Tirotax® 0.5 g/1 g/2 g – vials

SANDOZ

Composition
What does Tirotax® contain?

Tirotax® 0.5 g :
1 vial contains 0.5 g cefotaxime (as cefotaxime-sodium)
Sodium content: 24 mg/vial

Tirotax® 1 g :
1 vial contains 1 g cefotaxime (as cefotaxime-sodium)
Sodium content: 48 mg/vial

Tirotax® 2 g :
1 vial contains 2 g cefotaxime (as cefotaxime-sodium)
Sodium content: 96 mg/vial

Pharmaceutical form: Sterile, crystalline, white to pale yellow powder for preparing an injection solution.

Presentation: Single packs and hospital packs

Pharmaceutical and therapeutic category and mode of action
How does Tirotax® work?
Tirotax® is a third-generation, broad-spectrum bactericidal antibiotic from the cephalosporin family. Its bactericidal action is based on inhibition of synthesis of the bacterial cell wall.

Registered owner and manufacturer
Sandoz GmbH, Kundl- Austria

Indications
When is Tirotax® used?
Cefotaxime is indicated for treatment of the following severe infections, if it has been demonstrated or is suspected that they are caused by cefotaxime-sensitive bacteria:
- Bacterial pneumonia; cefotaxime is not effective against bacteria that cause atypical pneumonia, or against some other types of bacteria that can cause pneumonia, including *P. aeruginosa*
- Complicated kidney and upper urinary tract infections
- Severe infections of the skin and of the soft tissue
- Gonococcal infections of the genitals, especially if penicillin has failed or is unsuitable.
- Infections of the abdominal cavity (e.g. peritonitis). When treating infections of the abdominal cavity, cefotaxime should be used in conjunction with an antibiotic that is active against anaerobic bacteria.
- Acute, bacterial meningitis (especially if caused by *H. Influenzae, N. meningitidis, S. pneumoniae, E. Coli, Klebsiella spp.*)
- Septicaemic infections starting from the lungs, the urinary tract or the intestine (in the case of gram-negative microorganisms, a combination with another suitable antibiotic should be considered).

Official recommendations on the appropriate use of antibacterial products are to be taken into account.

Contraindications
When should Tirotax® not be used?
Tirotax® should not be used for patients with proven or suspected hypersensitivity to cefotaxime or cephalosporins.

Pregnancy and lactation
No suitable data are available for estimating possible harmfulness of cefotaxime during pregnancy. Animal tests have not so far given any indications of unwanted effects. Caution is advised when using this medicine for pregnant women.

Cefotaxime is transferred to breast milk at low concentrations. Its use during lactation can have an adverse effect on the intestinal tract of the infant and lead to diarrhoea and colonization with *Saccharomyces* and give rise to sensitivity. The attending doctor must weigh the possibility of weaning against discontinuing treatment with cefotaxime, taking into account the importance of cefotaxime for the breastfeeding mother.

Precautions for use and special warnings
- Particular caution is advised for patients with a history of hypersensitivity reactions to penicillin. Before prescribing cephalosporins the attending doctor must exclude possible hypersensitivity to penicillin or other lactam antibiotics, as cross allergies occur in 5-10% of cases. If there is an allergic reaction the treatment is to be discontinued immediately.
- In patients with severe impairment of renal function the attending doctor may need to adjust the dose (see Dosage).
- Tirotax® is to be used with caution in patients with an allergy and asthma.
- As with other broad-spectrum antibiotics, with longterm use there may be proliferation of pathogens that are not sensitive to the medicine used, and in some circumstances this may require discontinuation of the treatment. If such superinfection occurs during treatment, the attending doctor must initiate specific antimicrobial treatment, if he regards this as clinically necessary.
- There have been reports of the occurrence of a severe intestinal disease (pseudomembranous colitis) during treatment with broad-spectrum antibiotics. Therefore if there is severe and persistent diarrhoea during or after treatment with antibiotics it is important to consider this diagnosis. The attending doctor must check for the presence of *C. difficile* toxin, and if colitis is suspected the treatment with cefotaxime must be discontinued. The diagnosis can be confirmed by detection of the toxin; treatment with an antibiotic (e.g. oral vancamycin or metronidazole) is to be initiated if clinically necessary. Administration of preparations that stop bowel movement is to be avoided.
- Because blood abnormalities can develop during treatment with cefotaxime, the blood picture should be monitored if treatment lasts longer than 7 days. If there is a definite change in the blood picture (neutropenia (<1400 neutrophils/mm3)), treatment is to be discontinued by the doctor.
- Aminoglycosides and cefotaxime must not be mixed together in the same syringe or in the same infusion fluid.
- Rapid infusion into a central vein can cause disturbance of cardiac rhythm.
- The sodium content of cefotaxime (2.09 mmol/g) must be taken into account for patients requiring sodium retention.
- Cefotaxime prepared with lidocaine must never be used:
- intravenously
- in children under 30 months
- in patients with a previous history of hypersensitivity to this product
- in patients with heart block or with a pacemaker
- in patients with severe cardiac insufficiency

