CONTRAINdications (FOSMICIN-S is contraindicated in the following patients.)
Patients with a history of hypersensitivity to fosfomycin

DESCRIPTION
1. Composition
Each vial of FOSMICIN-S 0.5 g for Injection, FOSMICIN-S 1 g for Injection and FOSMICIN-S 2 g for Injection contains the following ingredients.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>FOSMICIN-S 0.5 g for Injection</th>
<th>FOSMICIN-S 1 g for Injection</th>
<th>FOSMICIN-S 2 g for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Fosfomycin Sodium 500 mg (potency)</td>
<td>Fosfomycin Sodium 1 g (potency)</td>
<td>Fosfomycin Sodium 2 g (potency)</td>
</tr>
<tr>
<td>Inactive ingredient</td>
<td>Anhydrous citric acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Product description
Dosage form: Crystalline powder
Color: White
pH: 6.5 – 8.5
Osmotic pressure ratio (OPR): 50 mg (potency)/mL (water)

DOSAGE AND ADMINISTRATION

<Indications>
Sepsis, acute bronchitis, pneumonia, lung abscess, pyothorax, secondary infections in chronic respiratory lesion, cystitis, pyelonephritis, peritonitis, Bartholinitis, intrauterine infection, uterine adnexitis, parametritis

[Intravenous drip infusion]
The usual daily dosage is 2 to 4 g (potency) of fosfomycin for adults and 100 to 200 mg (potency)/kg for children; both of these are given by intravenous drip infusion in 2 divided doses. Each dose is dissolved in 100 to 500 mL of infusion fluid and infused over a period of one to 2 hours.

[Intravenous injection]
The usual daily dosage is 2 to 4 g (potency) of fosfomycin for adults and 100 to 200 mg (potency)/kg for children; both of these are given by intravenous injection in 2 to 4 divided doses. As the solvent, 20 mL of water for injection (JP) or glucose injection (JP) is used to dissolve one to 2 g (potency) of the product. The injection must be performed over 5 minutes or more.

The dosage may be adjusted according to the patient’s age and symptoms in either case.

<Precautions>
As a general rule, the duration of administration of this drug should be limited to the minimum period required for the treatment of the patient’s condition, after susceptibility of the microorganism to the drug has been confirmed, in order to prevent the emergence of drug-resistant microorganisms.

PRECAUTIONS
1. Careful Administration (FOSMICIN-S should be administered with care in the following patients.)
(1) Patients with a personal or familial predisposition to allergic reactions such as bronchial asthma, rash or urticaria

(2) Patients with hepatic disorder [Hepatic disorder may worsen.]

2. Important Precautions

(1) Since no methods are available to reliably predict the potential occurrence of shock or anaphylactoid reaction due to this product, the following measures should be taken.

1) Patients should be carefully interviewed in advance to obtain any past history regarding the above reactions. Be sure to ascertain any history of allergy to antibiotics and other agents.

2) Emergency care must be prepared for treatment of shock etc., whenever using this product.

3) From the beginning of administration to after the end of administration of this product, patients should be kept at rest and observed carefully. Immediately after the beginning of administration, patients should be observed especially carefully.

(2) Since the product contains 14.5 mEq of sodium per g (potency), care should be taken when administering it to patients with cardiac failure, renal failure, hypertension, etc. that require the limited sodium intake.

3. Adverse Reactions

As the results of post-marketing drug-use results surveys, a total of 33,711 clinical cases were reported from 2,618 institutions nationwide. 710 episodes of adverse reactions were observed in 591 cases (1.75%). (At the end of reexamination)

The main adverse reactions were as follows.

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver and biliary system disorders [AST(GOT) increased, ALT(GPT) increased, etc.]</td>
<td>378</td>
</tr>
<tr>
<td>Skin and appendages disorders (Rash, pruritus, urticaria, etc.)</td>
<td>88</td>
</tr>
<tr>
<td>Gastrointestinal system disorders (Diarrhea, nausea, vomiting, abdominal pain, anorexia, etc.)</td>
<td>78</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders (Al-P increased, LDH increased, hypernatremia, etc.)</td>
<td>25</td>
</tr>
<tr>
<td>Vascular (extracardiac) disorders (Vascular pain, flushing)</td>
<td>15</td>
</tr>
<tr>
<td>Body as a whole-general disorders (Fever, malaise, etc.)</td>
<td>14</td>
</tr>
<tr>
<td>Urinary system disorders (Abnormal renal function etc.)</td>
<td>10</td>
</tr>
<tr>
<td>Central and peripheral nervous system disorders (Hypoaesthesia)</td>
<td>7</td>
</tr>
<tr>
<td>White cell and RES disorders (Leukopenia etc.)</td>
<td>7</td>
</tr>
</tbody>
</table>

