Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion

PL 22805/0001, 3-5

UKPAR

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LAY SUMMARY

On 9th October 2009, the MHRA granted Orchid Europe Limited Marketing Authorisations (licences) for Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion (PL 22805/0001, 3-5).

This medicine contains the active ingredient ceftriaxone. Ceftriaxone belongs to a group of antibacterial agents called cephalosporins, which act by killing bacteria.

Ceftriaxone is used when an infection is known to be or likely to be caused by bacteria that are sensitive to ceftriaxone. It is used for the treatment of the following conditions:
- Infection of the bloodstream by bacteria (septicaemia)
- Infection of the membranes and fluid surrounding the brain and spinal cord (meningitis)
- Chest infections such as pneumonia

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion outweigh the risks; hence Marketing Authorisations have been granted.
Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion

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SCIENTIFIC DISCUSSION

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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, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion (PL 22805/0001, 3-5) to Orchid Europe Limited on 9th October 2009. These products are prescription only medicines used in the treatment of the following serious infections when known or likely to be due to microorganisms that are susceptible to ceftriaxone and require parenteral treatment

- Septicaemia
- Acute bacterial meningitis
- Pneumonia.

These applications for Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Rocephin 250mg, 500mg, 1g and 2g Powder for Solution for Injection, first authorised to Roche Products Limited in September 1988.

The products contain the active substance ceftriaxone, a semi-synthetic cephalosporin antibacterial agent for parental administration.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Ceftriaxone sodium

INN/Ph.Eur name: Ceftriaxone sodium
Chemical name: Disodium (6R,7R)-7-[(Z)-(2-aminothiazol-4-y1)(methoxyimino)acetylamino]-3-[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulphonyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Molecular formula: C_{18}H_{16}N_{8}Na_{2}O_{7}S_{3} 3\frac{1}{2}H_{2}O

Appearance: Almost white or yellowish, crystalline powder, slightly hygroscopic
Solubility: Freely soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol
Molecular weight: 662

An appropriate specification based on the European Pharmacopoeia has been provided.

All aspects of the manufacture of the active substance ceftriaxone sodium from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance ceftriaxone sodium.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.
Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

**DRUG PRODUCT**
**Other ingredients**
None.

**Product development**
The objective of the development programme was to produce products that could be considered generic medicinal products of Rocephin 250mg, 500mg, 1g and 2g Powder for Solution for Injection (Roche Products Limited, September 1988).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on three consecutive commercial scale batches of each strength of finished product and the results appear satisfactory.

**Finished product specification**
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The 250mg and 500mg products are packaged in Type I clear glass 10ml vials sealed with gray bromo butyl rubber stoppers and a blue coloured flip off seal (250mg), or a white coloured flip off seal (500mg).

The 1g and 2g products are packaged in Type I clear glass 20ml vials sealed with gray bromo butyl rubber stoppers and a blue coloured flip off seal (1g), or a white coloured flip off seal (2g).

For Ceftriaxone 2g Powder for Solution for Infusion, the product is packaged in a Type I clear glass 100ml vial sealed with a gray bromobutyl rubber stopper and a white coloured flip off seal.

All products are packaged in cartons of 1 or 5 vials.

Specifications and Certificates of Analysis for the packaging types used have been provided. All primary product packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.
Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set. It is recommended that the reconstituted product should be used immediately. If not used immediately, then it has a shelf-life of 24 hours in a refrigerator (2 to 8°C), or 6 hours when stored at temperatures not exceeding 25°C. This is satisfactory.

General storage conditions are ‘Keep vial(s) in the outer carton to protect from light’.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
These are pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
These are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
These are pharmaceutically satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications for Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Rocephin 250mg, 500mg, 1g and 2g Powder for Solution for Injection, first authorised to Roche Products Limited in September 1988.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No bioequivalence studies have been performed and none are required for these applications, as the products are administered as parenteral aqueous solutions, distributed rapidly in vivo.

EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert reports have been written by a suitably qualified person and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
These are consistent with those for the reference products and are satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORM (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
A bioequivalence study with the reference products is not required for these products and its absence can be justified by the route of administration.

MEDICAL CONCLUSION
The grant of marketing authorisations are recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 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
Ceftriaxone sodium is a well-known drug and has been used for many years. Bioequivalence has been demonstrated between the applicant’s Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion and the reference products Rocephin 250mg, 500mg, 1g and 2g Powder for Solution for Injection (Roche Products Limited).

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with those for the reference products Rocephin 250mg, 500mg, 1g and 2g Powder for Solution for Injection.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data submitted supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with ceftriaxone sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
Ceftriaxone 250mg, 500mg, 1g and 2g Powder for Solution for Injection or Infusion

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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 18th January 2005.

2. Following standard checks and communication with the applicant, the MHRA considered the application valid on 31st July 2005.


5. The application was determined on 9th October 2009.
Ceftriaxone 250mg, 500mg, 1g and 2g Powder for Solution for Injection or Infusion

PL 22805/0001, 3-5

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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>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 250 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains:
250 mg Ceftriaxone as 298.3 mg hydrated disodium Ceftriaxone.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Powder for Solution for Injection.
Almost white or yellowish, slightly hygroscopic crystalline powder

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Ceftriaxone is indicated for the treatment of the following serious infections when known or likely to be
due to microorganisms that are susceptible to ceftriaxone and require parenteral treatment (see section
5.1):
Septicaemia
Acute bacterial meningitis
Pneumonia.
Treatment may be started before the results of susceptibility tests are known.
Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route and method of administration
Intravenous use
Ceftriaxone for Injection may be administered by intravenous bolus injection or by intravenous infusion
after reconstitution of the solution according to the directions in sections 6.2 and 6.6.
Dosage and mode of administration should be determined by the severity and site of infection,
susceptibility of the causative micro-organism and the patient's age and condition.
An intravenous injection should be administered over at least 2 – 4 minutes directly into the vein or via
the tubing of an intravenous infusion. Dose ≥50 mg/kg should be given as infusion over a period of at
least 30 minutes.

Normal dosage
Adults and adolescents aged over 12 years with a body weight ≥50 kg:
The usual dose is 1-2 g of ceftriaxone, administered once a day (every 24 hours). In cases of serious
infections or infections caused by moderately sensitive micro-organisms the dose can be raised up to 4 g,
administered once a day.

Newborn infants (age 0 – 14 days):
20 – 50 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 50 mg per kg bodyweight must not be exceeded.
Children 15 days-12 years of age with a body weight of < 50 kg:
20-80 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 80 mg per kg bodyweight must not be exceeded, except in
meningitis (see section 4.2.: Special dosage recommendations).
Children with a bodyweight of 50 kg or more receive the usual adult dosage once daily (see above).
For administration to neonates see 4.4.

Elderly:
The normal adult dose can usually be given to elderly patients, unless renal and hepatic function is
significantly impaired (see below).
Dosage in special situations
Meningitis:
In children with bacterial meningitis the therapy should be started with 100 mg/kg (not exceeding 4 g), administered once a day. After determining the sensitivity of the pathogen the dose may be reduced accordingly.
In new-born infants below 2 weeks of age the dose should not exceed 50 mg/kg/24 h.

Renal insufficiency:
In patients with impaired renal function, alteration of the ceftriaxone dose is not necessary, provided that the hepatic function is normal. Only in cases of extreme renal insufficiency (creatinine clearance < 10ml/min) the daily dose of the ceftriaxone should not exceed 2 g.
In co-existing severe renal and hepatic insufficiency, and in children with extreme renal insufficiency the serum ceftriaxone concentrations should be regularly monitored, and the dosage adjusted appropriately. Patients undergoing haemodialysis or peritoneal dialysis do not need an additional dose of ceftriaxone after 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.

Hepatic insufficiency:
The dose does not need to be altered in patients with a liver disease provided that the renal function is normal.

Duration of therapy
The normal duration of therapy depends on the response and causative micro-organism. As with antibiotic therapy in general, administration of ceftriaxone should be continued for at least 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

4.3 CONTRAINDICATIONS
Hypersensitivity to the active substance, to other cephalosporins.
Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products (see section 4.4).
Ceftriaxone should not be given to neonates with jaundice, or those who are hypoalbuminaemic or acidotic.
Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.
Calcium treatment because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
In suspected or proven infections with *Pseudomonas aeruginosa*, high resistance rates (> 60 %) for ceftriaxone in at least some European countries should be taken into consideration (see section 5.1).
In infections caused by *Pseudomonas aeruginosa* with proven sensitivity to ceftriaxone a combination with amino-glycosides is warranted to avoid secondary resistance.

