1.3 Labeling and packaging

1.3.1 Package Insert /Summary of Product Characteristics (SmPC)

SUMMARY OF PRODUCT CHARACTERISTICS

Table of Contents

Scheduling Status: S2

1. Name of the medicinal product
SANOTAX – 500 (Cefotaxime for Injection USP 500mg)

2. Qualitative and quantitative composition
Label claim:
Each vial contains: Sterile Cefotaxime Sodium USP equivalent to anhydrous Cefotaxime 500mg

Raw material	Specification	Qty / vial (mg)	Rationale
Cefotaxime sodium (sterile)	USP	573.0 *	Active

Remarks:
*Standard quantity of Cefotaxime Sodium is based on 90 % w/w assay and 3.0 % w/w water content.

3. Pharmaceutical form
Dry powder for injection
Description: Sterile, off white to pale yellow crystalline powder, distributed in sealed containers and which, when shaken with the prescribed volume of sterile liquid, rapidly form clear and practically particle- free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefotaxime for Injection is indicated in the treatment of the following infections either before the infecting organism has been identified or when caused by bacteria of established sensitivity.
Septicaemias.
Respiratory Tract Infections such as acute and chronic bronchitis, bacterial pneumonia, infected bronchietasis, lung abscess and post-operative chest infections.
Urinary Tract Infections such as acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria.
Soft-tissue Infections such as cellulitis, peritonitis and wound infections.
Bone and Joint Infections such as osteomyelitis, septic arthritis.
Obstetric and Gynaecological Infections such as pelvic inflammatory disease.
Gonorrhoea particularly when penicillin has failed or is unsuitable.
Other Bacterial infections meningitis and other sensitive infections suitable for parenteral antibiotic therapy.
BACTERIOLOGY: The following organisms have shown in vitro sensitivity to Cefotaxime for Injection.
GRAM POSITIVE:
Staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing strains.
Beta-haemolytic and other streptococci such as Streptococcus mitis (viridans) (many strains of

enterococci, eg. Streptococcus faecalis, are relatively resistant).
Streptococcus (Diplococcus) pneumonia.
Clostridium spp.
GRAM NEGATIVE:
Escherichia coli.
Haemophilus influenzae including ampicillin resistant strains.
Klebsiella spp.
Proteus spp. (both indole positive and indole negative).
Enterobacter spp.
Neisseria spp. (including ß-lactamase producing strains of N. gonorrhoea).
Salmonella spp. (including Sal. typhi).
Shigella spp.
Providencia spp.
Serratia spp.
Citrobacter spp.

4.2 Posology and method of administration

Cefotaxime for Injection may be administered intravenously, by bolus injection, by infusion or intramuscularly.

Adults: The recommended dosage for mild to moderate infections is 1g 12 hourly. However, dosage may be varied according to the severity of the infection, sensitivity of causative organisms and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

In severe infections dosage may be increased up to 12g daily given in 3 or 4 divided doses.

For infections caused by sensitive Pseudomonas spp. daily doses of greater than 6g will usually be required.

Children: The usual dosage range is 100–150mg/kg/day in 2 to 4 divided doses. However, in very severe infections doses of up to 200mg/kg/day may be required.

Neonates: The recommended dosage is 50mg/kg/day in 2 to 4 divided doses. In severe infections 150-200mg/kg/day, in divided doses, have been given.

Dosage in Gonorrhoea: A single injection of 1g may be administered intramuscularly or intravenously.

Dosage in Renal Impairment: Because of extra-renal elimination, it is only necessary to reduce the dosage of Cefotaxime for Injection in severe renal failure (GFR < 5ml/min = serum creatinine approximately 751 micromol/l). After an initial loading dose of 1g, daily dose should be halved without change in the frequency of dosing, i.e. 1g in 12 hourly becomes 0.5g 12 hourly, 1g 8 hourly becomes 0.5g 8 hourly, 2g 8 hourly becomes 1g 8 hourly etc. As in all other patients, dosage may require further adjustment according to the course of the infection and the general condition of the patient.

DIRECTION FOR USE

Intravenous and Intramuscular Administration: Reconstitute SANOTAX with Water for Injection, as given in the Dilution Table. Shake well until dissolved and then withdraw the entire contents of the vial into the syringe and use immediately.

