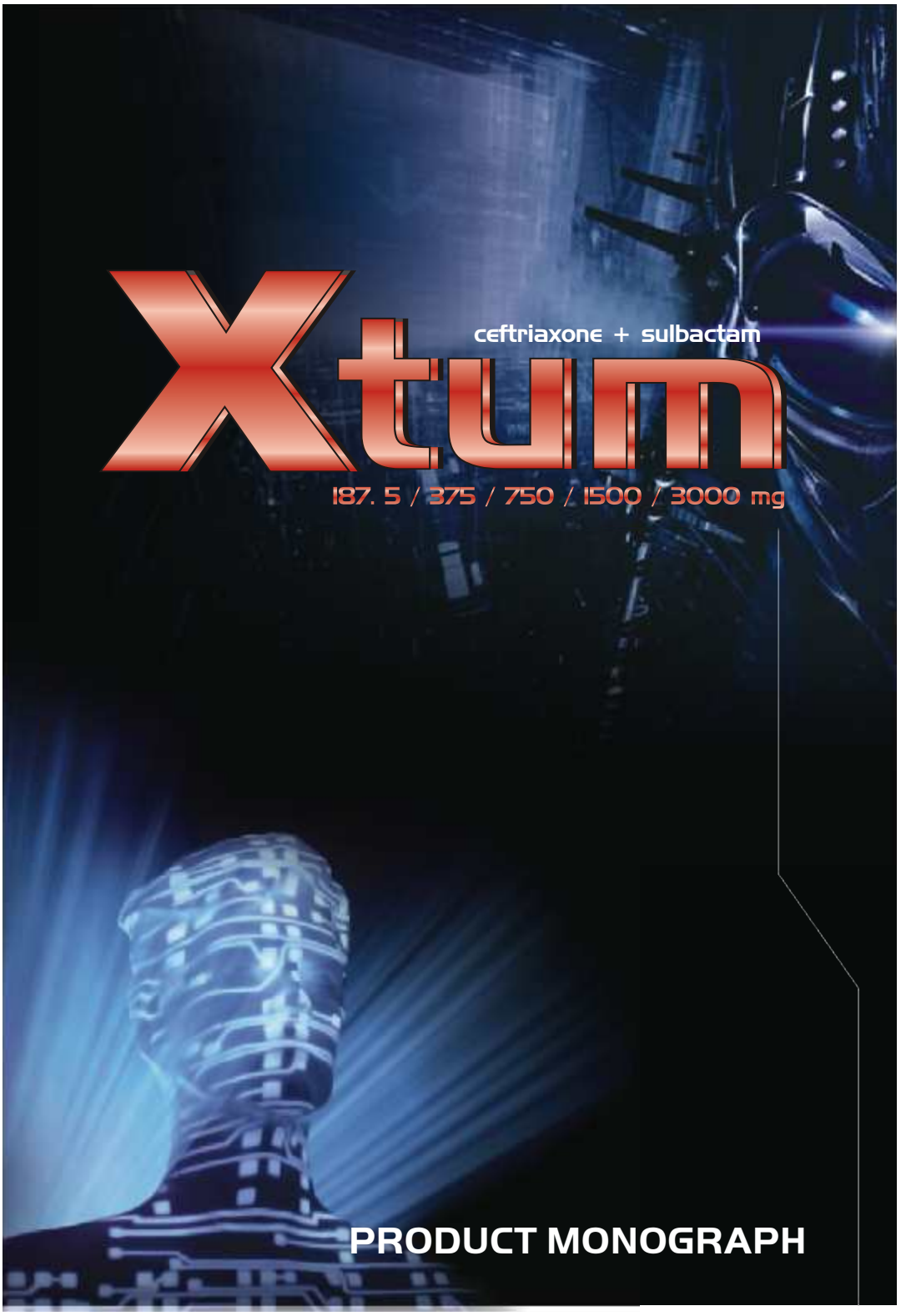

Xtum
ceftriaxone + sulbactam
187. 5 / 375 / 750 / 1500 / 3000 mg
PRODUCT MONOGRAPH

Index

INDEX

Introduction

For several years we have been faced 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. XTUM the combination of Ceftriaxone (3rd generation cephalosporin) and Sulbactam (beta-lactamase inhibitor) provides a solution for treatment of such bacterial infections caused by multi-drug resistant pathogens.

