CEFTRIAXONE 250MG POWDER FOR SOLUTION FOR INJECTION
PL 24780/0004

CEFTRIAXONE 500MG POWDER FOR SOLUTION FOR INJECTION
PL 24780/0005

CEFTRIAXONE 1G POWDER FOR SOLUTION FOR INJECTION
PL 24780/0006

CEFTRIAXONE 2G POWDER FOR SOLUTION FOR INJECTION OR INFUSION
PL 24780/0007

UKPAR

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LAY SUMMARY

The MHRA granted Villerton Invest SA Marketing Authorisations (licences) for the medicinal products Ceftriaxone 250mg, 500mg and 1g powder for solution for injection (PL 24780/0004, PL 24780/0005 and PL 24780/0006) and Ceftriaxone 2g powder for solution for injection or infusion (PL 24780/0007). These licenses were initially granted to ACS Dobfar Generics Italia Srl on 28 January 2008 and a Change of Ownership was approved on 29 January 2008. These are prescription only medicines (POM) for the treatment of infections of the chest, lungs, bones, joints and skin. The products may also be used to treat some sexually transmitted infections (gonorrhoea), meningitis and blood infections. They may also be given before operations to prevent infections.

Ceftriaxone 250mg, 500mg and 1g powder for solution for injection and Ceftriaxone 2g powder for solution for injection or infusion contain the active ingredient ceftriaxone, as ceftriaxone sodium, which is an antibiotic.

The products were considered to be equivalent to the original products Rocephin 250mg, 500mg, 1g and 2g vials (Roche Products Ltd) based on the data submitted.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Ceftriaxone 250mg, 500mg and 1g powder for solution for injection and Ceftriaxone 2g powder for solution for injection or infusion outweigh the risks, hence Marketing Authorisations have been granted.
CEFTRIAXONE 250MG POWDER FOR SOLUTION FOR INJECTION
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PL 24780/0007

SCIENTIFIC DISCUSSION

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Pharmaceutical assessment Page 5
Preclinical assessment Page 7
Clinical assessment (including statistical assessment) Page 8
Overall conclusion and risk benefit assessment Page 10
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Ceftriaxone 250mg, 500mg and 1g powder for solution for injection and Ceftriaxone 2g powder for solution for injection or infusion to Villerton Invest SA on 29 January 2008. These licenses were granted to ACS Dobfar Generics Italia Srl on 28 January 2008 prior to the Change of Ownership. The products are prescription only medicines.

Four strengths of ceftriaxone were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic products of Rocephin 250mg, 500mg, 1g and 2g vials (Roche Products Ltd). The reference products have been authorised in the UK since September 1988 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient ceftriaxone, as ceftriaxone sodium, and are indicated for the treatment of meningitis, infections in neutropenic patients, gonorrhoea, pneumonia, septicaemia, peri-operative prophylaxis of infections associated with surgery, bone, skin and soft tissue infections when known or likely to be due to one or more susceptible micro-organisms and when parenteral therapy is required. 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.

Ceftriaxone is a cephalosporin. The mechanism of the bacterial action is due to inhibition of bacterial cell wall synthesis which leads to cell death.

All applications were submitted at the same time and consequently, all sections of the Scientific Discussion refer to all applications.
UKPAR Ceftriaxone 250mg, 500mg & 1g powder for solution for injection and Ceftriaxone 2g powder for solution for injection or infusion

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The products are formulated as powders for solution for injection (or as a powder for solution for injection or infusion) containing 250mg, 500mg, 1g or 2g of the active pharmaceutical ingredient ceftriaxone, as ceftriaxone sodium. No excipients are present in the formulation.

Ceftriaxone 250mg, 500mg and 1g powder for solution for injection and Ceftriaxone 2g powder for solution for injection or infusion are presented in colorless Type III glass vials with bromobutyl rubber stoppers sealed with aluminium caps in packs of 1, 5, 10, 20, 50 or 100 vials.

DRUG SUBSTANCE

Ceftriaxone sodium
All aspects of the manufacture and control of ceftriaxone sodium are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of ceftriaxone sodium for inclusion in this medicinal product.

Stability data have been generated supporting a retest period of 2 years when stored in the proposed packaging.

DRUG PRODUCT

Manufacture
A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The proposed finished product specifications are acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification. Suitable reference standards were used.

Container Closure System
No compatibility issues were observed.

Stability
Finished product stability data support the proposed shelf-life of 36 months with storage conditions “Do not store above 25°C.” After reconstitution, it is recommended that the solution is used immediately but it may be used within 24 hours when stored at 2-8°C.
Bioequivalence/bioavailability
A bioequivalence study was not required for these applications.

SPC, PIL and Labels
The SPC and labels are pharmaceutically acceptable.

The marketing authorisation holder has provided a commitment to update the marketing authorisation with a patient information leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 01 July 2008.

CONCLUSION
It is recommended that Marketing Authorisations should be granted for these applications.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
INTRODUCTION AND BACKGROUND

These are generic abridged applications for powder for solution for injection containing 250mg, 500mg, 1g or 2g of ceftriaxone.

The applications are submitted under the provisions of Directive 2001/83/EC Article 10.1, claiming that Ceftriaxone 250mg, 500mg and 1g powder for solution for injection and Ceftriaxone 2g powder for solution for injection or infusion are generic products of Rocephin 250mg, 500mg, 1g and 2g vials (Roche Products Ltd) which were authorised in the UK in September 1988.

Ceftriaxone is a long half-life, once daily dosing cephalosporin.

INDICATIONS

The following indications have been approved:

Ceftriaxone is indicated for the following infections when known or likely to be due to one or more susceptible micro-organisms and when parenteral therapy is required:

- Meningitis
- Infections in neutropenic patients
- Gonorrhoea
- Pneumonia
- Septicaemia
- Peri-operative prophylaxis of infections associated with surgery.
- Bone, skin and soft tissue infections.

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.

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for these products to be used for the above indications are the same as those for the reference products.
CLINICAL PHARMACOLOGY

No studies or new data were presented in these applications and none are required.

CLINICAL EFFICACY

No new efficacy data were presented in these applications and none are required.

CLINICAL SAFETY

No formal safety data were presented in these applications and none are required.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified medical doctor. It is an adequate summary of the clinical data provided in the dossier.

SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSION

Marketing Authorisations should be granted for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Ceftriaxone 250mg, 500mg and 1g powder for solution for injection and Ceftriaxone 2g powder for solution for injection or infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
No new or unexpected safety concerns arose from these applications.

The SPC, PIL and labelling are satisfactory and are based on those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.
CEFTRIAXONE 250MG POWDER FOR SOLUTION FOR INJECTION
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CEFTRIAXONE 2G POWDER FOR SOLUTION FOR INJECTION OR INFUSION
PL 24780/0007

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 31 January 2002.

2 Following standard checks and communication with the applicant, the MHRA considered the applications valid on 25 February 2002.


5 The applications were determined on 28 January 2008.
CEFTRIAXONE 250MG POWDER FOR SOLUTION FOR INJECTION  
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CEFTRIAXONE 2G POWDER FOR SOLUTION FOR INJECTION OR INFUSION 
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STEPS TAKEN AFTER AUTHORISATION – SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 January 2008</td>
<td>Change of Ownership</td>
<td>To change the Marketing Authorisation Holder from ACS Dobfar Generics Italia Srl to Villerton Invest SA</td>
<td>Granted 29 January 2008</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 250mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 298.25mg Ceftriaxone sodium equivalent to 250mg Ceftriaxone

Also contains 0.9 mmol sodium.

3 PHARMACEUTICAL FORM
Powder for solution for injection

A white or almost white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ceftriaxone is indicated for the following infections when known or likely to be due to one or more susceptible micro-organisms (see section 5.1) and when parenteral therapy is required:

Meningitis
Infections in neutropenic patients
Gonorrhoea
Pneumonia
Septicaemia
Peri-operative prophylaxis of infections associated with surgery.
Bone, skin and soft tissue infections.

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.
4.2 Posology and method of administration

Ceftriaxone is for parenteral use only and may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution (see section 6.6). Following reconstitution, a colourless solution is produced.

Dosage and method of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Usually a once daily dose will give satisfactory therapeutic results. In some indications (see below), a single dose is sufficient.

Adults and children over 12 years of age

*Standard therapeutic dosage:* 1g once a day.

*Severe infections:* 2 - 4g daily, normally as a single dose every 24 hours.

The duration of therapy should be varied 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 as soon as there is evidence of bacterial eradication.

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

*Peri-operative prophylaxis:* Usually 1g as a single intramuscular or slow intravenous dose. In colorectal surgery, 2g should be given intramuscularly or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

**Elderly**

As for adult dose, subject to normal hepatic and renal function.

**Neonates, infants and children up to 12 years**

The following dosage schedules are recommended for once daily administration:

**Neonates**

A daily dose of 20 - 50mg/kg body weight, not to exceed 50mg/kg. 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 (see section 4.4).
Infants and children of up to 12 years

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

In severe infections up to 80mg/kg body weight daily may be given. For children with bodyweights of 50kg or more, the usual adult dosage should be given. 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 except in meningitis (see Special dosage recommendations).

**Special dosage recommendations:**

**Meningitis:**
Treatment is initiated with 100mg/kg bodyweight once daily – not exceeding 4g daily. After determining the sensitivity of the pathogen, the dose may be reduced accordingly. In new born infants 0-14 days of age the dose should not exceed 50mg/kg/24h

**Renal and hepatic impairment**

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is normal. 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 normal.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of ceftriaxone should be determined at regular intervals and dosage adjusted accordingly.

