Hospira™ CEFTRIAXONE SODIUM POWDER FOR INJECTION

NAME OF THE MEDICINE
Ceftriaxone sodium

DESCRIPTION
Hospira™ Ceftriaxone Sodium Powder for Injection is a sterile, semisynthetic, broad spectrum cephalosporin antibiotic for intravenous or intramuscular administration.

Ceftriaxone sodium is Disodium (6R,7R)-7-[(2Z)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulphanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 3.5 hydrate.

The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_{8}Na_{2}O_{7}S_{3} \ \frac{1}{2}H_{2}O$. It has a calculated molecular weight of 661.59 (CAS registry number: 104376-79-6).

Ceftriaxone sodium is a white or yellowish crystalline powder which is very soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 5% aqueous solution is approximately 6 to 8. Ceftriaxone sodium solutions may be light yellow to amber coloured in colour.

Hospira™ Ceftriaxone Sodium Powder for Injection contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

PHARMACOLOGY

Pharmacokinetics
Ceftriaxone is absorbed poorly from the gastrointestinal tract. 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 or 1 g dose in healthy subjects are presented in Table 1.
Table 1
Average Ceftriaxone Plasma Concentrations After Single Dose Administration.

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Average Plasma Concentrations (micrograms/mL) (Time from End of Administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 hour</td>
</tr>
<tr>
<td>0.5 g I.V.</td>
<td>82</td>
</tr>
<tr>
<td>0.5 g I.M.</td>
<td>30</td>
</tr>
<tr>
<td>1 g I.V.</td>
<td>151</td>
</tr>
<tr>
<td>1 g I.M.</td>
<td>40</td>
</tr>
<tr>
<td>2 g I.V.</td>
<td>257</td>
</tr>
</tbody>
</table>

I.V. = doses were infused at a constant rate over 30 minutes.
I.M. = doses were administered with lignocaine.
ND = Not determined.

Mean maximum plasma concentrations following I.M. injection occurred between two and three hours post-dosing. Multiple I.V. or I.M. doses ranging from 0.5 to 2 g at 12 to 24 hour intervals resulted in 15 to 36% accumulation of ceftriaxone above single dose values. Accumulation was more with the I.M. doses.

Ceftriaxone concentrations in urine are high, as shown in Table 2.

Table 2
Urinary Concentrations (micrograms/mL) of Ceftriaxone After Single Dose Administration.

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Average Urinary Concentrations (microgram/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-2 hour</td>
</tr>
<tr>
<td>0.5 g I.V.</td>
<td>526</td>
</tr>
<tr>
<td>0.5 g I.M.</td>
<td>115</td>
</tr>
<tr>
<td>1 g I.V.</td>
<td>995</td>
</tr>
<tr>
<td>1 g I.M.</td>
<td>504</td>
</tr>
<tr>
<td>2 g I.V.</td>
<td>2692</td>
</tr>
</tbody>
</table>

ND = Not determined.

Thirty three to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug. Substantial amounts are secreted in the bile and ultimately found in the faeces as microbiologically inactive compounds. A small fraction appears in the urine as an unidentified metabolite. Renal excretion of ceftriaxone is not affected by prior administration of probenecid. After a 1 g I.V. dose, average concentrations of ceftriaxone, determined from one to three hours after dosing, were 581 microgram/mL in the gallbladder bile, 788 microgram/mL in the common duct bile, 898 microgram/mL in the cystic duct bile, 78.2 microgram/g in the gallbladder wall and 62.1 microgram/mL in the concurrent plasma. There were, however, wide individual variations in levels.

Over a 0.15 to 3 g dose range in healthy adult subjects, the values of elimination half life ranged from 5.8 to 8.7 hours, apparent volume of distribution from 5.78 to 13.5 L; plasma clearance from 0.58 to 1.45 L/hr and renal clearance from 0.32 to 0.73 L/hr. Ceftriaxone is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of 25 microgram/mL to a value of 85% bound at 300 microgram/mL. Protein binding is reduced in children and in uremic patients. The in vitro activity of ceftriaxone is decreased 2 to 8 fold by the presence of human serum.