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

Antibiotic-Resistant Organisms of Major Concern to Health Professionals	
Hospital - Acquired	Community-Acquired
Methicillin-resistant Staphylococcus aureus(MRSA) Vancomycin-intermediate S. aureus(VISA) Vancomycin-resitant enterococcus(VRE) Enterobacter Pseudomonas Klebsiella	Penicillin-resistant pneumococcus (PRP) Escherichia coil- Extended-Spectrum B-lactamases(ESBL) Neisseria gonorrhoea Haemophilus influenza Mycobacterium tuberculosis

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, tolerability and safety.

The need for a beta-lactam beta lactamase inhibitor combination

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

development 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:

- Well established safety and efficacy profile
- Production of beta lactamase is the most common mechanism of resistance to beta lactam antibiotics, especially in gram negative bacteria
- 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
- 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:

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

Ceftriaxone /Sulbactam combination

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

Fantin et. al. in 1990, showed that the MIC and MBC of ceftriaxone was lowered by addition of sulbactam and the bacterial killing was enhanced proportionately.

They further showed that ceftriaxone sulbactam combination was more effective than single ceftriaxone therapy in treatment of E. coli bacterial endocarditis in experimental models of bacterial endocarditis. Sulbactam ceftriaxone (15mg/kg) induced a reduction of approximately 2 log10 CFU/g of vegetation greater than that induced by single drug therapy (5.7 + 2.4 verses 8.0 + 1.3 log10 CFU/g) and sulbactam ceftriaxone 30 mg/kg combination induced a reduction of almost 5 log10 CFU/g of vegetation compared with that of single drug therapy (3.1 verses 7.9 log10 CFU/g) and sterilized 62.5%vegetation indicating that the activities of the sulbactam ceftriaxone combination greatly depended on the ceftriaxone dose.

Caron et. al. 1990 showed that addition of sulbactam lowered the MBC of ceftriaxone for Klebsiella pneumoniae

TABLE 1.

MICs and MBCs of netilmicin, sulbactam, and ceftriaxone against a strain of E. coli **producinga SHV-2-like -lactamase**

Antibiotic	5×10^5 CFU/ml		5×10^7 CFU/ml	
	MIC (g/ml)	MBC (g/ml)	MIC (g/ml)	MBC (g/ml)
Netilmicin	1.00	1.00	2.00	2.00
Sulbactam	64.00	64.00	64.00	128.00
Ceftriaxone	2.00	4.00	256.00	256.00
Ceftriaxone + Sulbactam (4 g/ml)	0.12	0.25	8.00	32.00
Ceftriaxone + Sulbactam (16 g/ml)	0.06	0.06	0.50	2.00

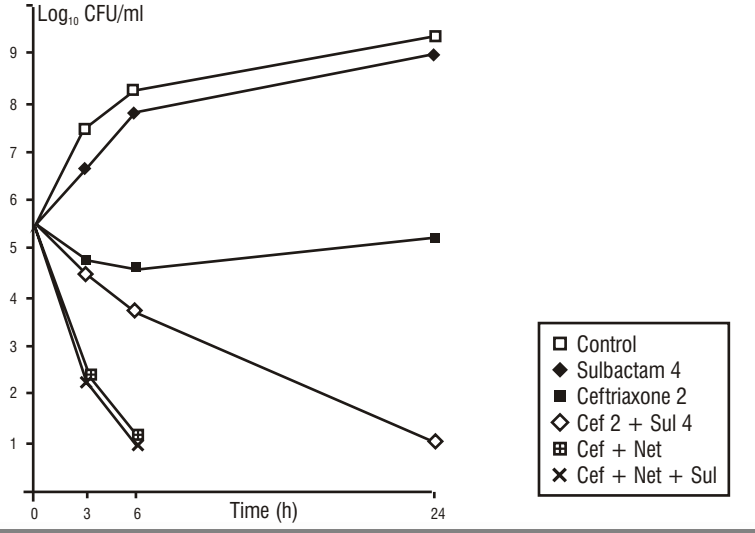


FIG. 1. In vitro killing rates of an *E. coli* strain producing a broad-spectrum -lactamase, SHV-2, incubated with various concentrations of ceftriaxone (Cef), netilmicin (Net), and sulbactam (Sul). A standard inoculum (5×10^5 CFU/ml) was used, Symbols and concentrations of each drug (in micrograms per milliliter) are indicated on the right.