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

**4.3 Contraindications**

Known hypersensitivity to ceftriaxone or to any of the cephalosporins.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam.

In neonates with jaundice or those who are hypoalbuminaemic, acidotic or have other conditions, such as prematurity, in which bilirubin binding is likely to be impaired.

In neonates who need calcium treatment due to the risk of precipitation of ceftriaxone-calcium salt.
4.4 Special warnings and precautions for use

Before therapy with ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftriaxone, any other cephalosporin, or to any penicillin or other beta-lactam drug. 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.

Ceftriaxone should be given with caution to patients who have other allergic diatheses

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.

As with other cephalosporins, prolonged use of ceftriaxone may result in the overgrowth of non-susceptible organisms, such as enterococci and Candida spp.

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined under section 4.2.

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 jaundiced new-borns or in those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is likely to be impaired. Particular caution should be exercised in babies born prematurely.

Ceftriaxone may precipitate in the gallbladder and kidneys and then be detectable as shadows on ultrasound (see section 4.8). 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 in 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. As the condition appears to be transient and reversible upon discontinuation, therapeutic procedures are not normally indicated.

Cephalosporin antibiotics 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.

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been rarely reported in patients treated with ceftriaxone. Most of these 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.

4.5 Interaction with other medicinal products and other forms of interaction

No impairment of renal function has been observed in man after simultaneous administration of ceftriaxone with diuretics.

No interference with the action or increase in nephrotoxicity of aminoglycosides has been observed during simultaneous administration with ceftriaxone.

The ceftriaxone molecule does not contain the N-methylthio-tetrazole substituent which has been associated with a disulfiram-like effect when alcohol is taken during therapy with certain cephalosporins.

In vitro, chloramphenicol has been shown to be antagonistic with respect to ceftriaxone and other cephalosporins. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

In patients treated with ceftriaxone, the Coombs' test may rarely become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

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 Pregnancy and lactation

Safety in human pregnancy has not been established. Therefore ceftriaxone should not be used in pregnancy unless absolutely indicated. Only minimal amounts of ceftriaxone are excreted in breast milk. However, caution is advised in nursing mothers.

4.7 Effects on ability to drive and use machines

Not applicable.
4.8 Undesirable effects

Rarely, severe adverse reactions have been reported in preterm and full-term newborns. These reactions have caused death in some cases. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone-calcium salt have been observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation was due to the low blood volume of the newborns. Moreover the half life is longer than in adults.

The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts.

**Infections and infestations**

Rare (≥ 0.01% - < 0.1%): Mycosis of the genital tract.

Superinfections of various sites with yeasts, fungi or other resistant organisms are possible.

**Blood and lymphatic system disorders**

Rare (≥ 0.01% - < 0.1%): Neutropenia, leucopenia, eosinophilia, thrombocytopenia, anaemia (including haemolytic anaemia), slight prolongation of prothrombin time.

Very rare (< 0.01 %) including isolated reports: Positive Coombs' test, coagulation disorders, agranulocytosis (< 500/m3), mostly after 10 days of treatment and following total doses of 20g ceftriaxone and more.

**Immune system disorders**

Rare (≥ 0.01% - < 0.1%): Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions (see section 4.4)

**Nervous system disorders**

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

**Gastrointestinal disorders**

Common (≥ 1% - < 10%): Loose stools or diarrhoea, nausea, vomiting.

Rare (≥ 0.01% - < 0.1%): Stomatitis, glossitis. These side effects are usually mild and commonly disappear during treatment or after discontinuation of treatment.

Very rare (< 0.01%) including isolated reports: Pseudomembranous colitis (mostly caused by Clostridium difficile), pancreatitis (possibly caused by obstruction of bile ducts).

**Hepato-biliary disorders**
Rare (≥ 0.01% - < 0.1%): Increase in serum liver enzymes (AST, ALT, alkaline phosphatase).

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed (see section 4.4), 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.

**Skin and subcutaneous tissue disorders**

Uncommon (≥ 0.1% - < 1%): Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritis, oedema.

Very rare (< 0.01%) including isolated reports: Erythema multiforme, Stevens Johnson Syndrome, Lyell's Syndrome/toxic epidermal necrolysis.

**Renal and urinary disorders**

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

Very rare (< 0.01%) including isolated reports: Renal precipitation, mostly in children older than 3 years who have been treated with either high daily doses (80 mg/kg/day and more) or total doses exceeding 10g and with other risk factors such as dehydration or immobilisation. Renal precipitation is reversible upon discontinuation of ceftriaxone. Anuria and renal impairment have been reported in association.

**General disorders and administration site conditions**

Rare (≥ 0.01% - < 0.1%): Phlebitis and injection site pain following intravenous administration. This can be minimised by slow injection over at least 2-4 minutes. Rigors, pyrexia.

An intramuscular injection without lidocaine is painful.

### 4.9 Overdose

There is no specific antidote. Treatment should be symptomatic. Haemodialysis or peritoneal dialysis will not reduce drug levels.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cephalosporins and related substances
ATC code: J01D 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 \( \beta \)-lactamases and is active against a broad spectrum of bacterial pathogens including both Gram-positive and Gram-negative species.

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 \textit{S. aureus} and \textit{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. The use of NCCLS breakpoints predominate and are the breakpoints used in data presented in the Table. Values quoted comprise mg/L (MIC testing) or mm (disk diffusion testing) using a 30mg/L drug concentration.

<table>
<thead>
<tr>
<th>National Committee for Clinical Laboratory Standards (NCCLS) (M100-S12) – 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Susceptible</strong></td>
</tr>
<tr>
<td>\textit{Enterobacteriaceae, P. aeruginosa and other non-}</td>
</tr>
<tr>
<td>\textit{Haemophilus} spp.</td>
</tr>
<tr>
<td>Disk: &gt; 26</td>
</tr>
<tr>
<td>\textit{Neisseria} spp.</td>
</tr>
<tr>
<td>Disk: &gt; 35</td>
</tr>
</tbody>
</table>
### Ceftriaxone Susceptibility among Gram-positive and Gram-negative bacterial species in Europe from January 1999-December 2001:

<table>
<thead>
<tr>
<th><strong>Streptococcus pneumoniae</strong> *</th>
<th>≤ 0.5</th>
<th>1</th>
<th>≥ 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other</strong></td>
<td>Beta strep</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Streptococcus spp.</strong> **</td>
<td>≤ 0.5 Disk:</td>
<td>Viridans group:</td>
<td>Viridans group:</td>
</tr>
<tr>
<td></td>
<td>≥ 24</td>
<td>1 Disk: 25-26</td>
<td>≥ 2 Disk:</td>
</tr>
<tr>
<td></td>
<td>Viridans group:</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

* Recent 2002 *S. pneumoniae* breakpoints (NCCLS M100-S12) defined as ≤ 1 (Sensitive), 2 (Intermediate) and ≥ 4 (Resistant) for non-meningitis specimens and ≤ 0.5 (Sensitive), 1 (Intermediate), and > 2 (Resistant) for meningitis specimens.

** Recent 2002 *Streptococcus viridans* group breakpoints (NCCLS M100-S12) defined ≤ 1 (Sensitive), 2 (Intermediate), and ≥ 4 (Resistant)

### 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:

<table>
<thead>
<tr>
<th><strong>Commonly susceptible species (i.e. resistance &lt; 10% in all EU Member States)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive aerobes</strong> :</td>
</tr>
<tr>
<td>MS coagulase negative <em>Staphylococcus</em> spp. (including <em>S. epidermidis</em>) *</td>
</tr>
<tr>
<td>MSb <em>Staphylococcus aureus</em> *</td>
</tr>
<tr>
<td>Group B (<em>Streptococcus agalactiae</em>)</td>
</tr>
<tr>
<td><em>Streptococcus bovis</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> *</td>
</tr>
<tr>
<td>Group A <em>Streptococcus (Streptococcus pyogenes)</em></td>
</tr>
<tr>
<td><em>Streptococcus viridans</em> *</td>
</tr>
<tr>
<td><strong>Gram-Negative aerobes</strong> :</td>
</tr>
<tr>
<td><em>Citrobacter</em> spp. (including <em>C.freundii</em> )</td>
</tr>
<tr>
<td>Species for which acquired resistance may be a problem (i.e. resistance ≥10% in at least one EU Member State)</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong>*</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> (including beta-lactamase positive isolates)*</td>
</tr>
<tr>
<td><em>Haemophilus para-influenzae</em></td>
</tr>
<tr>
<td><em>Klebsiella</em> spp. (including <em>K. pneumoniae</em> and <em>K. oxytoxa</em>)*</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td><em>Neisseria gonorrhoea</em> (including penicillin-resistant isolates)*</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td><em>Proteus</em> spp. (including <em>P. mirabilis</em> and <em>P. vulgaris</em>)*</td>
</tr>
<tr>
<td><em>Salmonella</em> spp. (including <em>S. typhimurium</em>)</td>
</tr>
<tr>
<td><em>Serratia</em> spp. (including <em>Serratia marsescens</em>)*</td>
</tr>
<tr>
<td><em>Shigella</em> spp.</td>
</tr>
<tr>
<td><strong>Anaerobes:</strong></td>
</tr>
<tr>
<td><em>Clostridium</em> spp.*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inherently resistant organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive aerobes:</strong></td>
</tr>
<tr>
<td>MR&lt;sup&gt;d&lt;/sup&gt; coagulase negative <em>Staphylococcus</em> spp. (including <em>S. epidermidis</em>)</td>
</tr>
<tr>
<td>MR&lt;sup&gt;e&lt;/sup&gt;* <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td><strong>Gram-Negative aerobes:</strong></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td><em>Mycoplasma</em> spp.</td>
</tr>
</tbody>
</table>
Stenotrophomonas maltophilia
Ureaplasma urealyticum

Others:
Chlamydia spp.