The average values of maximum plasma concentration, elimination half life, plasma clearance and volume of distribution after 50 mg/kg I.V. doses in paediatric patients suffering from bacterial meningitis are shown in Table 3.
Table 3
Average Pharmacokinetic Parameters of Ceftriaxone in Paediatric Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Plasma Concentrations (microgram/mL)</td>
<td>216</td>
</tr>
<tr>
<td>Elimination Half life (hr)</td>
<td>4.6</td>
</tr>
<tr>
<td>Plasma Clearance (mL/hr/kg)</td>
<td>49</td>
</tr>
<tr>
<td>Volume of Distribution (mL/kg)</td>
<td>338</td>
</tr>
<tr>
<td>CSF concentration - in purulent meningitis (microgram/mL)</td>
<td>5.6</td>
</tr>
<tr>
<td>Range (microgram/mL)</td>
<td>1.3-18.5</td>
</tr>
<tr>
<td>Time after dose (hour)</td>
<td>3.7 (±1.6)</td>
</tr>
</tbody>
</table>

The half life of ceftriaxone in neonates ranges from 7.2 to 19 hours and in infants over six weeks of age from 4.0 to 6.6 hours.

Ceftriaxone crosses the placenta and appears in the milk in low concentrations.

Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with hepatic dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients with ceftriaxone doses up to 2 g/day. However in some patients with severely impaired renal function the t\(_{1/2}\) of ceftriaxone may be prolonged (37 to 52 hours) and dosage adjustment should be considered. Peak serum levels should be held below 280 microgram/mL.

Ceftriaxone was not removed to any significant extent from the plasma by haemodialysis. Plasma concentrations of ceftriaxone should be monitored in these patients to determine if dosage adjustments are necessary.

Table 4
Average Pharmacokinetic Parameters of Ceftriaxone in Humans

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>Elimination Half Life (Hour)</th>
<th>Plasma Clearance (L/hour)</th>
<th>Volume of Distribution (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Subjects</td>
<td>5.8-8.7</td>
<td>0.58-1.45</td>
<td>5.8-13.5</td>
</tr>
<tr>
<td>Elderly Subjects (mean age, 70.5 years)</td>
<td>8.9</td>
<td>0.83</td>
<td>10.7</td>
</tr>
<tr>
<td>Patients with renal impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemodialysis patients (0.5 mL/min)*</td>
<td>14.7</td>
<td>0.65</td>
<td>13.7</td>
</tr>
<tr>
<td>Severe (5-15 mL/min)</td>
<td>15.7</td>
<td>0.56</td>
<td>12.5</td>
</tr>
<tr>
<td>Moderate (16-30 mL/min)</td>
<td>11.4</td>
<td>0.72</td>
<td>11.8</td>
</tr>
<tr>
<td>Mild (31-60 mL/min)</td>
<td>12.4</td>
<td>0.70</td>
<td>13.3</td>
</tr>
<tr>
<td>Patients with liver disease</td>
<td>8.8</td>
<td>1.1</td>
<td>13.6</td>
</tr>
</tbody>
</table>

*Creatinine clearance

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, types I, II & III, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. It is susceptible to type IV beta-lactamases at approximately 18% of the rate of cephaloridine. Ceftriaxone is usually active against the following microorganisms in vitro and in clinical infections (see INDICATIONS).

GRAM-NEGATIVE AEROBES: Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae (including ampicillin-resistant strains), Klebsiella species (including K. pneumoniae). Neisseria gonorrhoeae (including penicillinase and nonpenicillinase producing strains), Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii and Serratia marcescens.
Note: Strains of the above organisms that are multiply resistant to other antibiotics, eg penicillins, cephalosporins and aminoglycosides, may be susceptible to ceftriaxone sodium. Ceftriaxone is also active against some strains of Pseudomonas aeruginosa. Other pseudomonas species are usually resistant.

GRAM-POSITIVE AEROBES: Staphylococcus aureus (including penicillinase producing strains) and Staphylococcus epidermidis (Note: methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone), Streptococcus pyogenes (Group A beta-haemolytic streptococci), Streptococcus agalactiae (Group B streptococci) and Streptococcus pneumoniae, Group G streptococci, Streptococcus viridans and Streptococcus species (Note: Most species of Group D streptococci including Streptococcus faecalis and Streptococcus faecium are resistant).

