1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

CAPASTAT 1 g (Injection)

COMPOSITION:

Each vial contains 1 000 000 units of capreomycin sulphate (approximately equivalent to 1 g capreomycin base).

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.3 Tuberculostatics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Capreomycin is active against human strains of *Mycobacterium tuberculosis*.

Pharmacokinetic properties:

Capreomycin sulphate is not significantly absorbed from the gastrointestinal tract, and must be administered parenterally.

Following intramuscular injection of 1 g of capreomycin in human subjects peak serum concentration in the range of 20 – 47 µg/ml (average 28 and 32 µg/ml) are achieved after 1 – 2 hours. Serum concentrations are low at 24 hours and daily injections of 1 g for 30 days produced no significant accumulation in subjects with normal renal function.

Frequent cross-resistance occurs with capreomycin. Varying degrees of cross-resistance between capreomycin and kanamycin and neomycin have been reported. There is no recent information on cross-

resistance between capreomycin and isoniazid, para-aminosalicylic acid (PAS), cycloserine, streptomycin, ethionamide, or ethambutol exists.

Capreomycin is excreted in the urine, essentially unaltered, and approximately 50% of a 1 g intramuscular dose is excreted within 12 hours.

INDICATIONS:

CAPASTAT should be used concomitantly with other appropriate antituberculous agents for the treatment of pulmonary infections caused by CAPASTAT-susceptible strains of *Mycobacterium tuberculosis* when the primary agents (isoniazid, rifampicin, streptomycin and ethambutol) have been ineffective because of the presence of resistant tubercle bacilli.

CONTRA-INDICATIONS:

Hypersensitivity to CAPASTAT.

WARNINGS:

The use of CAPASTAT in patients with renal insufficiency or pre-existing, auditory impairment must be undertaken with great caution, and the risk of additional eighth cranial nerve impairment or renal injury should be weighed against the benefits to be derived from treatment.

CAPASTAT must be used only in conjunction with adequate doses of other antituberculous drugs. The use of CAPASTAT alone allows the rapid development of strains resistant to it.

As CAPASTAT is potentially ototoxic, audiometry and assessment of vestibular function should be performed before starting treatment and at regular intervals during treatment.

Regular tests of renal function should be made throughout the period of treatment. Elevation of urea above 10.7 mmol/litre or any other evidence of decreasing renal function with or without a rise in urea levels calls for careful evaluation of the patient, and the dosage should be reduced or completely withdrawn. (See “DOSAGE AND DIRECTIONS FOR USE”).

INTERACTIONS:

Simultaneous administration of other antituberculous drugs which also have ototoxic and nephrotoxic potential (e.g. streptomycin, viomycin) is not recommended. Also use with other medicines that are not given for the treatment of tuberculosis but have ototoxic or nephrotoxic potential (e.g. amikacin, gentamycin, tobramycin, vancomycin and kanamycin) should also be undertaken only with great caution.

PREGNANCY AND LACTATION:

The safety of this preparation in pregnancy and lactation has not been established. CAPASTAT has been shown to be teratogenic in rats when given at 3,5 times the human dose. There are no adequate and well controlled studies in pregnant women. CAPASTAT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether CAPASTAT is excreted in human milk. Caution should be exercised when administering CAPASTAT to a breastfeeding woman.

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

DOSAGE AND DIRECTIONS FOR USE:

The usual dose is 1 g daily (but 20 mg/kg/day should not be exceeded) given by deep intramuscular injection only for 60 to 120 days, followed by 1 g intramuscularly two or three times a week.
CAPASTAT is always administered in combination with at least two other antituberculous agents to which the patient's strain of tubercle bacillus is susceptible.

CAPASTAT should be dissolved in 2 ml of 0.9% Sodium Chloride Intravenous Infusion or Water for Injections. Two to three minutes should be allowed for complete solution. The reconstituted solution must be used immediately. Any unused portion of the reconstituted solution should be discarded.

For administration of a 1 g dose, the entire contents of the vial should be given.
For dosages of less than 1 g the following dilution table may be used:

Diluent to be added	Approximate volume of CAPASTAT solution	Approximate average concentration in terms of mg of CAPASTAT activity
2.15 ml	2.85 ml	370mg/ ml
2.63 ml	3.33 ml	315 mg/ml

3.3 ml	4.0 ml	260mg/ml
4.3 ml	5.0 ml	210 mg/ml

The elderly: As for adults. Reduce dosage if renal function is impaired.

