For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

TOROCEF XP

1. Generic Name

Ceftriaxone & Tazobactam for Injection

2. Qualitative and Quantitative Composition:

TOROCEF XP 500

Each composite pack contains: A & B
A) Each vial contains:
Ceftriaxone Sodium I.P. equivalent to
Anhydrous Ceftriaxone……500 mg
Tazobactam Sodium equivalent to
Tazobactam……62.5 mg
B) Each ampoule contains:
Sterile Water for Injection I.P. ……...10 ml

TOROCEF XP 1000

Each composite pack contains: A & B
A) Each vial contains:
Ceftriaxone Sodium I.P. equivalent to
Anhydrous Ceftriaxone……1000 mg
Tazobactam Sodium equivalent to
Tazobactam……125 mg
B) Each ampoule contains:
Sterile Water for Injection I.P. ……10 ml

3. Dosage form and strength

Dosage form: Intravenous/Intramuscular

Strength: Ceftriaxone 500 & Tazobactam 62.5 for Injection; Ceftriaxone 1000 & Tazobactam 125 for Injection

4. Clinical particulars

4.1. Therapeutic indication

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Torocef XP, it should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Torocef XP is mainly indicated in the following conditions: Lower respiratory tract infections and community acquired pneumonia acute bacterial otitis media, Skin and skin structure infections, Urinary tract infections, uncomplicated gonorrhoea, Pelvic inflammatory disease, Bacterial septicemia, Bone and joint infections, Intra-abdominal infections, Bacterial meningitis.

Surgical prophylaxis: The preoperative administration of a single 1gm dose of Torocef XP may reduce the incidence of postoperative infections in patients undergoing surgical procedures

classified as contaminated or potentially contaminated (e.g, vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, (such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (e.g, during coronary artery bypass surgery).

4.2. Posology and method of administration

Posology

Torocef XP is administered intravenously and intramuscularly.

Adults: The usual adult dose is 1000/125 mg of ceftriaxone/tazobactam givenonceaday (or in equally divided doses twice a day) depending upon the severity of the infection. The total daily dose should not exceed 4.5 gms (in terms of ceftriaxone).

Paediatric patients: For the treatment of serious infections the recommended dose is 50-75 mg/kg (in terms of ceftriaxone) given in divided doses every 12 hours. The total daily dose should not exceed 2.25 g (in terms of ceftriaxone).

Generally, ceftriaxone/tazobactam should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 7 to 14 days; in complicated infections longer therapy may be required. When treating *Streptococci* pyogenes the therapy should be continued for at least 10 days.

Method of administration

Reconstitute ceftriaxone/ tazobactam with the appropriate diluent for example water for injection I.P. normal saline, dextrose solutions.

For IV administration		**For IM aministration**	
Vial dosage size	Amount of diluent to be added (ml)	Vial dosage size	Amount of diluent to be added (ml)
1000 mg	9.6	1000 mg	2.1 to 3.6
500 mg	48	500 mg	1.0 to 1.8
250 mg	2.4	250 mg	0.5 to 0.9

Use Reconstituted Solution in the Vial Immediately

4.3. Contraindications

Hypersensitivity to cephalosporins and beta lactamase inhibitors.

4.4. Special warnings and precautions for use

Before therapy with Torocef XP is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. This product should be given cautiously to penicillin sensitive patients. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftriaxone/tazobactam and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of ceftriaxone/tazobactam is similar to that of other cephalosporins.

Alterations in prothrombin times have occurred rarely in patients treated with ceftriaxone/ tazobactam. Patients with impaired vitamin K synthesis or low vitamin K stores (eg. chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Torocef XP treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy. Prolonged use of ceftriaxone/tazobactam may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Torocef XP should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

There have been reports of sonographic abnormalities in the gallbladder of patients treated with ceftriaxone; some of these patients also had symptoms of gallbladder disease. These abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The chemical nature of the sonographically detected material has been determined to be predominantly a ceftriaxone-calcium sari. The condition appears to be transient and reversible upon discontinuation of ceftriaxone/tazobactam and institution of conservative management. Therefore, ceftriaxone/tazobactam should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Renal Impairment

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Torocef XP are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Hepatic impairment

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however in patients with both hepatic dysfunction and significant renal disease, Torocef XP dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

4.5. Drugs interactions

Vancomycin and Fluconazole are physically incompatible with ceftriaxone in admixture. When either of these drugs is to be administered concomitantly with ceftriaxone by intravenous infusion, it is recommended that they be given sequentially, with thorough flushing of the intravenous lines between the administrations.

4.6. Use in special populations (such as pregnant women, lactating women).)

Pregnancy

Category B. There are, no adequate and well controlled studies in pregnant women and hence this drug should be used during pregnancy only if clearly needed.

