APPROVED POFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAME (and dosage form):

SRATOP 250 mg (Powder for injection)

SRATOP 500 mg (Powder for injection)

SRATOP 1 g (Powder for injection)

COMPOSITION:

SRATOP 250 mg:

Each vial contains sterile cefazolin sodium equivalent to cefazolin 250 mg.

SRATOP 500 mg:

Each vial contains sterile cefazolin sodium equivalent to cefazolin 500 mg.

SRATOP 1 g:

Each vial contains sterile cefazolin sodium equivalent to cefazolin 1 g.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Cefazolin is a broad-spectrum bactericidal, semi-synthetic cephalosporin for parenteral administration.

Cefazolin is bactericidal against a wide range of gram-positive and gram-negative micro-organisms.

Most strains of indole-positive *Proteus* (*Proteus vulgaris*), *Enterobacter cloacae*, *Morganella morganii*, and *Providencia rettgeri* are resistant. Almost uniformly resistant to cefazolin are *Serratia*, *Pseudomonas* and *Acinetobacter calcoaceticus*. *In vitro* sensitivity does not necessarily imply *in vivo* efficacy.

Pharmacokinetics Properties:

Cefazolin given intramuscularly or intravenously produces notably high serum levels. Serum binding occurs at a rate of 74 %. Cefazolin is resistant to degradation in the body, is virtually not inactivated in the liver, and is primarily excreted in the urine unchanged. Following intramuscular injection of cefazolin 500 mg, 63 ± 17 % of the dose was recovered within 6 hours and approximately 80 % to 100 % within 24 hours. Peak urine concentrations of approximately 1000 micrograms/ml and 4000 micrograms/ml are achieved after intramuscular administration of 500 mg and 1 g doses, respectively. When cefazolin is administered to patients with unobstructed biliary tracts, high concentrations well over serum levels occur in the gallbladder tissue and bile. In the presence of obstruction, however, concentration in the bile is considerably lower than the serum level. Tissue distribution of cefazolin is greatest in the kidney, liver and lungs. The concentration of cefazolin in the joint space when the synovial membrane is inflamed is comparable to the concentration found in the serum due to the ease with which the antibiotic crosses the inflamed membrane.

INDICATIONS:

SRATOP is indicated in the treatment of the following infections when due to susceptible micro-organisms.

Respiratory tract infections due to *S. pneumoniae, Klebsiella* sp, *H. influenzae, Staph. aureus* (including penicillinase-producing strains), and Group A beta-haemolytic streptococci:

Tonsillitis, pharyngitis, pneumonia, bronchitis, pulmonary abscess, empyema, pleurisy, sinusitis, laryngitis and otitis media.

Skin, soft-tissue and postoperative infections due to *Staph. aureus* (including penicillinase-producing strains) and Group A beta-haemolytic streptococci and other strains of streptococci:

Lymphangitis, abscesses, cellulitis, decubitus ulcers, mastitis. (Surgical procedures should be performed where indicated).

Genitourinary tract infection due to *E. coli, P. mirabilis, Klebsiella* sp., and some strains of *Enterobacter* and enterococci:

Pyelonephritis, cystitis and adnexitis.

Other infections due to *Staph. aureus* (penicillin-susceptible and penicillin-resistant) and Group A beta-haemolytic streptococci, *S. pneumoniae, P. mirabilis, E. coli*, and *Klebsiella* spp.:
Bacteraemia, septicaemia, endocarditis, osteomyelitis, peritonitis, puerperal sepsis.

NOTE:

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to **SRATOP**. If the tests show that the causative organism is resistant of **SRATOP**, other appropriate therapy should be instituted.

CONTRAINDICATIONS:

SRATOP is contraindicated in patients hypersensitive to cephalosporins and its derivatives, or any components of the formulation.

WARNINGS AND SPECIAL PRECAUTIONS:

Pseudomembranous colitis has been reported with broad spectrum antibiotics including **SRATOP**, therefore, it is important to consider its diagnosis in patients who develop diarrhoea in association with its use. Such colitis may be life-threatening and appropriate measures should be taken, including discontinuation of the **SRATOP**. In individuals with a history of gastrointestinal disease, particularly colitis, broad spectrum antibiotics should be prescribed with caution.
Cefazolin as in **SRATOP** should be given with caution to penicillin sensitive patients. There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Careful inquiry should be made concerning previous hypersensitivity reactions of cephalosporins and penicillins, before **SRATOP** therapy is instituted. Any patient who has shown some form of allergy particularly to medicines should receive antibiotics cautiously and no exception should be made in this regard to **SRATOP**.
If an allergic reaction to **SRATOP** occurs the medicine should be discontinued and the patient treated with the appropriate therapy.
Prolonged use of **SRATOP** may result in the overgrowth of non-susceptible organisms. If superinfection

occurs during therapy, appropriate measures should be taken.

