PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrIVOZFO™
Fosfomycin for injection

Powder for solution, 2 g/vial, 4 g/vial and 8 g/vial Fosfomycin (as Fosfomycin Sodium), Intravenous

Antibiotic

ATC Code: J01XX01

VERITY PHARMACEUTICALS
2560 Matheson Blvd. E, Suite 220,
Mississauga, Ontario, L4W 4Y9

www.veritypharma.com

Date of Initial Approval:
May 1, 2019

Submission Control No: 219662

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

IVOZFO™ (fosfomycin for injection) is indicated for the treatment of the following infections in adults and children including neonates:

- 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

IVOZFO™ 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. Fosfomycin should usually be used as part of a combination antibacterial regimen (see **WARNINGS AND PRECAUTIONS, Susceptibility/Resistance**).

1.1 Pediatrics

Pediatrics (**<12 years)**: Based on the limited data submitted and reviewed by Health Canada, the safety and efficacy of IVOZFO™ (fosfomycin for injection) in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use. Safety and efficacy of fosfomycin in neonates and children with renal impairment have not been evaluated in clinical trials (see **DOSAGE AND ADMINISTRATION)**.

1.2 Geriatrics

Geriatrics (> 65 years of age): There was no difference in drug efficacy or tolerance for patients older than 65 years compared with patients younger than 65 years. Caution is advised when considering the use of doses at the higher end of the recommended range (see **WARNINGS AND PRECAUTIONS, Cardiovascular; Renal)**.

2 CONTRAINDICATIONS

IVOZFO™ (fosfomycin for injection) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.**

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- 1 g IVOZFO™ (fosfomycin for injection) contains 14 mmol (320 mg) sodium, equivalent to 16% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.
- There are limited safety data for doses in excess of 16 g/day; special caution is advised when such doses are prescribed.
- Plasma electrolytes (in particular sodium, potassium and phosphate) and fluid balance must be monitored regularly during therapy with IVOZFO, in particular when using the high dose regimen (>16 g/day in adults; > 300 mg/kg/day in children), and for all doses in neonates and premature infants due to variable renal sodium excretion.

(see **DOSAGE AND ADMINISTRATION; DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING; WARNINGS AND PRECAUTIONS, Cardiovascular, Monitoring and Laboratory Tests; and ADVERSE REACTIONS**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

Adults and adolescents ≥ 12 years of age (> 40 kg):
Fosfomycin is primarily excreted unchanged via the kidneys. The general dosage guidelines for adults with estimated creatinine clearance > 80 mL/min are provided in Table 1.

Table 1: General dosage guidelines for adults by indication

Indication	Daily dose
Osteomyelitis	12–24 g* in 2–3 divided doses
Complicated urinary tract infection	12–16 g in 2–3 divided doses
Nosocomial lower respiratory tract infection	12–24 g* in 2–3 divided doses
Bacterial meningitis	16–24 g* in 3–4 divided doses

*The high-dose regimen (> 16 g/day in 3 divided doses) should be used in severe infections expected or known to be caused by less susceptible bacteria (see **MICROBIOLOGY).**

Individual doses must not exceed 8 g.

There are limited safety data in particular for doses in excess of 16 g/day. Special caution is advised when such doses are prescribed.

Renal Impairment

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 IVOZFO™ (fosfomycin for injection) 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 by Cockroft and Gault:

$$\text{Creatinine clearance } (CL_{CR}) \text{ in men [mL/min]} = 1.2 \times \frac{(140 - \text{Age [years]}) \times \text{Body Weight [kg]}}{\text{Serum Creatinine [µmol/L]}}$$

$$\text{Creatinine Clearance } (CL_{CR}) \text{ in women (mL/min)} = \frac{(140 - \text{Age [years]}) \times \text{Body Weight [kg]}}{\text{Serum Creatinine [µmol/L]}}$$

Table 2: Dosage for patients with impaired renal function

CL_{CR} patient	Daily dosage recommended*
40 mL/min	70% (in 2–3 divided doses)
30 mL/min	60% (in 2–3 divided doses)
20 mL/min	40% (in 2–3 divided doses)
10 mL/min	20% (in 1–2 divided doses)

*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.

Dosage in patients undergoing renal replacement therapy
Patients undergoing chronic intermittent dialysis (every 48 hours) should receive 2 g of IVOZFO™ at the end of each dialysis session.