In infections caused by other bacteria in patients with neutropenic fever interventional treatment with ceftriaxone should be combined with an aminoglycoside.
Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-lactam-medicinal products because patients hypersensitive to these medicines may be hypersensitive to ceftriaxone as well (cross-allergy).

Hypersensitivity reactions against ceftriaxone are more likely in patients with any other type of hypersensitivity reaction or asthma bronchiale.
Injections with ceftriaxone should be used with special caution in patients with allergic diathesis, because hypersensitivity reactions emerge faster and proceed more severely after intravenous injection (see section 4.8).

Hypersensitivity reactions may occur in all degrees of severity up to anaphylactic shock (see section 4.8).
In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined in section 4.2.
In case of simultaneous impairment of renal and liver function, serum-level of ceftriaxone should be monitored in regular intervals. Monitoring of renal and hepatic function and haematological parameters at regular intervals are indicated during long-term treatment (see section 4.8).

Each administration of antibiotics can lead to multiplication of pathogens resistant to the active substance used. Signs of consecutive secondary infections with such pathogens (including candida and fungi) are to be heeded. Secondary infections are to be treated accordingly (see section 5.1).

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. Drugs that inhibit peristalsis must not be given.

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

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 80 mg/kg body weight should be avoided – except for meningitis – because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of ceftriaxone precipitate in the gallbladder is recommended.

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

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the medicinal product to produce a positive Coombs’ test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins. 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.

Ceftiraxone should therefore not be used in jaundiced new-borns or in those who are hypoalbuminaemic or acidicotic, in whom bilirubin binding is likely to be impaired. Particular caution should be exercised in babies born prematurely.

As with other antibiotics, incidental occurrences of vitamin K–deficiency should be considered. High intravenous doses (>1 g or ≥50 mg/kg bodyweight) of ceftriaxone should be administered slowly (over a minimum period of 30 minutes) in order to avoid high concentrations in the bile. This medicinal product contains 0.9 mmol (20.7mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

**Aminoglycosides:**
In case of concomitant administration of cephalosporins and aminoglycosides there has been reported an increased risk of oto- and nephrotoxicity. Dose adjustment may be necessary. Furthermore, these medicinal products must be administered separately to avoid physicochemical incompatibility between ceftriaxone and the aminoglycoside.

Bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may antagonise the activity of ceftriaxone, especially in acute infections accompanied by rapid proliferation of micro-organisms. Simultaneous use of ceftriaxone and bacteriostatic antibiotics is, therefore, not recommended.
Probenecid:
Contrary to other cephalosporins, probenecid does not impede tubular secretion of ceftriaxone.
Oral contraceptives:
Ceftriaxone may adversely affect the efficacy of hormonal contraceptives. Consequently, it is advisable to use supplementary non-hormonal contraceptive measures.

Other:
Laboratory-diagnostic tests
The Coombs test may be false-positive in rare cases during treatment with ceftriaxone (see section 4.4). Non-enzymatic methods for glucose determinations in urine may yield false-positive results. For this reason, urine glucose determination during therapy with ceftriaxone should be carried out enzymatically. Ceftriaxone may lead to false-positive results of galactose determination in blood. 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.

4.6 PREGNANCY AND LACTATION
There are no data on use of ceftriaxone in pregnant women. Ceftriaxone crosses the placenta. Animal studies indicate no reproductive toxicity (see section 5.3). As a precautionary measure, ceftriaxone should only be used during pregnancy after benefit/risk assessment by the physician in charge, especially during the first trimester.

Ceftriaxone is excreted in low concentrations in breast milk. Caution should be exercised when prescribing to breast-feeding women. Diarrhoea and fungal infection of the mucous membrane could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Usually, Ceftriaxone has no or negligible influence on the ability to drive and use machines. However, undesirable effects such as hypotension, dizziness or vertigo (see section 4.8) should be taken into account.

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 is due to the low blood volume of the newborns. Moreover half life is longer than in adults. The following adverse reactions, reversible spontaneously or after treatment discontinuation, have been observed in association with ceftriaxone use:

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common &gt; 1/10</th>
<th>Common &gt; 1/100 to &lt; 1/10</th>
<th>Uncommon &gt; 1/1,000 to &lt; 1/100</th>
<th>Rare &gt; 1/10,000 to &lt; 1/1,000</th>
<th>Very rare: &lt; 1/10,000</th>
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<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia, leucopenia, granulocytopenia</td>
<td>Agranulocytosis (&lt;500/mm³), mostly after 10 day treatment and a total dose of 20g ceftriaxone and more; Coagulation disorders. Thrombocytopenia. Minor prolongation in the prothrombin time has been described.</td>
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<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Headache, dizziness, vertigo.</th>
<th>Anaemia (including haemolytic anaemia)</th>
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<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Stomatitis, glossitis, anorexia, nausea, emesis, abdominal pain, loose stool or diarrhoea. These undesirable effects are mostly mild and frequently subside during, otherwise after discontinuation of therapy</td>
<td>Pseudomembranous enterocolitis (see section 4.4). If severe, persistent diarrhoea occurs during or after treatment, pseudomembranous colitis which is a serious, even life-threatening complication mostly caused by <em>clostridium difficile</em>, should be considered. Discontinuation of therapy with ceftriaxone depending on the indication should be considered and appropriate treatment measures should be initiated: e.g. intake of specific antibiotics/chemotherapeutics with clinically proven efficacy. Antiperistaltics are contraindicated.</td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Oliguria, increase in serum creatinine</td>
<td>Precipitates of ceftriaxone in the kidneys in paediatric patients, mostly in children older than 3 years treated either with high daily doses (e.g. 80 mg/kg BW per day and more) or with total doses above 10 g ceftriaxone and who presented several risk factors (e.g. restricted fluid supply). However,</td>
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<tr>
<td><strong>Infections and Infestations</strong></td>
<td><strong>General disorders and administration site conditions</strong></td>
<td><strong>Immune system disorders</strong></td>
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<td>Phlebitis following intravenous administration. This can be minimised by slow injection (over 2-4 minutes). Pain at the site of injection. In rapid intravenous injection intolerability reactions in the form of sensation of heat or nausea may occur. This can be avoided by slow injection (2-4 minutes).</td>
<td>Allergic skin reactions (e.g. dermatitis, urticaria, exanthema), pruritus, oedematous swelling of skin and joints</td>
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**Immune system disorders**

- **Allergic skin reactions** (e.g. dermatitis, urticaria, exanthema), pruritus, oedematous swelling of skin and joints
- **Severe acute hypersensitivity reactions up to anaphylactic shock.**
- **Lyell syndrome/toxic epidermolysis,** Stevens-Johnson syndrome or **Erythema multiforme.**
- **Severe acute hypersensitivity reactions and anaphylactic shock.**
shock require immediate discontinuation of the administration of ceftriaxone and the initiation of appropriate emergency measures.

| Hepatobiliary disorders | Symptomatic precipitation of ceftriaxone calcium sail in the gallbladder of children/ reversible cholelithiasis in children. This disorder is rare in adults (see below). | Elevated liver enzymes in serum (AST, ALT, alkaline phosphatase). | Pancreatitis (see section 4.4). Increase in liver enzymes. Symptomatic precipitation of ceftriaxone calcium sail in the gallbladder of adults, which disappeared after discontinuation or cessation of therapy with ceftriaxone. These opacities usually occurred only after administration of higher doses than the recommended standard doses. In the rare cases in which the precipitates are accompanied by clinical symptoms such as pain, symptomatic measures are recommended. Discontinuation of treatment should be considered too (see section 4.4). |

### 4.9 OVERDOSE

No case of overdose has been reported.

**Symptoms of intoxication**

Typical signs of overdose can be expected to correspond to the adverse reaction profile. Colics occurred very rarely in the presence of nephropathy or cholelithiasis when using high doses administered more frequently and more rapidly than recommended.

**Therapy of intoxication**

Excessive serum concentration of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Symptomatic therapeutic measures are indicated.
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmaco-therapeutic group

Cephalosporins and related substances, ATC code: J01DD04

Mechanism of action

Ceftriaxone has bactericidal activity that results from the inhibition of bacterial cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of β-lactamases produced by Gram-negative and Gram-positive bacteria. Synergistic effects of ceftriaxone and aminoglycosides on certain Gram-negative bacteria have been noted in vitro.

