AUSTRALIAN PRODUCT INFORMATION

CEFTRIAXONE VIATRIS

(ceftriaxone sodium) powder for injection

1 NAME OF THE MEDICINE

Ceftriaxone sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CEFTRIAXONE VIATRIS powder for injection vial contains ceftriaxone sodium equivalent to either 1000 mg or 2000 mg of ceftriaxone as a single ingredient.

Ceftriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

The product contains no excipients or preservatives.

3 PHARMACEUTICAL FORM

CEFTRIAXONE VIATRIS 1000 mg	:	For IM injection, IV injection and IV infusion. A white to slightly yellow crystalline powder for injection vial.
CEFTRIAXONE VIATRIS 2000 mg	:	For IV infusion. A white to slightly yellow crystalline powder for injection vial.

The colour of ceftriaxone sodium solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CEFTRIAXONE VIATRIS is indicated for the treatment of the following infections when caused by susceptible aerobic organisms:

- LOWER RESPIRATORY TRACT INFECTIONS: caused by *S. pneumoniae*, Streptococcus species (excluding enterococci), methicillin sensitive *S. aureus, H. influenzae, H. parainfluenzae*, Klebsiella species (including *K. pneumoniae*), *E. coli, E. aerogenes*, *Proteus mirabilis* and *Serratia marcescens*.

- SKIN AND SKIN STRUCTURE INFECTIONS: caused by methicillin sensitive *S. aureus*, methicillin sensitive *S. epidermidis*, Streptococcus Group B, Streptococcus Group G, *Streptococcus pyogenes, Streptococcus viridans*, Streptococcus species (excluding enterococci), Peptostreptococcus species, *E. coli, E. 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 *S. pneumoniae, E. coli* and *H. influenzae*.

- BONE INFECTIONS: caused by methicillin sensitive *S. aureus*, methicillin sensitive *S. epidermidis*, Streptococcus Group B, *S. pneumoniae*, Streptococcus species (excluding enterococci), *E. coli*, Enterobacter species, *P. mirabilis* and *K. pneumoniae*.

- JOINT INFECTIONS: caused by methicillin sensitive *S. aureus*, *S. 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 1000 mg 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

CEFTRIAXONE VIATRIS may be administered intravenously or intramuscularly. The recommended adult daily dose is 1000 to 2000 mg 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 mg 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 1000 mg administered ½ to 2 hours before surgery is recommended.

For the treatment of serious miscellaneous infections in children, the recommended total daily dose is 50 - 75 mg/kg (not to exceed 2000 mg), given once per day or in divided doses every 12 hours. In meningitis the dose should be divided and administered every twelve hours.

Generally, ceftriaxone therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4-14 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.

Each gram of ceftriaxone contains 3.6x mmol sodium. To be taken into consideration in patients on a controlled diet.

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 (e.g. dialysis patients) and in patients with both renal and hepatic dysfunction. Serum levels should not exceed 280 mcg/mL.

Ceftriaxone contains no antimicrobial preservative. It is for single use in one patient only. Discard any residue. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, store at 2-8°C for not more than 24 hours.

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 (See sections 4.3 Contraindications, 4.4 Special warnings and precautions and 4.8 Adverse effects (Undesirable effects**)**).

Ceftriaxone 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.

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 5°C). The solutions are yellowish in colour; this characteristic of the active ingredient is of no significance to the efficacy or tolerance of the drug. A slight opalescence may be seen in the reconstituted solution.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute CEFTRIAXONE VIATRIS vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same I.V. administration line. CEFTRIAXONE VIATRIS must not be administered simultaneously with calcium-containing I.V. 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 (see sections 4.3 Contraindications and 4.4 Special warnings and precautions – Paediatric Use).

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (I.V. or oral).

CEFTRIAXONE VIATRIS should also not be mixed with or piggybacked into solutions containing other antimicrobial medicines or into diluent solutions other than those listed below, owing to possible incompatibility. Specifically, the literature reports that ceftriaxone is incompatible with amsacrine, vancomycin and fluconazole and aminoglycosides.