Please inform your doctor if you become pregnant.

Keep out of the reach of children.

Interactions
Can Tirotax® be used at the same time as other medicines?

With other medicines:
- Co-administration of probenecid leads, through inhibition of cefotaxime excretion via the kidneys, to higher serum concentrations of cefotaxime, which persist for longer.
- During simultaneous use of cefotaxime, the efficacy of oral contraceptives may be reduced. Therefore additional contraceptive measures are recommended during treatment with Tirotax®.
- Simultaneous treatment with high doses of cephalosporins and drugs that are toxic to the kidneys, such as aminoglycosides or highly effective diuretics (e.g. furosemide), can impair renal function. Monitoring of renal function by the attending doctor is strongly recommended.
- Tirotax® must not be combined with antibiotics that have bacteriostatic action (e.g. tetracyclines, erythromycin or chloramphenicol), as an opposing effect is possible.

Other interactions:
- As with other cephalosporins, the Coombs test may be positive during treatment with cefotaxime. This phenomenon can also affect serological cross-matching.
- In the determination of glucose by reducing methods (Benedict's solution, Fehling's solution, Clinitest tablets), false-positive results are possible. This can be avoided by using specific enzymatic methods (glucose oxidase methods).

Incompatibilities
Cefotaxime must not be administered mixed with other antibiotics in the same syringe or infusion solution. This applies in particular to aminoglycosides.
Tirotax® must not be mixed with solutions containing sodium bicarbonate.

Dosage
How much Tirotax® should be used, and how often?
It must ONLY be administered by a doctor!

Tirotax® can be administered as an intravenous bolus injection, intravenous infusion or intramuscular injection after preparing the solution ready for use according to the instructions given below. The dosage and mode of administration depend on the severity of infection, the sensitivity of the causative agent and the patient's condition. Treatment can be initiated before the results of the sensitivity tests are available.
Tirotax® has mutually intensifying effects with aminoglycosides.

Adults and children over 12 years:
The usual dose for adults is 2 to 6 g daily. The daily dose is to be split up. The dosage can, however, be adjusted according to the severity of infection, the sensitivity of the pathogen and the patient's condition.

Dosage guidelines
Typical infection, proven to be caused (or suspected of being caused) by sensitive microorganisms: 1 g every 12 hours corresponding to a total daily dose of 2 g, intramuscular or intravenous.

An infection that has been proven to be caused (or is suspected of being caused) by various sensitive or moderately sensitive microorganisms: 1 - 2 g every 12 hours corresponding to a total daily dose of 2-4 g.

Severe infection, caused by unidentified microorganisms, or infections that cannot be localized: 2 - 3 g as separate doses every 6-8 hours up to a maximum daily dose of 12 g.

For severe infections, co-administration of Tirotax® with other antibiotics is indicated.

Infants and children (1 month to 12 years):
The usual dose for infants and children <50 kg is 50-150 mg/kg/day spread over 2 to 4 doses. For very severe infections it may be necessary to increase the dose up to 200 mg/kg/day divided over several separate doses. In the case of infants and children >50 kg, the normal dose for adults should be given, but not exceeding a maximum daily dose of 12 g.

Newborn and premature infants:
The recommended dose is 50 mg/kg/day spread over 2 to 4 doses.
In life-threatening situations it may be necessary to increase the daily dose. For severe infection, 150-200 mg/kg/day has been administered: in these situations the following table can offer guidance, as there are differences in development of the kidnes.

Age	Daily dose of cefotaxime
0 - 7 days	50 mg/kg every 12 h
8 days - 1 month	50 mg/kg every 8 h

Elderly patients:
No adjustment of dosage is required for elderly patients, provided renal and hepatic function is normal.