SRATOP should be administered with caution in patients with impaired renal function, as in these patients lower daily dosage is required **(See "DOSAGE AND DIRECTIONS FOR USE")**.

Safety and effectiveness for use in premature infants and infants under one month of age have not been established. **See "DOSAGE AND DIRECTIONS FOR USE"** for recommended dosage in children over one month.

As experience in premature infants and neonates is limited the use of **SRATOP** in these patients should only be undertaken with caution.

Intrathecal administration of **SRATOP** is not recommended. There have been reports of severe central nervous system toxicity including seizures when cefazolin was administered intrathecally.

SRATOP is presumed to be safe or unlikely to produce an effect on the ability to drive and use machines.

INTERACTIONS:

The renal tubular secretion of cephalosporins may be decreased by probenecid when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

The efficacy of oestrogen-containing contraceptives may be decreased by the concomitant administration of **SRATOP**.

*Concomitant administration of cephalosporins and aminoglycoside antibiotics has been associated with increased nephrotoxicity.

A false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or Clinitest tablets but not with enzyme based tests such as Clinistix and Tes-Tape.

Positive direct and indirect antiglobulin tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

PREGNANCY AND LACTATION:

The safety of **SRATOP** in pregnancy and lactation has not been established.

SRATOP has been found to readily cross the placental barrier into the cord blood and amniotic fluid.

SRATOP is present in very low concentrations in the milk of nursing women.

DOSAGE AND DIRECTIONS FOR USE:

The following dosages are recommended, for administration of constituted **SRATOP** preferably by intravenous infusion or alternatively by slow intravenous injection (over 3 to 5 minutes) or by intramuscular injection.

For the treatment of mild-to-moderately severe bacterial infections, 1, 5 to 2 g per day in equally divided doses, two or three times daily.

For the treatment of severe bacterial infection, 3 - 4 g per day in equally divided doses two or three times daily.

Higher and/or more frequent doses (up to 6 g daily) may be given in very severe, life-threatening infections. Doses of up to 12 grams have been used.

Children:

The following dosage chart is a useful guide* to **SRATOP** therapy in children.

PERCENTAGE of ADULT DOSE	AGE AND WEIGHT	TOTAL DAILY DOSE** MAXIMUM
100 %	Adult (65 kg)	1,5 g to 6 g
75 %	12 years (40 kg)	1,125 g to 4,5 g
50 %	7 years (23 kg)	750 mg to 3 g
25 %	1 year (10 kg)	375 mg to 1,5 g
20 %	4 months (6,5 kg)	300 mg to 1,2 g

For in-between ages, in-between percentages are used e.g. at 10 years, 66 % and at three years 33 % of the adult dose.

* Using the Percentage Method based on the following formula:

$$\frac{\text{Surface area of child}}{\text{Surface area of adult}} \times 100 = \text{Percentage of adult dose}$$

** The recommended total daily dose should be administered in two or three equally divided doses. The

maximum range is for very severe life-threatening infections.

The intravenous route by drip infusion is preferable when high doses are to be administered.

Safety and effectiveness for use in premature infants and infants under one month of age has not been established.

Note:

SRATOP may be nephrotoxic if given in excessive doses (more than 6 g daily in patients with normal renal function) or if administered without appropriate dosage reduction in patients with renal impairment. Although **SRATOP** is generally well tolerated in patients with impaired renal function it is nevertheless desirable to adjust the dosage as follows to prevent the accumulation of high blood levels.

Renal impairment:

Dosage adjustment for adults:

CREATININE CLEARANCE (ml/min)	**DOSAGE ADJUSTMENT**
≥ 55	Full doses
35 to 54	Full doses, but restricted to at least 8 hour intervals
11 to 34	Half the usual dose every 12 hours
≤ 10	Half the usual dose every 18 to 24 hours

Dosage adjustment for children:

CREATININE CLEARANCE (ml/min)	**DOSAGE ADJUSTMENT**
70 to 40	60 % of normal daily dose in equally divided doses every 12 hours
40 to 20	25 % of normal daily dose in equally divided doses every 12 hours
20 to 5	10 % of normal daily dose every 24 hours.

All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the

infection. Patients undergoing peritoneal dialysis: **(See "PHARMACOLOGICAL ACTION").**

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.

A MINIMUM OF 10 DAYS TREATMENT IS RECOMMENDED FOR ANY INFECTION CAUSED BY GROUP-A beta-HAEMOLYTIC STREPTOCOCCI TO HELP PREVENT THE OCCURRENCE OF ACUTE GLOMERULONEPHRITIS OR ACUTE RHEUMATIC FEVER.

For administration by intravenous infusion: Use sterile water for injection. Add 2 ml to the 250 mg vial, 500 mg vial and 4 ml to the 1 g vial.

