NATIONAL AGENCY FOR FOOD & DRUG ADMINISTRATION & CONTROL

(NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Annxone(Ceftriaxone for injection USP 1000mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains

Sterile Ceftriaxone sodium USP

Equivalent to Ceftriaxone anhydrous 1000 mg

Supplied with an ampoule of 10ml sterile Water for injection BP

3. PHARMACEUTICAL FORM

Powder for injection

4. Clinical particulars

Therapeutic indications

Ceftriaxone sodium is a broad-spectrum bactericidal cephalosporin antibiotic. Ceftriaxone is active in vitro against a wide range of Gram-positive and Gram-negative organisms, which include β-lactamase producing strains.

Ceftriaxone is indicated in the treatment of the following infections either before the infecting organism has been identified or when known to be caused by bacteria of established sensitivity.

Pneumonia

Septicaemia

Meningitis

Skin and soft tissue infections

Infections in neutropenic patients

Gonorrhoea

Peri-operative prophylaxis of infections associated with surgery

Treatment may be started before the results of susceptibility tests are known.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology and method of administration

Ceftriaxone may be administered by deep intramuscular injection, or as a slow intravenous injection**,** after reconstitution of the solution according to the directions given below. The 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, one dose will give satisfactory therapeutic results.

Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously .

Intramuscular injection: 1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection BP. The solution should be administered by deep intramuscular injection. Doses greater than 1g should be divided and injected at more than one site.

Intravenous injection: 1g ceftriaxone should be dissolved in 10ml of Water for Injections PhEur. The injection should be administered over at least 2-4 minutes, directly into the vein or via the tubing of an intravenous infusion.

Adults and children 12 years and over:

Standard therapeutic dosage: 1g once daily.

Severe infections: 2-4 g daily, normally as a once daily dose.

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Acute, uncomplicated gonorrhoea: One dose of 250mg intramuscularly should be administered. Simultaneous administration of probenecid is not indicated.

Peri-operative prophylaxis: Usually one dose of 1g given by intramuscular or slow intravenous injection. In colorectal surgery, 2g should be given intramuscularly (in divided doses at different injection sites), by slow intravenous injection or by slow intravenous infusion**,** in conjunction with a suitable agent against anaerobic bacteria.

Elderly: These dosages do not require modification in elderly patients provided that renal and hepatic function are satisfactory

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

Children under 12 years

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

Up to 80mg/kg body-weight daily may be given in severe infections, except in premature neonates where a daily dosage of 50mg/kg should not be exceeded. For children with body weights of 50kg or more, the usual dosage should be used. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. Doses greater than 80mg/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 ceftriaxone provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance <10ml per minute) should the daily dosage be limited to 2g 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 ceftriaxone should be determined at regular intervals and dosage adjusted.

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

Reconstitution:

Reconstitution table Water for Injection (Intravenous Injection):

Vial Dosage Size	Amount of Diluent to be Added
500 mg	4.8 mL
1 gm	9.6 mL

Reconstitution table 1% Lidocaine Injection BP (Intramuscular Injection):

Vial Dosage Size	Amount of Diluent to be Added	
	250 mg/mL	350 mg/mL
500 mg	1.8 mL	1.0 mL
1 gm	3.6 mL	2.1 mL

Ceftriaxone should not be mixed in the same syringe with any drug other than 1% Lidocaine Injection BP (for intramuscular injection only).

The reconstituted solution should be clear. Do not use if particles are present.

Ceftriaxone sodium when dissolved in Water for Injections BP forms a pale yellow to amber solution. Variations in the intensity of colour of the freshly prepared solutions do not indicate a change in potency or safety.

For single use only. Discard any unused contents.

Contraindications

Ceftriaxone 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.

Hyperbilirubinaemic newborns and preterm newborns 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 is contraindicated in:

premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),

full-term newborns (up to 28 days of age) with

who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired if they require (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium

Contraindications of lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine is used as a solvent.

Special warnings and precautions for use

The stated dosage should not be exceeded.