Mechanism of resistance

Ceftriaxone is active against organisms producing some types of beta-lactamase, for example TEM-1. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes. Ceftriaxone cannot be expected to be active against the majority of bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam medicinal products. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

Breakpoints

Ceftriaxone – EUCAST clinical MIC breakpoints

Enterobacteriaceae: S≤1 mg/L/R>2 mg/L\(^1\)

Staphylococcus: Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility.

Streptococcus A, B, C, G: S≤0.5 mg/L/R>0.5 mg/L\(^2\)

S. pneumoniae: S≤0.5 mg/L/R>2 mg/L\(^2\)

H. influenzae,

M. catarrhalis: S≤0.12 mg/L/R>0.12 mg/L\(^2\)

N. gonorrhoeae: S≤0.12 mg/L/R>0.12 mg/L\(^2\)

N. meningitides: S≤0.12 mg/L/R>0.12 mg/L\(^2\)

Non-species related breakpoints: S≤1 mg/L/R>2 mg/L\(^3\)

\(^1\) The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.

\(^2\) Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

\(^3\) Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species.

Microbiology

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.

Commonly susceptible species

**Gram-Positive aerobes**

*Staphylococcus aureus (MSSA)*

*Staphylococcus epidermidis (MSSA)*

*Streptococcus pyogenes*
Streptococcus pneumoniae
Viridans group streptococci

Gram-negative aerobes
Escherichia coli 1
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae 1
Klebsiella oxytoca 1
Moraxella catarrhalis
Neisseria meningitidis
Proteus mirabilis 1

Anaerobes
Bacteroides fragilis
Clostridium species
Peptostreptococcus spp.
Species for which acquired resistance may be a problem
Acinetobacter spp
Citrobacter freundii 1
Enterobacter spp. 1,2
Morganella morganii
Serratia marcescens

Inherently resistant organisms
Clostridium difficile
Enterococci
Listeria monocytogenes
Proteus vulgaris
Pseudomonas spp.
1) Some strains produce inducible or stably derepressed chromosomally-encoded cephalosporinases and ESBLs (extended spectrum beta-lactamases) and thus are clinically resistant to cephalosporins.
2) Clinical efficacy has been demonstrated for susceptible isolates of Enterobacter cloacae and Enterobacter aerogenes in approved clinical indications.

5.2 PHARMACOKINETIC PROPERTIES
Ceftriaxone is a cephalosporin for parenteral administration. Ceftriaxone is not absorbed after oral application.
After a dose of 1 – 2 g, concentrations have been shown to remain above the MIC values for most infection-causing pathogens for over 24 hours in over 60 different tissues (including lungs, heart, bile ducts, liver, tonsils, middle ear, nasal mucosa, bones) and in many tissue fluids (including cerebrospinal fluid, pleural fluid as well as prostatic and synovial fluid).

Distribution
Ceftriaxone distributes well in various compartments and also passes the placental barrier. The mean volume of distribution in healthy adults is 0.13 L/kg.
Ceftriaxone is reversibly bound to albumin. The binding is 95 % at plasma concentrations less than 100 mg/l with the binding percentage decreasing as the concentration increases (to 85 % at ceftriaxone plasma concentrations of 300 μg/ml).

Serum levels
Following an the intravenous infusion of 1 g ceftriaxone for 30 minutes, serum levels immediately after cessation of the infusion process were at 123.2 μg/ml, and at 94.81, 57.8, 20.2 and 4.6 μg/ml, respectively, 1.5, 4, 12 and 24 hours after the onset of infusion.
Ceftriaxone penetrates the inflamed meninges of newborn, infants and children. In CSF the peak concentrations of 18 mg/l are achieved, after a 50-100 mg/kg intravenous dose, in about four hours. In
adult patients with meningitis, therapeutic concentrations are achieved within 2-24 hours with the dose of 50 mg/kg.

Ceftriaxone crosses the placenta and is excreted in human milk at low concentrations.

Biotransformation
Ceftriaxone does not undergo systemic metabolism but it is broken down in the small intestine by bacterial action.

Elimination
Over a 0.15 to 3 g dose range, the values of elimination half-life range from 6 to 9 hours, total plasma clearance from 0.6-1.4 l/h and renal clearance from 0.3-0.7 l/h.

50-60 % of ceftriaxone is eliminated as an unchanged active substance in the urine whilst the remainder is excreted via the bile into the faeces as microbiologically inactive metabolites.

Ceftriaxone concentrates in the urine. The urine concentrations are 5-10 times higher than those found in the plasma.

Ceftriaxone cannot be removed by dialysis. This applies to both haemodialysis and peritoneal dialysis. Urinary excretion is via glomerular filtration. No tubular secretion takes place. For this reason, no increase in the serum levels is to be expected in coincident administration of probenecid and is actually – even at higher dosage e.g. with 1-2 g probenecid – not found.

Non-Linearity
The pharmacokinetics of ceftriaxone is non-linear with respect to the dose. This non-linearity is explained by a concentration dependent decrease of binding to plasma proteins which leads to a respective increase in distribution and elimination.

With the exception of elimination half-life, all pharmacokinetic parameters are dose-dependent. Repeat dosing of 0.5 to 2 g results in 15 % - 36 % accumulation above single dose values.

Special patient groups
Elderly above 75 years: the plasma elimination half-life of ceftriaxone is about 2 – 3 fold increased compared to young adults.

In newborn infants of 3 days of age, the half-life of ceftriaxone in the serum amounts to approximately 16 hours, and approximately 9 hours in newborn infants aged from 9 to 30 days.

Patients with impaired renal and/or liver function:
Patients with an impaired renal function have an increased excretion of ceftriaxone into the bile.
Patients with an impaired liver function have an increased renal excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is almost not increased in these patient groups. Patients with an impaired renal function, as well as an impaired liver function, may have an increased ceftriaxone plasma elimination half-life. In case of terminal renal insufficiency, the half-life is distinctively higher and reaches approximately 14 hours.

5.3 PRECLINICAL SAFETY DATA
The adverse reactions (e.g. gastrointestinal disturbances and nephrotoxicity) associated with high parenteral doses of cephalosporins have been shown to be reversible in animals during repeat dosing.

After high doses of ceftriaxone diarrhoea, formation of biliary calculi in the gall bladder and nephropathy were observed in monkeys and dogs.

Ceftriaxone has no effect on fertility or reproduction. It has not been shown to possess any mutagenic activity.

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 such as Hartmann's solution and Ringer's solution. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.
6.3 SHELF LIFE
Unopened: 24 months
After reconstitution:
For reconstituted solution, chemical and physical in-use stability has been demonstrated for at least 6 hours at or below 25°C or 24 hours at 2-8°C. Protect from light.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at or below 25°C or 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. Unused solution should be discarded.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.
Keep vial(s) in the outer carton to protect from light.
For storage conditions of the reconstituted/diluted product see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER
Filled in 10 mL clear glass molded Type I Vial, sealed with gray bromo butyl rubber stopper and blue coloured flip off seal.
Pack sizes: 1 or 5 vials per carton.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND HANDLING OF THE PRODUCT
Preparation of solutions for injection and infusion
The use of freshly prepared solutions is recommended. These maintain potency for at least 6 hours at or below 25°C in daylight, or 24 hours at 2 – 8°C.
When reconstituted in water for injections, ceftriaxone powder gives a light yellow to amber coloured clear solution.
Ceftriaxone for Injection should not be mixed in the same syringe with any drug other than 1.0% Lidocaine Hydrochloride BP solution (for intramuscular injection only).
Intramuscular injection: Ceftriaxone 250mg Powder for Solution for Injection should be dissolved in 1ml of 1.0% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection.
Solutions in Lidocaine should not be administered intravenously.
Intravenous injection: Ceftriaxone 250mg Powder for Solution for Injection should be dissolved in 5ml 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.
Add the recommended volume of reconstitution solution and shake well until the contents of the vial have dissolved completely. The solution should be visually inspected prior to use. Only clear solutions practically free from particles should be used.
For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER
Orchid Europe Limited,
Building 3, Chiswick Park, 566, Chiswick High Road,
Chiswick, London, W4 5YA, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 22805/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/10/2009

10 DATE OF REVISION OF THE TEXT
09/10/2009
1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 500 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains:
500 mg Ceftriaxone as 596.5 mg hydrated disodium Ceftriaxone.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Powder for Solution for Injection.
Almost white or yellowish, slightly hygroscopic crystalline powder

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Ceftriaxone is indicated for the treatment of the following serious infections when known or likely to be
due to microorganisms that are susceptible to ceftriaxone and require parenteral treatment (see section
5.1):
- Septicaemia
- Acute bacterial meningitis
- Pneumonia.
Treatment may be started before the results of susceptibility tests are known.
Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route and method of administration
Intravenous use
Ceftriaxone for Injection may be administered by intravenous bolus injection or by intravenous infusion
after reconstitution of the solution according to the directions in sections 6.2 and 6.6.
Dosage and mode of administration should be determined by the severity and site of infection,
susceptibility of the causative micro-organism and the patient's age and condition.
An intravenous injection should be administered over at least 2 – 4 minutes directly into the vein or via
the tubing of an intravenous infusion. Dose ≥50 mg/kg should be given as infusion over a period of at
least 30 minutes.