Withdraw the entire contents and add to one of the following intravenous solutions:

0,9 % sodium chloride injection

5 % or 10 % dextrose injection

5 % dextrose in lactated Ringers injection

dextrose in 0,9 % sodium chloride injection (also may be used with 5 % dextrose and 0,45 % or 0,2 % sodium chloride injection)

Lactated Ringers Injections

5 % or 10 % invert sugar in sterile water for injection

Ringers Injection

For administration by direct intravenous injection: After constitution with 2 ml (250 mg, 500 mg) or 4 ml (1 g) of water for injection, dilute in a minimum of 10 ml of water for injection. Inject solution slowly over 3-5 minutes either directly into a vein or through the tubing for a patient receiving the parenteral fluids mentioned above.

For administration by intramuscular injection: Add 2 ml (250 mg, 500 mg) or 4 ml

(1 g) of sterile water for injection or bacteriostatic water for injection. Withdraw the entire contents to the vial.

Constituted solutions are stable for 24 hours when kept at room temperature not exceeding 25 °C, or for 96 hours when kept in a refrigerator (2 - 8 °C).

SIDE EFFECTS:

Immune system disorders:

Less frequent:

Rash, pruritus, urticaria, drug fever, anaphylaxis, hypersensitivity

Frequency not known:

Angioedema

Blood and the lymphatic system disorders:

Frequent:

Eosinophilia

Less frequent:

Leukopenia, neutropenia, thrombocytopenia

Frequency not known:

Thrombocythemia. Positive direct and indirect Coombs' tests have occurred.

Hepato-biliary disorders:

Frequency not known:

Transient rises in AST, ALT and alkaline phosphatase levels.

Transient hepatitis, cholestatic jaundice

Renal and urinary disorders:

Frequency not known:

Transient rise in blood urea levels have been observed. Interstitial nephritis and other renal disorders. Most patients experiencing these reactions had been seriously ill and were receiving multiple medicine therapies. The role of **SRATOP** in the development of nephropathies has not been determined.

Gastrointestinal disorders:

Frequent:

Nausea and vomiting, diarrhoea, oral candidiasis

Less frequent:

Symptoms of pseudomembranous colitis may appear either during or after antibiotic therapy

Frequency not known:

Anorexia

Skin and subcutaneous tissue disorders:

Less frequent:

**Stevens-Johnson syndrome.

Reproductive system and breast disorders:

Frequent:

Vaginal candidiasis

Less frequent:

Genital pruritus, vaginitis

General disorders and administrative site conditions:

Less frequent:

SRATOP is well tolerated when administered by intravenous infusion, and the incidence of phlebitis with **SRATOP** is low.

Although pain was infrequently reported after intramuscular injection, it was seldom severe. Cefazolin rarely produced tenderness, induration or fever.

Frequency not known:

Anal pruritus.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Inappropriately large doses of parenteral cephalosporins may cause dizziness, paresthesias and headache. With some cephalosporins, seizures may occur following overdosage, particularly in patients with renal impairment in whom accumulation is likely to occur.

Dosage reduction is necessary when renal function is impaired. (**See "DOSAGE AND**

DIRECTIONS FOR USE"). If seizures occur, the drug should be promptly discontinued; anticonvulsant therapy may be administered if clinically indicated. Haemodialysis may be considered in cases of overwhelming overdosage.

Laboratory abnormalities that may occur after an overdose include elevations in creatinine, BUN, liver enzymes and bilirubin, a positive Coombs' tests, thrombocytosis, thrombocytopenia, eosinophilia, leukopenia and prolongation of the prothrombin time.

Treatment of overdosage should be symptomatic and supportive.

IDENTIFICATION:

A white or almost white powder. When reconstituted, a pale yellow to intense yellow, clear liquid is formed.

PRESENTATION:

SRATOP 250 mg:

10 ml clear transparent type I glass vials with grey bromo butyl rubber stoppers sealed with maroon coloured aluminium flip off seals.

Pack size: Single vial packed in printed carton with a package insert.

SRATOP 500 mg:

10 ml clear transparent type I glass vials with grey bromo butyl rubber stoppers sealed with light rose coloured aluminium flip off seals.

Pack size: Single vial packed in printed carton with a package insert.

SRATOP 1 g:

10 ml clear transparent type I glass vials with grey bromo butyl rubber stoppers sealed with violet coloured aluminium flip off seals.

Pack size: Single vial packed in printed carton with a package insert.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Reconstituted solution to be used within 24 hours if stored below 25 °C and within 96 hours if stored at 2

– 8 °C, in original vial.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

SRATOP 250 mg: 43/20.1.1/0637

SRATOP 500 mg: 43/20.1.1/0638

SRATOP 1 g: 43/20.1.1/0639

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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