Lactation

Low concentrations of ceftriaxone/tazobactam are excreted in human milk. Caution should be exercised when ceftriaxone is administered to a nursing woman.

Tazobactam concentration in milk have not been studied.

Paedlatric use

Ceftriaxone/tazobactam should not be administered to hyperbilirubinemia neonates, especially prematures.

4.7. Effects on ability to drive and use machines

No information available

4.8. Undesirable effects

Ceftriaxone/tazobactam is generally well tolerated.

Local Reactions: pain, induration and tenderness, phlebitis. Hypersensitivity, rash (1.7%). Less frequently reported (<1 %) were pruritus, fever or chills.

Hematologic. Eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%).

Gastrointestinal: diarrhoea (2.7%). Less frequently reported (< 1 %) were nausea or vomiting, and dysgeusia. Hepatic, elevations of AST or ALT. Less frequently reported (< 1 %) were elevations of alkaline phosphatase and bilirubin.

Renal: elevations of the BUN (1.2%).

Central Nervous System: headache or dizziness were reported occasionally (<1 %).

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting by reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Limited information is available on the acute toxicity of ceftriaxone/tazobactam. There is no specific antidote. If acute overdosage of ceftriaxone/tazobactam occurs, supportive and symptomatic treatment should be initiated. Haemodialysis or peritoneal dialysis are ineffective in reducing ceftriaxone concentration following overdosage.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Ceftriaxone is a 2-aminothiazolyl methoxyimino third-generation cephalosporin derivative.

Ceftriaxone, a bactericidal antimicrobial, inhibits bacterial cell wall synthesis of actively dividing cells by binding to one or more penicillin binding proteins (PBPs). These proteins are associated with the bacterial cell membrane and probably serve in synthesis. The result is formation of a defective cell wall that is osmotically unstable. Bacterial species have a unique set of PBPs. The affinity pattern of ceftriaxone for the PBPs for different bacterial species affects the drugs antimicrobial spectrum of activity. It is also felt that cephalosporins, as well as penicillins, may

increase the breakdown of the cell wall of bacteria by decreasing the availability of an inhibitor of murein hydrolase, an enzyme involved in cell division. If unimposed, this enzyme can destroy the integrity of the cell wall.

Tazobactam is a penicillinate sulfone, structurally related to sulbactam. Being a beta lactamase inhibitor, it is synergistic with many beta lactamase labile drugs such as penicillins and cephalosporins.

Tazobactam inhibits all beta lactamases inhibited by clavulanic acid, but in addition it also has some activity against chromosomally mediated induced (or derepressed) enzymes of *Morganellamorganii, Citrobacterfreundii, Enterobactercloacae, Serra Samarcescens* and *Pseudomonas aemginosa*. Tazobactam also appears to be a weaker enzyme inducer than other beta lactamase inhibitors.

The combination of tazobactam and ceftriaxone is active against all the organisms sensitive to ceftriaxone. In addition, it demonstrates synergistic activity (reduction in MICs for the combination versus those of each component) in a variety of organisms.

Gram-negative Aerobes:

Acinetobactercalcoaceticus

Enterobacter aerogenes

Enterobacter cloacae

Escherichiacoli

Haemophilus influenzae

(Including ampicillin-resistant and betalactamase producing strains)

Haemophilus parainfiuenzae

Klebsiellaoxytoca

Klebsiella pneumoniae

Moraxella catarrhalis

(Including beta-lactamase producing strains)

Morganella morganii

Neisseria gonorrhoeae

(Including penicillinase and nonpenicillinase-producing strains)

Neisseria meningitidis

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Ceftriaxone is also active against many strains of

Pseudomonas aeruginosa.

Gram-Positive Aerobes:

Staphylococcus aureus

(Including penicillinase-producing strains)

Staphylococcus epidermidis

Streptococcus pneumoniae

Streptococcus pyogenes

Viridans group streptococci

Anaerobes:

Bacteroides fragilis, Clostridium species, Peptostxeptococcus species

5.2. Pharmacokinetic properties

Average plasma concentrations of ceftriaxone are given in the table below:

Ceftriaxone plasma concentrations (mcg/ml) after single dose administration.

Dose/Route	1/2 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 gml V	82	59	48	37	29	23	15	10	5
1 gml V	151	111	88	67	53	43	28	18	9

Ceftriaxone achieved high concentrations in urine. 33% to 67% of ceftriaxone was excreted unchanged drug and the remainder was excreted in bile and feces. Average concentrations of ceftriaxone achieved after 1 g IV dose in gallbladder bile was 581 Meg/ ml, 788 mcg/ml in common bile duct, 898 mcg/ml in cystic bile duct, 78.2 mcg/ml in gall bladder wall and 62.1 mcg/ml in concurrent plasma.

