# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Capreomycin Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Capreomycin Sulphate (approximately equivalent to 1g Capreomycin base).

## 3 PHARMACEUTICAL FORM

Powder for solution for injection.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

Frequent cross-resistance occurs between capreomycin and viomycin. Varying degrees of cross-resistance between capreomycin and kanamycin and neomycin have been reported. No cross-resistance has been observed between capreomycin and isoniazid, aminosalicylic acid, cycloserine, streptomycin, ethionamide or ethambutol.

*Indications*: Capreomycin should be used concomitantly with other appropriate antituberculous agents for the treatment of pulmonary infections caused by capreomycin susceptible strains of *Mycobacterium tuberculosis* when the primary agents (isoniazid, rifampicin, streptomycin and ethambutol) have been ineffective or cannot be used because of toxicity or the presence of resistant tubercle bacilli.

### 4.2 Posology and method of administration

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

Capreomycin should be dissolved in 2ml of 0.9% Sodium Chloride Intravenous Infusion BP or Water for Injections PhEur. Two to three minutes should be allowed for complete solution.

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

| Diluent to be added (ml) | Appropriate volume of Capreomycin solution (ml) | Approximate average concentration (mg/ml) in terms of mg of capreomycin activity |
|---|---|---|
| 2.15 | 2.85 | 370 |
| 2.63 | 3.33 | 315 |
| 3.3 | 4.0 | 260 |
| 4.3 | 5.0 | 210 |

*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 capreomycin level of 10 micrograms/ml, at various levels of renal function:

| Creatinine Clearance | Capreomycin clearance | Half life | Dose for these dosing intervals (mg/kg) | | |
|---|---|---|---|---|---|
| (ml/min) | (l/kg/h x $10^2$) | (hours) | 24h | 48h | 72h |
| 0 | 0.54 | 55.5 | 1.29 | 2.56 | 3.87 |
| 10 | 1.01 | 29.4 | 2.43 | 4.87 | 7.30 |
| 20 | 1.49 | 20.0 | 3.58 | 7.15 | 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 | 12.70 | | |
| 110 | 5.78 | 5.2 | 13.90 | | |

*Paediatric population*
Not for paediatric use since the safety of capreomycin for use in infants and children has not been established. No data are available.

## 4.3 Contraindications

Hypersensitivity to the active substance.

## 4.4 Special warnings and precautions for use

*Warnings*

The use of capreomycin 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.

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

*Precautions*

As capreomycin 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, and reduced dosage should be used in patients known, or suspected, renal impairment (see "Dosage and Administration").

Since hypokalaemia may occur during capreomycin therapy, serum potassium levels should be determined frequently.

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

Capreomycin should be administered cautiously to patients with a history of allergy, particularly to drugs.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of capreomycin for use during pregnancy has not been established. Capreomycin 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. Capreomycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fertility

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

Breast-feeding

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

## 4.7 Effects on ability to drive and use machines

Not relevant.

## 4.8 Undesirable effects

*Renal:* Elevation of serum creatinine or blood urea and abnormal urine sediment have been observed. Toxic nephritis was reported in one patient with tuberculosis and portal cirrhosis who was treated with capreomycin (1g) and aminosalicylic acid 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.

*Hepatic:* A decrease in bromsulphthalein excretion without change in serum enzymes has been noted in the presence of pre-existing liver disease. Abnormal results in liver function tests have occurred in many patients receiving capreomycin in combination with other antituberculous agents which are also known to cause changes in hepatic function. Periodic determinations of liver function are recommended.

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

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

*Otic:* Clinical and subclinical auditory loss has been noted. Some audiometric changes have proved reversible and others, with permanent loss have not been progressive following withdrawal of capreomycin. Tinnitus and vertigo have occurred.

*Injection site reactions:* Pain and induration at injection sites have been observed. Excessive bleeding and sterile abscesses have also been reported at these sites.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

### 4.9 Overdose

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

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

*Treatment*: 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 capreomycin and have normal renal function should be hydrated to maintain a urine output of 3-5ml/kg/hr. Fluid balance electrolytes and creatinine clearance should be monitored.

Haemodialysis is effective in patients with significant renal disease.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, ATC code: J04AB30

Capreomycin is active against human strains of Mycobacterium tuberculosis.

### 5.2 Pharmacokinetic properties

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

Following intramuscular injection of 1g of capreomycin in human subjects, peak serum concentrations in the range of 20-50µg/ml are achieved after 1-2 hours. Serum concentrations are low at 24 hours and daily injections of 1g for 30 days produced no significant accumulation in subjects with normal renal function.

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

### 5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber in addition to those summarised in other sections of the Summary of Product Characteristics.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

Three years.
Reconstituted solutions of Capreomycin may be stored below 25$^{o}$C for 24 hours. Discard unused portion.

### 6.4 Special precautions for storage

Store below 25˚C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Rubber stoppered, clear glass vial, with aluminium or plastic seal, containing capreomycin sulphate equivalent to approximately 1g capreomycin base, as sterile white powder.

### 6.6 Special precautions for disposal and other handling

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.

No special requirements for disposal.

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

## 7 MARKETING AUTHORISATION HOLDER

King Pharmaceuticals Ltd
Donegal Street
Bailybofey
County Donegal
Ireland

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 14385/0006

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:19 November 1997
Date of latest renewal: 01 June 2010

## 10 DATE OF REVISION OF THE TEXT

19/11/2015