Other recommendations:
Gonorrhoea:
Single administration of an injection (intramuscular or intravenous) of 0.5 g to 1 g Tirotax®.
In the case of complicated infections, any official recommendations are to be taken into account. Syphilis is to be excluded before treatment is started.

Urinary tract infections:
For uncomplicated urinary tract infections, 1 g every 12 hours.

Bacterial meningitis:
The recommended daily dose is 6-12 g for adults and 150-200 mg/kg for children, spread over doses of equal amount every 6 to 8 hours. For neonates, 50 mg/kg cefotaxime can be administered every 12 h for infants in the age range 0-7 days, and every 8 h for infants in the age range 7-28 days.

Infections of the abdominal cavity
Infections of the abdominal cavity should be treated with cefotaxime in combination with other suitable antibiotics.

Duration of treatment:
The duration of treatment with Tirotax® depends on the patient's clinical condition and the progress of the disease. Treatment with Tirotax® should continue until the symptoms have subsided or it can be demonstrated that the bacteria have been eradicated. Infections that are caused by *Streptococcus pyogenes* require treatment lasting at least 10 days (parenteral treatment (infusion or injection) can be changed to a suitable oral treatment (e.g. ingestion of tablets) before the 10 days have elapsed.

Dosage when kidney function is impaired:
For adults with creatinine clearance of ≤5 ml/min the initial dose corresponds to the usual recommended dose, whereas the maintenance dose should be halved, without altering the dose interval.

Dosage in blood lavage (dialysis or peritoneal dialysis):
For patients undergoing haemodialysis or peritoneal dialysis, the administration of an i.v. injection of 0.5 g - 2 g after each dialysis treatment and every 24 hours is sufficient for effective treatment of most infections.

Mode of Administration
To avoid any risk of infection, the infusion must be prepared under strictly aseptic conditions. Once the solution has been prepared, the infusion is to be administered without delay.

- Intravenous Infusion:
  For *short-duration intravenous* infusion, 1 g or 2 g Tirotax® is dissolved in 40-50 ml of water for injection or some other compatible (i.e. compatible with Tirotax®) liquid (e.g. glucose 10%). After it has been prepared, the solution is administered as a 20-minute intravenous infusion.
  For *continuous intravenous drip*, 2 g Tirotax® is dissolved in 100 ml of a suitable liquid, e.g. in 0.9% sodium chloride or in isotonic glucose solution or other compatible fluids for infusions. After it has been prepared, the solution is administered as a 50-60—minute intravenous infusion.
- Intravenous Injection:
  For intravenous injection, Tirotax® 0.5 g is dissolved in 2 ml water for injection, Tirotax® 1 g in 4 ml water for injection and Tirotax® 2 g in 10 ml water for injection, and then injected over 3 to 5 minutes.
- Intramuscular Injection:
  For intramuscular injection, Tirotax® 0.5 g is dissolved in 2 ml water for injection or Tirotax® 1 g in 4 ml water for injection. The solution is to be administered by deep intramuscular injection. To avoid pain during injection, Tirotax® 0.5 g can be dissolved in 2 ml of 1% lidocaine hydrochloride solution or Tirotax® 1 g in 4 ml of 1% lidocaine hydrochloride solution (only for adults). Lidocaine-containing solutions must not be given intravenously. If the total daily dose exceeds 2 g, choose intravenous administration. Intramuscular injection is not recommended for severe infections.

The following table shows the dilution ratio for the various sizes of vials.

	Mode of Administration			
Vial size	Short-duration intravenous infusion	Continuous intravenous drip	Intravenous injection	Intramuscular injection
0.5 g	-	-	2 ml	2 ml
1 g	40 - 50 ml	-	4 ml	4 ml
2 g	40 - 50 ml	100 ml	10 ml	-

Instructions for Handling:
The solution is to be prepared using aseptic methods. Once it is ready, the solution should be used immediately.
Cefotaxime is compatible with a number of common intravenous infusion fluids:
- water for injection
- sodium chloride solution 0.9% glucose solution 5%
- glucose 5%/sodium chloride solution 0.9%
- Ringer's lactate solution
- metronidazole solution 5%
- dextran 40 in sodium chloride solution 0.9%
- dextran 40 in glucose solution 5%

The compatibility of cefotaxime with other infusion fluids is to be checked before they are used.
The solution ready for use should be clear and pale yellowish to yellowish-brown. Do not use if particles are visible. Only take out one dose.
Unused solution is to be destroyed.
For instructions for preparing the solution ready for use, see Mode of Administration.

