PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME and dosage form:

SAB-CEFOTAXIME 500 (injection)

SAB-CEFOTAXIME 1 g (injection)

COMPOSITION:

SAB-CEFOTAXIME 500

Each vial contains:

Cefotaxime sodium (Sterile)

equivalent to cefotaxime 500 mg

SAB-CEFOTAXIME 1 g

Each vial contains:

Cefotaxime sodium (Sterile)

equivalent to cefotaxime 1 g

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Mechanism of action:

Cefotaxime is a third-generation cephalosporin antibiotic. The bacterial action of cefotaxime results from inhibition of cell wall synthesis of the bacterial cell wall.

Antibacterial spectrum:

Cefotaxime has *in vitro* activity against a wide range of gram-positive and gram-negative organism. Cefotaxime has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria.

Cefotaxime is active against the following micro-organism *in vitro* (*in vitr*o sensitivity does not necessarily imply in vivo efficacy):

Gram-positive aerobes:

Staphylococcus aureus, including certain penicillinase and non-penicillinase producing strains, *Staphylococcus epidermidis*, *Streptococcus pyogenes* (Group A beta-hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) (Note: most strains of enterococci e.g. S. *faecalis* are resistant), *Streptococcus pneumoniae*.

Gram-negative aerobes:

*Citrobacter spp., Enterobacter spp., Escherichia coli, Haemophilus influenza (*including *ampicillin-resistant H influenza), Klebsiella spp, (*including *K. pneumonia), Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Proteus morganella, Proteus rettgeri, Providencia spp., Serratia spp., Salmonella spp, (including S. typhi), Shigella spp.*

Citrobacter spp.,

Anaerobes:

Bacteroides spp., Clostridium spp., (Note: most strains of C. difficile are resistant),

Peptococcus spp., Peptostreptococcus spp.

Resistant strains:

Most *Pseudomonas* species, most anaerobic bacteria, some *Klebsiella and Serratia* species and *Candida*, Most Enterococci, *Listeria monocytogenes*, most *Clostridium difficile* strains, penicillinase producing *Staphylococcus epidermidis* strains and methicillin resistant *Staphylococcus aureas*.

Chlamydia

S. faecallis

Pharmacokinetics

IM Injection

Following IM injection of doses of 0.25 g, 05 g and 1 g, peak plasma levels are reached at 30 minutes. The level increase according to the dose administered and is approximately 24 mcg/ml after the 1 g injection. Urinary excretion in the 24 hours after injection is 50-60 % of the dose administered. It is 44-55 % in the first 6 hours after IM injection. The plasma protein binding of the medicine is approximately 38 %.

IV Injection

The initial phase half-lives for whole blood and plasma are 4,5 and 8 minutes respectively. Terminal phase half-lives for whole blood and plasma are 1,3 and 2,2 hours respectively. Of the administered dose 85 to 90 % is excreted in the urine and 7-9,5 % in the faeces. Most of the dose is excreted within 4 hours of administration. Approximately 20-36 % of an IV administered dose of cefotaxime is excreted by the kidney as the unchanged cefotaxime and 15-25 % as the desacetyl derivative, the major metabolite. Desacetyl-cefotaxime has been shown to contribute to the bactericidal activity. Two other urinary metabolites (M2 and M3) account for 20-25 %. They lack bactericidal activity. After a single IV injection of cefotaxime 1 g, serum protein binding of the drug is approximately 44 %.

IV Infusion

Loading dose of 0.5 g, 1 g and 2 g administered over 15 minutes followed by sustaining infusions of 0.5 g, 1 g and 2 g per hour produces mean peak serum levels of 41, 93 and 160 mcg/ml respectively. The mean terminal half-life is 75± 7 minutes. 63± 9 % of the dose is excreted within 24 hours by the kidneys. Plasma protein binding is approximately 35 %.

INDICATIONS:

Cefotaxime is indicated for use primarily in the treatment of infections of the genito-urinary, gastro-intestinal and respiratory tracts, and in the skin and soft tissues and meningitis in children caused by susceptible strains of the following organism,

Staphylococcal infections (including infections caused by both penicillinase producing and non-penicillinase producing strains): abscess, furunculosis, bronchitis and impetigo.