Dilution table:

Vial Size	Diluent to be added
250mg	2ml
500mg	2ml
1g	4ml
2g	10ml

Intravenous Infusion: Cefotaxime for Injection may be administered by intravenous infusion. 1-2g are dissolved in 40-100ml of Water for Injection or in the infusion fluids The prepared infusion may be administered over 20-60 minutes.

Intravenous administration (injection or infusion):

For intermittent I.V. injections, the solution must be injected over a period of 3 to 5 minutes.

4.3 Contraindications

Hypersensitivity to cephalosporins.

In patients hypersensitive to penicillin the possibility of cross-sensitivity exists.

4.4 Special warnings and precautions for use

As with other antibiotics, the use of Cefotaxime, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Anaphylactic reactions

If a hypersensitivity reaction occurs, treatment must be stopped.

The use of Cefotaxime is strictly contraindicated in subjects with a history of immediate-type hypersensitivity to cephalosporins.

-Serious bullous reactions

Cases of serious bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Cefotaxime (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

-Clostridium difficile associated disease (e.g. pseudomembranous colitis)

Diarrhoea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment, may be symptomatic of Clostridium difficile associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis.

The diagnosis of this rare but potentially fatal condition can be confirmed by endoscopy and/or histology. It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of Cefotaxime.

If a diagnosis of pseudomembranous colitis is suspected, Cefotaxime should be stopped immediately and appropriate specific antibiotic therapy should be started without delay.

Clostridium difficile associated disease can be favoured by faecal stasis.

Medicinal products that inhibit peristalsis should not be given.

Haematological reactions: Leucopenia, neutropenia and more rarely, agranulocytosis, may develop during treatment with Cefotaxime, particularly if given over long periods. For treatment courses

lasting longer than 10 days, the blood counts should be monitored and treatment stopped in the event of neutropenia.
Some cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of haemolytic anaemia have also been reported (see section 4.8).
-Patients with renal insufficiency
The dosage should be modified according to the creatinine clearance calculated.
Caution should be exercised if Cefotaxime is administered together with aminoglycosides or other nephrotoxic drugs (see section 4.5). Renal function must be monitored in these patients, the elderly and those with pre-existing renal impairment.
-Neurotoxicity
High doses of beta lactam antibiotics including Cefotaxime, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if such reactions occur.
-Precautions for administration
During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of Cefotaxime through a central venous catheter. The recommended time for injection or infusion should be followed (see section 4.2). See section 4.3 for contraindications for formulations reconstituted with lidocaine.
-Effects on Laboratory Tests
As with other cephalosporins, a positive Coombs test has been found in some patients treated with Cefotaxime. This phenomenon can interfere with the cross-matching of blood.
Urinary glucose testing with non-specific reducing agents may yield false positive results. This phenomenon is not seen when a glucose-oxidase specific method is used.
-Sodium intake
The sodium content of this product should be taken into account when prescribing to patients requiring sodium restriction.

4.5 Interactions with other Medicinal Products and other forms of Interaction
Uricosurics: Probenecid interferes with the renal tubular transfer of cefotaxime, thereby increasing cefotaxime exposure about 2-fold and reducing renal clearance to about half at therapeutic doses. Due to the large therapeutic index of cefotaxime, no dosage adjustment is needed in patients with normal renal function. Dosage adjustment may be needed in patients with renal impairment.
Aminoglycoside antibiotics and diuretics: As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide). Renal function must be monitored in these patients.
Interference with Laboratory Tests: A positive Coombs test may be seen during treatment with cephalosporins. This phenomenon may occur during treatment with cefotaxime.
A false positive reaction to glucose may occur with reducing substances but not with the use of specific glucose oxidase methods.

4.6 Fertility, Pregnancy and Lactation
Pregnancy

The safety of Cefotaxime has not been established in human pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There are however no adequate and well controlled studies in pregnant women.
Cefotaxime passes through the human placenta. Therefore, Cefotaxime should only be used during pregnancy if the anticipated benefit outweighs any potential risks.

Lactation

Cefotaxime is excreted in human milk in low concentrations. Use during lactation can lead in infants to an effect on the physiological intestinal flora with diarrhoea, colonisation by yeast-like fungi and may also lead to sensitisation of the infant. Therefore a decision must be made whether to discontinue breast-feeding or to discontinue therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the mother.

4.7 Effects on Ability to Drive and Use Machines

High doses of cefotaxime, particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions). In the case of side effects such as dizziness the patient's ability to concentrate and to react properly may be impaired. In such cases patients should refrain from driving cars and using machines.