If lidocaine is used as a solvent ceftriaxone solutions should only be used for intramuscular injection.

As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken.

Before therapy with ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftriaxone, cephalosporins, penicillins, or other beta-lactam drugs. Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. 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. Ceftriaxone should be given with caution to patients who have had any other type of hypersensitivity reaction to a penicillin or any other beta-lactam drug. Care is required when administering ceftriaxone to patients who have previously shown hypersensitivity to penicillins or other non-cephalosporin beta-lactam antibiotics, as occasional instances of cross allergenicity between cephalosporins and these antibiotics have been recorded. Anaphylactic shock requires immediate counter measures.

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined under Posology and method of administration.

Safety and effectiveness of ceftriaxone in neonates, infants and children have been established for the dosages described under Dosage and administration. In vivo and in vitro studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Clinical data obtained in neonates have confirmed this finding. Ceftriaxone should therefore not be used in neonates (especially prematures) at risk of developing bilirubin encephalopathy.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. In vitro studies demonstrated that newborns have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing

TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions.

Shadows which have been mistaken for gallstones, have been detected on sonograms of the gallbladder, usually following doses of higher than the standard recommended dose . These shadows are, however, precipitates of calcium ceftriaxone which disappear on completion or discontinuation of ceftriaxone therapy. Rarely have these findings been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended. Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the physician. These shadows can appear in patients of any age, but are more likely in infants and small children who are usually given a larger dose of ceftriaxone on a body weight basis. In children, doses greater than 80mg/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.

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.

Regular blood counts (haemoglobin, erythrocyte, leucocyte and platelet counts and screening for prolongation of prothrombin time) should be carried out during treatment.

Cephalosporins may cause bleeding due to hypoprothrombinaemia and should be used with caution in patients with renal or hepatic impairment, malnourished patients or those with low vitamin K levels and also in patients receiving prolonged cephalosporin therapy who are at increased risk of developing hypoprothrombinaemia.

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been rarely reported in patients treated with ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor role of ceftriaxone-related biliary precipitation cannot be ruled out.

Superinfections with non-susceptible micro-organisms (such as yeasts, fungi) may occur as with other anti-bacterial agents. A rare side-effect is pseudomembranous colitis which has resulted from infection with Clostridium difficile during treatment with ceftriaxone.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains ofC.difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after 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.

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone. 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 discontinued until the aetiology is determined.

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.

Ceftriaxone should be used with caution in individuals with a previous history of gastro-intestinal disease, particularly colitis.

Interaction with other medicinal products and other forms of interaction

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone 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.

The elimination of ceftriaxone is not altered by probenecid.

Aminoglycoside antibiotics and diuretics: No impairment of renal function has so far been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g.furosemide). There is no evidence that ceftriaxone increases renal toxicity of aminoglycosides.

Alcohol: No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone. Ceftriaxone does not contain an N-

methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.

Antibiotics: In an in vitro study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

Anticoagulants: As ceftriaxone has an N-methylthiotriazine side-chain, it might have the potential to cause hypoprothrombinaemia (Refer to section 4.8, Undesirable effects) resulting in an increased risk of bleeding in patients treated with anticoagulants.

Oral 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.

Based on literature reports ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Pregnancy and lactation

Pregnancy: Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed. Therefore ceftriaxone should not be used in pregnancy unless absolutely indicated.

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

Effects on ability to drive and use machines

Ceftriaxone has been associated with dizziness, which may affect the ability to drive or operate machinery.

Undesirable effects

The undesirable effects usually are mild and short-term.

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 intravenous 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.

Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines.

Gastrointestinal

Common (≥ 1% - <10%): Loose stools or diarrhoea (diarrhoea may sometimes be a symptom of pseudomembranous colitis, see 4.4 Special warnings and precautions for use), nausea, vomiting, stomatitis and glossitis.

Rare (≥ 0.01% - < 0.1%): Abdominal pain.

