Nicholson healthcare
(A Division of Schwitz Biotech)

EXACEF-TZ INJECTION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

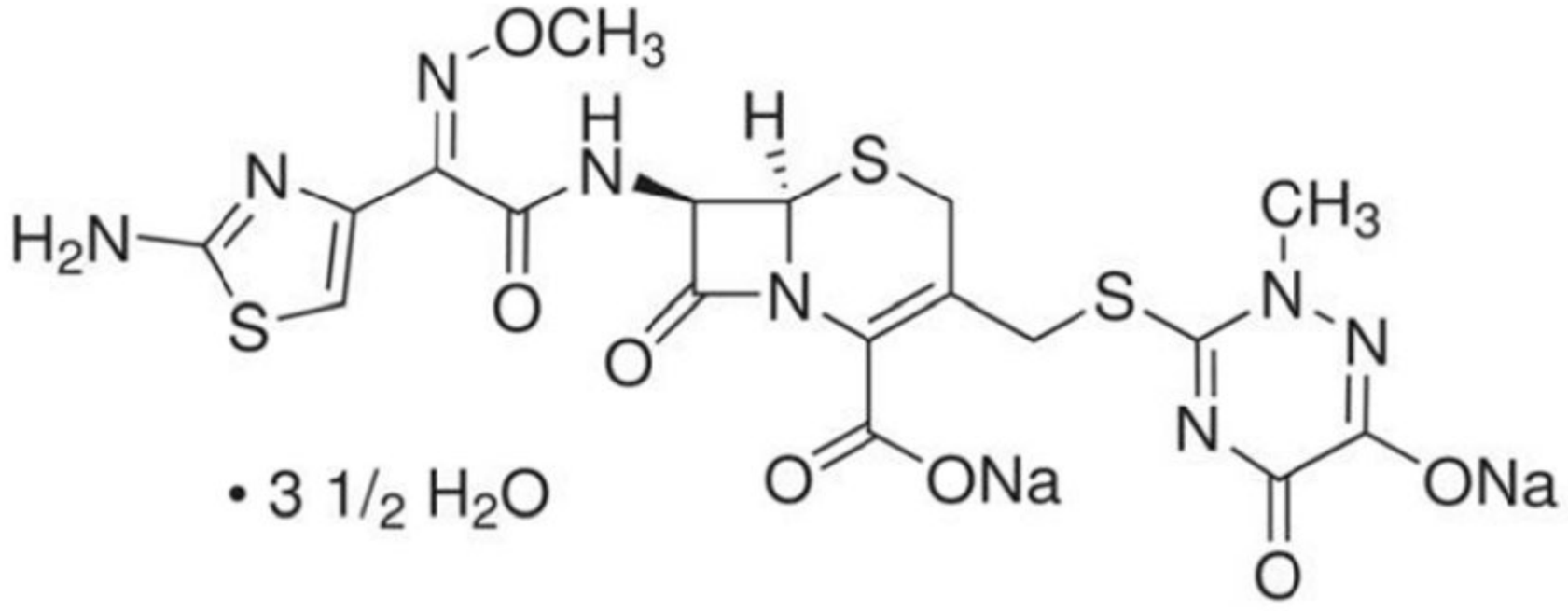
1 NAME OF THE MEDICINAL PRODUCT:
EXACEF-TZ INJECTION
COMBIPACK OF CEFTRIAXONE SODIUM & TAZOBACTAM SODIUM FOR INJECTION (1000 MG + 125 MG), STERILISED WATER FOR INJECTIONS BP 10

2 QUALITATIVE AND QUANTITATIVE COMPOSITIONS:
CHEMICAL NAME AND THE STRUCTURAL FORMULA OF EACH ACTIVE INGREDIENT:-

CEFTRIAXONE SODIUM USP

Chemical Name:
Sodium;(6R,7R)-7-[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-[(2-methyl-5,6-dioxo-1H-1,2,4-triazin-3-yl)sulfanylmethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

Chemical Structure:



Molecular Formula: $C_{18}H_{17}N_8NaO_7S_3$

Molecular Weight: 576.553 g/mol

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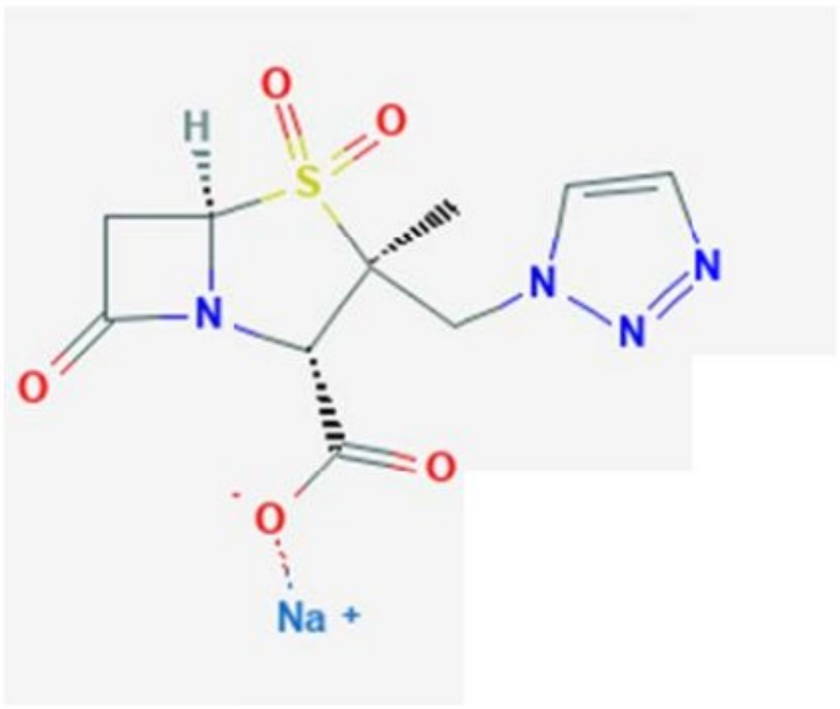
TAZOBACTAM SODIUM

Chemical Name:

4-Thia-1-azabicyclo [3.2.0]heptane-2-carboxylic acid, 3-methyl-7-oxo-3-(1*H* -1,2,3-triazol-1-ylmethyl)-, 4,4-dioxide, [2*S* -(2α,3β,5α)]-;
(2*S*, 3S ,5*R*) - 3 – Methyl – 7 – oxo – 3 - (1*H* -1 , 2 , 3 – triazol – 1 – ylmethyl) – 4 – thia – 1 - azabicyclo[3.2.0]heptane-2-carboxylic acid, 4,4-dioxide

Chemical Structure:



Molecular Formula: $C_{10}H_{11}N_4NaO_5S$

Molecular Weight: 300.28 g/mol

QUANTITATIVE FORMULA

RAW MATERIAL ASSEMBLY

Batch Size: 1,00,000 Vials

SR. NO.	L.C. per Vial	O.A. (%)	*INGREDIENTS*	PHARMA-COPIAL STATUS	*UNIT*	A.Q.R/ B In Kg.
1.	**1000 mg**	2%	Ceftriaxone sodium *(a)	USP	mg	102.00
2.	**125 mg**	2%	Tazobactam sodium *(b)	IHS	mg	12.75

* (a) Weight of Ceftriaxone Sodium USP eq. to Ceftriaxone

$$= \frac{1000 \times 100 \times 1000 \times \text{Batch Size in Vials}}{(\text{Assay mcg/mg}) \times (100 - \%\text{WATER})}$$

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*(b) Weight of Tazobactam Sodium eq. to Tazobactam

$$= \frac{125 \times 100 \times 100 \times \text{Batch Size in Vials}}{(\%\ \text{Assay}) \times (100 - \%\text{WATER})}$$

A.Q.R/B	=	Actual Quantity Required Per Batch
O.A. %	=	Overages in %.
L.C. per vial	=	Label Claim per vial

3 PHARMACEUTICAL FORMS:

White crystalline powder
(COMBIPACK OF CEFTRIAXONE SODIUM & TAZOBACTAM SODIUM FOR INJECTION (1000 MG + 125 MG), STERILISED WATER FOR INJECTIONS BP 10 ML

4 CLINICAL PARTICULARS:

4.1 INDICATIONS FOR USE:

Following Infections caused by the susceptible organisms in Bacterial meningitis, bone and joint infections, Community-acquired pneumonia, Intra-abdominal infections, Lower respiratory tract infections, Pelvic inflammatory disease, Uncomplicated gonorrhea, Skin and skin structure infections, Bacterial septicaemia, Urinary tract infections.

