PRODUCT MONOGRAPH – CEFERA T (CEFTRIAXONE-TAZOBACTAM)

INTRODUCTION

For several years we have been facing with the emergence and spread of microorganisms resistant to one or several antibiotics commonly used in the treatment of infections, such as respiratory tract infections or meningitis. In some cases, pathogens have become resistant to all anti-infectious drugs, leading to therapeutic failure. At the present time, this situation is not limited to the hospital ecosystem and nosocomial infections, but is spreading to the whole population and concerns community infections.

Antibacterial resistance is a global clinical and public health problem that has emerged with alarming rapidity in recent years and undoubtedly will increase in the near future. Resistance is a problem in the community as well as in health care settings, where transmission of bacteria is greatly amplified, in both developed and developing countries. Because multiple drug resistance is a growing problem, physicians are now confronted with infections for which there is no effective therapy. The morbidity, mortality, and financial costs of such infections pose an increasing burden for health care systems worldwide, but especially in countries with limited resources.

Resistance to antibiotics constitutes a major threat to public health and ought to be faced, by a better understanding of the numerous and "smart" mechanisms which bacteria have been developing with the passing years to escape the lethal effect of antibiotics.

Antibiotic-Resistant Organisms of Major Concern to Health Professionals

HOSPITAL-ACQUIRED	COMMUNITY-ACQUIRED
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Penicillin-resistant pneumococcus (PRP)
Vancomycin-intermediate *S. aureus* (VISA)	*Escherichia coli*– extended-spectrum ß-lactamases (ESBL)
Vancomycin-resistant enterococcus (VRE)	Neisseria gonorrhoae
Enterobacter	Haemophilus influenza
Pseudomonas	Mycobacterium tuberculosis
Klebsiella	

It is therefore critical to treat severe bacterial infections appropriately by starting antimicrobial treatment early in the course of infection, using the correct agent, at the most appropriate dose, and for an adequate duration. Indeed, early 'appropriate' antibiotic prescribing has been shown significantly to reduce mortality, length of intensive care unit and hospital stay and overall costs.

Early use of the correct antibiotic at the appropriate dose and for an adequate duration are key to initial appropriate antibiotic prescribing. Choosing the right antibiotic depends mainly on the likely pathogen(s) and the expected local susceptibility patterns. Selection of appropriate antimicrobial therapy requires a thorough understanding of the likely microbial cause of the infection, including local susceptibility patterns, as well as the properties of the antimicrobials available for treating these infections, namely spectrum of activity and potency (including activity versus known resistance mechanisms), pharmacokinetic profile and tolerability and safety.

Beta-lactamases

Beta-lactamases are a family of enzymes produced by many gram positive and gram negative bacteria that inactivate beta-lactam antibiotics by opening the beta-lactam ring and thereby hydrolyzing them. In gram negative bacteria, production of beta lactamases is considered to be a major determinant of antibiotic resistance. These enzymes have a higher affinity for the antibiotic than the antibiotic has for its target. Binding results in hydrolysis of the beta-lactam ring. Clinically important organisms that are resistant by virtue of beta-lactamases include *E. coli, Klebsiella,* all proteus species *H. influenzae, M. catarrhalis, Providencia, B. fragilis,* some species of S*taphylococcus* and, *Acinetobacter*.

Resistance in Enterobacteriaceae

Resistance strains of enterobacterriaceae have been established since the 1980s as a major cause of hospital-acquired infections. During the late 1990s as well as 2000s, *Enterobacteriaceae* (mostly *Escherichia coli*) producing novel ESBLs, the cefotaximases, have been identified predominantly from the community as a cause of urinary tract infections.

All members of *enterobacteriaceae* produce intrinsic chromosomal encoded beta-lactamases. *E. coli* and *Shigella* spp. produce a small amount of AmpC beta-lactamases and are susceptible to ampicillin and other beta-lactam antibiotic agents. *Enterobacter* spp, *C. freundii*, *Serratia* spp., *M. morganii*, *P. stuarti* and *P. rettgeri* produce small amounts of inducible AmpC beta-lactamases which are not inhibited by beta-lactamases inhibitors, causing intrinsic resistance to ampicillin, co-amoxiclav and first generation cephalosporins. They are susceptible to beta lactamase inhibitors. Antibiotics have caused the appearance of acquired or secondary beta-lactamases, with the sole function of protecting bacteria from antibiotics. The production of broad-spectrum beta-lactamases (TEM-1, TEM-2, SHV-1, OXA-1) results in resistance to ampicillin, ticarcillin, first-generation cephalosporins as well as piperacillin. A high level of beta-lactamases leads to resistance to their inhibitors.