Infections

Superinfection caused by microorganisms non-susceptible to ceftriaxone such as yeasts, fungi (mycosis of the genital tract) or other resistant microorganisms may develop. Pseudomembranous colitis is a rare undesirable effect caused by infection with Clostridium difficile during treatment with ceftriaxone. Therefore, the possibility of the disease should be considered in patients who present with diarrhoea following antibacterial agent use.

Hypersensitivity

Uncommon (≥ 0.1% - < 1%): Maculopapular rash or exanthema, pruritus, urticaria, oedema, shivering and anaphylactic or anaphylactoid reactions (e.g. bronchospasm) and allergic dermatitis have occurred.

Rare (≥ 0.01% - < 0.1%): Drug fever, shivering. Anaphylactic-type reactions such as bronchospasm are rare.

Very rare (< 0.01%): Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson Syndrome and Lyell's Syndrome/toxic epidermal necrolysis) have been reported.

Blood and lymphatic system disorders

Common (≥1% - ≤10%):

Haematological reactions have included anaemia (all grades), haemolytic anaemia, granulocytopenia, leucopenia, neutropenia, thrombocytopenia and eosinophilia. Coagulation disorders have been reported as very rare side effects.

Unknown frequency: Immune mediated haemolytic anaemia

Unknown frequency of agranulocytosis (<500/mm3) has been reported, mostly after 10 days of treatment and following total doses of 20g or more.

There have been rare reports of fatal haemolysis in association with ceftriaxone. Ceftriaxone has rarely been associated with prolongation of prothrombin time, however, bleeding and bruising due to hypoprothrombinaemia may be more prevalent in patients with renal or hepatic impairment, malnourished patients or those with low vitamin K levels and patients receiving prolonged ceftriaxone therapy.

Central Nervous system

Rare (≥ 0.01% - < 0.1%): Headache, vertigo and dizziness.

Administration of high doses of cephalosporins, particularly in patients with renal insufficiency, may result in convulsions.

Renal and Urinary

Rare (≥ 0.01% - < 0.1%): Glycosuria, oliguria, haematuria, increase in serum creatinine.

Very rare (< 0.01%): Cases of renal precipitation have been reported, mostly in children older than 3 years and who have been treated with either high daily doses (e.g.≥ 80mg/kg/day) or total doses exceeding 10 grams and presenting other risk factors (e.g. fluid restrictions, confinement to bed, etc.). The risk of precipitate formation is increased in immobilized or dehydrated patients. This event may be symptomatic or asymptomatic, may lead to renal insufficiency and anuria, and is reversible upon discontinuation of ceftriaxone.

Acute renal tubular necrosis may occur rarely with ceftriaxone.

Hepatobiliary system

Rare (≥ 0.01% - < 0.1%): Hepatitis and/or cholestatic jaundice, increase in liver enzymes.Transient elevations in liver function tests have been reported in a few cases.

Shadows which have been mistaken for gallstones, but which are precipitates of calcium ceftriaxone, have been detected by sonograms. These abnormalities are commonly observed after an adult daily dose of two grams per day or more, or its equivalent in children; these abnormalities were particularly observed in children with an incidence of above 30% in isolated reports. At doses of two grams a day or above these biliary precipitates may occasionally cause symptoms. Should patients develop symptoms, non-surgical management is recommended and discontinuation of ceftriaxone should be considered. The evidence suggests biliary precipitates usually disappear once ceftriaxone has been stopped. The risk of biliary precipitates may be increased by treatment duration greater than 14 days, renal failure, dehydration or total parenteral nutrition.

Pancreas

Very rare (< 0.01%): There have been isolated reports of pancreatitis although a causal relationship to ceftriaxone has not been established.

Local effects

Rare (≥ 0.01% - < 0.1%): Pain or discomfort may be experienced at the site of intramuscular injection immediately after administration but is usually well tolerated and transient. Intramuscular injection without lidocaine solution is painful. Local phlebitis has occurred rarely following intravenous administration but can be minimised by slow injection over at least 2-4 minutes.

Influence on diagnostic tests

In patients treated with ceftriaxone the Coombs' test rarely may become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosemia.