Susceptibility Tests: Standard susceptibility disk method. Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M; Antibiotic Susceptibility testing by Standardized Single Disk Method, Am J Clin Pathol 45:493-496, 1966; Standardized Disk Susceptibility Test, Federal Register 39: 19182-19184, 1974; National Committee for Clinical Laboratory Standards Approved Standard: ASM-2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to Ceftriaxone. Laboratory results of the standardised single-disk susceptibility test using a 30 microgram Ceftriaxone disk should be interpreted according to the following criteria:

1. Susceptible organisms produces zones of 21 mm or greater, indicating that the tested organism is likely to respond to therapy.
2. Organisms that product zones of 14 to 22 mm are expected to be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (e.g. urine) in which high antibiotic levels are attained.
3. Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

Organism should be tested with the ceftriaxone disk, since ceftriaxone has been shown to by in vitro tests to be active against certain strains found resistant to cephalosporin class disks.

Standardised procedures require use of control organisms. The 30 microgram ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains E. coli ATCC 25922, S. aureus ATCC 25923 and P. aeruginosa ATCC 27853, respectively.

Dilution techniques: A bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 8 micrograms/mL. Organisms are considered resistant to ceftriaxone if the MIC is greater than 32 micrograms/mL. Organisms having a MIC value of equal to or less than 32 microgram/mL, but less than 8 micrograms/mL are expected to be susceptible if a high dosage is used or if the infection is confirmed to tissues and fluids (e.g. urine), in which high antibiotic levels are attained. E. coli ATCC 25922, S. aureus ATCC 25823 and P. aeruginosa ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests. Greater than 95% of MICs for the E. coli strain should fall within the range of 0.016 at 0.5 microgram/mL. The range for the S. aureus strain should be 1 to 2 microgram/mL.

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (eg. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

INDICATIONS
Hospira™ Ceftriaxone Sodium Powder for Injection is indicated for the treatment of the following infections when caused by susceptible aerobic organisms.
Lower Respiratory Tract Infections caused by Streptococcus pneumoniae, Streptococcus species (excluding enterococci), methicillin sensitive Staphylococcus aureus, Haemophilus influenzae, H. parainfluenzae, Klebsiella species (including K. pneumoniae), E. coli, Enterobacter aerogenes, Proteus mirabilis and Serratia marcescens.

Skin and Skin Structure Infections caused by methicillin sensitive Staphylococcus aureus, methicillin sensitive Staphylococcus epidermidis, Streptococcus Group B, Streptococcus Group G, Streptococcus pyogenes, Streptococcus viridans, Streptococcus species (excluding enterococci), Peptostreptococcus species, E. coli, Enterobacter cloacae, Klebsiella species (including K. pneumoniae, K. oxytoca), Proteus mirabilis, Morganella morganii, Serratia marcescens.

Urinary Tract Infections (complicated and uncomplicated) caused by E. coli, Proteus mirabilis, Proteus vulgaris, M. morganii and Klebsiella species (including K. pneumoniae).

Uncomplicated Gonorrhoea (cervical/urethral and rectal) caused by Neisseria gonorrhoea, including both penicillinase and non penicillinase producing strains.

Bacterial Septicemia caused by Streptococcus pneumoniae, E. coli and H. influenzae.

Bone Infections caused by methicillin sensitive S. aureus, methicillin sensitive S. epidermidis, Streptococcus Group B, Streptococcus pneumoniae, Streptococcus species (excluding enterococci), E. coli, Enterobacter species, P. mirabilis and K. pneumoniae.

Joint Infections caused by methicillin sensitive S. aureus, Streptococcus pneumoniae, Streptococcus species (excluding enterococci), E. coli, P. mirabilis, K. pneumoniae and Enterobacter species.

Meningitis: The initial treatment, as a single agent, of meningitis in children and immunocompetent adults when presumed or proven to be caused by Haemophilus influenzae type b, Neisseria meningitidis, Streptococcus pneumoniae or Enterobacteriaceae pending culture and sensitivity results.

Surgical Prophylaxis: The preoperative administration of a single 1 g dose of ceftriaxone may reduce the incidence of post-operative infections in patients undergoing vaginal or abdominal hysterectomy or cholecystectomy in high risk patients, surgical procedures which are classified as contaminated or potentially contaminated and patients undergoing coronary artery bypass surgery. Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo controlled trials have been conducted.