The elimination half-life was 8.7 hours. Ceftriaxone was 98% bound to plasma proteins. Ceftriaxone crosses the blood brain barrier.

Tazobactam is metabolised to a single metabolite that lacks pharmacological and antibacterial activities. Tazobactam is eliminated via the kidney by glomerular filtration and tubular secretion. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose excreted as unchanged drug and the remainder as the single metabolite. Tazobactam is also secreted into the bile. Tazobactam is approximately 30% bound to plasma proteins. Protein binding of the tazobactam metabolite is negligible. Tazobactam is widely distributed to tissues and body fluids including intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary and fallopian tube), interstitial fluid, and bile.

6. Nonclinical properties

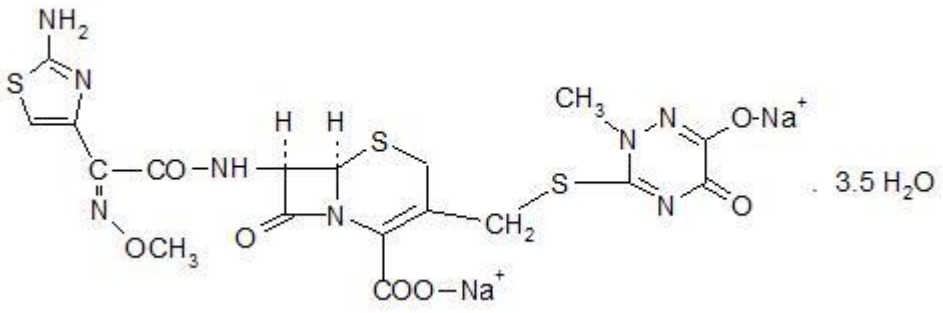
6.1. Animal Toxicology or Pharmacology

No information available.

7. Description

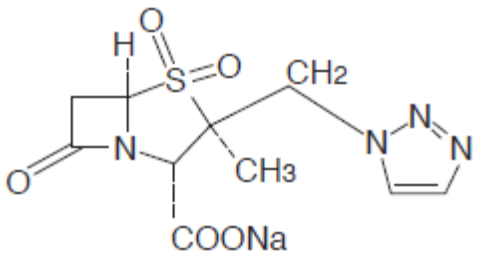
Ceftriaxone sodium is disodium(6R,7R)-7-[[(Z)-(2-aminothiazol- 4-yl)(methoxyimino)acetyl]amino]-3-[[(2-methyl-6-oxido-5-oxo-2, 5-dihydro-1,2,4-triazin-3-yl)sulphanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It has empirical formula of $C_{18}H_{16}N_8Na_2O_7S_3$, 3½H2O and molecular weight of 662.0. It is a white or yellowish, crystalline powder, slightly hygroscopic substance.

Ceftriaxone sodium is freely soluble in water, soluble in methanol, very slightly soluble in ethanol (95%), ether, ethyl acetate and chloroform.



Tazobactam sodium is [2S-(2α,3β,5α)]-3-Methyl-7-oxo-3-(1H-1,2,3- triazol-1-ylmethyl)-4-thia-1-azabicyclo[3,2,0]heptane-2-carboxylic acid 4,4-dioxide Sodium Salt.

It has empirical formula of $C_{10}H_{11}NO_5SNa$ and molecular weight of 322.30



8. Pharmaceutical particulars

8.1. Incompatibilities

Vancomycin and Fluconazole are physically incompatible with ceftriaxone in admixture. When either of these drugs is to be administered concomitantly with ceftriaxone by intravenous infusion, it is recommended that they be given sequentially, with thorough flushing of the intravenous lines between the administrations.

8.2. Shelf-life

24 Months.

8.3. Packaging information

Torocef XP 500 is available in a vial of 10 ml with 10 ml sterile water for injection.

Torocef XP 1000 is available in a vial of 20 ml with 10 ml sterile water for injection.

8.4. Storage and handing instructions

Store below 25ºC. Protect from light.

Keep out of reach of children. Do not freeze.

After reconstitution protection from normal light is not necessary.

The colour of solution ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

9. Patient Counselling Information

TOROCEF XP Ceftriaxone & Tazobactam for Injection)

- Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

9.1. What TOROCEF XP is and what it is used for?

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Torocef XP, it should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Torocef XP is mainly indicated in the following conditions: Lower respiratory tract infections and community acquired pneumonia acute bacterial otitis media, Skin and skin structure infections, Urinary tract infections, uncomplicated gonorrhoea, Pelvic inflammatory disease, Bacterial septicemia, Bone and joint infections, Intra-abdominal infections, Bacterial meningitis.