Likewise, nonenzymatic methods for the glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

Overdose

In the case of overdose nausea, vomiting, diarrhoea, can occur. Ceftriaxone concentration can not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

General Properties

ATC classification: JO1D A13

Mode of action

Ceftriaxone has bactericidal activity resulting from the inhibition of bacterial cell wall synthesis ultimately leading to cell death. Ceftriaxone is stable to a broad range of bacterial β-lactamases.

Mechanism of resistance

Ceftriaxone is stable to a wide range of both Gram-positive and Gram-negative beta-lactamases, including those which are able to hydrolyse advanced generation penicillin derivatives and other cephalosporins. Resistance to ceftriaxone is encoded mainly by the production of some beta-lactam hydrolysing enzymes (including carbapenemases and some ESBLs) especially in Gram-negative organisms. For Gram-positive organisms such as S. aureus and S. pneumoniae, acquired resistance is mainly encoded by cell wall target site alterations. Outside of the advanced generation parenteral cephalosporins, cross-resistance to other drug classes is generally not encountered.

Breakpoints

Current MIC breakpoints used to interpret ceftriaxone susceptibility data are shown below. Values quoted comprise mg/L (MIC testing).

European Committee on Antimicrobial Susceptibility Testing (EUCAST) Clinical MIC Breakpoints (V1.1, 31/03/2006)

	Susceptible/Resistant
Enterobacteriaceae[2]	1/2
Pseudomonas	--
Acinetobacter	--
Staphylococcus[3]	Note[3]
Enterococcus	--
Streptococcus A, B, C, G	0.5/0.5[4]
Streptococcus pneumoniae	0.5/2[4]
Haemophilus influenzae *Moraxella Catarrhalis*	0.12/0.12[4]
Neisseria gonorrhoea	0.12/0.12[4]
Neisseria Meningitidis	0.12/0.12[4]
Gram-negative, anaerobes	--
Non-species related breakpoints[1] S≤/>R	1/2

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).

2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.

3. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).

4. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

RD = rationale document listing data used by EUCAST for determining breakpoints.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Ceftriaxone susceptibility among Gram-positive and Gram-negative bacterial species in Europe from January 1999-December 2001:

Commonly susceptible species (i.e. resistance < 10% in all EU Member States)
Gram-Positive aerobes :
MS[a] coagulase negative *Staphylococcus* spp. (including *S. epidermis*)*

MS[b] *Staphylococcus aureus**
Group B (*Streptococcus agalactiae*)
Streptococcus bovis
*Streptococcus pneumoniae**
Group A *Streptococcus (Streptococcus pyogenes)**
*Streptococcus viridans**
Gram-Negative aerobes :
Citrobacter spp. (including *C.freundii*)
*Escherichia coli**
Haemophilus influenzae (including beta-lactamase positive isolates)[c*]
*Haemophilus para-influenzae**
Klebsiella spp. (including *K. pneumoniae* and *K. oxytoca*)*
*Moraxella catarrhalis**
*Morganella morganii**
Neisseria gonorrhoea (including penicillin-resistant isolates)*
*Neisseria meningitidis**
Proteus spp. (including *P. mirabilis* and *P. vulgaris*)*
Salmonella spp. (including *S. typhimurium*)
Serratia spp. (including *Serratia marsescens*)*
Shigella spp.
Anaerobes:
Clostridium spp.*
Species for which acquired resistance may be a problem (i.e. resistance ≥10% in at least one EU Member State)
Gram-Negative aerobes:
Pseudomonas aeruginosa +

Enterobacter spp. (including *E. aerogenes and E. cloacae*)*+
Acinetobacter spp. (including *A. baumanii* and *A. calcoaceticus*)*+
Anaerobes:
Bacteroides spp.*
Peptostreptococcus spp.*
Inherently resistant organisms
Gram-Positive aerobes:
MR[d] coagulase negative *Staphylococcus* spp. (including *S. epidermidis*)
MR[e]*Staphylococcus aureus*
Enterococcus spp.
Gram-Negative aerobes:
Listeria monocytogenes
Mycoplasma spp.
Stenotrophomonas maltophilia
Ureaplasma urealyticum
Others:
Chlamydia spp.