Beta-lactamase Inhibitors

Beta-lactamase-related resistance can be approached using multiple therapeutic interventions. One strategy that has been devised for circumventing resistance mediated

by beta-lactamases is to combine the susceptible beta-lactam with an inhibitor that avidly binds the inactivating enzyme, preventing its attack on the antibiotic.

Beta-lactamase inhibitors are compounds designed to inhibit or destroy the effectiveness of beta-lactamase enzymes. These inhibitors function by binding to the beta-lactamase enzymes more efficiently than the actual beta lactam antibiotic itself.

Two structurally distinct classes of beta-lactamase inhibitors, clavams represented by Clavulanic acid and pernicillanic sulfones represented by sulbactam and tazobactam have been widely used clinically. In combination with a ß-lactam antibiotic, these inhibitors have successfully overcome bacterial ß-lactam resistance caused by ß-lactamase – mediated ß-lactam hydrolysis. In particular, tazobactam, a triazolyl-substituted penicillanic sulfone, has potent inhibitory activity against class A ß-lactamases, including some ß-lactamases that are resistant to inactivation by Clavulanic acid and sulbactam. Extensive studies have demonstrated that the combination of tazobactam-piperacillin is an effective antimicrobiological agent against class A-lactamase producing isolates. Tazobactam has been shown to be a more effective beta-lactamase inhibitor than sulbactam and furthermore both tazobactam and Clavulanic acid are potent inhibitors of not only the conventional spectrum beta-lactamases but also of newer enzymes; tazobactam has been shown to be more active than Clavulanic acid against OXA-2 and OXA-5 enzymes.

THE NEED FOR A BETA-LACTAM- BETA LACTAM INHIBITOR COMBINATION ANTIBIOTIC

It has always been the naive hope that the continuous discovery of new antimicrobial agents would provide clinicians with the upper hand in the battle against pathogenic bacteria, but it is apparent that bacterial resistance is increasing at an alarming rate despite the creativity of the pharmaceutical industry. The hope now is to slow this process of drug resistance through infection control and intelligent antimicrobial prescribing practices until novel alternative approaches are developed to prevent and treat bacterial infections.
Additional efforts used to forestall the development of antimicrobial-resistant bacteria include the following;

Streamlining empiric antimicrobial treatment when culture results become available.
Replacing certain drugs, such as third-generation cephalosporins, with other agents that are *presumably* less likely to foster resistance, such as beta lactam beta lactamase inhibitor in combination with or without an aminoglycoside.
Cycling of antibiotics.

Among different antibiotics, beta lactam antibiotics account for approximately 50% of global antibiotic consumption because of their proven efficacy and safety. It is well documented fact that bacterial resistance to this group of antibiotic increased parallely with increasing use of these antibiotic. Strategy for overcoming bacterial resistance with newer cephalosporins has been successfully employed as it was possible to modify

structure of a cephalosporin nucleus easily to confer an additional advantage. However, it has become clear that such attempts have been not only short lived but has created an alarming situation that currently available antibiotics are not adequate to control infection due to resistant bacteria.

Among all the above mentioned strategies, cycling of antibiotics has led to developement of antibiotic policy in hospital set up and has delayed emergence of resistance to some extent but has failed to control the problem satisfactorily. Additionally, because it is not practical for application in the community, it has not made much impact on menace of spreading antibiotic resistance, particularly in gram negative bacteria.

For similar reasons, streamlining empiric antimicrobial treatment has not been successful.