4.2 CONTRAINDICATIONS:

Hypersensitivity to cephalosporins and b-lactamase inhibitors

5 SPECIAL PRECAUTIONS FOR USE:

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 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, EXACEF-TZ 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, EXACEF-TZ should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease.

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6 ADVERSE REACTIONS:

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.

7 USES DURING PREGNANCY, LACTATION:

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. Tazobactum: Reproduction studies have performed in rats and have revealed no evidence of imp aired 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.

8 DRUG INTERACTIONS:

Ceftriaxone interaction in seen with Chloramphenicol, Solutions and Solvents with Calcium, Vancomicin, fluconazole, aminoglycosides, hormonal contraceptives & Coomb's test

Tazobactam: Interaction is seen with Probenecid, heparin, warfarin, anti-coagulants, methotrexate

9 DOSAGES AND ADMINISTRATION:

EXACEF-TZ should be administered intravenously and intramuscularly. ADULTS: The usual adult daily dose of EXACEF-TZ 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 gm 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 given once a day (or in equally divided doses twice a day). The total daily doses of EXACEF-TZ should not exceed 2.250 grams.

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2. For the treatment of acute bacterial otitis media, a single intramuscular Ceftriaxone dose of 50 mg/kg (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, 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 (total combination dose not to exceed 4.5 gram).

10 OVERDOSAGE:
Symptomatic and supportive treatment should be initiated.

11 PHARMACOLOGY:
Ceftriaxone interferes with the biosynthesis of the peptidoglycan component of the bacterial cell way by binding to and inactivating penicillin-binding proteins (PBPs). Tazobactam is a penicilanic acid sulfone derivative with β-lactamases inhibitory properties. It enhances the activity of β-lactam antibacterials against β-lactamase-producing bacteria. 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 gram-positive bacteria. In an in vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. Ceftriaxone has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections – Aerobic gram-negative microorganisms: Acinetobactercalcoacetius. Enterobacteraerogenes
Enterobacter cloacae. Escherichia coli. Haemophilus influenza (including ampicillin-resistant and beta-lactamase producing strains). Haemophilusparainfluenzae. Klebsiellaoxytoca. Klebsiellapneumoniae. Moraxella catarrhalis (including beta-lactamase producing strains). Morganellamorganii. Neisseria gonorrhoeae (including Salmonella typhi). Shigella species. Aerobic gram-positive microorganisms: Streptococcus agalactiae. Anaerobic microorganisms: Prevotella (Bacterodes) bivius. Porphyromonas (Bacteroides) melaninogenicus. 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 those that are resistant to penicillins and third generation cephalosporins

12 PHARMACOKINETICS:
Average Pharmacokinetic Parameters of Ceftriaxone Absorption: Ceftriaxone was completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours post-dose. Distribution: Ceftriaxone: 98% bound plasma proteins; crosses the blood brain barrier. Excretion: Ceftriaxone 33-67% removed as unchanged drug.

Subject group	Elimination Half-life (hr)	Plasma clearance (L/hr)	VD(L)
Healthy Subjects	5.8-8.7	0.58-1.45	5.8-13.5
Elderly Subjects (mean age, 70.5 yrs)	8.9	0.83	10.7
Patients with renal impairment	14.7	0.65	13.7
Hemodialysis Patients (0-			

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5ml/min)*			
Severe (5-15 ml/min)	15.7	0.56	12.5
Moderate (16-30 ml/min)	11.4	0.72	11.8
Mild (31-60ml/min)	12.4	0.7	13.3
Patients with Liver Disease	8.8	1.1	13.6

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 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.
Lidocaine can reduce the amount of pain of an intramuscular injection of co-ceftriaxone when compared with sterile water as a diluent. These findings have implications not only for the treatment of gonorrhea but also for other situations where intramuscular injections utilizing a diluent may be necessary.

13 STORAGE:
Store below 25°C in a dry place in original package
Do not use later than the date of expiry.
KEEP OUT OF REACH OF CHILDREN.

14 SHELF-LIFE:
24 MONTHS

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