* Methicillin-susceptible Coagulase-Negative Staphylococcus
* Methicillin-susceptible Staphylococcus aureus
* Non-susceptible range (no resistant breakpoints defined)
* Methicillin-resistant Coagulase-Negative Staphylococcus
* 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

The table above comprises current levels of susceptibility according to routinely produced susceptibility test results in France, Germany, Greece, Italy, the Netherlands, Spain, and the United Kingdom. All data is presented using contemporary NCCLS derived susceptibility breakpoints except France (CA-SFM). Data is derived from The Surveillance Network™ (TSN) Databases in each respective region. The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether microorganisms will be susceptible to ceftriaxone or not.

5.2 Pharmacokinetic properties

The pharmacokinetics of ceftriaxone are largely determined by its concentration-dependent binding to serum 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 concentration 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 1.06% Lidocaine produces mean peak plasma concentrations of 40-70mg/l within 1 hour. Bioavailability after intramuscular injection is 100%

**Excretion:** The drug is eliminated mainly as unchanged ceftriaxone, 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 - 22ml/min. The renal clearance is 5 - 12ml/min. The elimination half-
life in adults is about 8 hours. 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 elderly person aged over 75 years, the average elimination half-life is usually 2 to 3 times longer than 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 data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Solutions containing ceftriaxone should not be mixed with or added to solutions containing other agents. In particular, ceftriaxone is not compatible with calcium-containing solutions (e.g. Hartmann's solution and Ringer's solution) and must not be given simultaneously with calcium-containing solutions – even via different infusion lines.

Ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.
6.3 Shelf life

36 months unopened.

Reconstituted solutions: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours below 25°C. 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 not normally be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C

For shelf-life of reconstituted solutions, see section 6.3.

6.5 Nature and contents of container

Colourless Type III glass vial closed with a bromobutyl rubber stopper and sealed with an aluminium cap.

Packs of 1, 5, 10, 20, 50 or 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Ceftriaxone should not be mixed in the same syringe with any drug other than 1.06% Lidocaine Hydrochloride BP solution (for deep intramuscular injection only).

**Intramuscular injection:** 250mg or 500mg ceftriaxone should be dissolved in 2ml of 1.06% Lidocaine Hydrochloride BP solution, or 1g in 3.5ml of 1% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection. Dosages greater than 1g should be divided and injected at more than one site.

Solutions reconstituted with Lidocaine Hydrochloride BP solution should not be administered intravenously.

**Intravenous injection:** 250mg or 500mg ceftriaxone should be dissolved in 5ml of Water for Injections BP or 1g in 10ml of Water for Injections BP. The injection should be administered over at least 2 - 4 minutes, directly into the vein or via the tubing of an intravenous infusion.

**Intravenous infusion:** 2g of ceftriaxone should be dissolved in 40ml of one of the following calcium-free solutions: Dextrose Injection BP 5% or 10%, Sodium Chloride Injection BP, Sodium Chloride and Dextrose Injection BP (0.45% Sodium Chloride and 2.5% Dextrose), Dextran 6% in Dextrose Injection BP 5%. The infusion should be administered over at least 30 minutes.
The displacement value of 250mg of ceftriaxone is 0.194ml.

7 MARKETING AUTHORISATION HOLDER
Villerton Invest SA
1, Allée Scheffer
L-2520 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)
PL 24780/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/01/2008

10 DATE OF REVISION OF THE TEXT
28/01/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 500mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 596.5mg Ceftriaxone sodium equivalent to 500mg Ceftriaxone

Also contains 1.8 mmol sodium.

3 PHARMACEUTICAL FORM
Powder for solution for injection

A white or almost white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ceftriaxone is indicated for the following infections when known or thought likely to be due one or more susceptible micro-organisms (see section 5.1) and when parenteral therapy is required:

Meningitis
Infections in neutropenic patients
Gonorrhoea
Pneumonia
Septicaemia
Peri-operative prophylaxis of infections associated with surgery.
Bone, skin and soft tissue infections.

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.
4.2 **Posology and method of administration**

Ceftriaxone is for parenteral use only and may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution (see section 6.6). Following reconstitution, a colourless solution is produced.

Dosage and method of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Usually a once daily dose will give satisfactory therapeutic results. In some indications (see below), a single dose is sufficient.

**Adults and children over 12 years of age**

*Standard therapeutic dosage:* 1g once a day.

*Severe infections:* 2 - 4g daily, normally as a single dose every 24 hours.

The duration of therapy should be varied 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 as soon as there is evidence of bacterial eradication.

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

*Peri-operative prophylaxis:* Usually 1g as a single intramuscular or slow intravenous dose. In colorectal surgery, 2g should be given intramuscularly or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

**Elderly**

As for adult dose, subject to normal hepatic and renal function.

**Neonates, infants and children up to 12 years**

The following dosage schedules are recommended for once daily administration:

**Neonates**

A daily dose of 20 - 50mg/kg body weight, not to exceed 50mg/kg. 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 (see section 4.4).
Infants and children of up to 12 years

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

In severe infections up to 80mg/kg body weight daily may be given. For children with bodyweights of 50kg or more, the usual adult dosage should be given. 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 except in meningitis (see Special dosage recommendations).

Special dosage recommendations:

Meningitis:
Treatment is initiated with 100mg/kg bodyweight once daily – not exceeding 4g daily. After determining the sensitivity of the pathogen, the dose may be reduced accordingly. In new born infants 0-14 days of age the dose should not exceed 50mg/kg/24h.

Renal and hepatic impairment

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is normal. 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 normal.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of ceftriaxone should be determined at regular intervals and dosage adjusted accordingly.

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

4.3 Contraindications

Known hypersensitivity to ceftriaxone or to any of the cephalosporins.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam

In neonates with jaundice or those who are hypoalbuminaemic, acidotic or have other conditions, such as prematurity, in which bilirubin binding is likely to be impaired.

In neonates who need calcium treatment due to the risk of precipitation of ceftriaxone-calcium salt.
4.4 Special warnings and precautions for use

Before therapy with ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftriaxone, any other cephalosporin, or to any penicillin or other beta-lactam drug. 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.

Ceftriaxone should be given with caution to patients who have other allergic diatheses

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.

As with other cephalosporins, prolonged use of ceftriaxone may result in the overgrowth of non-susceptible organisms, such as enterococci and Candida spp.

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined under section 4.2.

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 jaundiced new-borns or in those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is likely to be impaired. Particular caution should be exercised in babies born prematurely.

Ceftriaxone may precipitate in the gallbladder and kidneys and then be detectable as shadows on ultrasound (see section 4.8). 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 in 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. As the condition appears to be transient and reversible upon discontinuation, therapeutic procedures are not normally indicated.

Cephalosporin antibiotics 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.

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been rarely reported in patients treated with ceftriaxone. Most of these 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.

4.5 Interaction with other medicinal products and other forms of interaction

No impairment of renal function has been observed in man after simultaneous administration of ceftriaxone with diuretics.

No interference with the action or increase in nephrotoxicity of aminoglycosides has been observed during simultaneous administration with ceftriaxone.

The ceftriaxone molecule does not contain the N-methylthio-tetrazole substituent which has been associated with a disulfiram-like effect when alcohol is taken during therapy with certain cephalosporins.

*In vitro*, chloramphenicol has been shown to be antagonistic with respect to ceftriaxone and other cephalosporins. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

In patients treated with ceftriaxone, the Coombs' test may rarely become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

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 Pregnancy and lactation

Safety in human pregnancy has not been established. Therefore ceftriaxone should not be used in pregnancy unless absolutely indicated. Only minimal amounts of ceftriaxone are excreted in breast milk. However, caution is advised in nursing mothers.

4.7 Effects on ability to drive and use machines

Not applicable.
4.8 Undesirable effects

Rarely, severe adverse reactions have been reported in preterm and full-term newborns. These reactions have caused death in some cases. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone-calcium salt have been observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation was due to the low blood volume of the newborns. Moreover the half life is longer than in adults.

The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or other resistant organisms as well as changes in blood cell counts.

Infections and infestations

Rare (0.01% - < 0.1%): Mycosis of the genital tract. Superinfections of various sites with yeasts, fungi or other resistant organisms are possible.

Blood and lymphatic system disorders

Rare (0.01% - < 0.1%): Neutropenia, leucopenia, eosinophilia, thrombocytopenia, anaemia (including haemolytic anaemia), slight prolongation of prothrombin time. Very rare (< 0.01 %) including isolated reports: Positive Coombs' test, coagulation disorders, agranulocytosis (< 500/m3), mostly after 10 days of treatment and following total doses of 20g ceftriaxone and more.

Immune system disorders

Rare (0.01% - < 0.1%): Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions (see section 4.4)

Nervous system disorders

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

Gastrointestinal disorders

Common (1% - < 10%): Loose stools or diarrhoea, nausea, vomiting. Rare (0.01% - < 0.1%): Stomatitis, glossitis. These side effects are usually mild and commonly disappear during treatment or after discontinuation of treatment. Very rare (< 0.01%) including isolated reports: Pseudomembranous colitis (mostly caused by Clostridium difficile), pancreatitis (possibly caused by obstruction of bile ducts).

