

CEFBACT T Injection (Ceftriaxone + Tazobactam)

Ceftriaxone Plus Tazobactam For Injection

Cefbact T

COMPOSITION

CEFBACT T Injection 1g

Each vial contains:

Ceftriaxone Sodium, USP, equivalent to

Ceftriaxone $\square\square\square$ 1 g

Tazobactam Sodium equivalent to

Tazobactam $\square\square$. 125 mg

Supplied with 10 ml sterile Water for Injection, IP

DOSAGE FORM

Powder for reconstitution (intravenous [I.V]/intramuscular [I.M])

PHARMACOLOGY

Pharmacodynamics

Ceftriaxone is a 2-aminothiazolyl methoxylmino 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 the 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 drug's antimicrobial spectrum of activity. It is also felt that cephalosporins, as well as penicillins, may increase the breakdown of the cell wall of the 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.

Ceftriaxone has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Tazobactam is a penicillinate sulphone, 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 *Morganella morganii*, *Citrobacter freundii*, *Enterobacter cloacae*, *Serratia marcescens* and *Pseudomonas aeruginosa*. Tazobactam also appears to be a weaker enzyme inducer than other beta-lactamase inhibitors.

Combination of Ceftriaxone and Tazobactam

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

Gram-negative bacteria

Acinetobacter calcoaceticus

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella oxytoca

Klebsiella pneumoniae

Moraxella catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Neisseria meningitidis

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Pseudomonas aeruginosa

Gram-positive bacteria

Staphylococcus aureus

Staphylococcus epidermidis

Streptococcus pneumoniae

Streptococcus pyogenes

Viridans group streptococci

Anaerobes

Bacteroides fragilis

Clostridium species

Peptostreptococcus species

The *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit *in vitro* MIC less than or equal to susceptible breakpoint for ceftriaxone. However, the efficacy of ceftriaxone in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-negative bacteria

Citrobacter diversus

Citrobacter freundii

Providencia species (including *Providencia rettgeri*)

Salmonella species (including *Salmonella typhi*)
Shigella species

Gram-positive bacteria

Streptococcus agalactiae

Anaerobic bacteria

Prevotella (Bacteroides) bivia

Porphyromonas (Bacteroides) melaninogenicus

Pharmacokinetics

Adults

Average plasma concentrations of ceftriaxone after administration of a single dose are given in the table below:

Table 1: Ceftriaxone Plasma Concentrations After Single-Dose Administration

Dose/Route	½ hour	1 hour	2 hours	4 hours	6 hours	8 hours	12 hours	16 hours	24 hours
1 g I.V.*	151	111	88	67	53	43	28	18	9
1 g I.M.	40	68	76	68	56	44	29	ND	ND

*I.V. doses were infused at a constant rate over 30 minutes.

ND = Not determined.

Ceftriaxone was completely absorbed following I.M. administration, with mean maximum plasma concentrations occurring between 2 and 3 hours post-dose. Multiple I.V. or I.M. doses ranging from 0.5 to 2 g at 12- to 24-hour intervals resulted in 15-36% accumulation of ceftriaxone above single-dose values.

Ceftriaxone concentrations in urine are shown in Table 2.

Table 2: Urinary Concentrations of Ceftriaxone After Single-Dose Administration

Dose/Route	Average Urinary Concentrations (µg/mL)					
	0-2 hours	2-4 hours	4-8 hours	8-12 hours	12-24 hours	24-48 hours
1 g I.V.	995	855	293	147	132	32
1 g I.M	504	628	418	237	ND	ND
2 g I.V.	2692	1976	757	274	198	40

ND = Not determined.

Altogether, 33-67% of the ceftriaxone dose is excreted in the urine as unchanged drug and the remainder is excreted in the bile and the faeces. After a 1 g I.V. dose, average concentrations of ceftriaxone achieved in the gall bladder bile is 581 mcg/ml, 788 mcg/ml in the common bile duct, 898 mcg/ml in the cystic bile duct, 78.2 µg/g in the gall bladder wall and 62.1 µg/ml in concurrent plasma.

Over a 0.15 to 3 g dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8 to 8.7 hours; apparent volume of distribution from 5.78 to 13.5 L; plasma clearance from 0.58 to 1.45 L/hour; and renal clearance from 0.32 to 0.73 L/hour. Ceftriaxone is reversibly bound to

human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of <25 µg/mL to a value of 85% bound at 300 µg/mL. Ceftriaxone crosses the blood-placenta barrier.