In one clinical study, once daily sulbactam ceftriaxone for 5 days cured 96.6% patients with severe community acquired pneumonia. In another study one dose sulbactam ceftriaxone was more effective (97.17% cure rate) than 10 days oral amoxicillin (90.57% cure rate)

The above sited studies indicate that sulbactam can be used with ceftriaxone to enhance its antibacterial action especially in circumstances where infection with resistant bacteria is suspected or where bacterial infection could be catastrophic if not controlled completely.

TABLE 2.

MICs and MBCs of ceftriaxone with and without sulbactam against two strains of K. pneumoniae that produced or did not produce the TEM-3 extended-broad-spectrum -lactamase at two different inocula

K. pneumoniae strain and antibiotic	5×10^5 CFU/ml		1×10^7 CFU/ml	
	MIC (g/ml)	MBC (g/ml)	MIC (g/ml)	MBC (g/ml)
Susceptible (nonproducing)	0.25	0.25	0.25	0.50
Ceftriaxone	32.00	32.00	32.00	32.00
Sulbactam				
Resistant (producing)	32.00	128.00	>1000.00	>1000.00
Ceftriaxone	32.00	32.00	32.00	32.00
Sulbactam	0.25	0.25	4.00	16.00
Ceftriaxone + sulbactam (1 g/ml)	0.12	0.25	0.25	1.00
Ceftriaxone + sulbactam (10 g/ml)	ND *	ND *	0.12	0.5
Ceftriaxone + sulbactam (20 g/ml)				

* ND - Not Done

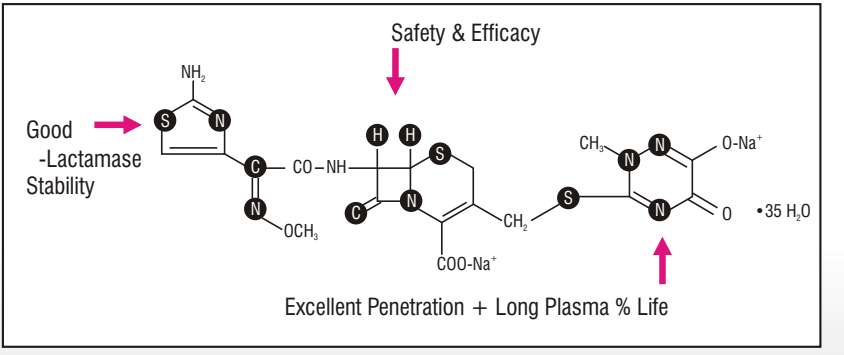
XTUM is a combination of Ceftriaxone sodium and Sulbactam Sodium available for parenteral administration.

Ceftriaxone is a parenteral third-generation cephalosporin with a long elimination half-life which permits once-daily administration and a good tolerability profile

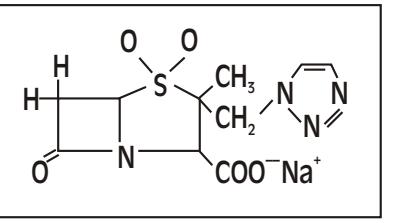
The unique molecular structure of Ceftriaxone provides the following advantages

- The aminothiazole-methoxyimino acyl side chain is responsible for beta-lactamase stability (more stable as compared to other third generation cephalosporins)
- The "triazine" ring confers greater efficacy against Neisseria, H.influenzae and Proteus mirabilis compared with such other third generations as Cefotaxime, Ceftazidime.
- The hydroxyl group in the triazine enhances the penetration power particularly into gram negative bacteria. Therefore rapid action and does not act as an inducer for production of beta-lactamases.The hydroxyl group is also responsible for long elimination half-life.

Sulbactam is a penicillanic acid sulfone derivative and has weak antibacterial activity, but is a potent inhibitor of many plasmid-encoded and some chromosomal beta-lactamases. It therefore restores antibacterial activity of cephalosporins and



penicillins which can be destroyed by beta-lactamases and ESBL's commonly produced by gram-positive and gram-negative organisms.



Mode of action

The bactericidal activity of XTUM is due to the Ceftriaxone component and the ability of Ceftriaxone to interfere with the biosynthesis of the peptidoglycan component of the bacterial cell wall by binding to and inactivating penicillin-binding proteins (PBPs).

Ceftriaxone induces filamentation in Escherichia coli and Pseudomonas aeruginosa, it binds primarily to PBP 3 which is responsible for formation of cross-wall or septum of dividing bacilli.