(1) Clinically significant adverse reactions

1) Shock or anaphylactoid reaction (<0.1%) may occur. Patients should be carefully monitored and if any symptoms such as distressed feeling of chest, dyspnea, decreased blood pressure, cyanosis, urticaria or feeling unwell occur, administration should be discontinued and appropriate measures should be taken.

2) Serious colitis with bloody stool such as pseudomembranous colitis (<0.1%) may occur. Patients should be carefully monitored and if abdominal pain or frequent diarrhea occurs, administration should be discontinued immediately and appropriate measures should be taken.

3) Pan cytopenia, agranulocytosis or thrombocytopenia (<0.1%) may occur. Patients should be carefully monitored and if any abnormality is observed, administration should be discontinued and appropriate measures should be taken.

4) Hepatic function disorder or jaundice (<0.1%) may occur. Patients should be carefully monitored and if any abnormality is observed, appropriate measures such as discontinuation of administration should be taken.

5) Convulsion (incidence unknown) may occur. If such a symptom is observed, administration should be discontinued and appropriate measures should be taken.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>5% &gt; 0.1%</th>
<th>&lt;0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic</td>
<td>AST(GOT) increased, ALT(GPT) increased, Al-P increased, LDH increased, γ-GTP increased, bilirubin increased</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia, granulocytopenia, leukopenia, eosinophilia</td>
</tr>
<tr>
<td>Renal</td>
<td>Abnormal renal function, edema, BUN increased, proteinuria, electrolyte abnormality</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea, Stomatitis, nausea, vomiting, abdominal pain, anorexia</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Rash, Erythema, urticaria, itching</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Cough, asthmatic attack</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Nummness, vertigo</td>
</tr>
<tr>
<td>Injection site</td>
<td>Vascular pain, Phlebitis</td>
</tr>
<tr>
<td>Others</td>
<td>Headache, thirst, redness, fever, malaise, chest discomfort, chest pressure sensation, palpitation</td>
</tr>
</tbody>
</table>
4. Use in the Elderly
This product is mainly excreted by the kidney. (See “PHARMACOKINETICS” section.) It should be administered with caution, because many elderly patients have generally reduced renal function and thus adverse reactions are more likely to occur in these patients. Care should be taken in dose selection particularly in elderly patients with cardiac failure, renal failure, hypertension, etc. that require the limited sodium intake. [See “Important Precautions” section.]

5. Use during Pregnancy, Delivery or Lactation
Use of this product in pregnant women or women who may possibly be pregnant is not recommended. [The safety of this product in pregnant women has not been established.]

6. Pediatric Use
The safety of this product in low birth weight infants and newborns has not been established.

7. Precautions concerning Use
(1) Route of administration
The product should be administered only by intravenous route. In addition, it is advisable for administration to be performed by intravenous drip infusion whenever possible.

(2) Precautions in administration
Intravenous injection may cause phlebitis or vascular pain. Inject the product as slowly as possible and take special care with respect to the injection site and the method of injection.

8. Other Precautions
In the case of patients on long-term therapy using this product, periodic testing of hepatic function, renal function, and hematological parameters is recommended.

PHARMACOKINETICS
1. Blood concentration
   (1) Adults 1,2)
   When this product was administered by intravenous injection or intravenous drip infusion, the serum concentrations and pharmacokinetic parameters were as follows.