Patients with reduced renal function: A reduced dosage should be given based on creatinine clearance using the guidance given in the following table. These dosages are designed to achieve a mean steady-state CAPASTAT level of 10 micrograms/ml, at various levels of renal function:

Creatinine clearance	**CAPASTAT clearance**	**Half life**	**Dose[a] for these dosing intervals (mg/kg)**		
(ml/min)	**(l/kg/h x 10 –2)**	**(hours)**	**24h**	**48 h**	**72h**
0	0.54	55.5	1.29	2.58	3.87
10	1.01	29.4	2.43	4.87	7.30
20	1.49	20.0	3.58	7.16	10.70
30	1.97	15.1	4.72	9.45	14.20
40	2.45	12.2	5.87	11.70	
50	2.92	10.2	7.01	14.00	
60	3.40	8.8	8.16		
80	4.35	6.8	10.40		
100	5.31	5.6	12.7		
110	5.78	5.2	13.9		

[a] For patients with renal impairment, initial maintenance dose estimates are given for optional dosing intervals are expected to provide greater peak and lower trough serum CAPASTAT levels than shorter dosing intervals.

Infants and children: Not for paediatric use since the safety of CAPASTAT for use in infants and children has not been established.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

Renal and urinary disorders:

Frequent: Elevation of serum creatinine or blood urea and abnormal urine sediment.

Less frequent: Toxic nephritis was reported in one patient with tuberculosis and portal cirrhosis who was treated with CAPASTAT (1 g) and para-aminosalicylic acid (PAS) daily for one month. This patient developed renal insufficiency and oliguria and died. The post-mortem showed subsiding acute tubular necrosis.

Electrolyte disturbances resembling Bartter's syndrome have been reported in one patient.
Nephrotoxicity – Cases of serious electrolyte disturbances including hypokalaemia, hypomagnesaemia and hypocalcaemia, some of which can be fatal may occur during treatment with CAPASTAT. Serum Potassium, magnesium and calcium levels must be monitored.

Hepatobiliary disorders:

Less frequent: Abnormal results in liver function tests have occurred in many patients receiving CAPASTAT in combination with other antituberculous agents which are also known to cause changes in hepatic function, periodic determinations of liver function are recommended.

Blood and lymphatic system disorders:

Frequent: Most patients receiving daily CAPASTAT have had eosinophilia exceeding 5%, but this has subsided with the reduction of CAPASTAT dosage to two or three times weekly.
Less frequent: Leucocytosis and leucopenia have been observed. Rare cases of thrombocytopenia have been reported.

Ear and labyrinth disorders:

Less frequent: Clinical and subclinical auditory loss has been noted. Some audiometric changes have proved reversible and other with permanent loss has not been progressive following withdrawal of CAPASTAT. Tinnitus and vertigo have occurred.

General disorders and administration site conditions:

Less frequent:

Hypersensitivity: Urticaria and maculopapular rashes associated in some cases with febrile reactions have been reported when CAPASTAT and other antituberculous medicines were given concomitantly.

Pain and induration at injection sites have been observed. Excessive bleeding and sterile abscesses have also been reported at these sites.

Precautions:

As CAPASTAT is potentially ototoxic, audiometry and assessment of vestibular function should be performed before starting treatment and at regular intervals during treatment.

Regular tests of renal function should be made throughout the period of treatment. Elevation of urea above 10.7 mmol/litre or any other evidence of decreasing renal function with or without a rise in urea levels calls for careful evaluation of the patient, and the dosage should be reduced or completely withdrawn. (See "DOSAGE AND DIRECTIONS FOR USE").

Since hypokalaemia, hypomagnesaemia and hypocalcaemia may occur during CAPASTAT therapy, serum electrolyte levels should be checked frequently.

A partial neuromuscular block can occur after large doses of CAPASTAT.

CAPASTAT should be administered cautiously to patients with a history of allergy, particularly to medicines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Hypokalaemia, hypocalcaemia, hypomagnesaemia and an electrolyte disturbance resembling Bartter's syndrome have been reported to occur in patients with CAPASTAT toxicity. Nephrotoxicity, including acute tubular necrosis; and ototoxicity including dizziness, tinnitus, vertigo and loss of high-tone acuity. Neuromuscular blockage or respiratory paralysis may occur following rapid intravenous administration.

If CAPASTAT is ingested, toxicity is unlikely because less then 1% is absorbed from an intact gastro-intestinal system.

Treatment is symptomatic and supportive therapy is recommended. Activated charcoal may be more effective than emesis or lavage in reducing absorption.

Patients who have received an overdose of CAPASTAT and have normal renal function should be hydrated to maintain a urine output of 3 – 5 ml/kg/hr. Fluid balance electrolytes and creatinine clearance should be monitored.

Haemodialysis may be effectively used to remove CAPASTAT in patients with significant renal disease.

IDENTIFICATION:

A white to off white plug in a clear vial with a grey stopper.

PRESENTATION:

Rubber stopper, clear glass vial, with aluminium or plastic seal, containing

1 000 000 units (1 g capreomycin base) as a sterile white powder.

STORAGE INSTRUCTIONS:

Store below 25°C.

The solution may acquire a pale straw colour and darken with time, but this is not associated with loss of potency or the development of toxicity.

Reconstituted product must be used immediately. Any unused portion of the solution must be discarded.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A40/20.2.3/0680

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