Reintroduction of currently available penicillins and cephalosporins with other agents such as beta lactamase inhibitors is an attractive preposition for many reasons;

1. Well established safety and efficacy profile
2. Production of beta lactamase is the most common mechanism of resistance to beta lactam antibiotics, especially in gram negative bacteria
3. Convenience of use, and more essentially an understanding that using such combination empirically may help in not only overcome therapeutic failures due to resistant bacteria but will also delay resistance development in susceptible bacteria
4. Minimize use of newer antibacterials so that they remain effective antibacterial for specific use

Therefore, Beta lactam-Beta lactamase inhibitor combinations offer a potential alternative to newer cephalosporins. As ESBLs are generally susceptible to available beta-lactamase inhibitors, such combinations often are seen as the only reliable antibacterial for treatment of ESBL producing bacterial infection. Often the beta lactamase extend the anti-bacterial action meaningfully to anaerobic bacteria, which otherwise were marginally sensitive to the beta lactam member of the combination.

Desired Properties of a beta lactam beta lactamase combination

Since the objective of a beta lactam beta lactamase combination is to provide an empiric therapy without increasing risk of development of bacterial resistance the combination should possess the following properties;

1. The combination should be bactericidal
2. It should have intrinsic broad spectrum of activity
3. Blood and tissue levels above MIC values should be maintained for long duration to inhibit bacterial growth between two doses during the treatment period
4. Should inhibit broad range of beta lactamase
5. Should not induce beta lactamase production
6. Should be suicidal inhibitor of beta lactamase
7. Should not affect the safety adversely

CEFTRIAXONE TAZOBACTAM COMBINATION

The combination of Ceftriaxone (3rd generation cephalosporin) and Tazobactam (beta-lactamase inhibitor) provides a solution for treatment of such bacterial infections caused beta lactam resistant pathogens.

Ceftriaxone has a broad spectrum of antibacterial activity is beta-lactamase stable and exhibits excellent activity against Streptococcus pneumoniae, methicillin-susceptible staphylococci, Haemophilus influenzae, Moraxella catarrhalis and Neisseria spp which are the most common cause of community acquired and hospital acquired infections. Ceftriaxone is more potent and hence less protection from a beta- lactamases inhibitor is required for the antibiotic and fewer drug molecules are needed for optimal activity.

Tazobactam (sodium), a triazolylmethyl penicillanic acid sulfone, is a new beta lactamase inhibitor with a range of activity that includes extended spectrum plasmid mediated beta lactamases.

Tazobactam lacks significant antibacterial activity of its own. It combines irreversibly with the common plasmid-encoded beta lactamases belonging to Richmond and Sykes class III and has been shown to inhibit many other enzymes of different classes, including the extended spectrum group of beta lactamases.
By rendering β–lactamase inactive, tazobactam is able to protect the activity of various β–lactam antibiotics. Tazobactam does not appear to have β–lactamase inducing properties.

Following intravenous administration of 500 mg of Tazobactam, the peak plasma levels of 24.3 mcg are reached in about half an hour. The estimated half-life of Tazobactam is approximately 1.3 hours. Tazobactam is metabolized and excreted as metabolite predominantly in the urine.

Tazobactam has been combined with various beta lactam antibiotics to enhance:-

1) Their antibacterial potency.
2) Overcome bacterial resistance due to beta lactamase production.

Combination of Tazobactam with penicillin derivative antibiotic is well established and is a very frequently used combination in clinical practice.

Recently, it has been shown that Tazobactam can also be combined with Ceftriaxone which protects Ceftriaxone from beta lactamases. The benefits of such combination are:-

1) Prevention of resistance to Ceftriaxone which has increased over a period of time due to its extensive use. A specific correlation between ceftriaxone use & development of resistance in *E. cloacae* clinical isolates has been demonstrated.

2) Increase the spectrum of activity of Ceftriaxone against microorganisms like anaerobic bacteria and pseudomonas which are not very susceptible to Ceftriaxone.

The efficacy of combination of ceftriazone with tazobactam has been evaluated in many in vivo and in vitro studies, since such a combination has been of considerable interest in the background of ESBL producing bacteria particularly the enterobacteriaceae family.

