DISCLAIMER

All labeling reflected on this website is for informational and promotional purposes only. It is not intended to be used by healthcare professionals or patients for the purpose of prescribing or administering these products. Questions regarding the current content of product labeling should be directed to Akorn's Customer Service department at 800.932.5676.
Capastat® Sulfate
Capreomycin for Injection, USP
For Intramuscular and Intravenous Infusion Only
Not for Pediatric Use

INDICATIONS AND USAGE

Susceptibility studies should be performed to determine the presence of a capreomycin-susceptible strain of M. tuberculosis.

CONTRAINDICATION

Capastat Sulfate is contraindicated in patients who are hypersensitive to capreomycin.

PRECAUTIONS

General

AUDIOMETRIC MEASUREMENTS AND ASSESSMENT OF VESTIBULAR FUNCTION

Audiometric measurements and assessment of vestibular function should be performed prior to initiation of therapy with Capastat Sulfate.

Renal injury, with tubular necrosis, elevation of the blood urea nitrogen (BUN) or serum creatinine, and abnormal urinary sediment, has been noted. Slight elevation of the BUN and serum creatinine has been observed in a significant number of patients receiving prolonged therapy. The appearance of casts, red cells, and white cells in the urine has been noted in a high percentage of these cases.

Elevation of the BUN above 30 mg/100 mL, or any other evidence of decreasing renal function with or without a rise in BUN levels calls for careful evaluation of the patient, and the dosage should be reduced or the drug completely withdrawn. The clinical significance of abnormal urine sediment and slight elevation in the BUN (or serum creatinine) observed during long-term therapy with Capastat Sulfate has not been established.

The peripheral neuromuscular blocking action that has been attributed to other polypeptide antibiotics (colistin, polymyxin A sulfate, polymyxin B sulfate, paromomycin, and viomycin) and to aminoglycoside antibiotics (streptomycin, dihydrostreptomycin, neomycin, and kanamycin) has been studied with Capastat Sulfate. A partial neuromuscular blockade was demonstrated after large intravenous doses of Capastat Sulfate. This action was enhanced by other anesthetics (as has been reported for neomycin) and was antagonized by neostigmine.

Caution should be exercised in the administration of antibiotics, including Capastat Sulfate, to any patient who has demonstrated some form of allergy, particularly to drugs.

Laboratory Tests

Regular tests of renal function should be made throughout the period of treatment, and reduced dosage should be employed in patients with known or suspected renal impairment.

Renal function studies should be made both before therapy with Capastat Sulfate is started and on a weekly basis during treatment.

Since hypokalemia, hypomagnesemia and hypocalcemia may occur during therapy, these serum electrolyte levels should be determined frequently.

Drug Interactions

For neuromuscular blocking action of this drug, see PRECAUTIONS, GENERAL.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been performed to determine potential for carcinogenicity, mutagenicity, or impairment of fertility.

Usage in Pregnancy

Capastat Sulfate has been shown to be teratogenic in rats when given in doses 3.1/2 times the human dose. There are no adequate and well-controlled studies in pregnant women. Capastat Sulfate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see boxed WARNINGS and ANIMAL PHARMACOLOGY).

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Capastat Sulfate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (see boxed WARNINGS).

Geriatric Use

Clinical studies of Capastat Sulfate did not analyze the safety and efficacy of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at lower than the usual adult dose. Age-related renal function studies should be made both before therapy with Capastat Sulfate is started and on a weekly basis during treatment.

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ADVERSE REACTIONS

Nephrotoxicity: In 36% of 722 patients treated with Capastat Sulfate, elevation of the BUN above 20 mg/100 mL has been observed. In many instances, there was also depression of PSP excretion and abnormal urine sediment. In 10% of patients, the BUN elevation exceeded 30 mg/100 mL.

Toxic nephritis was reported in 1 patient with tuberculosis and portal cirrhosis who was treated with Capastat Sulfate (1 g) and aminosalicylic acid daily for 1 month. This patient developed renal insufficiency and oliguria and died. Autopsy showed subacute tubular necrosis. Electrolyte disturbances including hypokalemia, hypomagnesemia and hypocalcemia, sometimes serious in nature, have been reported.

Otoxicity: Subclinical auditory loss was noted in approximately 11% of 722 patients undergoing treatment with Capastat Sulfate. This was a 5- to 10-decibel loss in the 4000- to 8000-Hz region.