Streptococcal infections: (both-hemolytic and group *D streptococci),* cellulitis, pneumonia, follicular tonsillitis, otitis media, pharyngitis, sinusitis, scarlet fever, septic sore throat, urinary tract infections (Enterococci) and meningitis in children.

Pneumococcal infections: Lobar pneumonia, bronchitis, cellulites and otitis media.

Haemophilus inflenzae infections: Otis media, laryngotracheobronchitis and meningitis in children.

E. coli infections: Lobar pneumonia, urinary tract infections and meningitis in children.

Shigella infections: Bacillary dysentery
Salmonella infections: Enteritis
Sensitive strains of Pseudomonas aeruginosa: Sepsis
Gonococcus: Gonorrhoea
Neisseria meningitis: Meningitis in children

Bacteriological studies to determine the causative organism and their sensitivity to cefotaxime should be performed.

Prophylactic uses: The administration of cefotaxime pre-operatively may reduce the incidence of certain post-operative infections in patients undergoing surgical procedures that are classified as potentially contaminated. The minimum effective dose has been found to be 1 g cefotaxime 30-90 minutes prior to surgery.

CONTRAINDICATIONS:

Cefotaxime is contraindicated in patients who are allergic to the cephalosporin group of antibiotics.

Pregnancy: There are no well controlled studies pertaining to the use of cefotaxime in pregnant woman, although animal studies have not shown any teratogenic effect.

Lactation: Cefotaxime is excreted in human milk in low concentrations. Caution should be exercised when cefotaxime is administered to a nursing woman.

WARNING:

Before therapy with cefotaxime is instituted, careful enquiry should be made to determine whether the patient had previous hypersensitivity reactions to cefotaxime sodium, cephalosporins or penicillin. If an allergic reaction to cefotaxime occurs, discontinue treatment with the drug. Strict medical supervision is required throughout the treatment.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics) therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotics use.

DOSAGE AND DIRECTIONS FOR USE:

Cefotaxime is given as deep intramuscular injection or by slow intravenous injection over 3-5 minutes or by infusion over 20-60 minutes.

Adults

Dosage and route of administration be determined by susceptible organisms, severity of the infection, and the condition of the patient. The maximum daily dose should not exceed 12 grams.

The usual dose is 2 g daily in 2 X 1 g injections. Severe cases may be given 3-4 daily in 2 to 4 administrations.

In the treatment of gonorrhoea a single 1 g dose of cefotaxime is given.

To prevent post-operative infection, the recommended dose is a single dose of 1 g IM or IV administered 30 to 90 minutes before surgery.

In the treatment of beta-hemolytic streptococcal infections, a therapeutic dose must be administered for at least 10 days.

Neonates, Infants and Children

Children and Infants

50 mg/kg/day in 2-4 divided doses. A maximum dose of 200 mg/kg/day in 2-4 divided doses may be given in exceptional cases.

Neonates

The following dosage schedule is recommended

- Up to 1 week of age 50 mg (base)/kg IV every 12 hourly.
- 1-4 weeks of age 50 mg (base)/kg IV every 8 hourly

Renal Failure

It is suggested that the dosage of cefotaxime be halved in patients with creatinine clearance less than 20 ml/min.

The dosage interval should be modified

Method of Preparation

Reconstitute the contents with sterile water for injection. Shake well until dissolved and then withdrawn the entire contents of the vial into the syringe and use immediately. The dilution table is given below:

Vial size	Volume of water for injection to be added	
	IM	IV*
500 mg	2 ml	10 ml
1 g	4 ml	10 ml

*For direct intravenous use, the resulting solution should be administered over 3 to 5 minutes period.

Intravenous infusion: Cefotaxime may be administered by intravenous infusion 1 to 2 g are dissolved in 40 to 100 ml of water for injection or in the infusion fluids (see “Stability”). The prepared infusion should be administered over 20 to 60 minutes.

Warning: Do not mix cefotaxime with another antibiotic in the same syringe or infusion.