Susceptibility Testing: Before instituting treatment with ceftriaxone, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS
Ceftriaxone is contraindicated in patients with known allergy to the cephalosporin class of antibiotics or a major allergy to penicillin (anaphylaxis, angioneurotic oedema, urticaria).

Lignocaine should not be used as a diluent for intramuscular injection in patients who are hypersensitive to lignocaine.

Hospira™ Ceftriaxone Sodium Powder for Injection must not be administered with calcium-containing solutions in newborns because of the risk of precipitation of ceftriaxone-calcium salt (see PRECAUTIONS: Calcium-containing Solutions; Paediatric Use, and ADVERSE EFFECTS). Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidney in newborns have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed.
Therefore, Hospira™ Ceftriaxone Sodium Powder for Injection and I.V. calcium-containing solutions must not be administered within 48 hours of each other in newborns.

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, leading to a possible risk of bilirubin encephalopathy in these patients.

**PRECAUTIONS**

**Hypersensitivity to Cephalosporins, Penicillins or other Drugs:**
BEFORE THERAPY WITH CEFTRIAXONE 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 ADRENALINE AND OTHER EMERGENCY MEASURES. IF AN ALLERGIC REACTION OCCURS CEFTRIAXONE SHOULD BE DISCONTINUED.

**Calcium-containing Solutions:**
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. See **CONTRAINDICATIONS** for information regarding newborns.

**Antibiotic Associated Pseudomembranous Colitis:** Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ceftriaxone. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Other causes of colitis should also be considered.

**History of Gastrointestinal Disease:** Ceftriaxone should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

**Immune mediated Haemolytic Anaemia**
Immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials. 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 etiology is determined.

**Overgrowth of Other Non-Susceptible Organisms:** Prolonged use of Hospira™ Ceftriaxone Sodium Powder for Injection may result in overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

**Pancreatitis and Biliary Precipitation:** Cases of pancreatitis (possibly of biliary obstruction aetiology) have been rarely reported in patients treated with Hospira™ Ceftriaxone Sodium for Injection. 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 Hospira™ Ceftriaxone Sodium Powder for Injection related biliary precipitation can therefore not be ruled out.

**Gall Bladder Concretions/Precipitates:** Ceftriaxone produces gall bladder concretions/precipitates in dogs and baboons, and rarely in human being (see **ADVERSE EFFECTS**)

**Renal Impairment and Toxicity:** Ceftriaxone has shown some evidence of renal toxicity in animals. Clinical studies have shown only transient elevations of serum urea and serum creatinine at the recommended dosages.

Ceftriaxone is excreted via both biliary and renal excretion (see **Pharmacokinetics**). The half-life of ceftriaxone may be prolonged in some patients with renal failure, adjustment in dosage may be required. Concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly. Dosage adjustments should not be necessary in patients with hepatic dysfunction. In patients with both hepatic dysfunction and significant renal disease, Hospira™ Ceftriaxone Sodium Powder for Injection dosage requires close monitoring of serum concentrations.

**Alterations in Clotting Time:** Alterations in prothrombin times have occurred rarely in patients treated with ceftriaxone. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g. chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during ceftriaxone treatment. Vitamin K administration (10 milligram weekly) may be necessary if the prothrombin time is prolonged before or during therapy. Prolonged prothrombin time may occur in patients receiving protracted antimicrobial therapy.

**Effects on ability to drive or operate machinery:** During treatment with ceftriaxone undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

**Use of Lignocaine Hydrochloride in Patients with Impaired Liver Function:** Repeated use of lignocaine hydrochloride should be avoided in patients with severe liver disease or decreased hepatic blood flow due to the possibility of lignocaine toxicity (resulting from decreased metabolism and accumulation).

**Carcinogenesis, genotoxicity, effects of fertility**

**Carcinogenesis:** Carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

**Genotoxicity:** Genetic toxicity 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.

**Effects of Fertility:** Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 milligram/kg/day.

**Use in pregnancy** Category B1.
Teratogenic Effects: Reproductive studies (Segment II) have been performed in mice and rats at doses up to 586 milligram/kg/day and no evidence of embryotoxicity, foetotoxicity or teratogenicity was seen. In primates, at doses up to 84 milligram/kg/day no embryotoxicity or teratogenicity was demonstrated.