<table>
<thead>
<tr>
<th>Subject</th>
<th>n</th>
<th>Dose [g (potency)]</th>
<th>Volume of solvent (mL)</th>
<th>Administration period</th>
<th>Cmax (μg/mL)</th>
<th>T1/2 (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patient</td>
<td>6</td>
<td>1.0</td>
<td>20</td>
<td>5 min</td>
<td>744(100)</td>
<td>1.7</td>
</tr>
<tr>
<td>Healthy adult</td>
<td>3</td>
<td>1.0</td>
<td>200</td>
<td>1 hr</td>
<td>87.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Healthy adult</td>
<td>3</td>
<td>2.0</td>
<td>300</td>
<td>1 hr</td>
<td>157.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Healthy adult</td>
<td>3</td>
<td>2.0</td>
<td>300</td>
<td>2 hr</td>
<td>98.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Note: Serum concentration 30 minutes after administration

(2) Children 3)
In 4 school children (body weight: 20 to 37 kg, mean 28 kg) receiving 4-minute intravenous injection of 1.0 g (potency) of the product, the blood concentration and T1/2 were 93.8 to 107 μg/mL and 1.3 hours, respectively, 30 minutes to 1 hour after administration.

2. Protein binding
Binding rate to human serum protein determined by equilibrium dialysis method was 2.16%.

3. Sputum concentration 1)
In 5 patients with respiratory tract infections, intravenous injection of 1.0 g (potency) of the product produced a peak sputum concentration of 7.0 μg/mL 3 hours after injection.

4. Metabolism and excretion 2)
Fosfomycin is not metabolized in vivo and is mostly excreted into the urine as an active-unchanged form. In 3 healthy adults receiving one-hour intravenous drip infusion of 1.0 g (potency) or 2-hour intravenous drip infusion of 2.0 g (potency) of fosfomycin sodium, the urinary excretion rate was 95 to 99% within the first 10 to 11 hours after the completion of intravenous drip infusion.

CLINICAL STUDIES
The results of comparative clinical studies and open clinical studies were as follows 4-11):
The efficacy rate was:
1. 40.0% (6/15 cases) for sepsis (sepsis, bacteremia).
2. 64.8% (107/165 cases) for pneumonia (pneumonia, bronchopneumonia), acute bronchitis and secondary infections in chronic respiratory lesion (bronchitis, bronchiolitis, bronchiectasis with infection), lung abscess (pulmonary suppuration) and pyothorax.
3. 67.6% (213/315 cases) for peritonitis, pyelonephritis and cystitis.
4. 93.5% (29/31 cases) for uterine adnexitis, 91.3% (42/46 cases) for intrauterine infection, 82.6% (19/23 cases) for parametritis (parametritis, inflammation of pelvic dead space) and 100% (15/15 cases) for Bartholinitis.

PHARMACOLOGY

1. In vitro antibacterial activity

Fosfomycin acts bactericidally on gram-positive and gram-negative bacteria. It is especially highly active against Pseudomonas aeruginosa, Proteus sp., Morganella morganii, Serratia marcescens and multi-drug resistant strains of Staphylococcus aureus and Escherichia coli.

2. Mechanism of action

The mechanism of action of fosfomycin is very unique. It is efficiently taken into bacterial cells via the active transport system in the cytoplasmic membrane and inhibits the early stage of cell wall peptidoglycan biosynthesis. (β-lactam antibiotics inhibit the final stage.)

PHYSICOCHEMISTRY

Nonproprietary name: Fosfomycin Sodium
Chemical name: Disodium (2R, 3S)-3-methyloxiran-2-ylphosphonate
Abbreviation: FOM
Molecular formula: C3H5Na2O4P
Molecular weight: 182.02
Structural formula:

```
H3C
O

|PO3Na2
H
H
```

Description:
Fosfomycin Sodium occurs as a white crystalline powder. It is very soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol (99.5).

Partition coefficient:

| pH 2.0 - 10.0 | < -3.0 |

PRECAUTIONS FOR HANDLING

When this product is dissolved, heat of dissolution is released; this has no detrimental effect on the product or its activity.

PACKAGING

FOSMICIN-S 0.5 g for Injection:
500 mg (potency)/vial × 10 vials
FOSMICIN-S 1 g for Injection:
1 g (potency)/vial × 10 vials
FOSMICIN-S 2 g for Injection:
2 g (potency)/vial × 10 vials

REFERENCES


REQUEST FOR LITERATURE SHOULD BE MADE TO:
Drug Information Center
Meiji Seika Kaisha, Ltd.
4-16, Kyobashi 2-chome, Chuo-ku, Tokyo 104-8002, Japan

Manufactured and distributed by:
Meiji Seika Kaisha, Ltd.
4-16, Kyobashi 2-chome, Chuo-ku, Tokyo 104-8002, Japan