During continuous veno-venous hemofiltration (post-dilution CVVHF), IVOZFO™ is effectively eliminated. Patients undergoing post-dilution CVVHF will not require any dose adjustment (see **PHARMACOKINETICS, Renal Insufficiency**).

No clinical data exist for intravenous IVOZFO™ 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 ***Dosage in renal insufficiency*** above).

Neonates, infants and children < 12 years of age (< 40 kg):
Dose recommendations are based on very limited data. Fosfomycin is primarily excreted unchanged by the kidneys. No dose recommendations can be made for children with renal impairment.

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

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

Table 3: general dosage guidelines for pediatrics < 12 years of age (< 40 kg)

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 (>300 mg/kg/day) 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 (see **MICROBIOLOGY)**.

4.3 Administration

Method of administration
IVOZFO™ (fosfomycin for injection) is intended for intravenous administration. The duration of infusion should be at least 15 minutes for a 2 gram dose, 30 minutes for a 4 gram dose and 60 minutes for an 8 gram dose. Isolated reports from the literature indicate that extending the infusion time to up to 4 hours might reduce the risk of hypokalemia. In patients with high risk of hypokalemia, an extended infusion time (up to 4 hours for the 4g and 8g strengths) might be considered.

Use only clear solutions.

As damaging effects can result from inadvertent intra-arterial administration of IVOZFO, it is essential to ensure that IVOZFO™ is only administered into veins.

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.

4.4 Reconstitution

Preparation of the solution for infusion
IVOZFO™ (fosfomycin for injection) must be reconstituted and diluted prior to administration. Use Dextrose 5% in Water (D5W) for reconstitution of the powder. It is not recommended to use Sodium Chloride containing solutions for reconstitution of IVOZFO™ due

to their additional sodium load (See **WARNINGS AND PRECAUTIONS)**.

Reconstitution
Shake the vial prior to reconstitution to loosen up the powder. Reconstitute the 2 gram vial with 10 mL of diluent. Reconstitute the 4 gram vial with 20 mL of the diluent. Reconstitute the 8 gram vial with 40 mL of diluent. Shake well to dissolve. A slight degree of warming occurs when the powder is dissolved. Visually ensure that the powder is completely dissolved.

Caution: This intermediate solution is not for direct infusion. Withdraw the solution completely from the original vial. Upon reconstitution with D5W, further dilute the product immediately (see below). If not used immediately, the reconstituted product should be protected from light and stored at 2-8°C in the vial for no longer than 48 hours.

Dilution
For a **2 gram** dose, transfer the reconstituted contents of the 2 gram vial into a D5W PVC bag with 50 mL D5W (Dextrose 5% in Water) to reach a total volume of 60 mL.

For a **4 gram** dose, transfer the reconstituted contents of the 4 gram vial into a D5W PVC bag with 100 mL D5W (Dextrose 5% in Water) to reach a total volume of 120 mL.

For an **8 gram** dose, transfer the reconstituted contents of the 8 gram vial into a D5W PVC bag with 250 mL D5W (Dextrose 5% in Water) to reach a total volume of 290 mL.

The diluted product should be used immediately. If not used immediately, the diluted product should be protected from light and stored at 2-8°C or 25°C in the PVC bags for no longer than 48 hours.

The reconstituted product should be protected from light.

Table 4- Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Volume of final solution	Infusion Time (minutes)
2 g	10 mL	60 mL D5W	15
4 g	20 mL	120 mL D5W	30
8 g	40 mL	290 mL D5W	60

The concentration of the final solution should not exceed 40 mg/mL.

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

Inspect the product visually for particulate matter and discoloration prior to administration. DO NOT use if solution appears hazy, contains particles. Discard unused portion.

Check the container for minute leaks prior to use by squeezing the bag firmly; ensure that the seal is intact. If leaks are found, discard solution as sterility may be impaired.

Incompatibilities
Although no chemical/pharmaceutical incompatibilities have been found, fosfomycin solutions should not be mixed together with other parenteral preparations.

4.5 Missed Dose

If a dose is missed, it should be given as soon as possible. However, if it is less than two hours before the time for the next dose, no additional dose should be given and the regular dosing schedule should be resumed.