M. tuberculosis agents, is indicated in pulmonary infections caused by capreomycin-susceptible strains of M. tuberculosis when the primary agents (isoniazid, rifampin, ethambutol, aminosalicylic acid, and streptomycin) have been ineffective or cannot be used because of toxicity or the presence of resistant tubercle bacilli.

Since other parenteral antituberculosis agents (streptomycin, viomycin) also have similar and sometimes irreversible toxic effects, particularly on cranial nerve VIII and renal function, simultaneous administration of these agents with Capastat Sulfate is not recommended. Use with nonantituberculosis drugs (polymyxin A sulfate, colistin sulfate, amikacin, gentamicin, tobramycin, vancomycin, kanamycin, and neomycin) having ototoxic or nephrotoxic potential should be undertaken only with great caution.

Usage in Pregnancy: The safety of the use of Capastat Sulfate in pregnancy has not been determined.

Pediatric Usage: Safety and effectiveness in pediatric patients have not been established.
8000-CPS range. Clinically apparent hearing loss occurred in 3% of the 722 subjects. Some audiometric changes were reversible. Other cases with permanent loss were not progressive following withdrawal of Capastat Sulfate.

Tinnitus and vertigo have occurred.

Liver: Serial tests of liver function have demonstrated a decrease in BSP excretion without change in AST (SGOT) or ALT (SGPT) in the presence of preexisting liver disease. Abnormal results in liver function tests have occurred in many persons receiving Capastat Sulfate in combination with other antituberculosis agents that also are known to cause changes in hepatic function. The role of Capastat Sulfate in producing these abnormalities is not clear; however, periodic determinations of liver function are recommended.

Blood: Leukocytosis and leucopenia have been observed. The majority of patients treated have had eosinophilia exceeding 5% while receiving daily injections of Capastat Sulfate. This has subsided with reduction of the Capastat Sulfate dosage to 2 or 3 g weekly.

Pain and induration at the injection site have been reported. Excessive bleeding at the injection site has been reported. Sterile abscesses have been noted. Rare cases of thrombophlebitis have been reported.

Hypersensitivity: Urticaria and maculopapular skin rashes associated in some cases with febrile reactions have been reported when Capastat Sulfate and other antituberculosis drugs were given concomitantly.

OVERDOSAGE

Signs and Symptoms
Nephrotoxicity following the parenteral administration of Capastat Sulfate is most closely related to the area under the curve of the serum concentration versus time graph. The elderly patient, patients with abnormal renal function or dehydration, and patients receiving other nephrotoxic drugs are at much greater risk for developing acute tubular necrosis.

Damage to the auditory and vestibular divisions of cranial nerve VIII has been associated with Capastat Sulfate given to patients with abnormal renal function or dehydration and in those receiving medications with additive auditory toxicities. These patients often experience dizziness, tinnitus, vertigo, and a loss of high-tone acuity.

Neuromuscular blockade or respiratory paralysis may occur following rapid intravenous infusion.

If capreomycin is ingested, toxicity would be unlikely because it is poorly absorbed (less than 1%) from an intact gastrointestinal system.

Hypokalemia, hypocalcemia, hypomagnesemia, and an electrolyte disturbance resembling Bartter’s syndrome have been reported to occur in patients with capreomycin toxicity.

The subcutaneous median lethal dose in mice was 514 mg/kg.

Treatment
To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians’ Desk Reference (PDR). In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Protect the patient’s airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient’s vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient’s airway when employing gastric emptying or charcoal.

Patients who have received an overdose of capreomycin and have normal renal function should be carefully hydrated to maintain a urine output of 3 to 5 mL/kg/h. Fluid balance, electrolytes, and creatinine clearance should be carefully monitored.

Hemodialysis may be effective provided to remove capreomycin in patients with significant renal disease.

DOSAGE AND ADMINISTRATION

Capastat Sulfate may be administered intramuscularly or intravenously following reconstitution. Reconstitution is achieved by dissolving the vial contents (1 g) in 2 mL of 0.9% Sodium Chloride Injection or Sterile Water for Injection. Two to 3 minutes should be allowed for complete dissolution.

**Intravenously** — For intravenous infusion, reconstituted Capastat Sulfate should be diluted in 100 mL of 0.9% Sodium Chloride Injection and administered over 60 minutes.

**Intramuscularly** — Reconstituted Capastat Sulfate should be given by deep intramuscular injection into a large muscle mass, since superficial injection may be associated with increased pain and the development of sterile abscesses.