Normal dosage
Adults and adolescents aged over 12 years with a body weight ≥50 kg:
The usual dose is 1-2 g of ceftriaxone, administered once a day (every 24 hours). In cases of serious
infections or infections caused by moderately sensitive micro-organisms the dose can be raised up to 4 g,
administered once a day.

Newborn infants (age 0 – 14 days):
20 – 50 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 50 mg per kg bodyweight must not be exceeded.
Children 15 days-12 years of age with a body weight of < 50 kg:
20-80 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 80 mg per kg bodyweight must not be exceeded, except in
meningitis (see section 4.2.: Special dosage recommendations).
Children with a bodyweight of 50 kg or more receive the usual adult dosage once daily (see above).
For administration to neonates see 4.4.

Elderly:
The normal adult dose can usually be given to elderly patients, unless renal and hepatic function is
significantly impaired (see below).
Dosage in special situations
Meningitis:
In children with bacterial meningitis the therapy should be started with 100 mg/kg (not exceeding 4 g), administered once a day. After determining the sensitivity of the pathogen the dose may be reduced accordingly.
In new-born infants below 2 weeks of age the dose should not exceed 50 mg/kg/24 h.

Renal insufficiency:
In patients with impaired renal function, alteration of the ceftriaxone dose is not necessary, provided that the hepatic function is normal. Only in cases of extreme renal insufficiency (creatinine clearance < 10ml/min) the daily dose of the ceftriaxone should not exceed 2 g.
In co-existing severe renal and hepatic insufficiency, and in children with extreme renal insufficiency the serum ceftriaxone concentrations should be regularly monitored, and the dosage adjusted appropriately. Patients undergoing haemodialysis or peritoneal dialysis do not need an additional dose of ceftriaxone after 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.

Hepatic insufficiency:
The dose does not need to be altered in patients with a liver disease provided that the renal function is normal.

Duration of therapy
The normal duration of therapy depends on the response and causative micro-organism. As with antibiotic therapy in general, administration of ceftriaxone should be continued for at least 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

4.3 CONTRAINDICATIONS
Hypersensitivity to the active substance, to other cephalosporins.
Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products (see section 4.4).
Ceftriaxone should not be given to neonates with jaundice, or those who are hypoalbuminaemic or acidotic.
Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.
Calcium treatment because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
In suspected or proven infections with Pseudomonas aeruginosa, high resistance rates (> 60 %) for ceftriaxone in at least some European countries should be taken into consideration (see section 5.1).
In infections caused by Pseudomonas aeruginosa with proven sensitivity to ceftriaxone a combination with aminoglycosides is warranted to avoid secondary resistance.

In infections caused by other bacteria in patients with neutropenic fever interventional treatment with ceftriaxone should be combined with an aminoglycoside.
Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-lactam-medicinal products because patients hypersensitive to these medicines may be hypersensitive to ceftriaxone as well (cross-allergy).

Hypersensitivity reactions against ceftriaxone are more likely in patients with any other type of hypersensitivity reaction or asthma bronchiale.
Injections with ceftriaxone should be used with special caution in patients with allergic diathesis, because hypersensitivity reactions emerge faster and proceed more severely after intravenous injection (see section 4.8).

Hypersensitivity reactions may occur in all degrees of severity up to anaphylactic shock (see section 4.8). In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined in section 4.2.
In case of simultaneous impairment of renal and liver function, serum-level of ceftriaxone should be monitored in regular intervals. Monitoring of renal and hepatic function and haematological parameters at regular intervals are indicated during long-term treatment (see section 4.8).

Each administration of antibiotics can lead to multiplication of pathogens resistant to the active substance used. Signs of secondary consecutive infections with such pathogens (including candida and fungi) are to be heeded. Secondary infections are to be treated accordingly (see section 5.1).

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. Drugs that inhibit peristalsis must not be given.

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

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 80 mg/kg body weight should be avoided – except for meningitis – because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of ceftriaxone precipitate in the gallbladder is recommended.

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

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the medicinal product to produce a positive Coombs’ test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins. 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.

As with other antibiotics, incidental occurrences of vitamin K deficiency should be considered.

High intravenous doses (>1 g or ≥50 mg/kg bodyweight) of ceftriaxone should be administered slowly (over a minimum period of 30 minutes) in order to avoid high concentrations in the bile.

This medicinal product contains 1.8 mmol (41.4 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Aminoglycosides: In case of concomitant administration of cephalosporins and aminoglycosides there has been reported an increased risk of ototoxicity and nephrotoxicity. Dose adjustment may be necessary. Furthermore, these medicinal products must be administered separately to avoid physicochemical incompatibility between ceftriaxone and the aminoglycoside.
Bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may antagonise the activity of ceftriaxone, especially in acute infections accompanied by rapid proliferation of micro-organisms. Simultaneous use of ceftriaxone and bacteriostatic antibiotics is, therefore, not recommended.

Probenecid:  
Contrary to other cephalosporins, probenecid does not impede tubular secretion of ceftriaxone. 

Oral contraceptives:  
Ceftriaxone may adversely affect the efficacy of hormonal contraceptives. Consequently, it is advisable to use supplementary non-hormonal contraceptive measures.

Other:  
Laboratory-diagnostic tests  
The Coombs test may be false-positive in rare cases during treatment with ceftriaxone (see section 4.4). Non-enzymatic methods for glucose determinations in urine may yield false-positive results. For this reason, urine glucose determination during therapy with ceftriaxone should be carried out enzymatically. Ceftriaxone may lead to false-positive results of galactose determination in blood. 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.

4.6 PREGNANCY AND LACTATION  
There are no data on use of ceftriaxone in pregnant women. Ceftriaxone crosses the placenta. Animal studies indicate no reproductive toxicity (see section 5.3). As a precautionary measure, ceftriaxone should only be used during pregnancy after benefit/risk assessment by the physician in charge, especially during the first trimester.

Ceftriaxone is excreted in low concentrations in breast milk. Caution should be exercised when prescribing to breast-feeding women. Diarrhoea and fungal infection of the mucous membrane could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES  
Usually, Ceftriaxone has no or negligible influence on the ability to drive and use machines. However, undesirable effects such as hypotension, dizziness or vertigo (see section 4.8) should be taken into account.

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 is due to the low blood volume of the newborns. Moreover half life is longer than in adults. The following adverse reactions, reversible spontaneously or after treatment discontinuation, have been observed in association with ceftriaxone use:

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common &gt; 1/10</th>
<th>Common &gt; 1/100 to &lt; 1/10</th>
<th>Uncommon &gt; 1/1,000 to &lt; 1/100</th>
<th>Rare &gt; 1/10,000 to &lt; 1/1,000</th>
<th>Very rare: &lt; 1/10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Eosinophilia, leucopenia, granulocytopenia</td>
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<tr>
<td>Agranulocytosis (&lt;500/mm³), mostly after 10 day treatment and a total dose of 20g ceftriaxone and more; Coagulation disorders. Thrombocytopenia. Minor prolongation in the prothrombin time</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Symptoms Category</td>
<td>Undesirable Effects</td>
<td>Notes</td>
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</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness, vertigo.</td>
<td>Anaemia (including haemolytic anaemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Stomatitis, glossitis, anorexia, nausea, emesis, abdominal pain, loose stool or diarrhea. These undesirable effects are mostly mild and frequently subside during, otherwise after discontinuation of therapy</td>
<td>Pseudomembranous enterocolitis (see section 4.4). If severe, persistent diarrhoea occurs during or after treatment, pseudomembranous colitis which is a serious, even life-threatening complication mostly caused by <em>clostridium difficile</em>, should be considered. Discontinuation of therapy with ceftriaxone depending on the indication should be considered and appropriate treatment measures should be initiated: e.g. intake of specific antibiotics/chemotherapeutics with clinically proven efficacy. Antiperistaltics are contraindicated.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Oliguria, increase in serum creatinine</td>
<td>Precipitates of ceftriaxone in the kidneys in paediatric patients, mostly in children older than 3 years treated either with high daily doses (e.g. 80 mg/kg BW per day and more) or with total doses above 10 g ceftriaxone and who presented several risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Mycosis of the genital tract.</td>
<td>Superinfections with non-susceptible micro-organisms.</td>
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<td>-----------------------------------------------------</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>Phlebitis following intravenous administration. This can be minimised by slow injection (over 2-4 minutes).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain at the site of injection. In rapid intravenous injection intolérability reactions in the form of sensation of heat or nausea may occur. This can be avoided by slow injection (2-4 minutes).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Allergic skin reactions (e.g. dermatitis, urticaria, exanthema), pruritus, oedematous swelling of skin and joints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe acute hypersensitivity reactions up to anaphylactic shock. Lyell syndrome/toxic epidermolysis, Stevens-Johnson syndrome or Erythema multiforme.</td>
</tr>
<tr>
<td></td>
<td>Severe acute</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Symptomatic precipitation of ceftriaxone calcium sail in the gallbladder of children/ reversible cholelithiasis in children. This disorder is rare in adults (see below).</td>
</tr>
</tbody>
</table>

4.9 **OVERDOSE**
No case of overdose has been reported.

*Symptoms of intoxication*
Typical signs of overdose can be expected to correspond to the adverse reaction profile. Colics occurred very rarely in the presence of nephropathy or cholelithiasis when using high doses administered more frequently and more rapidly than recommended.
Therapy of intoxication
Excessive serum concentration of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis.
There is no specific antidote. Symptomatic therapeutic measures are indicated.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group
Cephalosporins and related substances, ATC code: J01DD04
Mechanism of action
Ceftriaxone has bactericidal activity that results from the inhibition of bacterial cell wall synthesis.
Ceftriaxone has a high degree of stability in the presence of β-lactamases produced by Gram-negative and Gram-positive bacteria.
Synergistic effects of ceftriaxone and aminoglycosides on certain Gram-negative bacteria have been noted in vitro.

Mechanism of resistance
Ceftriaxone is active against organisms producing some types of beta-lactamase, for example TEM-1. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes. Ceftriaxone cannot be expected to be active against the majority of bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam medicinal products. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

Breakpoints
Ceftriaxone – EUCAST clinical MIC breakpoints
Enterobacteriaceae: S≤1 mg/L/R>2 mg/L
Staphylococcus: Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility.
Streptococcus A, B, C, G: S≤0.5 mg/L/R>0.5 mg/L
S. pneumoniae: S≤0.5 mg/L/R>2 mg/L
H. influenzae, M. catarrhalis: S≤0.12 mg/L/R>0.12 mg/L
N. gonorrhoeae: S≤0.12 mg/L/R>0.12 mg/L
N. meningitides: S≤0.12 mg/L/R>0.12 mg/L
Non-species related breakpoints: S≤1 mg/L/R>2 mg/L

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

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

3 Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species.

Microbiology
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.

Commonly susceptible species
Gram-Positive aerobes
Staphylococcus aureus (MSSA)
Staphylococcus epidermidis (MSSA)
Streptococcus pyogenes
Streptococcus pneumoniae
Viridans group streptococci

Gram-negative aerobes
Escherichia coli 1
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae 1
Klebsiella oxytoca 1
Moraxella catarrhalis
Neisseria meningitidis
Proteus mirabilis 1

Anaerobes
Bacteroides fragilis
Clostridium species
Peptostreptococcus spp.
Species for which acquired resistance may be a problem
Acinetobacter spp
Citrobacter freundii 1
Enterobacter spp. 1,2
Morganella morganii
Serratia marcescens

Inherently resistant organisms
Clostridium difficile
Enterococci
Listeria monocytogenes
Proteus vulgaris
Pseudomonas spp.
1) Some strains produce inducible or stably derepressed chromosomally-encoded cephalosporinases and ESBLs (extended spectrum beta-lactamases) and thus are clinically resistant to cephalosporins.

2) Clinical efficacy has been demonstrated for susceptible isolates of Enterobacter cloacae and Enterobacter aerogenes in approved clinical indications.

5.2 PHARMACOKINETIC PROPERTIES
Ceftriaxone is a cephalosporin for parenteral administration. Ceftriaxone is not absorbed after oral application.

After a dose of 1 – 2 g, concentrations have been shown to remain above the MIC values for most infection-causing pathogens for over 24 hours in over 60 different tissues (including lungs, heart, bile ducts, liver, tonsils, middle ear, nasal mucosa, bones) and in many tissue fluids (including cerebrospinal fluid, pleural fluid as well as prostatic and synovial fluid).

Distribution
Ceftriaxone distributes well in various compartments and also passes the placental barrier. The mean volume of distribution in healthy adults is 0.13 l/kg.

Ceftriaxone is reversibly bound to albumin. The binding is 95 % at plasma concentrations less than 100 mg/l with the binding percentage decreasing as the concentration increases (to 85 % at ceftriaxone plasma concentrations of 300 μg/ml).

Serum levels
Following an the intravenous infusion of 1 g ceftriaxone for 30 minutes, serum levels immediately after cessation of the infusion process were at 123.2 μg/ml, and at 94.81, 57.8, 20.2 and 4.6 μg/ml, respectively, 1.5, 4, 12 and 24 hours after the onset of infusion.
Ceftriaxone penetrates the inflamed meninges of newborns, infants, and children. In CSF, the peak concentrations of 18 mg/l are achieved, after a 50-100 mg/kg intravenous dose, in about four hours. In adult patients with meningitis, therapeutic concentrations are achieved within 2-24 hours with the dose of 50 mg/kg.

Ceftriaxone crosses the placenta and is excreted in human milk at low concentrations.

**Biotransformation**
Ceftriaxone does not undergo systemic metabolism but is broken down in the small intestine by bacterial action.

**Elimination**
Over a 0.15 to 3 g dose range, the values of elimination half-life range from 6 to 9 hours, total plasma clearance from 0.6-1.4 l/h and renal clearance from 0.3-0.7 l/h.

50-60% of ceftriaxone is eliminated as an unchanged active substance in the urine whilst the remainder is excreted via the bile into the faeces as microbiologically inactive metabolites.

Ceftriaxone concentrates in the urine. The urine concentrations are 5-10 times higher than those found in the plasma.

Ceftriaxone cannot be removed by dialysis. This applies to both haemodialysis and peritoneal dialysis. Urinary excretion is via glomerular filtration. No tubular secretion takes place. For this reason, no increase in the serum levels is to be expected in coincident administration of probenecid and is actually - even at higher dosage e.g. with 1-2 g probenecid – not found.

**Non-Linearity**
The pharmacokinetics of ceftriaxone is non-linear with respect to the dose. This non-linearity is explained by a concentration dependent decrease of binding to plasma proteins which leads to a respective increase in distribution and elimination.

With the exception of elimination half-life, all pharmacokinetic parameters are dose-dependent. Repeat dosing of 0.5 to 2 g results in 15% - 36% accumulation above single dose values.

**Special patient groups**
- **Elderly above 75 years**: the plasma elimination half-life of ceftriaxone is about 2 – 3 fold increased compared to young adults.
- **In newborn infants of 3 days of age**: the half-life of ceftriaxone in the serum amounts to approximately 16 hours, and approximately 9 hours in newborn infants aged from 9 to 30 days.
- **Patients with impaired renal and/or liver function**:
  - Patients with an impaired renal function have an increased excretion of ceftriaxone into the bile.
  - Patients with an impaired liver function have an increased renal excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is almost not increased in these patient groups. Patients with an impaired renal function, as well as an impaired liver function, may have an increased ceftriaxone plasma elimination half-life. In case of terminal renal insufficiency, the half-life is distinctively higher and reaches approximately 14 hours.

5.3 **PRECLINICAL SAFETY DATA**
The adverse reactions (e.g. gastrointestinal disturbances and nephrotoxicity) associated with high parenteral doses of cephalosporins have been shown to be reversible in animals during repeat dosing. After high doses of ceftriaxone diarrhoea, formation of biliary calculi in the gall bladder and nephropathy were observed in monkeys and dogs.