Tazobactam is metabolized to a single metabolite that lacks pharmacological and antibacterial activities. Tazobactam is eliminated via the kidneys 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 a 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 the intestinal mucosa, gall bladder, lungs, female reproductive tissues (uterus, ovary and fallopian tube), interstitial fluid, and bile.

Compared with that in healthy adult subjects, the pharmacokinetics of ceftriaxone is only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (Table 3); therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2 g per day. Ceftriaxone was not removed to any significant extent from the plasma by haemodialysis; in 6 of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced.

Table 3: Average Pharmacokinetic Parameters of Ceftriaxone in Humans

Subject Group	Elimination Half-Life (hr)	Plasma Clearance (L/hr)	Volume of Distribution (L)
Healthy subjects	5.8-8.7	0.58-1.45	5.8-13.5
Elderly subjects (mean age, 70.5 years)	8.9	0.83	10.7
Patients with Renal Impairment			
Haemodialysis patients (0 to 5 mL/min)*	14.7	0.65	13.7
Severe (5-15 mL/min)	15.7	0.56	12.5
Moderate (16-30 mL/min)	11.4	0.72	11.8
Mild (31-60 mL/min)	12.4	0.70	13.3
Patients with liver disease	8.8	1.1	13.6

*Creatinine clearance.

The elimination of ceftriaxone is not altered when ceftriaxone is co-administered with probenecid.

INDICATIONS

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

CEFBACT T Injection is mainly indicated in the following conditions:

Surgical Prophylaxis: The pre-operative administration of a single 1 g dose of **CEFBACT T Injection** may reduce the incidence of post-operative 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 a serious risk (e.g. during coronary artery bypass surgery).

When administered prior to surgical procedures for which it is indicated, a single 1 g dose of **CEFBACT T Injection** provides protection from most infections due to susceptible organisms throughout the course of the procedure.

Although **CEFBACT T Injection** has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

DOSAGE AND ADMINISTRATION

CEFBACT T Injection may be administered by the I.V. or I.M. Route.

Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Under most circumstances a once-daily dose — or, in the specified indications, a single dose — will give satisfactory therapeutic results.

Note: The dosage recommendations are in terms of ceftriaxone alone.

Adults and Children Aged 12 Years and Over

The usual adult dose is 1 g given once a day (or in equally divided doses twice a day), depending upon the severity of the infection.

For severe infections, 2–4 g daily, normally as a single dose every 24 hours.

For infections caused by *Staphylococcus aureus* (methicillin-susceptible *S. Aureus* [MSSA]), the recommended daily dose is 2–4 g, in order to achieve >90% target attainment. The total daily dose should not exceed 4 g.

If *Chlamydia trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism.

For the treatment of uncomplicated gonococcal infections, a single I.M. dose of 250 mg is recommended.

Simultaneous administration of probenecid is not indicated.

For pre-operative use (surgical prophylaxis), a single I.V. dose of 1 g administered half-hour to 2 hours before surgery is recommended. In colorectal surgery, a 2 g I.M. dose should be given (dosages greater than 1 g should be divided and injected at more than one site), or by slow I.V.

infusion, in conjunction with a suitable agent against anaerobic bacteria.

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 4–14 days; in complicated infections, longer therapy may be required. When treating *Streptococci pyogenes*, the therapy should be continued for at least 10 days.

Elderly Patients

These dosages do not require modification in elderly patients provided that renal and hepatic functions are satisfactory.

Paediatric Patients

Neonates

A daily dose of 20–50 mg/kg body weight, not to exceed 50 mg/kg.

In the neonate, the I.V. dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy.

Infants and Children Aged up to 12 Years

Standard therapeutic dosage: 20–50 mg/kg body weight once daily.

For the treatment of skin and skin structure infections, the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 g.

For the treatment of acute bacterial otitis media, a single I.M. dose of 50 mg/kg (not to exceed 1 g) is recommended.

For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50–75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 g.

In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 g). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 g daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7–14 days.

In severe infections, up to 80 mg/kg body weight daily may be given. For children with body weights of 50 kg or more, the usual adult dosage should be used. Doses of 50 mg/kg or over should be given by slow I.V. infusion over at least 30 minutes. Doses greater than 80 mg/kg body weight should be avoided because of the increased risk of biliary precipitates.

Renal and Hepatic Impairment

In patients with impaired renal function, there is no need to reduce the dosage of **CEFBACT T Injection** provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance <10 ml per minute) should the daily dosage be limited to 2 g or less.

In patients with liver damage there is no need for the dosage to be reduced provided renal function

is intact.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of **CEFBACT T Injection** should be determined at regular intervals and dosage adjusted.