[a]Methicillin-susceptible Coagulase-Negative *Staphylococcus*

[b]Methicillin-susceptible *Staphylococcus aureus*

[c]Non-susceptible range (no resistant breakpoints defined)

[d]Methicillin-resistant Coagulase-Negative *Staphylococcus*

[e]Methicillin-resistant *Staphylococcus aureus*

* Species for which the efficacy of ceftriaxone has been demonstrated both *in vitro* and *in vivo*

+ Species for which high rates of resistance have been observed in one or more regions within the EU.

5.2 Pharmacokinetic properties

The pharmacokinetics of ceftriaxone are largely determined by its concentration-dependent binding to plasma albumin. The plasma free (unbound) fraction of the drug in man is approximately 5% over most of the therapeutic concentration range, increasing to 15% at concentrations of 300mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

Plasma concentrations: Mean peak concentrations after bolus intravenous injection are about 120mg/l following a 500mg dose and about 200mg/l following a 1g dose; mean levels of 250mg/l are achieved after infusion of 2g over 30 minutes. Intramuscular injection of 500mg ceftriaxone in 1% Lidocaine Injection BP produces mean peak plasma concentrations of 40-70 mg/l within one hour. Bioavailability after intramuscular injection is 100%.

Excretion: Ceftriaxone is eliminated mainly as unchanged drug, approximately 60% of the dose being excreted in the urine (almost exclusively by glomerular filtration) and the remainder via the biliary and intestinal tracts. The total plasma clearance is 10-22 ml/min. The renal clearance is 5-12 ml/min. A notable feature of ceftriaxone is its relatively long plasma elimination half-life of approximately eight hours which makes single or once daily dosage of the drug appropriate for most patients. The half-life is not significantly affected by the dose, the route of administration or by repeated administration.

Pharmacokinetics in special clinical situations: In the first week of life, 80% of the dose is excreted in the urine; over the first month, this falls to levels similar to those in the adult. In infants aged less than 8 days the average elimination half-life is usually two to three times longer than that of young adults.

In elderly persons aged over 75 years, the average elimination half-life is usually two to three times longer that in the young adult group. As with all cephalosporins, a decrease in renal function in the elderly may lead to an increase in half-life. Evidence gathered to date with ceftriaxone however, suggests that no modification of the dosage regimen is needed.

In patients with *renal or hepatic dysfunction*, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

Cerebrospinal fluid: Ceftriaxone crosses non-inflamed and inflamed meninges, attaining concentrations 4-17% of the simultaneous plasma concentration.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber that are additional to those included in other sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

No excipients are used in the formulation of Annxone(Ceftriaxone for injection USP 1000mg).

6.2 Incompatibilities

Solutions containing ceftriaxone should not be mixed with or added to solutions containing other agents except 1% Lidocaine Injection BP (for intramuscular injection only). In particular, diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions .Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides, pentamidine, clindamycin phosphate and labetalol.

6.3 Shelf life

2years

Reconstituted product: Chemical and physical in-use stability has been demonstrated for 6 hours at or below 25°C or 24 hours at 2-8°C. The product must be protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

Keep all medicines out of the reach of the children.

6.5 Nature and contents of container

Annxone (Ceftriaxone for injection USP 1000mg) is filled in 10 ml USP Type III flint glass vial with grey butyl rubber stopper and red colour flip off seal.

6.6 Special precautions for disposal and other handling

Each vial is for single use only.

Standard aseptic techniques should be used for solution preparation and administration.

The solution should be shaken before use.

Any unused product or waste material should be disposed of in accordance with local requirements.

7.Applicant/manufacturer

YELURI FORMULATIONS PVT LTD

Sy.No.296/7/6, IDA Bollaram,

Sangareddy District-502 325,

Telangana, India.