5 OVERDOSAGE

Experience regarding overdose with IVOZFO™ (fosfomycin for injection) is limited. Cases of hypotonia, somnolence, electrolytes disturbances (including hypernatremia, hypokalemia, hypophosphatemia), 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 hemodialysis with a mean elimination half-life of approximately 4 hours.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5– Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
intravenous	Powder for solution 2 g, 4 g and 8 g	Succinic acid

Each vial with 2.69 g of powder contains 2.64 g fosfomycin sodium, corresponding to 2 g fosfomycin and 0.64 g sodium.

Each vial with 5.38 g of powder contains 5.28 g fosfomycin sodium, corresponding to 4 g fosfomycin and 1.28 g sodium.

Each vial with 10.76 g of powder contains 10.56 g fosfomycin sodium, corresponding to 8 g fosfomycin and 2.56 g sodium.

IVOZFO™ (fosfomycin for injection) is supplied in clear type-I glass vials with a rubber stopper (bromobutyl rubber) and pull-off cap containing 2 g (in 30 mL vial), 4 g (in 30 mL vial) or 8 g (in 50 mL vial) of fosfomycin, respectively, in packs of 10 vials each.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

Cardiovascular
1 g IVOZFO™ (fosfomycin for injection) (equivalent to 1.32 g fosfomycin sodium) contains 14 mmol (320 mg) sodium, equivalent to 16% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult. Due to the additional sodium load, caution is advised when IVOZFO™ is used in patients with cardiac insufficiency, hypertension, hyperaldosteronism, hypernatremia or pulmonary edema. A high sodium load may also result in decreased levels of potassium in serum or plasma. Blood potassium levels should also be monitored, in particular in digitalized heart failure patients (see **ADVERSE REACTIONS, Monitoring and Laboratory Tests).**

The action of cardiac glycosides can be potentiated by potassium deficiency.

Gastrointestinal
Clostridium difficile-associated disease
Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including IVOZFO™ (see **ADVERSE REACTIONS**). CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *C. difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C. difficile*. Surgical evaluation should be instituted as clinically indicated; as surgical intervention may be required in certain severe cases.

Hepatic/Biliary/Pancreatic
Liver injury, usually reversible upon discontinuation of therapy, has been seen with use of fosfomycin, including steatosis and hepatitis. Liver function should be monitored periodically during intravenous fosfomycin treatment.

Patients with hepatic cirrhosis should be closely monitored for sodium overload.

Immune
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 IVOZFO™ (fosfomycin for injection) 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.

Monitoring and Laboratory Tests
1 g IVOZFO™ (fosfomycin for injection) (equivalent to 1.32 g fosfomycin sodium) 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 vial with 2 g of IVOZFO™ contains 28 mmol (640 mg)

sodium, one vial with 4 g IVOZFO™ contains 56 mmol (1,280 mg) sodium and one vial with 8 g of IVOZFO™ contains 111 mmol (2,560 mg) sodium.

A high sodium load associated with the use of IVOZFO™ 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 regularly during therapy (see **WARNINGS AND PRECAUTIONS, Cardiovascular; and ADVERSE REACTIONS**).

Hypokalemia may result in varied symptoms such as weakness, tiredness or edema 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 edema (see **WARNINGS AND PRECAUTIONS, Cardiovascular; and ADVERSE REACTIONS).**

Renal
Fosfomycin is primarily excreted unchanged by the kidneys. In patients with severe renal insufficiency (creatinine clearance ≤ 40mL/min), the elimination of IVOZFO™ (fosfomycin for injection) is substantially slowed. (See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, *Dosage in renal insufficiency***).

Data on fosfomycin clearance by continuous veno-venous hemofiltration is very limited and fosfomycin clearance may be extensive. Patients undergoing renal replacement therapy should be closely monitored for clinical efficacy and for adverse events.

Susceptibility/Resistance
Consideration should be given to co-administering IVOZFO™ (fosfomycin for injection) with another antibacterial agent, especially when treating multidrug-resistant pathogens, taking into account the remaining susceptibilities of the pathogen(s) under treatment. As it is unknown whether the development of resistance to IVOZFO™ is higher when it is used as a monotherapy, co-administration with other antibacterials should also be considered in order to prevent the emergence of resistance.