Hepato-biliary disorders
Rare (≥ 0.01% - < 0.1%): Increase in serum liver enzymes (AST, ALT, alkaline phosphatase).

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed (see section 4.4), 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.

Skin and subcutaneous tissue disorders

Uncommon (≥ 0.1% - < 1%): Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritis, oedema.

Very rare (< 0.01%) including isolated reports: Erythema multiforme, Stevens Johnson Syndrome, Lyell's Syndrome/toxic epidermal necrolysis.

Renal and urinary disorders

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

Very rare (< 0.01%) including isolated reports: Renal precipitation, mostly in children older than 3 years who have been treated with either high daily doses (80 mg/kg/day and more) or total doses exceeding 10g and with other risk factors such as dehydration or immobilisation. Renal precipitation is reversible upon discontinuation of ceftriaxone. Anuria and renal impairment have been reported in association.

General disorders and administration site conditions

Rare (≥ 0.01% - < 0.1%): Phlebitis and injection site pain following intravenous administration. This can be minimised by slow injection over at least 2-4 minutes. Rigors, pyrexia.

An intramuscular injection without lidocaine is painful.

4.9 Overdose

There is no specific antidote. Treatment should be symptomatic. Haemodialysis or peritoneal dialysis will not reduce drug levels.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmatherapeutic group: Cephalosporins and related substances
ATC code: J01DA13

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 \( \beta \)-lactamases and is active against a broad spectrum of bacterial pathogens including both Gram-positive and Gram-negative species.

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. The use of NCCLS breakpoints predominate and are the breakpoints used in data presented in the Table. Values quoted comprise mg/L (MIC testing) or mm (disk diffusion testing) using a 30mg/L drug concentration.

National Committee for Clinical Laboratory Standards (NCCLS) (M100-S12) – 2002

<table>
<thead>
<tr>
<th></th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Enterobacteriaceae) , ( P. ) aeruginosa and other non- ( Enterobacteriaceae) , ( Staphylococcus) spp.</td>
<td>( \leq 8 )</td>
<td>16-32</td>
<td>( &gt;64 )</td>
</tr>
<tr>
<td>Disk: ( \leq 13 )</td>
<td>Disk: 14 – 20</td>
<td>Disk: ( \geq 21 )</td>
<td></td>
</tr>
<tr>
<td>( Haemophilus) spp.</td>
<td>( \leq 2 )</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disk: ( \geq 26 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( Neisseria) spp.</td>
<td>( \leq 0.25 )</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disk: ( \geq 35 )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ceftriaxone susceptibility among Gram-positive and Gram-negative bacterial species in Europe from January 1999-December 2001:

**Streptococcus pneumoniae** *
- Beta strep
  - 0.5 Disk: ²<sub>24</sub>
  - Viridans group:
    - 1 Disk: 25-26

Other *Streptococcus* spp.**
- Viridans group:
  - 0.5 Disk: ²²<sub>27</sub>

---

* Recent 2002 *S. pneumoniae* breakpoints (NCCLS M100-S12) defined as ≤ 1 (Sensitive), 2 (Intermediate) and ≥ 4 (Resistant) for non-meningitis specimens and ≤ 0.5 (Sensitive), 1 (Intermediate), and > 2 (Resistant) for meningitis specimens.

** Recent 2002 *Streptococcus viridans* group breakpoints (NCCLS M100-S12) defined ≤ 1 (Sensitive), 2 (Intermediate), and ≥ 4 (Resistant)

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<sup>a</sup> coagulase negative *Staphylococcus* spp. (including *S. epidermis*)*
- MS<sup>b</sup> *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)*

*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<sup>+</sup> coagulase negative *Staphylococcus* spp. (including *S. epidermidis*)

MR<sup>+</sup>*Staphylococcus aureus*

*Enterococcus* spp.

**Gram-Negative aerobes:**

*Listeria monocytogenes*

*Mycoplasma* spp.
Stenotrophomonas maltophilia
Ureaplasma urealyticum

Others:
Chlamydia spp.

* Methicillin-susceptible Coagulase-Negative Staphylococcus
+ Methicillin-susceptible Staphylococcus aureus

- Non-susceptible range (no resistant breakpoints defined)
- Methicillin-resistant Coagulase-Negative Staphylococcus
- 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

The table above comprises current levels of susceptibility according to routinely produced susceptibility test results in France, Germany, Greece, Italy, the Netherlands, Spain, and the United Kingdom. All data is presented using contemporary NCCLS derived susceptibility breakpoints except France (CA-SFM). Data is derived from The Surveillance Network™ (TSN) Databases in each respective region. The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether microorganisms will be susceptible to ceftriaxone or not.

5.2 Pharmacokinetic properties

The pharmacokinetics of ceftriaxone are largely determined by its concentration-dependent binding to serum 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 concentration 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 1.06% Lidocaine produces mean peak plasma concentrations of 40-70mg/l within 1 hour. Bioavailability after intramuscular injection is 100%

**Excretion:** The drug is eliminated mainly as unchanged ceftriaxone, 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 - 22ml/min. The renal clearance is 5 - 12ml/min. The elimination half-life in adults is about 8 hours. 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 elderly person aged over 75 years, the average elimination half-life is usually 2 to 3 times longer than 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 data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None

6.2 Incompatibilities
Solutions containing ceftriaxone should not be mixed with or added to solutions containing other agents. In particular, ceftriaxone is not compatible with calcium-containing solutions (e.g. Hartmann's solution and Ringer's solution) and must not be given simultaneously with calcium-containing solutions – even via different infusion lines.

Ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.
6.3 Shelf life
36 months unopened.

Reconstituted solutions: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours below 25°C. 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 not normally be longer than 24 hours at 2-8°C, unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Do not store above 25°C

For shelf-life of reconstituted solutions, see section 6.3.

6.5 Nature and contents of container
Colourless Type III glass vial closed with a bromobutyl rubber stopper and sealed with an aluminium cap.

Packs of 1, 5, 10, 20, 50 or 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Ceftriaxone should not be mixed in the same syringe with any drug other than 1.06% Lidocaine Hydrochloride BP solution (for deep intramuscular injection only).

Intramuscular injection: 250mg or 500mg ceftriaxone should be dissolved in 2ml of 1.06% Lidocaine Hydrochloride BP solution, or 1g in 3.5ml of 1% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection. Dosages greater than 1g should be divided and injected at more than one site. Solutions reconstituted with Lidocaine Hydrochloride BP solution should not be administered intravenously.

Intravenous injection: 250mg or 500mg ceftriaxone should be dissolved in 5ml of Water for Injections BP or 1g in 10ml of Water for Injections BP. The injection should be administered over at least 2 - 4 minutes, directly into the vein or via the tubing of an intravenous infusion.

Intravenous infusion: 2g of ceftriaxone should be dissolved in 40ml of one of the following calcium-free solutions: Dextrose Injection BP 5% or 10%, Sodium Chloride
UKPAR Ceftriaxone 250mg, 500mg & 1g powder for solution for injection and  Ceftriaxone 2g powder for solution for injection or infusion

Injection BP, Sodium Chloride and Dextrose Injection BP (0.45% Sodium Chloride and 2.5% Dextrose), Dextran 6% in Dextrose Injection BP 5%. The infusion should be administered over at least 30 minutes.

The displacement value of 250mg of ceftriaxone is 0.194ml.

7 MARKETING AUTHORISATION HOLDER
Villerton Invest SA
1, Allée Scheffer
L-2520 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)
PL 24780/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/01/2008

10 DATE OF REVISION OF THE TEXT
28/01/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 1g powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1.19g Ceftriaxone sodium equivalent to 1g Ceftriaxone

Also contains 3.6mmol sodium.

3 PHARMACEUTICAL FORM
Powder for solution for injection

A white or almost white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ceftriaxone is indicated for the following infections when known or likely to be due to one or more susceptible micro-organisms (see section 5.1) and when parenteral therapy is required:

Meningitis
Infections in neutropenic patients
Gonorrhoea
Pneumonia.
Septicaemia
Peri-operative prophylaxis of infections associated with surgery.
Bone, skin and soft tissue infections.

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.

4.2 Posology and method of administration

Ceftriaxone is for parenteral use only and may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution (see section 6.6). Following reconstitution, a colourless solution is produced.

Dosage and method of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Usually a once daily dose will give satisfactory therapeutic results. In some indications (see below), a single dose is sufficient.

Adults and children over 12 years of age

*Standard therapeutic dosage:* 1g once a day.

*Severe infections:* 2 - 4g daily, normally as a single dose every 24 hours.

The duration of therapy should be varied 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 as soon as there is evidence of bacterial eradication.

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

*Peri-operative prophylaxis:* Usually 1g as a single intramuscular or slow intravenous dose. In colorectal surgery, 2g should be given intramuscularly or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

**Elderly**

As for adult dose, subject to normal hepatic and renal function.

**Neonates, infants and children up to 12 years**

The following dosage schedules are recommended for once daily administration:

**Neonates**

A daily dose of 20 - 50mg/kg body weight, not to exceed 50mg/kg. 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 (see section 4.4).

**Infants and children of up to 12 years**

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

In severe infections up to 80mg/kg body weight daily may be given. For children with bodyweights of 50kg or more, the usual adult dosage should be given. 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 except in meningitis (see Special dosage recommendations).