Ceftriaxone has no effect on fertility or reproduction. It has not been shown to possess any mutagenic activity.

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 such as Hartmann's solution and Ringer's solution. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

6.3 SHELF LIFE
Unopened: 24 months
After reconstitution:
For reconstituted solution, chemical and physical in-use stability has been demonstrated for at least 6 hours at or below 25°C or 24 hours at 2-8°C. Protect from light.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at or below 25°C or 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. Unused solution should be discarded.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light. For storage conditions of the reconstituted/diluted product see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER
Filled in 10 mL clear glass Type I vial, sealed with gray bromo butyl rubber stopper and white coloured flip off seal.
Pack sizes: 1 or 5 vials per carton.
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND HANDLING OF THE PRODUCT
Preparation of solutions for injection and infusion
The use of freshly prepared solutions is recommended. These maintain potency for at least 6 hours at or below 25°C in daylight, or 24 hours at 2 – 8°C.
When reconstituted in water for injections, ceftriaxone powder gives a light yellow to amber coloured clear solution.
Ceftriaxone for Injection should not be mixed in the same syringe with any drug other than 1.0% Lidocaine Hydrochloride BP solution (for intramuscular injection only).

Intramuscular injection: Ceftriaxone 500mg Powder for Solution for Injection should be dissolved in 2ml of 1.0% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection.
Solutions in Lidocaine should not be administered intravenously.

Intravenous injection: Ceftriaxone 500mg Powder for Solution for Injection should be dissolved in 5ml 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.
Add the recommended volume of reconstitution solution and shake well until the contents of the vial have dissolved completely. The solution should be visually inspected prior to use. Only clear solutions practically free from particles should be used.
For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER
Orchid Europe Limited,
Building 3, Chiswick Park, 566, Chiswick High Road,
Chiswick, London, W4 5YA, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 22805/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
UKPAR Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and
2g Powder for Solution for Injection or Infusion

09/10/2009

10 DATE OF REVISION OF THE TEXT

09/10/2009
1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 1g Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains:
1 g Ceftriaxone as 1.19 g hydrated disodium Ceftriaxone.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Powder for Solution for Injection.
Almost white or yellowish, slightly hygroscopic crystalline powder

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Ceftriaxone is indicated for the treatment of the following serious infections when known or likely to be
due to microorganisms that are susceptible to ceftriaxone and require parenteral treatment (see section 5.1):
- Septicaemia
- Acute bacterial meningitis
- Pneumonia.
Treatment may be started before the results of susceptibility tests are known.
Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route and method of administration
Intravenous use
Ceftriaxone for Injection may be administered by intravenous bolus injection or by intravenous infusion
after reconstitution of the solution according to the directions in sections 6.2 and 6.6.
Dosage and mode of administration should be determined by the severity and site of infection,
susceptibility of the causative micro-organism and the patient’s age and condition.
An intravenous injection should be administered over at least 2 – 4 minutes directly into the vein or via
the tubing of an intravenous infusion. Dose \( \geq 50 \text{ mg/kg} \) should be given as infusion over a period of at
least 30 minutes.

Normal dosage
- Adults and adolescents aged over 12 years with a body weight \( \geq 50 \text{ kg} \):
The usual dose is 1-2 g of ceftriaxone, administered once a day (every 24 hours). In cases of serious
infections or infections caused by moderately sensitive micro-organisms the dose can be raised up to 4 g,
administered once a day.
- Newborn infants (age 0 – 14 days):
20 – 50 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 50 mg per kg bodyweight must not be exceeded.
- Children 15 days-12 years of age with a body weight of \(< 50 \text{ kg} \):
20-80 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 80 mg per kg bodyweight must not be exceeded, except in
meningitis (see section 4.2.: Special dosage recommendations).
Children with a bodyweight of 50 kg or more receive the usual adult dosage once daily (see above).
For administration to neonates see 4.4.

Elderly:
The normal adult dose can usually be given to elderly patients, unless renal and hepatic function is
significantly impaired (see below).
Dosage in special situations
Meningitis:
In children with bacterial meningitis the therapy should be started with 100 mg/kg (not exceeding 4 g), administered once a day. After determining the sensitivity of the pathogen the dose may be reduced accordingly.
In new-born infants below 2 weeks of age the dose should not exceed 50 mg/kg/24 h.

Renal insufficiency:
In patients with impaired renal function, alteration of the ceftriaxone dose is not necessary, provided that the hepatic function is normal. Only in cases of extreme renal insufficiency (creatinine clearance < 10ml/min) the daily dose of the ceftriaxone should not exceed 2 g.
In co-existing severe renal and hepatic insufficiency, and in children with extreme renal insufficiency the serum ceftriaxone concentrations should be regularly monitored, and the dosage adjusted appropriately.
Patients undergoing haemodialysis or peritoneal dialysis do not need an additional dose of ceftriaxone after 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.

Hepatic insufficiency:
The dose does not need to be altered in patients with a liver disease provided that the renal function is normal.

Duration of therapy
The normal duration of therapy depends on the response and causative micro-organism. As with antibiotic therapy in general, administration of ceftriaxone should be continued for at least 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

4.3 CONTRAINDICATIONS
Hypersensitivity to the active substance, to other cephalosporins.
Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products (see section 4.4).
Ceftriaxone should not be given to neonates with jaundice, or those who are hypoalbuminaemic or acidotic.

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.
Calcium treatment because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
In suspected or proven infections with Pseudomonas aeruginosa, high resistance rates (> 60 %) for ceftriaxone in at least some European countries should be taken into consideration (see section 5.1).
In infections caused by Pseudomonas aeruginosa with proven sensitivity to ceftriaxone a combination with amino-glycosides is warranted to avoid secondary resistance.

In infections caused by other bacteria in patients with neutropenic fever interventional treatment with ceftriaxone should be combined with an aminoglycoside.
Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-lactam-medicinal products because patients hypersensitive to these medicines may be hypersensitive to ceftriaxone as well (cross-allergy).

Hypersensitivity reactions against ceftriaxone are more likely in patients with any other type of hypersensitivity reaction or asthma bronchiale.
Injections with ceftriaxone should be used with special caution in patients with allergic diathesis, because hypersensitivity reactions emerge faster and proceed more severely after intravenous injection (see section 4.8).

Hypersensitivity reactions may occur in all degrees of severity up to anaphylactic shock (see section 4.8).
In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined in section 4.2.
In case of simultaneous impairment of renal and liver function, serum-level of ceftriaxone should be monitored in regular intervals.

Monitoring of renal and hepatic function and haematological parameters at regular intervals are indicated during long-term treatment (see section 4.8).

Each administration of antibiotics can lead to multiplication of pathogens resistant to the active substance used. Signs of consecutive secondary infections with such pathogens (including candida and fungi) are to be heeded. Secondary infections are to be treated accordingly (see section 5.1).

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. Drugs that inhibit peristalsis must not be given.

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

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 80 mg/kg body weight should be avoided – except for meningitis – because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of ceftriaxone precipitate in the gallbladder is recommended.

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

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the medicinal product to produce a positive Coombs’ test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins. 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.

As with other antibiotics, incidental occurrences of vitamin K –deficiency should be considered.

High intravenous doses (>1 g or ≥50 mg/kg bodyweight) of ceftriaxone should be administered slowly (over a minimum period of 30 minutes) in order to avoid high concentrations in the bile.

This medicinal product contains 3.6 mmol (82.8 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Aminoglycosides:

In case of concomitant administration of cephalosporins and aminoglycosides there has been reported an increased risk of oto- and nephrotoxicity. Dose adjustment may be necessary. Furthermore, these medicinal products must be administered separately to avoid physicochemical incompatibility between ceftriaxone and the aminoglycoside.
Bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may antagonise the activity of ceftriaxone, especially in acute infections accompanied by rapid proliferation of micro-organisms. Simultaneous use of ceftriaxone and bacteriostatic antibiotics is, therefore, not recommended.

Probenecid:
Contrary to other cephalosporins, probenecid does not impede tubular secretion of ceftriaxone.

Oral contraceptives:
Ceftriaxone may adversely affect the efficacy of hormonal contraceptives. Consequently, it is advisable to use supplementary non-hormonal contraceptive measures.

Other:
Laboratory-diagnostic tests
The Coombs test may be false-positive in rare cases during treatment with ceftriaxone (see section 4.4). Non-enzymatic methods for glucose determinations in urine may yield false-positive results. For this reason, urine glucose determination during therapy with ceftriaxone should be carried out enzymatically. Ceftriaxone may lead to false-positive results of galactose determination in blood. 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.