In a recent study this combination was found to have efficacy against 94.6% of Ceftriaxone resistant strains. One hundred and five consecutive isolates of Escherichia coli and Klebsiella spp. That had been recovered from various high-risk areas of the hospital were included in the study. By the MIC studies, 88.6% of the strains appeared to be resistant to Ceftriaxone with the MIC_{90} value being >256 micro/ml. When the MIC were done to Ceftriaxone in combination with tazobactam, the resistance rate dropped to 4.8% with the MIC value being 4.0 micro/ml (Table 1).(*Prakash SK, Arora V. Prashad R. Sharma VK. In vitro activity of ceftriazone plus tazobactam against members of Enterobacteriaceae. J. Assoc Physicians India 2005 Jul;53: 595-8*)

Table 1. MIC values of strains to Ceftriaxone in combination with tazobactam

	(In µg/ml)	**(In µg/ml)**	**(In µg/ml)**	**resistant**
Antimicrobial	**MIC Range**	**MIC_{50}**	**MIC_{90}**	**% of strains**
Ceftriaxone	≤0.25->256	256	>256	88.6
Ceftriaxone + Tazobactam	≤0.25-128	2.0	4.0	4.8
Note: Value of: ≤ 8 µg/ml have been taken as sensitive and ≥ 64µg/m as resistant.				

CLINICAL STUIDES

1. Aldridge KE et al showed: In vitro study carried out in 461 clinical strains of anaerobes were tested using a broth microdilution test to determine the activity of the combination of ceftriaxone and tazobactam and other antimicrobials against these isolates. Ceftriaxone was combined with tazobactam in ratios of 1:1, 2:1, 4:1 and 8:1 and twofold dilutions of ceftriaxone in constant concentrations to tazobactam of 2, 4, 8, 16 and 32 mcg/ml. The results of this study showed that all combinations of ceftriaxone and tazobactam showed enhanced in vitro activity and were more active than ceftriaxone alone.

Fixed concentrations of tazobactam at 2 and 4 mcg/ml appear to be most suitable for susceptibility testing and are within the pharmacological profile of this inhibitor, pharmacological and toxicity studies will further define the role of ceftriaxone and tazobactam in infectious diseases.

2. Wust J. & Hardegger U. showed in another study that: In vitro activity of ceftriaxone combined with tazobactam against 190 strains of anaerobic bacteria was compared with that of amoxicillin with clavulanic acid, ampicillin with sulbactam, piperacillin alone and with tazobactam, cefoxitin, and imipenem, i.e. beta-lactam antibiotics established in the treatment of anaerobic infections. The results of this study showed that all anaerobes tested were susceptible to < or = mg/l ceftriaxone when tazobactam was added at fixed ratios (ceftriaxone to tazobactam) of 2:1 and 8:1 and at constant concentrations of 2, 4 and 8 mg/l, respectively. When 4 mg/l tazobactam was added, the MICs of ceftriaxone for 83 of 94 strains of the *Bacteroides fragilis* group were reduced by a factor of 8 to 512; for eight strains, this reduction was two to fourfold. Only the MICs of ceftriaxone for three *Bacteroides fragilis* strains were not influenced.

3. Eldstein and Eldstein in 1994 observed that Ceftriaxone and Tazobactam has synergistic action against Legionella species when combined in a ratio ranging from 1:1 to 8:1. In vitro extracellular and intracellular activities of clavulanic acid and those of piperacillin and ceftriaxone alone and in combination with tazobactam against clinical isolates of Legionella species were measured by broth microdilution and macrodilution methods and in macrophages.

The broth microdilution MICs that inhibited 90% of strains tested were 2 and 1 mcg/ml for ceftriaxone and tazobactam, respectively. Broth macrodilution MICs were 8 and 1 microgram/ml, respectively, for the two Legionella pneumophila strains tested with piperacillin and were 0.25 and 0.5 mg/ml, respectively, for clavulanate. The results of this study showed that:

- No significant intracellular anti-*L. pneumophila* activity was observed.
- Extracellular drug activity. Ceftriaxone and tazobactam broth microdiluation MICs for the 22 *Legionella* spp. Strains tested are shown in Table 2.

TABLE 2. Broth microdiluation susceptibilities of 22 *Legionella* spp. strains to ceftriaxone and tazobactam alone and in combination.