**Special dosage recommendations:**

**Meningitis:**
Treatment is initiated with 100mg/kg bodyweight once daily – not exceeding 4g daily. After determining the sensitivity of the pathogen, the dose may be reduced accordingly. In new born infants 0-14 days of age the dose should not exceed 50mg/kg/24h

**Renal and hepatic impairment**

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is normal. 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 normal.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of ceftriaxone should be determined at regular intervals and dosage adjusted accordingly.

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

**4.3 Contraindications**

Known hypersensitivity to ceftriaxone or to any of the cephalosporins.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam

In neonates with jaundice or those who are hypoalbuminaemic, acidotic or have other conditions, such as prematurity, in which bilirubin binding is likely to be impaired.
Calcium treatment because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

4.4 Special warnings and precautions for use

Before therapy with ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftriaxone, any other cephalosporin, or to any penicillin or other beta-lactam drug. 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.

Ceftriaxone should be given with caution to patients who have other allergic diatheses

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.

As with other cephalosporins, prolonged use of ceftriaxone may result in the overgrowth of non-susceptible organisms, such as enterococci and Candida spp.

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined under section 4.2.

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 jaundiced new-borns or in those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is likely to be impaired. Particular caution should be exercised in babies born prematurely

Ceftriaxone may precipitate in the gallbladder and kidneys and then be detectable as shadows on ultrasound (see section 4.8). 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 in 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. As the condition appears to
be transient and reversible upon discontinuation, therapeutic procedures are not normally indicated.

Cephalosporin antibiotics 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.

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been rarely reported in patients treated with ceftriaxone. Most of these 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.

4.5 Interaction with other medicinal products and other forms of interaction

No impairment of renal function has been observed in man after simultaneous administration of ceftriaxone with diuretics.

No interference with the action or increase in nephrotoxicity of aminoglycosides has been observed during simultaneous administration with ceftriaxone.

The ceftriaxone molecule does not contain the N-methylthio-tetrazole substituent which has been associated with a disulfiram-like effect when alcohol is taken during therapy with certain cephalosporins.

In vitro, chloramphenicol has been shown to be antagonistic with respect to ceftriaxone and other cephalosporins. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

In patients treated with ceftriaxone, the Coombs' test may rarely become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

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 Pregnancy and lactation
Safety in human pregnancy has not been established. Therefore ceftriaxone should not be used in pregnancy unless absolutely indicated. Only minimal amounts of ceftriaxone are excreted in breast milk. However, caution is advised in nursing mothers.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
Rarely, severe adverse reactions have been reported in preterm and full-term newborns. These reactions have caused death in some cases. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone-calcium salt have been observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation was due to the low blood volume of the newborns. Moreover the half life is longer than in adults.

The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts.

Infections and infestations
Rare (≥ 0.01% - < 0.1%): Mycosis of the genital tract.
Superinfections of various sites with yeasts, fungi or other resistant organisms are possible.

Blood and lymphatic system disorders
Rare (≥ 0.01% - < 0.1%): Neutropenia, leucopenia, eosinophilia, thrombocytopenia, anaemia (including haemolytic anaemia), slight prolongation of prothrombin time.
Very rare (< 0.01 %) including isolated reports: Positive Coombs' test, coagulation disorders, agranulocytosis (< 500/m3), mostly after 10 days of treatment and following total doses of 20g ceftriaxone and more.

Immune system disorders
Rare (≥ 0.01% - < 0.1%): Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions (see section 4.4)

Nervous system disorders
Rare (≥ 0.01% - < 0.1%): Headache, dizziness.

Gastrointestinal disorders
Common (⩾ 1% - < 10%): Loose stools or diarrhoea, nausea, vomiting.
Rare (⩾ 0.01% - < 0.1%): Stomatitis, glossitis. These side effects are usually mild and commonly disappear during treatment or after discontinuation of treatment.
Very rare (< 0.01%) including isolated reports: Pseudomembranous colitis (mostly caused by Clostridium difficile), pancreatitis (possibly caused by obstruction of bile ducts).

Hepato-biliary disorders
Rare (⩾ 0.01% - < 0.1%): Increase in serum liver enzymes (AST, ALT, alkaline phosphatase).
Precipitation of ceftriaxone calcium salt in the gallbladder has been observed (see section 4.4), 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.

Skin and subcutaneous tissue disorders
Uncommon (⩾ 0.1% - < 1%): Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritis, oedema.
Very rare (< 0.01%) including isolated reports: Erythema multiforme, Stevens Johnson Syndrome, Lyell's Syndrome/toxic epidermal necrolysis.

Renal and urinary disorders
Rare (⩾ 0.01% - < 0.1%): Increase in serum creatinine, oliguria, glycosuria, haematuria.
Very rare (< 0.01%) including isolated reports: Renal precipitation, mostly in children older than 3 years who have been treated with either high daily doses (80 mg/kg/day and more) or total doses exceeding 10g and with other risk factors such as dehydration or immobilisation. Renal precipitation is reversible upon discontinuation of ceftriaxone. Anuria and renal impairment have been reported in association.

General disorders and administration site conditions
Rare (⩾ 0.01% - < 0.1%): Phlebitis and injection site pain following intravenous administration. This can be minimised by slow injection over at least 2-4 minutes. Rigors, pyrexia.

An intramuscular injection without lidocaine is painful.
4.9 Overdose
There is no specific antidote. Treatment should be symptomatic. Haemodialysis or peritoneal dialysis will not reduce drug levels.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cephalosporins and related substances
ATC code: J01D 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 and is active against a broad spectrum of bacterial pathogens including both Gram-positive and Gram-negative species.

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. The use of NCCLS breakpoints predominate and are the breakpoints used in data presented in the Table. Values quoted comprise mg/L (MIC testing) or mm (disk diffusion testing) using a 30mg/L drug concentration.

| National Committee for Clinical Laboratory Standards (NCCLS) (M100-S12) – 2002 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| **Enterobacteriaceae, P. aeruginosa and other non-Enterobacteriaceae, Staphylococcus spp.** | **Susceptible** | **Intermediate** | **Resistant** |
| Disk: ≤ 13 | 8 | 16-32 | ≥ 64 |
| Disk: 14 – 20 | | | Disk: ≥ 21 |
| Disk: | | | |

| **Haemophilus spp.** | **Susceptible** | - | - |
UKPAR Ceftriaxone 250mg, 500mg & 1g powder for solution for injection and Ceftriaxone 2g powder for solution for injection or infusion

**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:

<table>
<thead>
<tr>
<th><strong>Commonly susceptible species (i.e. resistance &lt; 10% in all EU Member States)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive aerobes:</strong></td>
</tr>
<tr>
<td>MS&lt;sup&gt;a&lt;/sup&gt; coagulase negative <em>Staphylococcus</em> spp. (including <em>S. epidermis</em>)*</td>
</tr>
<tr>
<td>MS&lt;sup&gt;b&lt;/sup&gt;<em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Group B (<em>Streptococcus agalactiae</em>)</td>
</tr>
<tr>
<td><em>Streptococcus bovis</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>Group A <em>Streptococcus (Streptococcus pyogenes)</em></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th><strong>Disk:</strong> ≥26</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neisseria spp.</strong></td>
<td>Disk: ≥35</td>
</tr>
<tr>
<td>≥ 0.25</td>
<td>-</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>≤ 0.5</td>
<td>≥2</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th><strong>Other Streptococcus spp.</strong>&lt;sup&gt;**&lt;/sup&gt;</th>
<th>Beta strep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disk: ≥24</td>
<td>Viridans group:</td>
</tr>
<tr>
<td>≤ 0.5 Disk: ≥27</td>
<td>1 Disk: 25-26</td>
</tr>
<tr>
<td>≥ 2 Disk: ≥24</td>
<td>Viridans group:</td>
</tr>
</tbody>
</table>

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* Recent 2002 *S. pneumoniae* breakpoints (NCCLS M100-S12) defined as ≤1 (Sensitive), 2 (Intermediate) and ≥4 (Resistant) for non-meningitis specimens and ≤0.5 (Sensitive), 1 (Intermediate), and ≥2 (Resistant) for meningitis specimens.

** Recent 2002 *Streptococcus viridans* group breakpoints (NCCLS M100-S12) defined ≤1 (Sensitive), 2 (Intermediate), and ≥4 (Resistant)
**Streptococcus viridans**

### Gram-Negative aerobes:
- *Citrobacter* spp. (including *C. freundii*)
- *Escherichia coli* *
- *Haemophilus influenzae* (including beta-lactamase positive isolates) *
- *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* coagulate negative *Staphylococcus* spp. (including *S. epidermidis*)
- MR* *Staphylococcus aureus*
- *Enterococcus* spp.
UKPAR Ceftriaxone 250mg, 500mg & 1g powder for solution for injection and Ceftriaxone 2g powder for solution for injection or infusion

<table>
<thead>
<tr>
<th>Gram-Negative aerobes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Mycoplasma spp.</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
</tr>
<tr>
<td>Ureaplasma urealyticum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia spp.</td>
</tr>
</tbody>
</table>

*Methicillin-susceptible Coagulase-Negative Staphylococcus

*Methicillin-susceptible Staphylococcus aureus

*Non-susceptible range (no resistant breakpoints defined)

*Methicillin-resistant Coagulase-Negative Staphylococcus

*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

The table above comprises current levels of susceptibility according to routinely produced susceptibility test results in France, Germany, Greece, Italy, the Netherlands, Spain, and the United Kingdom. All data is presented using contemporary NCCLS derived susceptibility breakpoints except France (CA-SFM). Data is derived from The Surveillance Network™ (TSN) Databases in each respective region. The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether microorganisms will be susceptible to ceftriaxone or not.