In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

Directions for Use

The use of freshly prepared solutions is recommended.

Ceftriaxone may be administered by deep I.M. injection, or as a slow I.V. injection/infusion, after reconstitution of the solution according to the directions given below:

I.V. injection should be administered over at least 2–4 minutes.

I.V. infusion should be over a period of 30 minutes.

After reconstitution, the solution should be administered by deep **I.M. injection**. Doses greater than 1 g should be divided and injected at more than one site. As with all I.M. preparations, ceftriaxone/tazobactam should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

Reconstitute ceftriaxone/tazobactam with the appropriate diluent, e.g. Water for Injection, IP, Normal Saline Water, or Dextrose Solutions.

- Lower respiratory tract infections
- Acute bacterial otitis media
- Skin and skin structure infections
- Urinary tract infections (complicated and uncomplicated)
- Uncomplicated gonorrhea (cervical/urethral and rectal)
- Pelvic inflammatory disease
- Bacterial septicaemia
- Bone and joint infections
- Intra-abdominal infections
- Bacterial meningitis
- Peri-operative prophylaxis of infections associated with surgery
- Infections in neutropenic patients

Strength	1,000 mg
Amount of diluent (ml) I.V. administration	9.6
Amount of diluent (ml) I.M. administration	3.6

CONTRAINDICATIONS

CEFBACT T Injection is contraindicated in patients with known hypersensitivity to beta-lactam antibiotics. In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind. It is also contraindicated in patients who have had a previous immediate and/or any severe hypersensitivity reaction to any penicillin or to any other beta-lactam drug

Neonates (≤ 28 days)

Hyperbilirubinaemic neonates, especially prematures, should not be treated with ceftriaxone. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients. Ceftriaxone/tazobactam is contraindicated in premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life).

CEFBACT T Injection is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing I.V. solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone calcium.

It is contraindicated in

In some of these cases, the same I.V. infusion line was used for both ceftriaxone and calcium-containing fluids and, in some, a precipitate was observed in the I.V. infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone and calcium-containing fluids were administered at different time points via different I.V. lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

WARNINGS AND PRECAUTIONS

Before therapy with ceftriaxone/tazobactam is instituted, a detailed 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.

Ceftriaxone should be given with caution to patients who have other allergic diatheses.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone/tazobactam injection vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of ceftriaxone calcium can also occur when ceftriaxone/tazobactam injection is mixed with calcium-containing solutions in the same I.V. administration line. Ceftriaxone/tazobactam injection must not be administered simultaneously with calcium-containing I.V. solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone/tazobactam injection and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. *In vitro* studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone calcium.

Clostridium difficile-associated diarrhoea (CDAD) has been reported with nearly all antibacterial agents, including ceftriaxone/tazobactam, and may range in severity from mild to life-threatening. **Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*.** Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need

to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Superinfections with non-susceptible microorganisms may occur as with other antibacterial agents.

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of ceftriaxone. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Ceftriaxone should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.

As with other cephalosporins, prolonged use of ceftriaxone may result in the overgrowth of non-susceptible organisms, such as *Enterococci* and *Candida* spp.

An immune-mediated haemolytic anaemia has been observed in patients receiving cephalosporin class-antibacterials, including ceftriaxone/tazobactam. Severe cases of haemolytic anaemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin-associated anaemia should be considered and ceftriaxone stopped until the aetiology is determined.

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 infrequently in patients treated with ceftriaxone/tazobactam. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g. chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during ceftriaxone/tazobactam injection 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 the overgrowth of non-susceptible organisms. Hence, careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Ceftriaxone/tazobactam injection should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis. There have been reports of sonographic abnormalities in the gall bladder of patients treated with ceftriaxone/tazobactam; some of these patients also had symptoms of gall bladder disease. On a sonography, these abnormalities appear 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 salt. The condition appears to be transient and reversible upon the discontinuation of ceftriaxone/tazobactam and the institution of conservative non-surgical management. Therefore, ceftriaxone/tazobactam should be discontinued in patients who develop signs and symptoms suggestive of gall bladder disease and/or the sonographic findings described above.

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported rarely in patients treated with ceftriaxone/tazobactam. Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, total parenteral nutrition). A trigger/co-factor role of ceftriaxone/tazobactam-related biliary precipitation cannot be ruled out. As with other cephalosporins, anaphylactic shock/fatal outcomes cannot be ruled out even if a thorough patient history is taken and even if the patient is not known to be allergic or previously exposed.