Ceftriaxone has a high degree of stability against the beta-lactamases, both penicillinases and cephalosporinases produced by both gram -ve and gram +ve bacteria but not against chromosomally and plasmid mediated ESBL's produced by some strains of Klebsiella, Escherichia coli, Enterobacter spp and Serratia spp.

Sulbactam irreversibly blocks the destruction of beta-lactam ring of Ceftriaxone by these wide variety of ESBLs and chromosomally mediated beta-lactamases by attaching to these enzymes and acting as a suicide substrate that forms a stable intermediate, rendering the enzyme inactive.

Sulbactam is a broader-spectrum beta-lactamase inhibitor than clavulanic acid. Sulbactam does not induce chromosomal beta-lactamases like clavulanic acid, nor does it select for derepressed beta-lactamase-producing bacteria. Thus the full potential of Ceftriaxone against Klebsiella, pseudomonas, Eschericia coli spp is restored by addition of Sulbatam.

Antimicrobial spectrum of XTUM (ceftriaxone-sulbactam)

The combination of Ceftriaxone sodium and Sulbactam sodium is active against all the organisms sensitive to Ceftriaxone. In addition it demonstrates synergistic activity (reduction in minimum inhibitory concentrations, for the combination versus those of each component) in a variety of organisms.

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.

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

Ceftriaxone also demonstrates in vitro activity against most strains of the

following microorganism like Citrobacter diversus , Citrobacter freundii, Providencia species (including Providencia rettgeri , Salmonella species (including S. typhi), Shigella species

Gram-Positive Aerobes

- Staphylococcus aureus (including penicillinase-producing strains and methicillin sensitive strains but not methicillin resistant strains)
- Staphylococcus epidermidis
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Viridans group streptococci

Anaerobes:
Bacteroides fragilis, Clostridium species , Peptostreptococcus species.

Pharmacokinetics

XTUM can be administered IM or IV.

Following intramuscular administration, peak serum concentrations of Ceftriaxone and Sulbactam are seen between 15 minutes to 2 hrs.

The maximum plasma conc of Ceftriaxone after a single IM dsoe of 1.0 g is about 81mg/L and is reached 2-3 hrs after the dose while that of Sulbactam sodium is 6-24 mg/L and is reached approximately 1 hr after the dose. Hence effective amount of beta-lactamases are destroyed by the time peak concentration of Ceftriaxone is reached allowing full potential of action of Ceftriaxone against ESBL producing Klebsiella, E coli spp. Serum concentrations have been shown to be proportional to the amount of dose administered.
The area under curve (AUC) after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered Ceftriaxone sodium.

On intravenous administration Ceftriaxone sodium diffuses into the tissue fluid where if given in the recommended doses bactericidal concentrations are maintained for upto 24 hrs. Ceftriaxone is highly bound to human serum protein by about 83-90%.

Distribution

The volume of distribution of Ceftriaxone sodium is 7-12 L and that of Sulbactam is 18-27.6 L.

Ceftriaxone sodium penetrates well into the extravascular spaces, tissue fluid and the synovial fluid of inflamed joints. The concentrations in most extracellular foci reach or exceed several times the MIC of most pathogens for at least 24 hours after a single administration.

Ceftriaxone sodium reaches therapeutically effective concentrations in patients with bacterial meningitis which are at least ten-fold the MICs of common pathogens such as, Enterobacteriaceae, H.influenzae, Meningococci, Pneumococci and Group B Streptococci.

Ceftriaxone crosses placenta and is distributed in the amniotic fluid. It is also distributed in the milk.

Metabolism and excretion

Ceftriaxone is not metabolised in the body and is eliminated unchanged via two pathways, urine and bile. 40-50% of parenterally administered dose is excreted into the urine within 48 hours as active drug. Thus, high concentrations are attained in urine, whatever is not excreted via kidney is excreted through bile. Metabolism of sulbactam is less than 25%. 70-80% of Sulbactam is excreted by the kidney biliary excretion is minimal and. renal excretion is blocked by probenecid. Sulbactam and Ceftriaxone can be removed by hemodialysis.