For administration of a 1-g dose, the entire contents of the vial should be given. For doses lower than 1 g, the following dilution table may be used.

**DILUTION TABLE**

<table>
<thead>
<tr>
<th>Diluent Added to 1-g, 10-mL Vial</th>
<th>Volume of Capastat Sulfate Solution</th>
<th>Concentration (Approx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.15 mL</td>
<td>2.65 mL</td>
<td>370 mg/mL</td>
</tr>
<tr>
<td>2.63 mL</td>
<td>3.33 mL</td>
<td>315 mg/mL</td>
</tr>
<tr>
<td>3.3 mL</td>
<td>4 mL</td>
<td>260 mg/mL</td>
</tr>
<tr>
<td>4.3 mL</td>
<td>5 mL</td>
<td>210 mg/mL</td>
</tr>
</tbody>
</table>

* Equivalent to capreomycin activity. Approximated concentration takes into account the retention volume.

The solution may acquire a pale straw color and darken with time, but this is not associated with loss of potency or the development of toxicity. After reconstitution, all solutions of Capastat Sulfate may be stored for up to 24 hours under refrigeration.

Capreomycin is always administered in combination with at least 1 other antituberculosis agent to which the patient’s strain of tubercle bacilli is susceptible. The usual dose is 1 g daily (not to exceed 20 mg/kg/day) given intramuscularly or intravenously for up to 10 days, followed by 1 g by either route 2 or 3 times weekly. (Note — Therapy for tuberculosis should be maintained for 12 to 24 months. If facilities for administering injectable medication are not available, a change to appropriate oral therapy is indicated on the patient’s release from the hospital.)

Patients with reduced renal function should have dosage reduction based on creatinine clearance using the guidelines included in Table 1. These dosages are designed to achieve a mean steady-state capreomycin level of 10 μg/mL.

**Table 1. Estimated Dosages to Attain Mean Steady-State Serum Capreomycin Concentration of 10 mg/mL (Based on Creatinine Clearance)**

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Capreomycin Clearance (L/kg/h x 10(^{-2}))</th>
<th>Half-life (hours)</th>
<th>Dose(^{a}) (mg/kg) for the Following Dosing Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1.01</td>
<td>29.4</td>
<td>2.43</td>
</tr>
<tr>
<td>30</td>
<td>1.49</td>
<td>20.0</td>
<td>3.58</td>
</tr>
<tr>
<td>40</td>
<td>1.97</td>
<td>15.1</td>
<td>4.72</td>
</tr>
<tr>
<td>50</td>
<td>2.45</td>
<td>12.2</td>
<td>5.87</td>
</tr>
<tr>
<td>60</td>
<td>2.92</td>
<td>10.2</td>
<td>7.01</td>
</tr>
<tr>
<td>80</td>
<td>3.40</td>
<td>8.8</td>
<td>8.16</td>
</tr>
<tr>
<td>100</td>
<td>4.35</td>
<td>6.8</td>
<td>9.45</td>
</tr>
<tr>
<td>110</td>
<td>5.78</td>
<td>5.2</td>
<td>13.9</td>
</tr>
</tbody>
</table>

* For patients with renal impairment, initial maintenance dose estimates are given for optimal dosing intervals; longer dosing intervals are expected to provide greater peak and lower trough serum capreomycin levels than shorter dosing intervals.

The usual dosage for patients with normal renal function is 1000 mg daily, not to exceed 20 mg/kg/day, for 60 to 120 days, then 1000 mg 2 to 3 times weekly.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**HOW SUPPLIED**

Capastat \(^{\circledR}\) Sulfate, Capreomycin for Injection, USP, is available in:

Vials: 1 g*, 10 mL size (No. 718) (1s) NDC 17478-080-50

*Equivalent to capreomycin activity.

Store at controlled room temperature 15° to 30°C (59° to 86°F) prior to reconstitution.

**ANIMAL PHARMACOLOGY**

In addition to renal and cranial nerve VIII toxicity demonstrated in animal toxicology studies, cataracts developed in 2 dogs on doses of 62 mg/kg and 100 mg/kg for prolonged periods. In teratology studies, a low incidence of “wavy ribs” was noted in litters of female rats treated with daily doses of 50 mg/kg or more of capreomycin.

**REFERENCES**


2. Unpublished data on file at Akorn.

Manufactured by: Akorn, Inc.
Lake Forest, IL 60045

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