Drug	MIC (mcg/ml) [a]		
	50%	**90%**	**Range**
Ceftriaxone	1	2	0.06-2
Tazobactam	0.5	1	0.25-1
Ceftriaxone-Tazobactam (1:1)	0.25 [b]	0.3 [b]	0.06-0.5 [b]
Ceftriaxone-Tazobactam (8:1)	0.25 [b]	1 [b]	0.06-1 [b]

[a] 50% & 90%, MICs for 50 & 90% of organisms tested, respectively
[b] MICs are for the ceftriaxone component

An additive effect was observed when ceftriaxone was combined with tazobactam for 16 strains when ration was 1:1 and for 15, when ratio was 8:1.

4. In 2005, Krishna Prakash et al published his findings in *J. Assoc. Phys. India* showing that Ceftriaxone on combination with Tazobactam in the ratio of 8:1, 105 bacterial isolates resistant to Ceftriaxone became sensitive.

5. Georgopoulos et al in 1999 showed that combination of Ceftriaxone with Tazobactam was rapidly bactericidal over a period of 6 hours when tested in animal models of peritonitis in rabbits.

6. Pefanis et al in 1993 reported in *Journal of Antimicrobial Chemotherapy* that inspite of the pharmacokinetic differences, the administration of Ceftriaxone Tazobactam combination significantly enhances activity of Ceftriaxone against anaerobic bacteria, *Bacteroides fragilis* in rat model of intra abdominal abscess.

Thus above, and other in vitro and in vivo data have confirmed that combination of Ceftriaxone Tazobactam has a synergistic effect on antibacterial activity of Ceftriaxone.

IN VITRO STUDIES

- Tazobactam inhibits penicillinases as well as oxylminocephalosporinases produced by Proteus vulgaris more strongly than sulbactam. [1]
- Tazobactam has demonstrably better inhibitory capability than Sulbactam against Cephalosporinases. [1]
- Tazobactam has the ability to inhibit intracellular beta-lactamases also. [1]
- Tazobactam has been found to be 10-25-fold more potent than clavulanate of sulbactam against TEM-30 and TEM-31 beta-lactamases. [2]

References:

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Clinical Advantages

- **Tazobactam enhances the antibacterial spectrum of cephalosporins to include bacterial that are otherwise resistant.**

- **Tazobactam-ceftriaxone combination has demonstrably better clinical success rates than cephalosporins used alone.**

- **Beta-lactam/beta-lactamase combinations in general yield better clinical outcomes than comparators.**

- **Tazobactam-ceftriaxone combination has the unique properties of a broad spectrum antibiotic with the added advantage of a wide-spectrum beta-lactamase inhibitor.**

This combination exhibits a synergy that is not influenced by the presence or absence of oxygen. In addition, this synergy remains excellent at neutral pH. (*Konig C. Blaser J. Effect of pO2 and pH on synergy of tazobactam and beta-lactam antibiotics against beta-lactamase producing Enterobacteriaceae. J.Antimicrob Chemother.1995 Sep:36(3):513-9*)

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CEFERA - T OVERVIEW (CEFTRIAXONE-TAZOBACTAM)

Ceftriaxone & Tazobactam Combination for Injection

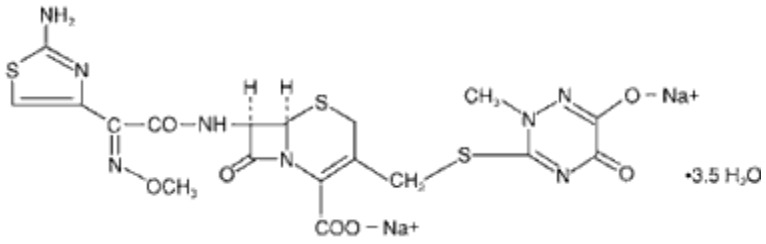
This is an injectable antibacterial combination consisting of the cephalosporin antibiotic ceftriaxone sodium and the β-lactamase inhibitor tazobactam sodium for parenteral administration.

COMPOSITION
Each vial (562.5 mg) Contains
Ceftriaxone Sodium USP 500 mg
Tazobactam Sodium USP 62.5 mg

Each vial (1125 mg) Contains
Ceftriaxone Sodium USP 1000 mg
Tazobactam Sodium USP 125 mg

Each vial (2250 mg) Contains
Ceftriaxone Sodium USP 2000 mg
Tazobactam Sodium USP 250 mg

DESCRIPTION
Ceftriaxone is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3- [[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo- as-triazin-3-yl)thio]methyl] -5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxyalic acid,7²-(Z)-(O-methyloxime), disodium salt, sesquaterhydrate.
The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5\ H_2O$. It has a calculated molecular weight of 661.59 and the following structural formula:



Ceftriaxone is a third generation cephalosporin belonging to beta lactam group of antibiotics. It is a broad spectrum bactericidal parenteral cephalosporin. The bactericidal action of Ceftriaxone is believed to be due to inhibition of cell wall synthesis leading to lysis of the bacterial cell.