There are, however, no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-Teratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behaviour and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

Australian categorisation definition of:

Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Use in lactation
Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when ceftriaxone is administered to a breastfeeding woman.

Paediatric Use
Safety and effectiveness of ceftriaxone in infants and children have been established for the dosages described in the DOSAGE AND ADMINISTRATION section. In vitro studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should not be given to neonates who may be at risk of developing bilirubin encephalopathy (especially premature infants). See CONTRAINDICATIONS

Interactions with other medicines
Ceftriaxone does not contain an N-methylthiotetrazole moiety which has been associated with significant impairment of Vitamin K dependent coagulation by some other cephalosporins. Probenecid does not cause clinically significant changes in the elimination of ceftriaxone. Concomitant use does not confer a therapeutic benefit.

In an in vitro study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.
Hospira™ Ceftriaxone Sodium Powder for Injection must not be administered with calcium-containing solutions in newborns because of the risk of precipitation of ceftriaxone-calcium salt (see CONTRAINDICATIONS). 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 (see PRECAUTIONS: Calcium-containing Solutions).

Effects on Laboratory tests
In patients treated with ceftriaxone the Coombs' test may become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosemia. Likewise, non-enzymatic 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.

ADVERSE EFFECTS
Ceftriaxone is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone therapy or of uncertain aetiology, were observed. Their incidence was somewhat higher in children and with higher doses.

Version 3.0
Local Effects: infrequent pain, induration or tenderness at the site of injection. Less frequently reported was phlebitis after IV administration. These may be minimised by slow injection over 2 to 4 minutes. Local reactions were increased if water was used as the diluent instead of lignocaine.

Hypersensitivity: infrequent rash. Less frequently reported were pruritus, fever or chills, severe dermatitis including exfoliative erythroderma, anaphylaxis, anaphylactoid reaction, erythema multiforme, urticaria, exanthema, allergic dermatitis. Cutaneous vasculitis may occur.

Haematological: occasional eosinophilia, thrombocytosis and leukopenia. Less frequently reported were haemolytic anaemia, neutropenia, lymphopenia, granulocytopenia, thrombocytopenia and prolongation of the prothrombin time and bleeding. In very rare cases agranulocytosis (below 500/mm3) has been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

Gastrointestinal: occasional diarrhoea. Less frequently reported were nausea or vomiting, stomatitis, glossitis and dysgeusia. Incidence of diarrhoea was higher in women and children. Pseudomembranous colitis has been reported rarely. Pancreatitis has been reported very rarely. Enterocolitis has been reported very rarely.

Hepatic: occasional elevations of SGOT or SGPT. Less frequently reported were elevations of alkaline phosphatase, bilirubin. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gall bladder, usually following doses higher than the standard recommended dose (See Precautions). 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 non surgical management is recommended. Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the clinician.

Renal: infrequent elevations of the serum urea. Less frequently reported were elevations of creatinine and the presence of casts in the urine. Crystalluria and oliguria have been reported very rarely. Renal adverse effects were somewhat more frequent in the elderly.

Central Nervous System: headache or dizziness were reported occasionally.

Genitourinary: moniliasis or vaginitis were reported occasionally. Genital mycosis has been reported rarely.

Miscellaneous: diaphoresis, flushing and fever were reported occasionally.

Other rarely observed adverse reactions include leukocytosis, lymphocytosis, monocytosis, basophilia, jaundice, glycosuria, haematuria, bronchospasm, oedema, shivering, serum sickness, abdominal pain, flatulence, dyspepsia, palpitations and epistaxis. Coagulation disorders have been reported as very rare side effects.

Isolated cases of severe cutaneous reactions (Stevens Johnson syndrome or Lyell's Syndrome/toxic epidermal necrolysis) have been reported.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidney in neonates and premature infants have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines (see Contraindications).

DOSAGE AND ADMINISTRATION
Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.
Dosage
Hospira™ Ceftriaxone Sodium Powder for Injection may be administered intravenously or intramuscularly. The recommended adult daily dose is 1 to 2 g given once a day or in equally divided doses twice a day depending on the type and severity of the infection. The lower dose would be appropriate for less severe infections.

For the treatment of uncomplicated gonococcal infections a single intramuscular dose of 250 milligrams is recommended.