4.6 PREGNANCY AND LACTATION
There are no data on use of ceftriaxone in pregnant women. Ceftriaxone crosses the placenta. Animal studies indicate no reproductive toxicity (see section 5.3). As a precautionary measure, ceftriaxone should only be used during pregnancy after benefit/risk assessment by the physician in charge, especially during the first trimester.

Ceftriaxone is excreted in low concentrations in breast milk. Caution should be exercised when prescribing to breast-feeding women. Diarrhoea and fungal infection of the mucous membrane could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Usually, Ceftriaxone has no or negligible influence on the ability to drive and use machines. However, undesirable effects such as hypotension, dizziness or vertigo (see section 4.8) should be taken into account.

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 is due to the low blood volume of the newborns. Moreover half life is longer than in adults. The following adverse reactions, reversible spontaneously or after treatment discontinuation, have been observed in association with ceftriaxone use:

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common &gt; 1/10</th>
<th>Common &gt; 1/100 to &lt; 1/10</th>
<th>Uncommon &gt; 1/1,000 to &lt; 1/100</th>
<th>Rare &gt; 1/10,000 to &lt; 1/1,000</th>
<th>Very rare: &lt; 1/10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia, leucopenia, granulocytopenia</td>
<td>Agranulocytosis (&lt;500/mm³), mostly after 10 day treatment and a total dose of 20g ceftriaxone and more; Coagulation disorders. Thrombocytopenia. Minor prolongation in the prothrombin time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>System</td>
<td>Undesirable Effects</td>
<td>Pseudomembranous enterocolitis (see section 4.4).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness, vertigo.</td>
<td>If severe, persistent diarrhoea occurs during or after treatment. pseudomembranous colitis which is a serious, even life-threatening complication mostly caused by <em>clostridium difficile</em>, should be considered. Discontinuation of therapy with ceftriaxone depending on the indication should be considered and appropriate treatment measures should be initiated: e.g. intake of specific antibiotics/chemotherapeutics with clinically proven efficacy. Antiperistaltics are contraindicated.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Stomatitis, glossitis, anorexia, nausea, emesis, abdominal pain, loose stool or diarrhoea. These undesirable effects are mostly mild and frequently subside during, otherwise after discontinuation of therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Oliguria, increase in serum creatinine</td>
<td>Precipitates of ceftriaxone in the kidneys in paediatric patients, mostly in children older than 3 years treated either with high daily doses (e.g. 80 mg/kg BW per day and more) or with total doses above 10 g ceftriaxone and who presented several risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Infections and Infestations** | Mycosis of the genital tract.  
Superinfections with non-susceptible micro-organisms. |  |
| --- | --- |  |
| **General disorders and administration site conditions** | Phlebitis following intravenous administration. This can be minimised by slow injection (over 2-4 minutes).  
Pain at the site of injection.  
In rapid intravenous injection intolérability reactions in the form of sensation of heat or nausea may occur. This can be avoided by slow injection (2-4 minutes). |  |
| **Immune system disorders** | Allergic skin reactions (e.g. dermatitis, urticaria, exanthema), pruritus, oedematous swelling of skin and joints | Severe acute hypersensitivity reactions up to anaphylactic shock.  
Lyell syndrome/toxic epidermolysis, Stevens-Johnson syndrome or Erythema multiforme.  
Severe acute |
**4.9 OVERDOSE**

No case of overdose has been reported.

*Symptoms of intoxication*

Typical signs of overdose can be expected to correspond to the adverse reaction profile. Colics occurred very rarely in the presence of nephropathy or choledolithiasis when using high doses administered more frequently and more rapidly than recommended.

| Hepatobilary disorders | Symptomatic precipitation of ceftriaxone calcium sail in the gallbladder of children/ reversible choledolithiasis in children. This disorder is rare in adults (see below). | Elevated liver enzymes in serum (AST, ALT, alkaline phosphatase). | Pancreatitis (see section 4.4). Increase in liver enzymes. Symptomatic precipitation of ceftriaxone calcium sail in the gallbladder of adults, which disappeared after discontinuation or cessation of therapy with ceftriaxone. These opacities usually occurred only after administration of higher doses than the recommended standard doses. In the rare cases in which the precipitates are accompanied by clinical symptoms such as pain, symptomatic measures are recommended. Discontinuation of treatment should be considered too (see section 4.4). |
Therapy of intoxication
Excessive serum concentration of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis.
There is no specific antidote. Symptomatic therapeutic measures are indicated.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group
cephalosporins and related substances, ATC code: J01DD04
Mechanism of action
Ceftriaxone has bactericidal activity that results from the inhibition of bacterial cell wall synthesis.
Ceftriaxone has a high degree of stability in the presence of β-lactamases produced by Gram-negative and Gram-positive bacteria.
Synergistic effects of ceftriaxone and aminoglycosides on certain Gram-negative bacteria have been noted in vitro.

Mechanism of resistance
Ceftriaxone is active against organisms producing some types of beta-lactamase, for example TEM-1. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes. Ceftriaxone cannot be expected to be active against the majority of bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam medicinal products. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

Breakpoints
Ceftriaxone – EUCAST clinical MIC breakpoints
Enterobacteriaceae: S≤1 mg/L/R>2 mg/L¹
Staphylococcus: Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility.
Streptococcus A, B, C, G: S≤0.5 mg/L/R>0.5 mg/L²
S. pneumoniae: S≤0.5 mg/L/R>2 mg/L²
H. influenzae,
M. catarrhalis: S≤0.12 mg/L/R>0.12 mg/L²
N. gonorrhoeae: S≤0.12 mg/L/R>0.12 mg/L²
N. meningitides: S≤0.12 mg/L/R>0.12 mg/L²
Non-species related breakpoints: S≤1 mg/L/R>2 mg/L³

¹ The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.

² Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

³ Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species.

Microbiology
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.

Commonly susceptible species
Gram-Positive aerobes
Staphylococcus aureus (MSSA)
Staphylococcus epidermidis (MSSA)
Streptococcus pyogenes
Streptococcus pneumoniae
Viridans group streptococci

**Gram-negative aerobes**
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Klebsiella oxytoca
Moraxella catarrhalis
Neisseria meningitidis
Proteus mirabilis

**Anaerobes**
Bacteroides fragilis
Clostridium species
Peptostreptococcus spp.
Species for which acquired resistance may be a problem
Acinetobacter spp
Citrobacter freundii
Enterobacter spp.
Morganella morgani
Serratia marcescens

**Inherently resistant organisms**
Clostridium difficile
Enterococci
Listeria monocytogenes
Proteus vulgaris
Pseudomonas spp.

1) Some strains produce inducible or stably derepressed chromosomally-encoded cephalosporinases and ESBLs (extended spectrum beta-lactamases) and thus are clinically resistant to cephalosporins.

2) Clinical efficacy has been demonstrated for susceptible isolates of Enterobacter cloacae and Enterobacter aerogenes in approved clinical indications.

**5.2 PHARMACOKINETIC PROPERTIES**

Ceftriaxone is a cephalosporin for parenteral administration. Ceftriaxone is not absorbed after oral application.

After a dose of 1 – 2 g, concentrations have been shown to remain above the MIC values for most infection-causing pathogens for over 24 hours in over 60 different tissues (including lungs, heart, bile ducts, liver, tonsils, middle ear, nasal mucosa, bones) and in many tissue fluids (including cerebrospinal fluid, pleural fluid as well as prostatic and synovial fluid).

Distribution
Ceftriaxone distributes well in various compartments and also passes the placental barrier. The mean volume of distribution in healthy adults is 0.13 l/kg.
Ceftriaxone is reversibly bound to albumin. The binding is 95 % at plasma concentrations less than 100 mg/l with the binding percentage decreasing as the concentration increases (to 85 % at ceftriaxone plasma concentrations of 300 μg/ml).

Serum levels
Following an intravenous infusion of 1 g ceftriaxone for 30 minutes, serum levels immediately after cessation of the infusion process were at 123.2 μg/ml, and at 94.81, 57.8, 20.2 and 4.6 μg/ml, respectively, 1.5, 4, 12 and 24 hours after the onset of infusion.

Ceftriaxone penetrates the inflamed meninges of newborn, infants and children. In CSF the peak concentrations of 18 mg/l are achieved, after a 50-100 mg/kg intravenous dose, in about four hours. In adult patients with meningitis, therapeutic concentrations are achieved within 2-24 hours with the dose of 50 mg/kg.