Stability: The stability of cefotaxime in a concentration of 1 g per 250 ml in the following infusions is satisfactory for 24 hours in a refrigerator or 12 hours at a temperature not exceeding 25˚C: 0.9 % sodium chloride, 5 % dextrose, Ringer’s sterile solutions.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects

The most common adverse effects are hypersensitivity reactions including skin rashes, skin eruptions, urticaria, eosinophilia, fever, reactions resembling serum sickness, and anaphylaxis. Acute interstitial nephritis is also a possibility as a manifestation of hypersensitivity.

There may be a positive response to Coombs' test although hemolytic anemia rarely occurs. Neutropenia and thrombocytopenia have occasionally been reported with cefotaxime. Agranulocytosis has been associated rarely with some cephalosporins including cefotaxime. As in the case of some other cephalosporins, bleeding complications related to hypoprothrombinemia and/or platelet dysfunction may occur.

Transient increase in liver enzyme values including transaminases and alkaline phosphatases have been reported.

Gastrointestinal adverse effects such as nausea, vomiting and diarrhea have been reported rarely.

Prolonged use may result in overgrowth of non-susceptible organism and, as with other broad-spectrum antibiotics, pseudomembranous colitis may develop.

Deep phlebitis after IV injection has been reported occasionally.

Precautions

General

The broad spectrum third generation cephalosporins have the potential for colonisation and super-infection with resistant organisms such as *Pseudomonas aeruginosa*, *Enterobacter spp.*, Candida and enterococci, at various sites in the body, although the incidence has generally been low with cefotaxime.

As high and prolonged serum antibiotics concentration can occur from usual doses in patients with transient or persistent reduction of urinary output because of renal insufficiency, the total daily dosage should be reduced when cefotaxime is administered to such patients.

About 10 % of penicillin-sensitive patients may also be allergic to cephalosporins although the true incidence is uncertain. Great care should be taken if cefotaxime is to be given to such patients, Care is also necessary in patients with known histories of allergies.

Geriatrics

Elderly patients are more likely to have an age-related decrease in renal function necessitating dosage adjustment.

Interactions

Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics. There is also some evidence for enhanced nephrotoxicity with a loop diuretic like furosemide.

Concomitant administration of probenecid with cephalosporins decreases tubular secretion of cephalosporins resulting in their increased and prolonged serum concentration.

There may be antagonism between cefotaxime and bacteriostatic antibacterial agents. Cefotaxime may interfere with the Jaffe method of measuring creatine concentrations and may produce falsely high values; this should be borne in mind when measuring renal functions.

Laboratory Value Alterations

A positive Coombs' reaction frequently appears in patients who received large doses of cephalosporin.

A false positive reaction may occur on testing for glucose in the urine with reducing substances, but this can be avoided with the use of methods that are specific to gluco-oxidase.

KNOWN SYMTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See side effects. Treatment is symptomatic and supportive.

IDENTIFICATION:

SAB-CEFOTAXIME 500

White or slightly yellow powder, hygroscopic, filled in 15 ml USP type I clear, colourless glass vial with grey rubber plug and coloured flip-off seal.

SAB-CEFOTAXIME 1 g:

White or slightly yellow powder, hygroscopic, filled in 15 ml USP type I clear, colourless glass vial with grey rubber plug and coloured flip-off seal.

PRESENTATION:

SAB-CEFOTAXIME 500: Carton containing vial of 500 mg in clear, colourless glass USP Type 1 vial.

SAB-CEFOTAXIME 1 g: Carton containing vial of 1 g in clear, colourless glass USP Type 1 vial.

STORAGE INSTRUCTIONS:

Store below 25 ˚C, protected from light. Store in the carton until required for use. Reconstituted solution to be used within 24 hours if stored at 2-8 ˚C in a refrigerator or within 12 hours is stored below 25 ˚C. Do not freeze the reconstituted solution.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

SAB-CEFOTAXIME 500: 34/20.1.1/0259

SAB-CEFOTAXIME 1 g: 34/20.1.1/0260

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

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

October 2001

DATE OF REVISION OF THE TEXT

18 December 2025