Prescribing ceftriaxone/tazobactam injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Ceftriaxone/tazobactam may precipitate in the gallbladder and then be detectable as shadows on ultrasound. This can happen in patients of any age, but is more likely in infants and small children who are usually given a larger dose of ceftriaxone/tazobactam on a body weight basis. In children, doses greater than 80 mg/kg body weight should be avoided because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone/tazobactam. As the condition appears to be transient and reversible upon discontinuation, therapeutic procedures are not normally indicated.

Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. During prolonged treatment, a complete blood count should be performed at regular intervals.

Cephalosporins, as a class, tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the drug to produce a positive Coombs' test and, occasionally, a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins.

Drug Interactions

Other Antibiotics

No interference with the action or increase in nephrotoxicity of aminoglycosides has been observed during simultaneous administration with ceftriaxone/tazobactam.

In an *in vitro* study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

Diuretics

No impairment of renal function has so far been observed after concurrent administration of large doses of ceftriaxone/tazobactam and potent diuretics (e.g. furosemide).

Disulfiram/ Probenecid

No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone/tazobactam. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins. The elimination of ceftriaxone/tazobactam is not altered by probenecid.

Contraceptives

Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.

Renal Impairment

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no dosage adjustment when the usual doses of ceftriaxone/tazobactam injection are administered, but concentrations of the drug in the serum should be monitored periodically. If evidence of accumulation exists, the dosage should be decreased accordingly. No data are available in the case of paediatric patients with impaired renal function.

Hepatic Impairment

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, the dosage of ceftriaxone/tazobactam injection should not exceed 2 g daily without close monitoring of serum concentrations. No data are available in the case of paediatric patients with impaired hepatic function.

Pregnancy

For ceftriaxone, limited clinical data on exposed pregnancies are available. Ceftriaxone crosses the placental barrier. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Low concentrations of ceftriaxone/tazobactam are excreted in human milk. Hence, caution should be exercised when ceftriaxone/tazobactam is administered to a nursing mother.

Paediatric Use

Safety and effectiveness of ceftriaxone/tazobactam in neonates, infants and paediatric patients have been established for the dosages described in the **DOSAGE AND ADMINISTRATION** section. *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone/tazobactam should not be administered to hyperbilirubinaemic neonates, especially premature.

Geriatric Use

The pharmacokinetics of ceftriaxone/tazobactam were only minimally altered in geriatric patients compared with healthy adult subjects, and dosage adjustments are not necessary for geriatric patients with ceftriaxone/tazobactam dosages up to 2 g per day.

UNDESIRABLE EFFECTS

Ceftriaxone/tazobactam is generally well tolerated.

The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts.

Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full-

term newborns (aged <28 days) who had been treated with I.V. ceftriaxone and calcium. Precipitations of ceftriaxone calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in newborns is due to their low blood volume and the longer half-life of ceftriaxone compared with adults.

General Disorders and Administration Site Conditions

Pain, indurations and tenderness was 1% overall.

Rare (≥ 0.01 □ $< 0.1\%$): Phlebitis and injection site pain following I.V. administration. This can be minimized by slow injection over at least 2□4 minutes. Rigors, pyrexia.

An I.M. injection *without* lidocaine solution is painful.

Hypersensitivity

Rash (1.7%). Less frequently reported ($< 1\%$) were pruritus, fever or chills.

Infections and Infestations

Rare (≥ 0.01 □ $< 0.1\%$): Mycosis of the genital tract.

Superinfections of various sites with yeasts, fungi or other resistant organisms are possible.

Blood and Lymphatic System Disorders

Eosinophilia (6%), thrombocytosis (5.1%) and leucopenia (2.1%).

Less frequently reported ($< 1\%$) were anaemia, haemolytic anaemia, neutropenia, lymphopenia, thrombocytopenia, and prolongation of the prothrombin time.

Rare (≥ 0.01 - $< 0.1\%$): Agranulocytosis ($< 500/m^3$).

Very rare ($< 0.01\%$), including isolated reports: Positive Coombs' test, coagulation disorders, mostly after 10 days of treatment and following total doses of 20 g ceftriaxone and more.

Immune System Disorders

Rare (≥ 0.01 □ $< 0.1\%$): Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions.

Nervous System Disorders

Uncommon ($< 1\%$): Headache, dizziness.

Gastrointestinal Disorders

Common (≥ 1 □ $< 10\%$): Loose stools or diarrhoea, nausea, vomiting.

Uncommon ($< 1\%$): Dysgeusia.

Rare (≥ 0.01 □ $< 0.1\%$): Stomatitis, glossitis. These side effects are usually mild and commonly disappear during treatment or after discontinuation of treatment.