Surgical prophylaxis: The preoperative administration of a single 1gm dose of Torocef XP may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g, vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, (such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (e.g, during coronary artery bypass surgery).

9.2. What you need to know before you take TOROCEF XP?

TOROCEF XP is contraindicated with cephalosporins and beta lactamase inhibitors as it causes hypersensitivity.

Warning and Precautions

Before therapy with Torocef XP is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. This product should be given cautiously to penicillin sensitive patients. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftriaxone/tazobactam and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

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Alterations in prothrombin times have occurred rarely in patients treated with ceftriaxone/ tazobactam. Patients with impaired vitamin Ksynthesis or low vitamin K stores (eg. chronic hepatic

disease and malnutrition) may require monitoring of prothrombin time during Torocef XP treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy. Prolonged use of ceftriaxone/tazobactam may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Torocef XP should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

There have been reports of sonographic abnormalities in the gallbladder of patients treated with ceftriaxone; some of these patients also had symptoms of gallbladder disease. These abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The chemical nature of the sonographically detected material has been determined to be predominantly a ceftriaxone-calcium sari. The condition appears to be transient and reversible upon discontinuation of ceftriaxone/tazobactam and institution of conservative management. Therefore, ceftriaxone/tazobactam should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Renal Impairment

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Torocef XP are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Hepatic impairment

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however in patients with both hepatic dysfunction and significant renal disease, Torocef XP dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

9.3. How to take TOROCEF XP?

Posology

Torocef XP is administered intravenously and intramuscularly.

Adults: The usual adult dose is 1000/125 mg of ceftriaxone/tazobactam givenonceaday (or in equally divided doses twice a day) depending upon the severity of the infection. The total daily dose should not exceed 4.5 gms (in terms of ceftriaxone).

Paediatric patients: For the treatment of serious infections the recommended dose is 50-75 mg/kg (in terms of ceftriaxone) given in divided doses every 12 hours. The total daily dose should not exceed 2.25 g (in terms of ceftriaxone).

Generally, ceftriaxone/tazobactam should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 7 to 14 days; in complicated infections longer therapy may be required. When treating Streptococci pyogenes the therapy should be continued for at least 10 days.

Method of administration

Reconstitute ceftriaxone/ tazobactam with the appropriate diluent for example water for injection I.P. normal saline, dextrose solutions.

For IV administration		For IM aministration	
Vial dosage size	Amount of diluent to be added (ml)	Vial dosage size	Amount of diluent to be added (ml)
1000 mg	9.6	1000 mg	2.1 to 3.6
500 mg	48	500 mg	1.0 to 1.8
250 mg	2.4	250 mg	0.5 to 0.9

Use Reconstituted Solution in the Vial Immediately

If you take more Torocef XP than you should

If you take too many Torocef XP injection, talk to a doctor or pharmacist immediately. Medical attention may be necessary. If you have to go to a doctor or hospital, take the pack and this leaflet with you.

If you forget to take Torocef XP

If you forget to take a tablet. Do not take a double dose (two injection at once) to make up for a forgotten tablet.

If you stop taking Torocef XP

Continue to take this medicine as long as your doctor prescribes it. Do not stop taking Torocef XP unless your doctor tells you to. If you have any questions about how long to take this medicine, talk to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

9.4. Possible side effects

Ceftriaxone/tazobactam is generally well tolerated.

Local Reactions: pain, induration and tenderness, phlebitis. Hypersensitivity, rash (1.7%). Less frequently reported (<1 %) were pruritus, fever or chills.

Hematologic. Eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%).

Gastrointestinal: diarrhoea (2.7%). Less frequently reported (< 1 %) were nausea or vomiting, and dysgeusia. Hepatic, elevations of AST or ALT. Less frequently reported (< 1 %) were elevations of alkaline phosphatase and bilirubin.

Renal: elevations of the BUN (1.2%).

Central Nervous System: headache or dizziness were reported occasionally (<1 %).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5. How to store TOROCEF XP?

Store below 25ºC. Protect from light.

Keep out of reach of children. Do not freeze.

After reconstitution protection from normal light is not necessary.

The colour of solution ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

9.6. Contents of the pack and other information

Torocef XP 500 is available in a vial of 10 ml with 10 ml sterile water for injection.

Torocef XP 1000 is available in a vial of 20 ml with 10 ml sterile water for injection.

10. Details of manufacturer

Nitin Lifesciences Ltd.

Rampur Road, Paonta Sahib,

Dist. Sirmour (H.P.)-173 025

11. MARKETED BY

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.

Indrad-382 721, Dist. Mehsana, INDIA.

IN/ TOROCEF XP 500/TOROCEF XP 1000/Jun-22/02/PI