Sexual Health
Fertility: To date, in humans no reduction in fertility after therapy with fosfomycin has been reported. In male and female rats, reduced fertility was observed after the oral administration of fosfomycin at supra-therapeutic doses (see **NON-CLINICAL TOXICOLOGY**).

7.1 Special Populations

7.1.1 Pregnant Women

No clinical studies of fosfomycin use in pregnant women are available. Fosfomycin crosses the placental barrier. IVOZFO™ should therefore not be prescribed to pregnant women unless the benefit to the mother outweighs the risk to the fetus.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see **NON-CLINICAL TOXICOLOGY**).

7.1.2 Breast-feeding

Fosfomycin is excreted in human milk in low concentrations. No information is available on the effects of fosfomycin on the breast-fed child or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IVOZFO™ and any potential adverse effects on the breastfed child from IVOZFO™ or from the underlying maternal condition.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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 **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, *Dosage in renal impairment***).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

8.2 Post-Market Adverse Reactions

Adverse drug reactions are listed by body system and frequency in accordance with the following classification:

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

Table 6: Adverse Drug Reactions reported by System Organ Class

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
Metabolism and nutrition disorders	Common	Hypernatremia and/or hypokalemia
	Uncommon	Decreased appetite, edema
	Frequency not known	Hypophosphatemia
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, congestive cardiac failure
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnea
	Frequency not known	Asthmatic attack
Gastrointestinal disorders	Common	Retching, stomach ache
	Uncommon	Nausea, vomiting, diarrhea
	Frequency not known	Pseudomembranous colitis
Hepatobiliary disorders	Uncommon	Blood alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase increased (transient)
	Very rare	Fatty liver (completely reversible after discontinuation of IVOZFO™)
	Frequency not known	Hepatitis, cholestatic hepatitis, icterus, gamma-GT increased
Skin and subcutaneous tissue disorders	Common	Erythematous eruption
	Uncommon	Rash
	Frequency not known	Angioedema, facial edema, pruritus, urticaria

Table 6: Adverse Drug Reactions reported by System Organ Class

System Organ Class	Frequency Category	Adverse Drug Reactions
General disorders and administration site conditions	Common	Injection site phlebitis
	Uncommon	Fatigue

Adverse Reactions (Pediatrics)
Limited safety information is available from the pediatric population. Frequency, type and severity of adverse reactions may be expected to be similar to the adult population.

9 DRUG INTERACTIONS

9.1 Drug-Drug 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. The action of cardiac glycosides can be potentiated by hypokalemia, which may be seen with use of intravenous fosfomycin (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Combination with other antibiotics
In-vitro tests have shown that the combination of fosfomycin with a β-lactam antibiotic such as penicillin, ampicillin, cefazolin or the class of carbapenems, usually shows an additive to synergistic effect. The same applies to the combination of fosfomycin with most anti-staphylococcal (linezolid, quinupristin/dalfopristin, moxifloxacin) agents in the treatment of staphylococcal infections. The combination of fosfomycin with aminoglycosides has predominantly indifferent to additive effects.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 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).

10.2 Pharmacodynamics

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

10.3 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 µg/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 µg/mL and 3.6–3.8 h, respectively.

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

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 IVOZFO™ (fosfomycin for injection) administered to healthy adults is eliminated renally within 10 hours after a single intravenous administration. 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.

Special Populations and Conditions

Pediatrics: 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, depending on the stage of renal maturation.

Geriatrics: 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 **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, *Dosage in renal insufficiency***).

Hepatic Insufficiency: Since fosfomycin is not metabolised by the liver, the pharmacokinetics remain unaffected in this patient group.

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 **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, *Dosage in renal insufficiency***).

In a study investigating 12 patients under CVVHF customary polyethylene sulfone hemofilters 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 12 h, respectively.

11 STORAGE, STABILITY AND DISPOSAL

Shelf life of IVOZFO™: 4 years

Store IVOZFO™ at 15-30°C.

Following dilution into D5W (Dextrose 5% in Water), the product should be used immediately. If not used immediately, the product should be stored protected from light for no longer than 48 hours at 25°C in PVC bags and at 2-8°C in the vial and in PVC bags.

For single use only.
Any unused product or waste material should be disposed as biohazardous waste.