Tazobactam (sodium), a triazolylmethyl penicillanic acid sulfone, is a new beta lactamase inhibitor with a range of activity that includes extended spectrum plasmid mediated beta lactamases.

Tazobactam lacks significant antibacterial activity of its own. It combines irreversibly with the common plasmid-encoded beta lactamases belonging to Richmond and Sykes class III and has been shown to inhibit many other enzymes of different classes, including the extended spectrum group of beta lactamases.

By rendering β–lactamase inactive, tazobactam is able to protect the activity of various β–lactam antibiotics. Tazobactam does not appear to have β–lactamase inducing properties.

CLINICAL PHARMACOLOGY

Average plasma concentrations of ceftriaxone following a single 30-minute intravenous (IV) infusion of a 0.5, 1 or 2 g dose and intramuscular (IM) administration of a single 0.5 (250 mg/mL or 350 mg/mL concentrations) or 1 g dose in healthy subjects are presented in Table 1.

TABLE 1: Ceftriaxone Plasma Concentrations After Single Dose Administration

Dose/Route	Average Plasma Concentrations (µg/mL)								
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 gm IV*	82	59	48	37	29	23	15	10	5
0.5 gm IM 250 mg/mL	22	33	38	35	30	26	16	ND	5
0.5 gm IM 350 mg/mL	20	32	38	34	31	24	16	ND	5
1 gm IV*	151	111	88	67	53	43	28	18	9
1 gm IM	40	68	76	68	56	44	29	ND	ND
2 gm IV*	257	192	154	117	89	74	46	31	15

* IV doses were infused at a constant rate over 30 minutes.
ND = Not determined.

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

Thirty-three percent to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug and the remainder was secreted in the bile and ultimately found in the feces as microbiologically inactive compounds. After a 1 gm IV dose, average concentrations of ceftriaxone determined from 1 to 3 hours after dosing, were 581 µg/mL in the gallbladder bile, 788 µg/mL in the common duct bile, 898 µg/mL in the cystic duct bile, 78.2 µg/gm in the gallbladder wall and 62.1 µg/mL in the concurrent plasma.

TABLE 2: 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			
Hemodialysis patients (0-5 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.

Pharmacokinetic Parameters of Tazobactam

Plasma half life	:	Mean (dose dependent): 0.35-0.67 h
Volume of distribution	:	141 L
Plasma protein binding	:	23%
Excretion	:	Renal route

Tazobactam is used in combination with other beta lactam antibiotics like piperacillin and internationally this combination is in clinical use.

Tazobactam is metabolized to a single metabolite which lacks pharmacological and antibacterial activities. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the dose as unchanged drug and the remainder as the single metabolite.

Tazobactam is widely distributed into tissues and body fluids including, intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary and fallopian tube) interstitial fluid and bile. Mean tissue concentrations is generally 50 to 100% of those in plasma.

Microbiology

The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases of gram-negative and positive bacteria.

Ceftriaxone has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections described in the **INDICATIONS.**

Gram-Negative Aerobes:
Acinetobacter calcoaceticus
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant and beta-lactamase producing strains)
Haemophilus parainfluenzae
Klebsiella oxytoca
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.

NOTE: Many strains of the above organisms that are multiply resistant to other antibiotics, eg, penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone.

Gram-Positive Aerobes:
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci, e.g., *Enterococcus (Streptococcus) faecalis*, are resistant.

Anaerobes:
Bacteroides fragilis
Clostridium species
Peptostreptococcus species

NOTE: Most strains of *C. difficile* are resistant.

In vitro data have demonstrated synergistic activity with ceftriaxone in combination with tazobactam.