For preoperative use (surgical prophylaxis) in cardiovascular surgery, biliary tract surgery in high risk patients and in vaginal and abdominal hysterectomy a single dose of 1 g administered 30 minutes to 2 hours before surgery is recommended.

For the treatment of serious miscellaneous infections in children, the recommended total daily dose is 50 to 75 milligrams/kg (not to exceed 2 grams), given once per day or in divided doses every 12 hours. In meningitis the dose should be divided and administered every 12 hours. For neonates (up to 14 days of age) a daily dose of 20 to 50 mg/kg bodyweight is recommended. The daily dose should not exceed 50 mg/kg on account of the immaturity of the neonate’s enzyme systems.

Generally, ceftriaxone therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days. In special conditions e.g. endocarditis, osteomyelitis, infected joints etc., treatment may be continued for a longer duration. Prolonged therapy results in a higher incidence of adverse effects particularly diarrhoea, rash, eosinophilia, elevated liver enzymes and to a lesser extent neutropenia.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of hepatic function; however, blood levels should be monitored in patients with severe renal impairment (eg dialysis patients) and in patients with both renal and hepatic dysfunction. Serum levels should not exceed 280 microgram/mL.

Administration
The use of freshly prepared solutions is recommended. These retain their efficacy for at least six hours at room temperature (or 24 hours at 2 to 8°C). The solutions are yellowish in colour. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 to 8°C for not more than 24 hours.

Hospira™ Ceftriaxone Sodium Powder for Injection should not be added to solutions containing calcium such as Hartmann's solution and Ringer's solution (see PRECAUTIONS: Calcium-containing Solutions). Hospira™ Ceftriaxone Sodium Powder for Injection should also not be mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed below, owing to possible incompatibility. Specifically, the literature reports that ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

*Intramuscular injection*: Hospira™ Ceftriaxone Sodium Powder for Injection 1 g in 3.5 mL of 1% lignocaine solution, and administered by deep intragluteal injection. It is recommended that no more than 1 g be injected on either side. The lignocaine solution must never be administered intravenously. Hospira™ Ceftriaxone Sodium Powder for Injection should be injected well into the body of a relatively large muscle mass. Intramuscular injection of Hospira™ Ceftriaxone Sodium Powder for Injection without lignocaine solution is painful.

*Intravenous injection*: Hospira™ Ceftriaxone Sodium Powder for Injection 1 g in 10 mL of water for injections, and then administered by direct intravenous injection lasting two to four minutes.
**Intravenous infusion:** Hospira™ Ceftriaxone Sodium Powder for Injection 2 g is dissolved in approximately 40 mL of one of the following infusion solutions:

- Sodium chloride 0.9%
- Sodium chloride 0.45% + glucose 2.5%
- Glucose 5%
- Glucose 10%
- Dextran 6% in glucose 5%

The infusion should be given over a period of at least 30 minutes.

**Stability**
At the concentrations indicated under Administration (above), solutions of Hospira™ Ceftriaxone Sodium Powder for Injection reconstituted in the injection or infusion media listed above, are stable for six hours at room temperature (25°C) and for twenty four hours if stored under refrigeration (2 to 8°C). As the reconstituted injection/infusion solutions do not contain a preservative, they should be used as soon as practical after reconstitution.

**OVERDOSAGE**
Excessive serum concentrations of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. Treatment of overdosage should be symptomatic.

In case of overdose, immediately contact the Poisons Information Centre for advice, call 0800 764 766.

**PRESENTATION AND STORAGE CONDITIONS**
- Hospira™ Ceftriaxone Sodium Powder for Injection 1 g
  1.19 g ceftriaxone sodium equivalent to 1 g ceftriaxone in a 20 mL molded glass Type I Clear 20 ml vial with bromo butyl rubber stopper – 1 vial per pack AUST R 167648

- Hospira™ Ceftriaxone Sodium Powder for Injection 2 g
  2.39 g ceftriaxone sodium equivalent to 2 g ceftriaxone in a 20 mL molded glass Type I Clear 20 ml vial with bromo butyl rubber stopper – 1 vial per pack AUST R 167651

Store below 25°C. Protect from light.

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**MEDICINE CLASSIFICATION**
Prescription Medicine

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