Intramuscular injection: CEFTRIAXONE VIATRIS 1000 mg is dissolved in 3.5 mL of 1% lidocaine (lignocaine) solution, and administered by deep intragluteal injection. It is recommended that no more than 1000 mg be injected on either side. The lidocaine (lignocaine) solution must never be administered intravenously. CEFTRIAXONE VIATRIS should be injected well into the body of a relatively large muscle mass. Intramuscular injection of CEFTRIAXONE VIATRIS *without* lidocaine (lignocaine) solution is painful.

Intravenous injection: CEFTRIAXONE VIATRIS 1000 mg is dissolved in 10 mL of water for injection, and then administered by direct intravenous injection lasting two to four minutes.

Intravenous infusion: Two grams of CEFTRIAXONE VIATRIS are 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%

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

4.3 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 neonates, especially premature, 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.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in newborns have been described. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates (see **4.8 Adverse effects (Undesirable effects) - Post-marketing experience**).

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 jaundice, or 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 (see 4.4 Special warnings and precautions, 4.8 Adverse effects (Undesirable effects) and 4.5 Interactions with other medicines and other forms of interactions).

Lidocaine (lignocaine) should not be used as a diluent for intramuscular injection in patients who are hypersensitive to lidocaine (lignocaine).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity to Cephalosporins, Penicillins or other Drugs

BEFORE THERAPY WITH CEFTRIAXONE IS INITIATED, 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. ANAPHYLACTIC REACTIONS WITH FATAL OUTCOME HAVE BEEN REPORTED, EVEN IF A PATIENT IS NOT KNOWN TO BE ALLERGIC OR PREVIOUSLY EXPOSED TO CEFTRIAXONE OR OTHER CEPHALOSPORINS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS ADRENALINE (EPINEPHRINE) AND OTHER EMERGENCY MEASURES.

IF AN ALLERGIC REACTION OCCURS CEFTRIAXONE SHOULD BE DISCONTINUED.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, ceftriaxone should be discontinued immediately and an alternative treatment should be considered.

Calcium-containing Solutions

In the available scientific data, there are no reports of intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing products. 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 sections 4.3 Contraindications, 4.8 Adverse effects (Undesirable effects), 5.2 Pharmacokinetic properties and 4.5 Interactions with other medicines and other forms of interactions.

Antibiotic associated pseudomembranous colitis

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibiotics agents, including ceftriaxone and may range in severity from mild diarrhoea 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. Toxin hyperproducing strains of *C. 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 diarrhoea 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, antibacterial agent effective against *C. difficile* and surgical evaluation should be instituted as clinically indicated.

Drugs which delay peristalsis, for example, opiates and diphenoxylate with atropine, 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 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 etiology is determined.

Overgrowth of Other Non-Susceptible Organisms

Prolonged use of CEFTRIAXONE VIATRIS may result in overgrowth of non-susceptible organisms (candida, fungi or other resistant microorganisms). Pseudomembraneous 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 diarrhea following antibacterial agent use. 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 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 can therefore not be ruled out.

Gall Bladder and Kidney Concretions/Precipitates

Ceftriaxone may precipitate in the gallbladder and kidneys and then be detectable as shadows on ultrasound. This can happen in patients of any age, but is 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 – except for meningitis – 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, and conservative management of ceftriaxone precipitate in the gallbladder is recommended. (see section 4.8 Adverse effects (Undesirable effects)).

Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the physician.

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 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone (see section 4.8 Adverse effects (Undesirable effects)), particularly in elderly patients with severe renal impairment or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include seizures and/or myoclonus. Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity.

Use in Hepatic Impairment

Repeated use of lidocaine (lignocaine) hydrochloride should be avoided in patients with severe hepatic disease or decreased hepatic blood flow due to the possibility of lidocaine (lignocaine) toxicity (resulting from decreased metabolism and accumulation).

Use in Renal Impairment

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 section 5.2 Pharmacokinetic properties).

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, ceftriaxone dosage requires close monitoring of serum concentrations.

Use in the Elderly

See sections 4.8 Adverse Effects (Undesirable effects) and 5.2 Pharmacokinetic properties.