Impaired renal function and Hepatic insufficiency: Ceftriaxone is excreted via

both renal and biliary pathways therefore patients with renal failure normally require no adjustments of dose however concentration of the drug should be monitored in such patients and if there is evidence of drug accumulation then dosage adjustments should be made accordingly. Dosage adjustments are not necessary in patients with hepatic dysfunction, however in patients with both hepatic dysfunction and significant renal failure, dosage should not exceed more than 2 gm daily with close monitoring of serum concentrations.

Indication s

XTUM is indicated for the treatment of following infections when caused by susceptible bacteria.

- Meningitis
- For treatment of Nosocomial infections surgical prophylaxis
- Urinary tract infections (complicated by underlying urological abnormalities)
- Skin and soft tissue infections Like cellulites, erysepalis etc.
- Cholecystitis
- Osteomyelitis
- Sexually transmitted diseases (Gonorrhoea, Chancroid, Syphilis)
- Chronic suppurative bacterial otitis media
- Infections in dialysis unit

Safety & tolerability profile

Clinical studies of the combination of sulbactam plus beta-lactam antibiotics or penicillins have revealed no major hematologic, renal, hepatic, or central nervous system reactions. Diarrhea has not been a major problem after intravenous use.

Incidence of side-effects due to Ceftriaxone is as follows: G.I. effects- 2-3%, cutaneous reactions 1-3%, haemotological 1-2%, miscellaneous 1.5-3%

Contraindication

XTUM is contraindicated in patients with known allergy to penicillins and cephalosporins.

Warnings

Serious or occasionally fatal anaphylactic reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of hypersensitivity reactions to multiple allergens.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics), therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Precautions

General

Transient elevations of BUN and serum creatinine have been observed, at recommended doses, the nephrotoxic potential of ceftriaxone is same as other cephalosporins. Since Ceftriaxone is excreted both via renal and bile patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone are administered.

Dosage adjustments are not necessary in patients with hepatic dysfunction; however in patients with both renal failure and hepatic dysfunction, dosage should not exceed more than 2 g daily with close monitoring of serum concentrations.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Genetic toxicological 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 mutagenic activity in these studies

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

Pregnancy

Teratogenic effects: Pregnancy category B. Reproductive studies have been performed in mice and rats at doses upto 20 times the usual human dose and no evidence of embryo toxicity, fetotoxicity or teratogenicity. In primates no teratogenicity or embryogenicity was demonstrated at a dose approximately 3 times the human dose.

There are however no 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.

Nursing Mothers
Low concentrations of Ceftriaxone are excreted in human milk. No risk to nursing infants have been reported but caution should be exercised when ceftriaxone-sulbactam is administered to nursing women.

Paediatric use
XTUM (Ceftriaxone-Sulbactam) should not be administered to hyperbilirubinemic neonates, especially premature.

Mode of administration

XTUM (Ceftriaxone-Sulbactam) may be administered intramuscularly or intravenously.

Dosage and administration:

Adults

The usual adult daily dose (in terms of Ceftriaxone) is 1-2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

Dosage regimen for XTUM (Ceftriaxone-Sulbactam) should be adjusted in patients with marked decrease in renal function (creatinine clearance of < 30ml/min) and to compensate for reduced clearance less than 15ml/min patient should receive a maximum of 500mg of sulbactam every 12 hours(maximum dose 1 gram of sulbactam)

Paediatric patients

For treatment of Skin and Soft tissue infections the recommended total daily dose (in terms of Ceftriaxone) is 50-75mg/kg given once a day or (in equally divided doses twice a day). The total daily dose should not exceed 1 gram.

For treatment of acute bacterial otitis media: A single intramuscular dose of 50 mg/kg (not to exceed 1gram) is recommended.

In treatment of Meningitis: The initial therapeutic dose in terms of Ceftriaxone should be 100 mg/kg (not to exceed 4 grams) Daily dose may be administered once a day or in equally divided doses 12 hourly. The usual duration of therapy is 7-14 days.

For treatment of serious infections other than meningitis: Recommended total daily dose in terms of Ceftriaxone is 50-75 mg/kg given in divided doses every 12 hors. The total daily dose (in terms of Ceftriaxone) should not exceed more than 2 grams.

Storage and stability

XTUM (Ceftriaxone-Sulbactam) is a sterile powder to be stored at or below 25 degrees centigrade (77 degree F) and protected from light

Note

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

SHREYA

SHREYA LIFE SCIENCES PVT LTD
Shreya House, 301/A, Pereira Hill Road, Andheri (East), Mumbai 400099