5.2 Pharmacokinetic properties

The pharmacokinetics of ceftriaxone are largely determined by its concentration-dependent binding to serum 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 concentration 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 1.06% Lidocaine produces mean peak plasma concentrations of 40 - 70mg/l within 1 hour. Bioavailability after intramuscular injection is 100%
**Excretion:** The drug is eliminated mainly as unchanged ceftriaxone, 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 - 22ml/min. The renal clearance is 5 - 12ml/min. The elimination half-life in adults is about 8 hours. 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 elderly person aged over 75 years, the average elimination half-life is usually 2 to 3 times longer than 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 data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

None

#### 6.2 Incompatibilities

Solutions containing ceftriaxone should not be mixed with or added to solutions containing other agents. In particular, ceftriaxone is not compatible with calcium-containing solutions (e.g. Hartmann's solution and Ringer's solution) and must not be given simultaneously with calcium-containing solutions – even via different infusion lines.
Ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

6.3 Shelf life
36 months unopened.

Reconstituted solutions: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours below 25°C. 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 not normally be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Do not store above 25°C.

For shelf-life of reconstituted solutions, see section 6.3.

6.5 Nature and contents of container
Colourless Type III glass vial closed with a bromobutyl rubber stopper and sealed with an aluminium cap.

Packs of 1, 5, 10, 20, 50 or 100 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Ceftriaxone should not be mixed in the same syringe with any drug other than 1.06% Lidocaine Hydrochloride BP solution (for deep intramuscular injection only).

Intramuscular injection: 250mg or 500mg ceftriaxone should be dissolved in 2ml of 1.06% Lidocaine Hydrochloride BP solution, or 1g in 3.5ml of 1.06% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection. Dosages greater than 1g should be divided and injected at more than one site.

Solutions reconstituted with Lidocaine Hydrochloride BP solution should not be administered intravenously.

Intravenous injection: 250mg or 500mg ceftriaxone should be dissolved in 5ml of Water for Injections BP or 1g in 10ml of Water for Injections BP. The injection should be administered over at least 2 - 4 minutes, directly into the vein or via the tubing of an intravenous infusion.
**Intravenous infusion:** 2g of ceftriaxone should be dissolved in 40ml of one of the following calcium-free solutions: Dextrose Injection BP 5% or 10%, Sodium Chloride Injection BP, Sodium Chloride and Dextrose Injection BP (0.45% Sodium Chloride and 2.5% Dextrose), Dextran 6% in Dextrose Injection BP 5%. The infusion should be administered over at least 30 minutes.

The displacement value of 250mg of ceftriaxone is 0.194ml.

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Ceftriaxone 2g powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 2.39g Ceftriaxone sodium equivalent to 2g Ceftriaxone

Also contains 7.2 mmol sodium

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion.

A white or almost white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ceftriaxone is indicated for the following infections when known or likely to be due to one or more susceptible micro-organisms (see section 5.1) and when parenteral therapy is required:

Meningitis
Infections in neutropenic patients
Gonorrhoea
Pneumonia
Septicaemia
Peri-operative prophylaxis of infections associated with surgery.
Bone, skin and soft tissue infections.

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.
4.2 Posology and method of administration

Ceftriaxone is for parenteral use only and may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution (see section 6.6). Following reconstitution, a colourless solution is produced.

Dosage and method of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Usually a once daily dose will give satisfactory therapeutic results. In some indications (see below), a single dose is sufficient.

Adults and children over 12 years of age

*Standard therapeutic dosage:* 1g once a day.

*Severe infections:* 2 - 4g daily, normally as a single dose every 24 hours.

The duration of therapy should be varied 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 as soon as there is evidence of bacterial eradication.

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

*Peri-operative prophylaxis:* Usually 1g as a single intramuscular or slow intravenous dose. In colorectal surgery, 2g should be given intramuscularly or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

Elderly

As for adult dose, subject to normal hepatic and renal function.

Neonates, infants and children up to 12 years

The following dosage schedules are recommended for once daily administration:

**Neonates**

A daily dose of 20 - 50mg/kg body weight, not to exceed 50mg/kg. 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 (see section 4.4).
Infants and children of up to 12 years

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

In severe infections up to 80mg/kg body weight daily may be given. For children with bodyweights of 50kg or more, the usual adult dosage should be given. 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 except in meningitis (see Special dosage recommendations).

**Special dosage recommendations:**

Meningitis:
Treatment is initiated with 100mg/kg bodyweight once daily – not exceeding 4g daily. After determining the sensitivity of the pathogen, the dose may be reduced accordingly. In new born infants 0-14 days of age the dose should not exceed 50mg/kg/24h

Renal and hepatic impairment

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is normal. 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 normal.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of ceftriaxone should be determined at regular intervals and dosage adjusted accordingly.

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

4.3 **Contraindications**

Known hypersensitivity to ceftriaxone or to any of the cephalosporins.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam

In neonates with jaundice or those who are hypoalbuminaemic, acidotic or have other conditions, such as prematurity, in which bilirubin binding is likely to be impaired.

In neonates who need calcium treatment due to the risk of precipitation of ceftriaxone-calcium salt.
4.4 Special warnings and precautions for use

Before therapy with ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftriaxone, any other cephalosporin, or to any penicillin or other beta-lactam drug. 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.

Ceftriaxone should be given with caution to patients who have other allergic diatheses

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.

As with other cephalosporins, prolonged use of ceftriaxone may result in the overgrowth of non-susceptible organisms, such as enterococci and Candida spp.

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined under section 4.2.

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 jaundiced new-borns or in those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is likely to be impaired. Particular caution should be exercised in babies born prematurely.

Ceftriaxone may precipitate in the gallbladder and kidneys and then be detectable as shadows on ultrasound (see section 4.8). 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 in 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. As the condition appears to be transient and reversible upon discontinuation, therapeutic procedures are not normally indicated.

Cephalosporin antibiotics 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.

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been rarely reported in patients treated with ceftriaxone. Most of these 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.

4.5 Interaction with other medicinal products and other forms of interaction

No impairment of renal function has been observed in man after simultaneous administration of ceftriaxone with diuretics.

No interference with the action or increase in nephrotoxicity of aminoglycosides has been observed during simultaneous administration with ceftriaxone.

The ceftriaxone molecule does not contain the N-methylthio-tetrazole substituent which has been associated with a disulfiram-like effect when alcohol is taken during therapy with certain cephalosporins.

In vitro, chloramphenicol has been shown to be antagonistic with respect to ceftriaxone and other cephalosporins. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

In patients treated with ceftriaxone, the Coombs' test may rarely become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

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 Pregnancy and lactation

Safety in human pregnancy has not been established. Therefore ceftriaxone should not be used in pregnancy unless absolutely indicated. Only minimal amounts of ceftriaxone are excreted in breast milk. However, caution is advised in nursing mothers.
4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
Rarely, severe adverse reactions have been reported in preterm and full-term newborns. These reactions have caused death in some cases. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone-calcium salt have been observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation was due to the low blood volume of the newborns. Moreover the half life is longer than in adults.

The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts.

Infections and infestations
Rare (≥ 0.01% - < 0.1%): Mycosis of the genital tract.
Superinfections of various sites with yeasts, fungi or other resistant organisms are possible.

Blood and lymphatic system disorders
Rare (≥ 0.01% - < 0.1%): Neutropenia, leucopenia, eosinophilia, thrombocytopenia, anaemia (including haemolytic anaemia), slight prolongation of prothrombin time.
Very rare (< 0.01 %) including isolated reports: Positive Coombs' test, coagulation disorders, agranulocytosis (< 500/m3), mostly after 10 days of treatment and following total doses of 20g ceftriaxone and more.

Immune system disorders
Rare (≥ 0.01% - < 0.1%): Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions (see section 4.4)

Nervous system disorders
Rare (≥ 0.01% - < 0.1%): Headache, dizziness.

Gastrointestinal disorders
Common (≥ 1% - < 10%): Loose stools or diarrhoea, nausea, vomiting.
Rare (≥ 0.01% - < 0.1%): Stomatitis, glossitis. These side effects are usually mild and commonly disappear during treatment or after discontinuation of treatment.
Very rare (< 0.01%) including isolated reports: Pseudomembranous colitis (mostly caused by Clostridium difficile), pancreatitis (possibly caused by obstruction of bile ducts).
**Hepato-biliary disorders**

Rare (≥ 0.01% - < 0.1%): Increase in serum liver enzymes (AST, ALT, alkaline phosphatase).

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed (see section 4.4), 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.

**Skin and subcutaneous tissue disorders**

Uncommon (≥ 0.1% - < 1%): Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritis, oedema.

Very rare (< 0.01%) including isolated reports: Erythema multiforme, Stevens Johnson Syndrome, Lyell's Syndrome/toxic epidermal necrolysis.

**Renal and urinary disorders**

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

Very rare (< 0.01%) including isolated reports: Renal precipitation, mostly in children older than 3 years who have been treated with either high daily doses (80 mg/kg/day and more) or total doses exceeding 10g and with other risk factors such as dehydration or immobilisation. Renal precipitation is reversible upon discontinuation of ceftriaxone. Anuria and renal impairment have been reported in association.

**General disorders and administration site conditions**

Rare (≥ 0.01% - < 0.1%): Phlebitis and injection site pain following intravenous administration. This can be minimised by slow injection over at least 2-4 minutes. Rigors, pyrexia.