Paediatric Use

Safety and effectiveness of ceftriaxone in infants and children have been established for the dosages described in section 4.2 Dose and Method of Administration. *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 section 4.3 Contraindications).

Because of the risk of precipitation of ceftriaxone-calcium (see section 4.5 Interactions with other medicines and other forms of interactions). Ceftriaxone is contraindicated in neonates requiring (or expected to require) treatment with calcium-containing I.V. solutions (including continuous calcium-containing infusions such as parenteral nutrition) (see section 4.3 Contraindications).

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.

Haematological changes such as eosinophilia, leukopenia, granulocytopenia, hemolytic anaemia, thrombocytopenia. Isolated cases of agranulocytosis ($< 500/mm^3$) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more. During prolonged treatment the complete blood count should be done at regular intervals.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No impairment of renal function has so far been observed after concurrent administration large doses of ceftriaxone and potent diuretics (e.g. furosemide (frusemide)). Healthy adults treated with 3 mg ceftriaxone and 3 mg/kg per day of tobramycin for three days did not show any enzymatic evidence of impaired renal function. There is no evidence that ceftriaxone increases renal toxicity of aminoglycosides. 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 which has been associated with significant impairment of Vitamin-K dependent coagulation by some other cephalosporins and possible ethanol intolerance and bleeding problems of certain 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.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute CEFTRIAXONE VIATRIS vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form.

Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same I.V. administration line.

CEFTRIAXONE VIATRIS must not be administered simultaneously with calcium-containing I.V. 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 (see sections 4.2 Dosage and method of administration and 4.3 Contraindications).

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses of up to 586 mg/kg/day.

Use in Pregnancy

Pregnancy Category: B1

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.

Teratogenic Effects: Reproductive studies (Segment II) have been performed in mice and rats at doses up to 586 mg/kg/day and no evidence of embryotoxicity, fetotoxicity or teratogenicity was seen. In primates, at doses up to 84 mg/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.

Use in Lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since Ceftriaxone sometimes induces dizziness, the ability to drive and use machines can be impaired.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Ceftriaxone is generally well tolerated. In clinical trials, the following adverse effects, 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.

Local Reactions - infrequent pain, induration or tenderness at the site of injection. Less frequently reported was phlebitis after I.V. administration. These may be minimised by slow (2-4 minutes) injection. Local reactions were increased if water was used as the diluent instead of lidocaine (lignocaine).

Hypersensitivity - infrequent rash. Less frequently reported were pruritus, fever or chills, severe dermatitis including exfoliative erythroderma, anaphylaxis, erythema multiforme, urticaria, exanthema, allergic dermatitis.

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 has been reported (most of them after 10 days of treatment and following total doses of 20g 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.

Hepatic - occasional elevations of ALT or AST. Less frequently reported were elevations of alkaline phosphatase and bilirubin. Symptomatic precipitation of ceftriaxone calcium salt in the gall bladder. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder, usually following doses higher than the standard recommended dose. These shadows are, however, precipitates of calcium ceftriaxone which disappear on completion or discontinuation of ceftriaxone therapy.

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.

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, mostly in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application, in some studies to above 30%. The incidence seems to be lower with slow infusion (20-30 minutes). This effect is usually asymptomatic, but in rare cases, the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

This disorder is rare in adults. In symptomatic cases, conservative nonsurgical 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. Very rare 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. ≥ 80 mg/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.

There have been isolated reports of pancreatitis.

Central Nervous System - headache or dizziness were reported occasionally.

Skin and other subcutaneous tissue disorders – severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in beta-lactam antibiotics.

Genitourinary – candidiasis or vaginitis were reported occasionally.

Miscellaneous – diaphoresis, flushing and fever were reported occasionally.

Other rarely observed adverse effects include vertigo, leukocytosis, lymphocytosis, monocytosis, basophilia, jaundice, glycosuria, haematuria, anaphylactic or anaphylactoid reactions e.g. bronchospasm, oedema, shivering, serum sickness, abdominal pain, flatulence, dyspepsia, palpitations, epistaxis and superinfections with non-susceptible micro-organisms.