INDICATIONS

Cefera T is indicated for the treatment of the following infections when caused by susceptible organisms:

- **Lower Respiratory Tract Infections**
- **Acute Bacterial Ottitis Media**
- **Skin and Skin Structure Infections**
- **Urinary Tract Infections**
- **Uncomplicated Gonorrhea**
- **Pelvic Inflammatory Disease**
- **Bacterial Septicemia**
- **Bone and Joint Infections**
- **Intra-Abdominal Infections**
- **Meningitis**
- **Surgical Prophylaxis**

DOSAGE AND ADMINISTRATION
CEFERA T should be administered intravenously and intramuscularly.
ADULTS
The usual adult daily dose of **CEFERA T** is 1.125 to 2.250 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4.5 grams.
For preoperative use (surgical prophylaxis), a single dose of 1.125 gram administered intravenously ½ to 2 hours before surgery is recommended.

PEDIATRIC PATIENTS
1. For the treatment of **skin and skin structure infections**, the recommended total daily dose of ceftriaxone is 50 to 75 mg/kg (i.e. 56.25 to 84.375 mg/kg of **CEFERA T**) given once a day (or in equally divided doses twice a day). The total daily doses of **CEFERA T** should not exceed 2.250 grams.
2. For the treatment of **acute bacterial otitis media**, a single intramuscular Ceftriaxone dose of 50 mg/kg (i.e. 56.25 mg/kg of **CEFERA T**, total combination dose not to exceed 1.125 gram) is recommended.
3. For the treatment of **serious miscellaneous infections** other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (i.e. 56.25 to 84.375 mg/kg of **CEFERA T**), given in divided doses every 12 hours. The total daily dose of combination should not exceed 2.250 grams.
4. In the treatment of **meningitis**, it is recommended that the initial therapeutic dose of ceftriaxone be 100 mg/kg (i.e. 112.5 mg/kg of **CEFERA T**, total combination dose not to exceed 4.5 gram). The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.
Generally, **CEFERA T** therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least 10 days. **CEFERA T** blood levels should be monitored in patients with severe renal impairment (eg, dialysis patients) and in patients with both renal and hepatic dysfunctions.

STABILITY

CEFERA T sterile powder should be stored at room temperature—77°F (25°C)—or below and protected from light. After reconstitution, protection from normal light is not necessary. The color of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

SIDE EFFECTS

Ceftriaxone/Tazobactam is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Ceftriaxone therapy or of uncertain etiology, were observed:

Local Reactions: pain, induration and tenderness was 1% overall. Phlebitis was reported in <11% after IV administration.

Hypersensitivity: rash (1.7%). Less frequently reported (<1%) were pruritus, fever or chills.

Hematologic: eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (<1%) were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

Gastrointestinal: diarrhea (2.7%). Less frequently reported (<1%) were nausea or vomiting, and dysgeusia. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment.

Hepatc: elevations of SGOT/AST (3.1%) or SGPT/ALT (3.3%).

Renal: elevations of the BUN (1.2%). Less frequently reported (<1%) were elevations of creatinine and the presence of casts in the urine.

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

Genitourinary: moniliasis or vaginitis were reported occasionally (<1%).

Miscellaneous: diaphoresis, flushing were reported occasionally (<1%).

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

WARNINGS

BEFORE THERAPY WITH CEFTRIAXONE/TAZOBACTAM 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. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

PRECAUTIONS

General

Prescribing Ceftriaxone/Tazobactam 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.

Patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone/Tazobactam are administered but concentrations of drug in the serum should be monitored periodically.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, **CEFERA T** dosage should not exceed 2.250 gm daily without close monitoring of serum concentrations.

Ceftriaxone 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. Therefore, **CEFERA T** should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

Pregnancy

Teratogenic Effects: *Pregnancy Category B.* Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Tazobactam: Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to tazobactam administered up to a dose 3 times the human dose based on body-surface area.

Nursing Mothers

Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Ceftriaxone is administered to a nursing woman. Tazobactam concentrations in milk have not been studied.

Pediatric Use

Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described above. *In vitro* studies have shown that ceftriaxone

like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should not be administered to hyperbilirubinemic neonates, especially prematures.

OVERDOSE

In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

CONTRAINDICATIONS

CEFERA T combination is contraindicated in patients with known allergy to the cephalosporin or beta lactam class of antibiotics.