12 SPECIAL HANDLING INSTRUCTIONS

Keep out of sight and reach of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

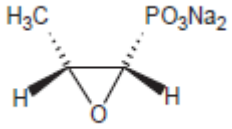
Drug Substance

Proper name: fosfomycin sodium

Chemical name: Disodium (2R, 3S)-(3-methyloxiran-2-yl) phosphonate

Molecular formula and molecular mass: C_3-H_5-Na_2-O_4-P and 182.02

Structural formula:



Physicochemical properties: Fosfomycin sodium is a white or almost white, very hygroscopic powder. It is very soluble in water, sparingly soluble in methanol, practically insoluble in ethanol and in methylene chloride.

14 MICROBIOLOGY

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 multi-resistant *Pseudomonas*.

Susceptibility Testing

The minimum inhibitory concentration (MIC) assessment method approved for fosfomycin by the US Clinical & Laboratory Standards Institute (CLSI) is the agar dilution method with the agar supplemented with 25 µg/ml of glucose-6-phosphate. The gradient diffusion test (commercialized as, e.g. E-test) is also available for MIC determination for fosfomycin.

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 (EUCAST breakpoint table version 9.0 Jan 2019) are provided in Table 7.

Table 7: Susceptibility* breakpoints established by EUCAST for fosfomycin

Species	susceptible	resistant
Enterobacterales	≤ 32 mg/L	> 32 mg/L
Staphylococcus spp.	≤ 32 mg/L	> 32 mg/L

*Agar dilution is the reference method for fosfomycin. MICs must be determined in the presence of glucose-6-phosphate (25 mg/L in the medium). Follow the manufacturers' instructions for commercial systems.

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
Table 8 is based on the breakpoint according to EUCAST and comprises organisms relevant for the approved indications:

Table 8: 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.

15 NON-CLINICAL TOXICOLOGY

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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

IVOZFO™
fosfomycin for injection

Read this carefully before you start taking **IVOZFO™**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IVOZFO™**.

Serious Warnings and Precautions

- IVOZFO™ contains sodium.
- Each gram of IVOZFO™ contains 320 mg of sodium. This is equal to 16 % of the recommended maximum daily dietary intake of sodium for an adult.
- Your doctor will be especially careful with this medicine if you are receiving more than 16 g of IVOZFO™ a day.
- Your doctor will monitor the electrolytes in your blood, including your sodium levels, while you are receiving IVOZFO™.
- Before you receive IVOZFO™, tell your doctor if you have any of the following health conditions: heart problems, high blood pressure, hyperaldosteronism which is a condition where you have too much of a hormone called aldosterone, cirrhosis (scar tissue) of the liver, kidney problems, high levels of sodium in your blood, or fluid in your lungs. .
- IVOZFO™ contains sodium that could make these conditions worse.

What is IVOZFO™ used for?

IVOZFO™ is used in adults and children to treat infections of the:
- lung
- bones
- kidney and bladder
- brain (called meningitis)
- blood that are caused by any of the infections listed above

It is used when other antibiotics cannot be used or have not worked.

This medicine is usually given in combination with other antibiotics.

Antibacterial drugs like IVOZFO™ treat only bacterial infections. They do not treat viral infections such as the common cold.

How does IVOZFO™ work?

IVOZFO™ belongs to a group of medicines called antibiotics. It works by killing a type of germ called bacteria that causes serious infections.

What are the ingredients in IVOZFO™?

Medicinal ingredients: fosfomycin sodium
Non-medicinal ingredients: succinic acid

IVOZFO™ does not contain any preservatives.

IVOZFO™ comes in the following dosage forms:

As a powder for solution. It comes in vials containing 2g, 4 g or 8 g fosfomycin (as fosfomycin sodium).

Do not use IVOZFO™ if you are:

- allergic to fosfomycin
- allergic to succinic acid, which is the non-medicinal ingredient in IVOZFO™
- allergic to any part of the container

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IVOZFO™. Talk about any health conditions or problems you may have, including if you:

- have heart problems
- have high blood pressure
- have hyperaldosteronism which is a condition where you have too much of a hormone called aldosterone
- high levels of sodium in your blood
- have too much fluid in your lungs which is a condition called pulmonary edema
- have kidney problems since your doctor may need to change the dose you receive
- have cirrhosis (scar tissue) of the liver
- are pregnant or thinking of becoming pregnant
- are breastfeeding or are planning to breastfeed

Other warnings you should know about:

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this medicine. If you are pregnant, IVOZFO™ may pass to your baby in the womb. It may also pass to your baby through your breast milk. If you are pregnant or breastfeeding your doctor will decide if you can receive this medicine.