Post-marketing experience

Nervous system disorders: Seizures, myoclonus – frequency not known.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys 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.

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 (see Sections 4.3 Contraindications, 4.4 Special warnings and precautions and 5.2 Pharmacokinetic properties).

Interaction with calcium

Two *in vitro* studies, one using adult plasma and the other neonatal plasma from umbilical cord blood have been carried out to assess interaction of ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved *in vivo* following administration of 2 grams ceftriaxone infused over 30 minutes) were used in combination with calcium concentrations up to 12 mM (48 mg/dL). Recovery of ceftriaxone from plasma was reduced with calcium concentrations of 6 mM (24 mg/dL) or higher in adult plasma or 4 mM (16 mg/dL) or higher in neonatal plasma. This may be reflective of ceftriaxone-calcium precipitation (see section 4.3 Contraindications).

Hepatobiliary disorders

Frequency "Not known": hepatitis[b], hepatitis cholestatic[b,c]

[b]: See Section 4.4 Special Warnings and Precautions for Use.

[c]: Usually reversible upon discontinuation of ceftriaxone

Central Nervous System

Rare: encephalopathy

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Excessive serum concentrations of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. Treatment of overdosage should be symptomatic and consist of general supportive measures. In the case of overdose; nausea, vomiting and diarrhoea can occur. There is no specific antidote for ceftriaxone overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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 section 4.1 Therapeutic 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, e.g. 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 Testing

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. Clinical and Laboratory Standards Institute [CLSI]). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation.

A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Dilution Techniques

A bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 8 mcg/mL. Organisms are considered resistant to ceftriaxone if the MIC is greater than 32 mcg/mL. Organisms having a MIC value of equal to or less than 32 mcg/mL, but greater than 8 mcg/mL, 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. *E. coli* ATCC 25922, *S. aure*us ATCC 25923 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 to 0.5 mcg/mL. The range for the *S. aureus* strain should be 1 to 2 mcg/mL.

Clinical Trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Ceftriaxone is poorly absorbed from the gastrointestinal tract. Average plasma concentrations of ceftriaxone following a single 30 minute intravenous (I.V.) infusion of a 0.5, 1 or 2 g dose and intramuscular (I.M.) 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

Dose/Route	Average Plasma Concentrations (mcg/mL) (Time from End of Administration)								
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 g i.v.	82	59	48	37	29	23	15	10	5
0.5 g i.m.	30	41	43	39	31	25	16	ND*	ND*
1 g i.v.	151	111	88	67	53	43	28	18	9
1 g i.m.	40	68	76	68	56	44	29	ND*	ND*
2 g i.v.	257	192	154	117	89	74	46	31	15

I.V. doses were infused at a constant rate over 30 minutes.
I.M. doses were administered with lidocaine (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 (mcg/mL) of Ceftriaxone After Single Dose Administration

Dose/Route	Average Urinary Concentrations (mcg/mL)				
	0-2 hr	2-4 hr	4-8 hr	8-12 hr	12-24 hr
0.5 g i.v.	526	366	142	87	70
0.5 g i.m.	115	425	308	127	96
1 g i.v.	995	855	293	147	132
1 g i.m.	504	628	418	237	ND*
2 g i.v.	2692	1976	757	274	198

*ND = Not determined.

Between 33 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 mcg/mL in the gallbladder bile, 788 mcg/mL in the common

duct bile, 898 mcg/mL in the cystic duct bile, 78.2 mcg/g in the gallbladder wall and 62.1 mcg/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 mcg/mL to a value of 85% bound at 300 mcg/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

	50 mg/kg i.v.
Maximum plasma concentrations (mcg/mL)	216
Elimination half-life (hr)	4.6
Plasma clearance (mL/hr/kg)	49
Volume of distribution (mL/kg)	338
CSF concentrations – in purulent meningitis (mcg/mL)	5.6
Range (mcg/mL)	1.3 - 18.5
Time after dose (hr)	3.7 (±1.6)