Overdose
Symptoms of overdose:
Cefotaxime has very low toxicity. No cases of acute poisoning with cefotaxime are known so far. The symptoms of an overdose should largely correspond to the profile of side effects. In the case of overdose (especially when renal function is impaired) there is a risk of a curable encephalopathy.

Treatment of overdose:
No specific antidote for overdose is known. The serum concentration of cefotaxime can be lowered by haemodialysis or peritoneal dialysis (blood lavage).

Treatment of hypersensitivity reactions:
In the case of anaphylactic shock, immediate countermeasures are required. At the first signs of hypersensitivity reactions (e.g. skin reactions such as skin rash or urticaria, headache, nausea, agitation), administration of Tirotax® should be discontinued. If there are severe hypersensitivity reactions or anaphylactic reactions, appropriate emergency measures must be initiated immediately, for example the administration of adrenaline and/or glucocorticoids. Additional measures (e.g. artificial respiration, administration of histamine receptor antagonists) may be necessary, depending on the clinical severity of the reactions. If there is circulatory collapse, emergency measures must be initiated in accordance with the current guidelines.

Undesirable effects
What unwanted effects (undesirable effects) - which do not necessarily occur in every patient - can Tirotax® have?

Frequent (1 - 10%); rare (<0.1%); very rare (<0.01%)

Infections and Infestation:
Rare
- Long-term use can lead to increased proliferation of non-sensitive organisms (see Precautions for Use and Special Warnings).

Blood and disturbances of the lymphatic system:
Rare
- During treatment with cefotaxime there may be development of granulocytopenia and, more rarely, of agranulocytosis, especially with administration over an extended period. Some cases of eosinophilia and neutropenia have been described; these, however, were curable after discontinuing the treatment. Haemolytic anaemia was described in rare instances. Eosinophilia and thrombocytopenia were observed in rare instances, and these too were quickly reversible after discontinuation of treatment. Therefore it is advisable to monitor the blood picture if treatment lasts longer than 7 days.

Disturbances of the nervous system:
Rare
- High-dosage administration of antibiotics of this group can lead to an encephalopathy (brain lesion) (especially in patients with impaired renal function) which is manifested in the form of dizziness, cramps and tiredness.

Heart trouble:
Very rare
- Very rarely, arrhythmias were observed after a fast bolus infusion through a centralvein catheter.

Gastrointestinal tract:
Frequent
- Patients treated with cefotaxime frequently develop disorders of the gastrointestinal tract, such as blastomycosis, nausea, vomiting, abdominal pains and diarrhoea. If diarrhoea is severe and persistent, the possibility of pseudomembranous colitis must be considered. If pseudomembranous colitis is proven or suspected, treatment with Tirotax® must be discontinued at once and suitable treatment must be initiated.

Disturbances of the liver and gallbladder:
Rare
- A slight, transient increase of bilirubin, liver transaminases and other enzymes (SGOT, SGPT, LDH, γ-GT, alkaline phosphatase) has been observed rarely.

Disturbances of the skin and of the subcutaneous tissue:
Frequent
- Hypersensitivity reactions described comprise skin reactions, for example rash, pruritus and urticaria
- Drug fever.

Very rare
- Severe skin diseases such as erythema multiforme exudativum, Stevens-Johnson syndrome, toxic epidermal necrolysis,
- allergic shock (see Section 4.9).

Patients with an allergy are more susceptible to hypersensitivity reactions after administration of Tirotax®.
There may be a Herxheimer-like reaction during treatment of spirochaetal infections. This can lead to fever, chill, headache and joint pains.

Kidney and urinary disturbances:
Rare
- There may be a temporary increase in serum creatinine and urea values

Very rare
- Very rarely, reversible interstitial nephritis has been reported.

General symptoms and symptoms at the site of administration:
Frequent
- There may be transient, localized pain at the injection site. The likelihood of this increases with the level of the dose. Superficial phlebitis has sometimes been observed after intravenous administration of cefotaxime. However, this has seldom necessitated discontinuation of the treatment.

If you have any other undesirable effect not given in the user information, please inform your doctor or pharmacist.

Note on expiry date and storage
Please note the expiry date on the pack.
Tirotax® must not be used after this date.

Do not store above 25 °C.
Keep the container in the outer packaging.
Once prepared, the solution must be used immediately.

Date of the information:
October 2002

If you have any other questions about Tirotax®, please ask your doctor or pharmacist.

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