4.8 Undesirable Effects

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/1000)	Very rare (<1/10000)
Infections and infestations					
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia		
Immune system disorders			Jarisch-Herxheimer reaction		
Nervous system disorders			Convulsions (See section 4.4)		
Cardiac disorders					
Gastro-intestinal disorders			Diarrhea		
Hepatobilary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase)		

			amd/or bilirubin		
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria		
Renal and Urinary disorders			Decrease in renal function/increase of creatinine (particularly when co-prescribed with aminoglycosides)		
General disorders and administration on site conditions	For IM formulations: Pain at the injection site		Fever Inflammatory reactions at the injection site, including phlebitis/thrombophlebitis		

4.9 Overdose

Symptoms of Overdose

Symptoms of overdose may largely correspond to the profile of side effects. With certain risk patterns and with the administration of very high doses, there is a risk of reversible encephalopathy, central nervous system excitation conditions, myoclonia and cramp, as have been described for other beta lactams.

No specific antidote exists. Plasma levels of Cefotaxime can be reduced by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cefotaxime is a broad spectrum bactericidal cephalosporin antibiotic. Cefotaxime is exceptionally active in vitro against Gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram positive bacteria.

5.2 Pharmacokinetic properties

After a 1000 mg intravenous bolus, mean peak plasma concentrations of Cefotaxime usually range between 81 and 102 microgram/ml. Doses of 500 mg and 2000 mg produce plasma concentrations of 38 and 200 microgram /ml, respectively. There is no accumulation following administration of 1000 mg intravenously or 500 mg intramuscularly for 10 or 14 days.

The apparent volume of distribution at steady-state of Cefotaxime is 21.6 litres/1.73 m^2 after 1 g intravenous 30 minute infusion. Concentrations of Cefotaxime (usually determined by non-selective assay) have been studied in a wide range of human body tissues and fluids.

Cerebrospinal fluid concentrations are low when the meninges are not inflamed, but are between 3 and 30 microgram/ml in children with meningitis. Cefotaxime usually passes the blood-brain barrier at levels above the MIC of common sensitive pathogens when the meninges are inflamed. Concentrations (0.2-5.4 microgram/ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive

organs, otitis media effusions, prostatic tissue, interstitial fluid, renal tissue, peritoneal fluid and gall bladder wall, after usual therapeutic doses. High concentrations of Cefotaxime and desacetyl-Cefotaxime are attained in bile. Cefotaxime is partially metabolised prior to excretion. The principal metabolite is the microbiologically active product, desacetyl-Cefotaxime. Most of a dose of Cefotaxime is excreted in the urine about 60% as unchanged drug and a further 24% as desacetyl-Cefotaxime. Plasma clearance is reported to be between 260 and 390 ml/minute and renal clearance 145 to 217 ml/minute.

After intravenous administration of Cefotaxime to healthy adults, the elimination half-life of the parent compound is 0.9 to 1.14 hours and that of the desacetyl metabolite, about 1.3 hours.

In neonates the pharmacokinetics are influenced by gestational and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

In severe renal dysfunction the elimination half-life of Cefotaxime itself is increased minimally to about 2.5 hours, whereas that of desacetyl-Cefotaxime is increased to about 10 hours. Total urinary recovery of Cefotaxime and its principal metabolite decreases with reduction in renal function.

5.3. Preclinical Safety Data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at temperature below 30°C. Protect from light.

Reconstituted solution should be used immediately after preparation.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

The drug product is available in 10ml clear USP Type III glass vial with 20mm Grey butyl rubber stopper and 20 mm taxim blue flip off seal. It is supplied in Monopack (1's) and also in Combi pack (Single vial with SWFI in a carton). Each pack contains package insert in a carton.

6.6 Special precautions for disposal and other handling

None

7. Marketing authorization holder

Sance Laboratories Private Limited,
VI/51B, P.B. No: 2, Kozhuvanal - 686573,

Pala, Kottayam District,
Kerala, India.
Ph: 0091-4822- 267799
Fax: 0091-4822-269406
Email: info@sancepharma.com
Web site:www.sancepharma.com

8. Marketing authorization number(s)
Botswana Reg. No.: xxxx

9. Date of first authorization/renewal of the authorization

10. Date of revision of the text