Sodium content

Each gram of IVOZFO contains 320 mg sodium (salt). This is equal to 16 % of the recommended maximum daily dietary intake of sodium for an adult. Your doctor will monitor the electrolytes in your blood, including your sodium levels, while you are receiving IVOZFO™. You should be on a low sodium diet while you are receiving IVOZFO™.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take IVOZFO™:

- IVOZFO™ will be given to you by a healthcare professional.
- Your healthcare professional will reconstitute and further dilute IVOZFO™ before giving it to you.
- It is usually given 2, 3 or 4 times a day.
- It will be infused directly into your vein.
- It will be infused over a period of 15 – 60 minutes, depending on the dose you are given.
- If you are at risk for low levels of potassium in your blood, the infusion might take up to 4 hours.
- Follow all instructions given to you by your healthcare professional.

Usual dose:

- Your doctor will decide how much IVOZFO™ you will be given and how often and for how long you will receive it.
- The dose you are given will depend on the type and severity of your infection.
- If you have kidney problems or require dialysis, your dose may be reduced.
- For children, the dose they are given depends on their weight and age.

Overdose:

If you think you have been given too much IVOZFO™, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

IVOZFO™ is administered by a healthcare professional. If you suspect a missed dose, talk to your healthcare professional.

What are possible side effects from using IVOZFO™?

These are not all the possible side effects you may feel when taking IVOZFO™. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Nausea, retching, vomiting, stomach ache or mild diarrhea

- Taste disturbances
- Shortness of breath
- Rash
- Decreased appetite
- Headache
- Feeling of dizziness or a “spinning” sensation
- Tiredness
- Confusion
- Swelling due to fluid retention (edema)
- Visual impairment

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Hypokalemia (low level of potassium in the blood): constipation, confusion, cramping, feeling of skipped heartbeat or palpitations, fatigue, trouble breathing, muscle weakness, muscle spasms or twitching.		√	
Hypernatremia (high level of sodium in the blood): coma, confusion, thirst, muscle twitches, seizure.		√	
Pain, burning, redness or swelling along the vein being used for infusion of this medicine		√	
UNCOMMON			
Liver problems: abdominal pain, dark urine, fatigue, light-coloured stool, loss of appetite, nausea, vomiting, yellowing of the skin or eyes (jaundice).		√	
RARE			
Anemia (decreased red blood cells): dizziness, feeling tired and weak, loss of energy, pale complexion, shortness of breath.		√	
Eosinophilia (increased numbers of certain white blood		√	

cells): abdominal pain, rash, weight loss, wheezing.			
VERY RARE			
Allergic reaction: difficulty breathing, difficulty swallowing, fever, hives, itchy skin, rash, swelling of your tongue, throat or face.		√	
UNKNOWN			
Clostridium difficile colitis (bowel inflammation): abdominal pain or tenderness, fever, severe diarrhea (bloody or watery).		√	
Asthma attack or heart failure: shortness of breath, wheezing or a tight feeling in the chest.		√	
Tachycardia (faster heart beat)		√	
Neutropenia (decreased white blood cells): aches, feeling tired, fever, flu-like symptoms, infections.		√	
Thrombocytopenia (decreased platelets in the blood): bleeding, bruising, fatigue, weakness.		√	
Hypophosphatemia (low level of phosphate in the blood): confusion, coma, fatigue, muscle weakness.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of the reach and sight of children.
- Store at 15-30°C.
- Do not use this medicine after the expiry date which is stated on the carton and label after "EXP". The expiry date refers to the last day of that month.
- Following dilution into Dextrose 5% in Water, the product should be used immediately. If not used immediately, the diluted product should be protected from light and stored at 2-8°C or at 25°C in the PVC bags or at 2-8°C in the vial for no longer than 48 hours.

If you want more information about IVOZFO™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.veritypharma.com, or by calling 1-888-877-4414.

This leaflet was prepared by Verity Pharmaceuticals.

Last Revised May 1, 2019