An intramuscular injection without lidocaine is painful.

### 4.9 Overdose

There is no specific antidote. Treatment should be symptomatic. Haemodialysis or peritoneal dialysis will not reduce drug levels.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cephalosporins and related substances
ATC code: J01DA13

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 and is active against a broad spectrum of bacterial pathogens including both Gram-positive and Gram-negative species.

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. The use of NCCLS breakpoints predominate and are the breakpoints used in data presented in the Table. Values quoted comprise mg/L (MIC testing) or mm (disk diffusion testing) using a 30mg/L drug concentration.

<table>
<thead>
<tr>
<th></th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em>, <em>P. aeruginosa</em> and other non- <em>Enterobacteriaceae</em>, <em>Staphylococcus</em> spp.</td>
<td>≤ 8 Disk: ≤ 13</td>
<td>16-32 Disk: 14 – 20</td>
<td>≥ 64 Disk: ≥ 21</td>
</tr>
<tr>
<td><em>Haemophilus</em> spp.</td>
<td>≤ 2 Disk: 26</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Neisseria</em> spp.</td>
<td>≤ 0.25 Disk: ≤ 35</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>Commonly susceptible species (i.e. resistance &lt; 10% in all EU Member States)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive aerobes:</strong></td>
</tr>
<tr>
<td>MS\textsuperscript{a} coagulase negative <em>Staphylococcus</em> spp. (including <em>S. epidermis</em>)*</td>
</tr>
<tr>
<td>MS\textsuperscript{b} <em>Staphylococcus aureus</em>*</td>
</tr>
<tr>
<td>Group B (<em>Streptococcus agalactiae</em>)</td>
</tr>
<tr>
<td><em>Streptococcus bovis</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>Group A <em>Streptococcus (Streptococcus pyogenes)</em></td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
</tr>
<tr>
<td><strong>Gram-Negative aerobes:</strong></td>
</tr>
<tr>
<td><em>Citrobacter</em> spp. (including <em>C. freundii</em>)</td>
</tr>
</tbody>
</table>

---

* Recent 2002 *S. pneumoniae* breakpoints (NCCLS M100-S12) defined as ≤ 1 (Sensitive), 2 (Intermediate) and ≥ 4 (Resistant) for non-meningitis specimens and ≤ 0.5 (Sensitive), 1 (Intermediate), and > 2 (Resistant) for meningitis specimens.

** Recent 2002 *Streptococcus viridans* group breakpoints (NCCLS M100-S12) defined ≤ 1 (Sensitive), 2 (Intermediate), and ≥ 4 (Resistant)
**Escherichia coli***

**Haemophilus influenzae** (including beta-lactamase positive isolates)*

**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.*

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem (i.e. resistance ≥ 10% in at least one EU Member State)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Negative aerobes:</strong></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> +</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp. (including <em>E. aerogenes</em> and <em>E. cloacaec</em>)*+</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp. (including <em>A. baumanii</em> and <em>A. calcoaceticus</em>)*+</td>
</tr>
<tr>
<td><strong>Anaerobes:</strong></td>
</tr>
<tr>
<td><em>Bacteroides</em> spp.*</td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> spp.*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inherently resistant organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive aerobes:</strong></td>
</tr>
<tr>
<td>MR&lt;sup&gt;4&lt;/sup&gt; coagulase negative <em>Staphylococcus</em> spp. (including <em>S. epidermidis</em>)</td>
</tr>
<tr>
<td>MR&lt;sup&gt;5&lt;/sup&gt;* <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-Negative aerobes:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td><em>Mycoplasma</em> spp.</td>
</tr>
</tbody>
</table>
Stenotrophomonas maltophilia
Ureaplasma urealyticum

Others:
Chlamydia spp.

5\(^\text{a}\) Methicillin-susceptible Coagulase-Negative Staphylococcus
5\(^\text{b}\) Methicillin-susceptible Staphylococcus aureus
5\(^\text{c}\) Non-susceptible range (no resistant breakpoints defined)
5\(^\text{d}\) Methicillin-resistant Coagulase-Negative Staphylococcus
5\(^\text{e}\) 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

The table above comprises current levels of susceptibility according to routinely produced susceptibility test results in France, Germany, Greece, Italy, the Netherlands, Spain, and the United Kingdom. All data is presented using contemporary NCCLS derived susceptibility breakpoints except France (CA-SFM). Data is derived from The Surveillance Network™ (TSN) Databases in each respective region. The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether microorganisms will be susceptible to ceftriaxone or not.

5.2 Pharmacokinetic properties
The pharmacokinetics of ceftriaxone are largely determined by its concentration-dependent binding to serum 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 concentration 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 1.06% Lidocaine produces mean peak plasma concentrations of 40-70mg/l within 1 hour. Bioavailability after intramuscular injection is 100%

Excretion: The drug is eliminated mainly as unchanged ceftriaxone, 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 - 22ml/min. The renal clearance is 5 - 12ml/min. The elimination half-
life in adults is about 8 hours. 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 elderly person aged over 75 years, the average elimination half-life is usually 2 to 3 times longer than 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 data of relevance to the prescriber which are additional to that already included in other sections of the SPC

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

None

**6.2 Incompatibilities**

Solutions containing ceftriaxone should not be mixed with or added to solutions containing other agents. In particular, ceftriaxone is not compatible with calcium-containing solutions (e.g. Hartmann's solution and Ringer's solution) and must not be given simultaneously with calcium-containing solutions – even via different infusion lines.

Ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.
6.3 **Shelf life**  
36 months unopened.

Reconstituted solutions: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours below 25°C. 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 not normally be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 **Special precautions for storage**  
Do not store above 25°C  
For shelf-life of reconstituted solutions, see section 6.3.

6.5 **Nature and contents of container**  
Colourless Type III glass vial closed with a bromobutyl rubber stopper and sealed with an aluminium cap.  
Packs of 1, 5, 10, 20, 50 or 100 vials.  
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**  
Ceftriaxone should not be mixed in the same syringe with any drug other than 1.06% Lidocaine Hydrochloride BP solution (for deep intramuscular injection only).

*Intramuscular injection:* 250mg or 500mg ceftriaxone should be dissolved in 2ml of 1.06% Lidocaine Hydrochloride BP solution, or 1g in 3.5ml of 1% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection. Dosages greater than 1g should be divided and injected at more than one site. Solutions reconstituted with Lidocaine Hydrochloride BP solution should not be administered intravenously.

*Intravenous injection:* 250mg or 500mg ceftriaxone should be dissolved in 5ml of Water for Injections BP or 1g in 10ml of Water for Injections BP. The injection should be administered over at least 2 - 4 minutes, directly into the vein or via the tubing of an intravenous infusion.

*Intravenous infusion:* 2g of ceftriaxone should be dissolved in 40ml of one of the following calcium-free solutions: Dextrose Injection BP 5% or 10%, Sodium Chloride Injection BP, Sodium Chloride and Dextrose Injection BP (0.45% Sodium Chloride and 2.5% Dextrose), Dextran 6% in Dextrose Injection BP 5%. The infusion should be administered over at least 30 minutes.
The displacement value of 250mg of ceftriaxone is 0.194ml.

7 MARKETING AUTHORISATION HOLDER
Villerton Invest SA
1, Allée Scheffer
L-2520 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)
PL 24780/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/01/2008

10 DATE OF REVISION OF THE TEXT
28/01/2008
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Ceftriaxone 250 mg, 500 mg, 1g Powder for Solution for Injection
Ceftriaxone 2g Powder for Solution for Injection/Infusion
Ceftriaxone as ceftriaxone sodium

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do NOT pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

In this leaflet:
1. What Ceftriaxone Injection is and what it is used for
2. Before you are given Ceftriaxone Injection
3. How Ceftriaxone Injection is given
4. Possible side effects
5. How to store Ceftriaxone Injection

The name of your medicine is Ceftriaxone Powder for Solution for Injection or Infusion, referred to as Ceftriaxone Injection throughout this leaflet.

1. WHAT CEFTRIAXONE INJECTION IS AND WHAT IT IS USED FOR

Ceftriaxone vials contain either 250 mg, 500 mg, 1g, or 2g ceftriaxone (as ceftriaxone sodium). Ceftriaxone is the active ingredient. The injection contains no other ingredients. Ceftriaxone is one of a group of medicines known as cephalosporins which are antibiotics. These are used to kill the bacteria or ‘germs’ that cause infections.

Ceftriaxone Injection is used to treat infections of the chest, lungs, bones, joints and skin. It may also be used to treat some sexually transmitted infections (gonorrhoea), meningitis and blood infections. It is sometimes given before operations to prevent infections.

Marketing Authorisation Holder: Vilberton Invest SA
1, Allee Schellen
L-2520 Luxembourg

Manufacturer: Anfarm Hellas
Schimatari Vokias, 32009 Schimatari
Greece

Ceftriaxone Injection is a white or almost white powder in a glass vial. The vials are for single use only. Ceftriaxone Injection is supplied in cartons of 1, 5, 10, 20 or 50 vials. Not all pack sizes may be marketed.

2. BEFORE YOU ARE GIVEN CEFTRIAXONE INJECTION

Do not take Ceftriaxone Injection:
- If you are allergic (hypersensitive) to ceftriaxone or other similar antibiotics (called "cephalosporins")
- If you have had a severe allergic reaction to penicillin or other similar antibiotics (called "beta-lactams")
- If you had an immediate allergic reaction when given penicillin or similar antibiotics.

If you are unsure about any of these, ask your doctor.