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

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 $t_{½}$ of ceftriaxone may be prolonged (37 - 52 hours) and dosage adjustment should be considered. Peak serum levels should be held below 280 mcg/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

Subject Group	Elimination Half-Life (hr)	Plasma Clearance (L/hr)	Volume of Distribution (L)
Healthy subjects	5.8-8.7	0.58-1.45	5.8-13.5
Elderly subjects (mean age, 70.5 years)	8.9	0.83	10.7

Patients with renal impairment			
Haemodialysis patients (0.5 mL/min)*	14.7	0.65	13.7
Severe (5-15 mL/min)	15.7	0.56	12.5
Moderate (16-30 mL/min)	11.4	0.72	11.8
Mild (31-60 mL/min)	12.4	0.70	13.3
Patients with liver disease	8.8	1.1	13.6
* Creatinine clearance.			

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The product contains no excipients or preservatives.

6.2 INCOMPATIBILITIES

See sections 4.2 Dose and method of administration and 4.5 Interactions with other medicines and other forms of interactions

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC. Protect from light. Store in original container.

CEFTRIAXONE VIATRIS is sensitive to light. Keep the vial in the outer carton in order to protect from light.

Storage condition for reconstituted solutions: Reconstituted solutions should be used immediately. If necessary, the solutions may be stored for 6 hours below 25°C or for 24 hours between 2°C to 8°C.

The product is for single use in one patient only. Discard any residue.

6.5 NATURE AND CONTENTS OF CONTAINER

CEFTRIAXONE VIATRIS 1000 mg	:	type I or II clear glass vials with a halobutyl stopper, sealed by an aluminium flip-off cap.

CEFTRIAXONE VIATRIS 2000 mg	:	type II or III clear glass vials with a halobutyl stopper, sealed by an aluminium flip-off cap.

Pack sizes of both products: 1 vial, 5 vials, 10 vials.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 164920 – CEFTRIAXONE VIATRIS ceftriaxone (as sodium) 1 g powder for injection vial

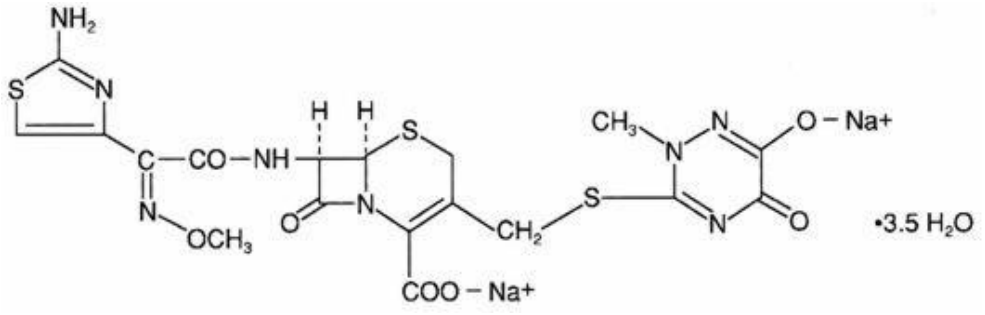
AUST R 164917 – CEFTRIAXONE VIATRIS ceftriaxone (as sodium) 2 g powder for injection vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name	disodium(*Z*)-(*6R, 7R*)-7-[2-(2-amino-1, 3-thiazol-4-yl)-2-(methoxyimino)acetamido]-8-oxo-3-[(2, 5-dihydro-2-methyl-6-oxido-5-oxo-1, 2, 4-triazin-3-yl)thiomethyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate hemiheptahydrate.
Molecular formula	$C_{18}H_{16}N_8Na_2O_7S_3, 3.5H_2O$
Molecular weight	661.59

CEFTRIAXONE VIATRIS contains ceftriaxone sodium, an almost white to yellowish crystalline powder which is freely soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 12% aqueous solution is approximately 6.0 to 8.0.

CAS Number

104376-79-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

20/01/2012

10 DATE OF REVISION

12/01/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial updates throughout
4.4	Neurotoxicity reports added
4.8	Nervous system disorders added

CEFTRIAXONE VIATRIS_pi\Jan24/00