Very rare (<0.01%), including isolated reports: Pseudomembranous colitis (mostly caused by *Clostridium difficile*), pancreatitis (possibly caused by obstruction of bile ducts). Therefore, the possibility of the disease should be considered in patients who present with diarrhoea following antibacterial agent use.

Hepato-Biliary Disorders

Elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, mostly in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with I.V. application, in some studies to above 30%. The incidence seems to be lower with slow infusion (20–30 minutes). This effect is usually asymptomatic, but, in rare cases, the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

Skin and Subcutaneous Tissue Disorders

Common ($\geq 1\%$ <math>\leq 10\%): Allergic dermatitis.

Uncommon ($\geq 0.1\%$ <math>\leq 1\%): Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritus, oedema.

Very rare (<0.01%), including isolated reports: Erythema multiforme, Stevens Johnson Syndrome, Lyell's Syndrome/toxic epidermal necrolysis.

Renal and Urinary Disorders

Uncommon (<1%): Increase in serum creatinine and the presence of casts in the urine. Moniliasis or vaginitis was reported occasionally.

Rare ($\geq 0.01\%$ <math>\leq 0.1\%): Oliguria, glycosuria, haematuria.

Very rare (<0.01%), including isolated reports: Renal precipitation, mostly in children older than 3 years who had been treated with either high daily doses (80 mg/kg/day and more) or total doses exceeding 10 g and with other risk factors such as dehydration or immobilization. Renal precipitation is reversible upon discontinuation of ceftriaxone. Anuria and renal impairment have been reported in association.

Miscellaneous

Diaphoresis and flushing were reported occasionally (<1%).

Other rarely observed adverse reactions (<0.1%) include abdominal pain, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, jaundice, leucocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, seizures, vertigo, and serum sickness.

Postmarketing Experience

In addition to the adverse reactions reported during clinical trials, the following adverse experiences

have been reported during clinical practice in patients treated with ceftriaxone/tazobactam. Data are generally insufficient to allow an estimate of incidence or to establish causation.

Gastrointestinal: Stomatitis and glossitis.

Genitourinary: Oliguria.

Dermatologic: Exanthema, allergic dermatitis, urticaria, oedema. As with many medications, isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

Cephalosporin-Class Adverse Reactions

In addition to the adverse reactions listed above, which have been observed in patients treated with ceftriaxone, the following adverse reactions and altered laboratory test results have been reported for cephalosporin-class antibiotics:

Adverse Reactions

Allergic reactions, drug fever, serum sickness-like reaction, renal dysfunction, toxic nephropathy, reversible hyperactivity, hypertonia, hepatic dysfunction, including cholestasis, aplastic anaemia, haemorrhage, and super-infection.

Altered Laboratory Tests

Positive direct Coombs's test, false-positive test for urinary glucose, and elevated LDH.

In patients treated with ceftriaxone/tazobactam, the Coombs's test may rarely become false-positive. Ceftriaxone/tazobactam, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone/tazobactam should be done enzymatically.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.

OVERDOSAGE

In the case of overdosage, nausea, vomiting and diarrhoea can occur. The drug concentration would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

INCOMPATIBILITY

Vancomycin, ampicillin, aminoglycosides, and fluconazole are physically incompatible with ceftriaxone/tazobactam in admixtures. When any of these drugs are to be administered concomitantly with ceftriaxone/tazobactam by intermittent I.V. infusion, it is recommended that they

be given sequentially, with thorough flushing of the I.V. lines (with one of the compatible fluids) between the administrations.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone/tazobactam vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of ceftriaxone calcium can also occur when ceftriaxone/tazobactam is mixed with calcium-containing solutions in the same I.V. administration line.

Ceftriaxone/tazobactam must not be administered simultaneously with calcium-containing I.V. solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone/tazobactam and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between I.M. ceftriaxone and calcium-containing products (I.V. or oral).

Ceftriaxone/tazobactam should not be physically mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, due to possible incompatibility.

NOTE: Parenteral drug products should be inspected visually for particulate matter before administration.

SHELF-LIFE

24 months

STORAGE AND HANDLING INSTRUCTIONS

Store below 25°C. Protect from light. After reconstitution, protection from normal light is not necessary. The colour of the solution ranges from light yellow to amber, depending on the length of storage, concentration and diluent used. Any unused portions of solution should be discarded.

PACKAGING INFORMATION

CEFBACT T Injection 1 g: Vial of 15 ml with 10 ml of sterile Water for Injection

Last Updated: February 2014

Last Reviewed: March 2014

- premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life); and,
- in full-term newborns (up to 28 days of age) with jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired.