SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

SANOTAX – 1000

Cefotaxime for Injection USP 1000mg

2. Qualitative and quantitative composition

Label claim:

Each vial contains: Sterile Cefotaxime Sodium USP equivalent to anhydrous Cefotaxime 1000mg.

Composition:

Sr. No	Material	Specification	Qty. /unit (mg)	Rationale
1	Cefotaxime Sodium (Sterile)	USP	1145.0*	Active pharmaceutical ingredient

Remarks:

*: Standard quantity of Cefotaxime sodium is based on 90.0 % assay value as cefotaxime and 30% 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 forms 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.

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.

ADMINISTRATION:

Cefotaxime and aminoglycosides should not be mixed in the same syringe or perfusion fluid.

Intravenous and Intramuscular Administration: Reconstitute Cefotaxime for injection 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
1g	4ml

Intravenous Infusion: Cefotaxime for injection may be administered by intravenous infusion. 1-2g are dissolved in 40-10Oml of Water for Injection or in the infusion fluids listed under 'Pharmaceutical Particulars'. The prepared infusion may be administered over 20-60 minutes. To produce an infusion using vials with an infusion connector, remove the safety
cap and directly connect the infusion bag. The needle in the closure will automatically pierce the vial stopper. Pressing the infusion bag will transfer solvent into the vial.
Reconstitute by shaking the vial and finally, transfer the reconstituted solution back to the infusion bag ready for use.

Intravenous administration (injection or infusion):

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

4.3 Contraindications

Hypersensitivity to cephalosporins.
- In patients with a history of hypersensitivity to Cefotaxime and/or to any component of Cefotaxime for injection.

Allergic cross reactions can exist between penicillins and cephalosporins (see section 4.4)
For pharmaceutical forms containing lidocaine:
- known history of hypersensitivity to lidocaine or other local anesthetics of the amide type
- non-paced heart block
- severe heart failure
- administration by the intravenous route
- infants aged less than 30 months of age

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.
- Anaphalactic reactions

Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime (see sections 4.3 and 4.8).
If a hypersensitivity reaction occurs, treatment must be stopped.
The use of cefotaxime is strictly contra-indicated in subjects with a previous history of immediate-type hypersensitivity to cephalosporins.
Since cross allergy exists between penicillins and cephalosporins, use of the latter should be undertaken with extreme caution in penicillin sensitive subjects.
- 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.

-Blood disorders

Leucopenia, neutropenia and more rarely,bone marrow failure, pancytopenia, or agranulocytosis may develop during reatment with Cefotaxime (see section 4.8) For courses of treatment lasting longer than 10 days, blodd counts should therefore be monitored and treatment discontinuation should be considered in case of abnormal results.

Some cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of haemolytic anemia 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 (48.2 mg/g) should be taken into account.

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.(see sections 4.4 and 4.2)

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 (see section 4.4)

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 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 crosses the placental barrier. Therefore, Cefotaxime should only be used during pregnancy if the anticipated benefit outweighs any potential risks.

Lactation

Cefotaxime passes into human milk.

Effects on the physiological intestinal flora of brest-fed infant leading to diarrhoea, colonisation by yeast-like fungi, and sensitisation of the infant cannot be excluded.

Therefore a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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)	Not known (cannot be estimated from available data)*
Infections and infestations						Superinfection (see section 4.4)
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Bone marrow failure Pancytopenia Agranulocytosis (see section 4.4) Haemolytic anaemia
Immune system disorders			Jarisch-Herxheimer reaction			Anaphylactic reactions Angioedema Bronchospasm Anaphylactic shock
Nervous system disorders			Convulsions (See section 4.4)			Headache Dizziness Encephalopathy (eg;impairment of consciousness, abnormal movements) (see section 4.4)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter
Gastro-intestinal disorders			Diarrhea			Nausea Vomiting Abdominal Pain Pseudomembranous colitis (see section 4.4) Candidiasis

Hepatobiliary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) amd/or bilirubin			Hepatitis*(sometimes with jaundice)
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria			Erythema multiforme Stevens-johnson syndrome Toxic epidermal necrolysis(see section 4.4) Acute generalized exanthematous pustulosis (AGEP)
Renal and Urinary disorders			Decrease in renal function/increase of creatinine (particularly when co-prescribed with aminoglycosides)			Acute renal failure (see section 4.4) Interstitial nephritis
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			For IM formulations (since the solvent contains lidocaine): Ssytemic reactions to lidocaine

*postmarketing experience

Jarisch-Herxheimer reaction

For the treatment of borreliosis (Lyme's Disease), a Jarisch-Herxheimer reaction may develop during the first days of treatment.

The occurrence of one or more of the following symptoms has been reported after several week's treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty of breathing, joint discomfort.

Hepatobiliary disorders

Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been observed. These laboratory abnormalities may rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.
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.

4.9 Overdose

Symptoms of overdose may largely correspond to the profile of side effects.
There is a risk of reversible encephalopathy in cases of administration of high doses of ß-lactam antibiotics including cefotaxime.
In case of overdose, cefotaxime must be discontinued, and supportive treatment initiated, which includes measures to accelerate elimination, and symptomatic treatment of adverse reactions (e.g. convulsions).
No specific antidote exists. Serum 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

Pharmacokinetics in adults

	Healthy adults i.v (5 min)	Healthy adults i.m
1. Dose	1g	1g
2. Absorbtion		
Bioavailability in %	100	90 – 95
3. Kinetic parameters		
Tmax (h)		0.5
Cmax (µg/ml)	100	20-30
Terminal half-life (h)	0.9 – 1.1	1.3
Volume of distribution (liters/Kg)	0.30	
Protein binding		
- Type	Albumin	
- %	25-40	
4. Metabolism		
Liver	+	
Kidney		
Other tissues %		

- Product - Metabolites		
M1	Desacetyl CTX*	
M2	Lactamine form	
M3	Lactamine form	
5. Excretion		
Urine	90% CTX:50% Desacetyl CTX: 15-25% M2 + m3: 15-30%	
Faeces %	10%	

*The half-life of desacetylcefotaxime in healthy subjects is approximatively 2h. Its antibacterial activity is synergistic with that of cefotaxime.

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

The apparent volume of distribution at steady-state of cefotaxime is 21.6L/1.73m2 after 1g 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 30mg/ml in children with meningitis. Cefotaxime usually passes the blood-brain barrier in levels above the MIC of common sensitive pathogens when the meninges are inflamed. Concentrations (0.2-5.4mg/ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2g. 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 desacetylcefotaxime.

Plasma clearance is reported to be between 260 and 390ml/minute and renal clearance 145 to 217ml/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
24 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
10 ml USP Type III clear glass vials sealed with 20 mm Grey Butyl rubber stopper and 20 mm colored flip off aluminum seal (Taxim Blue). The drug product is available in Monopack (1's) along with package insert.

6.6 Special precautions for disposal and other handling
None

7. MARKETING AUTHORISATION HOLDER :

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8. MARKETING AUTHORISATION NUMBER(S)

SAN/IND/031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION :
04/11/2019

10. Date of Revision of the text
25/07/2023