Ceftriaxone is NOT suitable for premature babies or newborn babies with jaundice or conditions known as acidosis (high levels of acid in the blood) and hyperalbuminaemia (high levels of the protein albumin in the blood).

Ceftriaxone should not be given to newborn babies who need calcium treatment.

Take special care with Ceftriaxone Injection

Before starting treatment, make sure your doctor knows if you:
- have ever had an allergic reaction to an antibiotic
- have both liver and kidney problems
- have a history of gastro-intestinal problems e.g. colitis
- are on a low sodium diet

If you are being treated with ceftriaxone, or have been treated with it recently, tell your doctor before having any laboratory tests e.g. blood or urine tests

Taking other medicines

Tell your doctor if you are taking any of the following medicines as they may interact with ceftriaxone:
- chloramphenicol (used in eye drops)
- oral contraceptives ("the pill").

Please tell your doctor or pharmacist if you are taking or have recently taken, any other medicines including medicines obtained without a prescription.

Pregnancy and breast-feeding

If you are pregnant, likely to become pregnant or are breast-feeding, you must tell your doctor before you are given this medicine.

Driving and using machines

This medicine has no known effects on the ability to drive or use machines.

Important information about some of the ingredients of Ceftriaxone Injection:
This medicine contains 0.9 mmol (230mg vial), 1.8 mmol (500mg vial), 3.6 mmol (1g vial) or 7.2 mmol (2g vial) of sodium. This should be taken into consideration by patients on a controlled sodium diet.
UKPAR Ceftriaxone 250mg, 500mg & 1g powder for solution for injection and
Ceftriaxone 2g powder for solution for injection or infusion

3. HOW CETRAXONE INJECTION IS GIVEN

Ceftriaxone injection will usually be given by a doctor or nurse who will dissolve the powder before injecting it, either directly into a vein or into a muscle. In some cases, it may be added to an intravenous infusion (“drip”).
The correct dose will be decided by your doctor and depends on the type of infection and your weight and age.
Ceftriaxone injection is usually continued for 2-3 days after you start to recover from your illness or after your operation.

Adults and children over 12 years old:
The usual adult dose is 1g every day. In some patients where infections are severe, the doctor may give a higher dose up to 4g every day.

Infants and children up to 12 years of age:
The recommended daily dose is 20-50mg per kg of bodyweight. In severe infections, a daily dose of 50-80mg/kg bodyweight may be infused over at least 30 minutes. More than 80mg per kg must not be given, even in severe infections - except meningitis. For children with bodyweights of 50kg or more, the usual adult dosage should be used.

Young babies (neonates)
The recommended daily dose is 20-50mg per kg of bodyweight. The maximum dose is 50mg/kg. The intravenous dose should be given over 60 minutes.

Patients with kidney problems:
Patients on dialysis machines will be monitored for the correct dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ceftriaxone injection can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. Any rashes (slightly raised, itchy, skin patches that are paler or redder than the surrounding skin), sudden swelling of the hands, feet, ankles, or swelling of the face, lips, mouth or throat, which may cause difficulty swallowing or breathing, should be reported to a doctor immediately.

The following side effects may occur in some patients treated with Ceftriaxone injection:

Common side effects (probably affecting more than 1 in 100 patients)
• Feeling sick
• Being sick
• Loose stools or diarrhoea

Uncommon side effects (probably affecting less than 1 in 100 patients)
• Rash with small, raised, red areas of skin (which may be itchy and/or scaly)
• Itching
• Swelling of hands, feet or ankles

Rare side effects (probably affecting less than 1 in 1,000 patients)
• Headache
• Dizziness
• Fungal infections affecting the genital regions
• Yeast infections e.g. thrush
• Fewer red blood cells which can make the skin pale and cause weakness or breathlessness
• Reduction in blood platelets which increases risk of bruising or bleeding
• Reduction in number of white blood cells which makes infections more likely
• Increase in number of white blood cells
• Slow blood clotting time
• Serious allergic reaction which causes difficulty in breathing or dizziness
• Sore on the lining of the mouth
• Inflamed tongue
• Increased liver enzymes
• Pain, redness and swelling at the injection site
• Fever and shivering
• Sugar or blood in the urine
• Reduced volume of urine produced
• Kidney stones in children

Higher doses of ceftriaxone (more than 2g per day) may cause deposits of ceftriaxone calcium in the gall bladder, which look like gall stones. These can cause pain, nausea and vomiting but usually disappear after treatment is stopped.

Very rare side effects (probably affecting less than 1 in 10,000 patients)
• Severe reduction in number of white blood cells which makes infections more likely
• Inflamed pancreas
• Diarrhoea containing blood (which may be a sign of a condition called pseudomembranous colitis)
• False positive blood tests
• Problems with kidney function
• Complete lack of urine production
• Serious illness with blistering of the skin, mouth, eyes and genitals

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

5. HOW TO STORE CETRAXONE INJECTION

Keep out of the reach and sight of children.
Do not use Ceftriaxone injection after the expiry date which is printed on the label and carton.
Do not store above 25°C.
Your doctor, pharmacist or nurse will know how to store Ceftriaxone injection properly.
UKPAR Ceftriaxone 250mg, 500mg & 1g powder for solution for injection and
Ceftriaxone 2g powder for solution for injection or infusion

PL 24780/0004-7

INFORMATION FOR THE HEALTHCARE PROFESSIONAL
The following information is intended for medical or healthcare professionals only.

Instructions for use and handling:
This medicinal product is for single use only. Discard any unused contents.

Ceftriaxone should not be mixed in the same syringe with any drug other than 1.06% Lidocaine Hydrochloride BP solution (for deep intramuscular injection only).

Intramuscular injection: 250mg or 500mg ceftriaxone should be dissolved in 2ml of 1.06% Lidocaine Hydrochloride BP solution, or 1g in 3.5ml of 1.06% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection. Dosages greater than 1g should be divided and injected at more than one site.

Solutions reconstituted with Lidocaine Hydrochloride BP solution should not be administered intravenously.

Intravenous injection: 250mg or 500mg ceftriaxone should be dissolved in 5ml of Water for Injections BP or 1g in 10ml of Water for Injections BP. The injection should be administered over at least 2 - 4 minutes, directly into the vein or via the tubing of an intravenous infusion.

Intravenous infusion: 2g of ceftriaxone should be dissolved in 40ml of one of the following calcium-free solutions: Dextrose Injection BP 5% or 10%, Sodium Chloride Injection BP, Sodium Chloride and Dextrose Injection BP (0.45% Sodium Chloride and 2.5% Dextrose), Dextran 6% in Dextrose Injection BP 5%. The infusion should be administered over at least 30 minutes.

The displacement value of 250mg of ceftriaxone is 0.194ml

Incompatibilities
Solutions containing ceftriaxone should not be mixed with or added to solutions containing other agents. In particular, ceftriaxone is not compatible with calcium-containing solutions (e.g. Hartmann’s solution and Ringer’s solution) and must not be given simultaneously with calcium-containing solutions - even via different infusion lines.

Storing Ceftriaxone Injection:
Do not store above 25°C.
Reconstituted solutions: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours below 25°C. 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 not normally be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Posology and method of administration
Ceftriaxone is for parenteral use only and may be administered by deep intramuscular injection; slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution. Following reconstitution, a colourless solution is produced.

Dosage and method of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Usually a once daily dose will give satisfactory therapeutic results. In some indications (see below), a single dose is sufficient.
Adults and children over 12 years of age

Standard therapeutic dosage: 1g once a day. Severe infections: 2 - 4g daily, normally as a single dose every 24 hours.

The duration of therapy should be varied 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 as soon as there is evidence of bacterial eradication.

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

Peri-operative prophylaxis: Usually 1g as a single intramuscular or slow intravenous dose. In colorectal surgery, 2g should be given intramuscularly or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

Elderly
As for adult dose, subject to normal hepatic and renal function.

Neonates, infants and children up to 12 years

The following dosage schedules are recommended for once daily administration:

**Neonates**
A daily dose of 20 - 50mg/kg body weight, not to exceed 500mg/kg. 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.

**Infants and children of up to 12 years**
Standard therapeutic dosage: 20 - 50mg/kg body weight once daily. In severe infections up to 80mg/kg body weight daily may be given. For children with bodyweights of 50kg or more, the usual adult dosage should be given. 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 except in meningitis [see below].

**Meningitis**
Treatment is initiated with 100mg/kg bodyweight once daily - not exceeding 4g daily. After determining the sensitivity of the pathogen, the dose may be reduced accordingly. In neonates 0-14 days of age, the dose should not exceed 50mg/kg/24h.

**Renal and hepatic impairment**
In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is normal. 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 normal.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of ceftriaxone should be determined at regular intervals and dosage adjusted accordingly.

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

L0801400
Each vial contains 1 g Ceftriaxone (as ceftriaxone sodium).
Also contains 3.6 mmol sodium per vial.
Reconstitute before use and use immediately.
Once reconstituted any unused solution should be discarded.
For single use only.
For full directions for use see enclosed leaflet.
Do not store above 25°C.
Do not use after the expiry date on the label.
Keep out of the reach and sight of children.

PL 24780/0006
Ceftriaxone 250mg, 500mg & 1g powder for solution for injection and infusion

Ceftriaxone 2g powder for solution for injection or infusion

Each vial contains 2.39 g ceftriaxone sodium equivalent to 2 g ceftriaxone. For IV infusion and IM injection.

Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 25°C. MAH: Villerton Invest S.A. PL24780/0007 E0801500

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