Ceftriaxone crosses the placenta and is excreted in human milk at low concentrations.

Biotransformation
Ceftriaxone does not undergo systemic metabolism but it is broken down in the small intestine by bacterial action.

Elimination
Over a 0.15 to 3 g dose range, the values of elimination half-life range from 6 to 9 hours, total plasma clearance from 0.6-1.4 l/h and renal clearance from 0.3-0.7 l/h. 50-60 % of ceftriaxone is eliminated as an unchanged active substance in the urine whilst the remainder is excreted via the bile into the faeces as microbiologically inactive metabolites. Ceftriaxone concentrates in the urine. The urine concentrations are 5-10 times higher than those found in the plasma.

Ceftriaxone cannot be removed by dialysis. This applies to both haemodialysis and peritoneal dialysis. Urinary excretion is via glomerular filtration. No tubular secretion takes place. For this reason, no increase in the serum levels is to be expected in coincident administration of probenecid and is actually – even at higher dosage e.g. with 1-2 g probenecid – not found.

Non-Linearity
The pharmacokinetics of ceftriaxone is non-linear with respect to the dose. This non-linearity is explained by a concentration dependent decrease of binding to plasma proteins which leads to a respective increase in distribution and elimination. With the exception of elimination half-life, all pharmacokinetic parameters are dose-dependent. Repeat dosing of 0.5 to 2 g results in 15 % - 36 % accumulation above single dose values.

Special patient groups
Elderly above 75 years: the plasma elimination half-life of ceftriaxone is about 2 – 3 fold increased compared to young adults.

In newborn infants of 3 days of age, the half-life of ceftriaxone in the serum amounts to approximately 16 hours, and approximately 9 hours in newborn infants aged from 9 to 30 days.

Patients with impaired renal and/or liver function:
Patients with an impaired renal function have an increased excretion of ceftriaxone into the bile. Patients with an impaired liver function have an increased renal excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is almost not increased in these patient groups. Patients with an impaired renal function, as well as an impaired liver function, may have an increased ceftriaxone plasma elimination half-life. In case of terminal renal insufficiency, the half-life is distinctively higher and reaches approximately 14 hours.

5.3 PRECLINICAL SAFETY DATA
The adverse reactions (e.g. gastrointestinal disturbances and nephrotoxicity) associated with high parenteral doses of cephalosporins have been shown to be reversible in animals during repeat dosing. After high doses of ceftriaxone diarrhoea, formation of biliary calculi in the gall bladder and nephropathy were observed in monkeys and dogs.

Ceftriaxone has no effect on fertility or reproduction. It has not been shown to possess any mutagenic activity.

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 such as Hartmann's solution and Ringer's solution. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

6.3 SHELF LIFE
Unopened: 24 months
After reconstitution:
For reconstituted solution, chemical and physical in-use stability has been demonstrated for at least 6 hours at or below 25°C or 24 hours at 2-8°C. Protect from light.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at or below 25°C or 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. Unused solution should be discarded.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light.
For storage conditions of the reconstituted/diluted product see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER
Filled in 20 mL clear glass molded Type I Vial, sealed with gray bromo butyl rubber stopper and Blue coloured flip off seal.
Pack sizes: 1 or 5 vials per carton.
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING OF THE PRODUCT
Preparation of solutions for injection and infusion
The use of freshly prepared solutions is recommended. These maintain potency for at least 6 hours at or below 25°C in daylight, or 24 hours at 2 – 8°C.
When reconstituted in water for injections, ceftriaxone powder gives a light yellow to amber coloured clear solution.
Ceftriaxone for Injection should not be mixed in the same syringe with any drug other than 1.0% Lidocaine Hydrochloride BP solution (for intramuscular injection only).

Intramuscular injection: Ceftriaxone 1g Powder for Solution for Injection should be dissolved in 2ml of 1.0% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection.
Solutions in Lidocaine should not be administered intravenously.

Intravenous injection: Ceftriaxone 1g Powder for Solution for Injection should be dissolved 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.

Add the recommended volume of reconstitution solution and shake well until the contents of the vial have dissolved completely. The solution should be visually inspected prior to use. Only clear solutions practically free from particles should be used.
For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER
Orchid Europe Limited,
Building 3, Chiswick Park, 566, Chiswick High Road,
Chiswick, London, W4 5YA, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 22805/0004
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/10/2009

10 DATE OF REVISION OF THE TEXT
09/10/2009
1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 2 g Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains:
2 g Ceftriaxone as 2.39 g hydrated disodium Ceftriaxone.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Powder for Solution for Injection or infusion
Almost white or yellowish, slightly hygroscopic crystalline powder

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Ceftriaxone is indicated for the treatment of the following serious infections when known or likely to be
due to microorganisms that are susceptible to ceftriaxone and require parenteral treatment (see section
5.1):
Septicaemia
Acute bacterial meningitis
Pneumonia.
Treatment may be started before the results of susceptibility tests are known.
Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route and method of administration
Intravenous use
Ceftriaxone for Injection may be administered by intravenous bolus injection or by intravenous infusion
after reconstitution of the solution according to the directions in sections 6.2 and 6.6.
Dosage and mode of administration should be determined by the severity and site of infection,
susceptibility of the causative micro-organism and the patient's age and condition.
An intravenous injection should be administered over at least 2 – 4 minutes directly into the vein or via
the tubing of an intravenous infusion. Dose ≥50 mg/kg should be given as infusion over a period of at
least 30 minutes.

Normal dosage
Adults and adolescents aged over 12 years with a body weight ≥50 kg:
The usual dose is 1-2 g of ceftriaxone, administered once a day (every 24 hours). In cases of serious
infections or infections caused by moderately sensitive micro-organisms the dose can be raised up to 4 g,
administered once a day.

Newborn infants (age 0 – 14 days):
20 – 50 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 50 mg per kg bodyweight must not be exceeded.
Children 15 days-12 years of age with a body weight of < 50 kg:
20-80 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 80 mg per kg bodyweight must not be exceeded, except in
meningitis (see section 4.2.: Special dosage recommendations).
Children with a bodyweight of 50 kg or more receive the usual adult dosage once daily (see above).
For administration to neonates see 4.4.

Elderly:
The normal adult dose can usually be given to elderly patients, unless renal and hepatic function is
significantly impaired (see below).
Dosage in special situations
Meningitis:
In children with bacterial meningitis the therapy should be started with 100 mg/kg (not exceeding 4 g), administered once a day. After determining the sensitivity of the pathogen the dose may be reduced accordingly.
In new-born infants below 2 weeks of age the dose should not exceed 50 mg/kg/24 h.

Renal insufficiency:
In patients with impaired renal function, alteration of the ceftriaxone dose is not necessary, provided that the hepatic function is normal. Only in cases of extreme renal insufficiency (creatinine clearance < 10ml/min) the daily dose of the ceftriaxone should not exceed 2 g.
In co-existing severe renal and hepatic insufficiency, and in children with extreme renal insufficiency the serum ceftriaxone concentrations should be regularly monitored, and the dosage adjusted appropriately.
Patients undergoing haemodialysis or peritoneal dialysis do not need an additional dose of ceftriaxone after 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.

Hepatic insufficiency:
The dose does not need to be altered in patients with a liver disease provided that the renal function is normal.

Duration of therapy
The normal duration of therapy depends on the response and causative micro-organism. As with antibiotic therapy in general, administration of ceftriaxone should be continued for at least 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

4.3 CONTRAINDICATIONS
Hypersensitivity to the active substance, to other cephalosporins.
Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products (see section 4.4).
Ceftriaxone should not be given to neonates with jaundice, or those who are hypoalbuminaemic or acidotic.
Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.
Calcium treatment because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
In suspected or proven infections with Pseudomonas aeruginosa, high resistance rates (> 60 %) for ceftriaxone in at least some European countries should be taken into consideration (see section 5.1).
In infections caused by Pseudomonas aeruginosa with proven sensitivity to ceftriaxone a combination with amino-glycosides is warranted to avoid secondary resistance.

In infections caused by other bacteria in patients with neutropenic fever interventional treatment with ceftriaxone should be combined with an aminoglycoside.
Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-lactam-medicinal products because patients hypersensitive to these medicines may be hypersensitive to ceftriaxone as well (cross-allergy).

Hypersensitivity reactions against ceftriaxone are more likely in patients with any other type of hypersensitivity reaction or asthma bronchiale.
Injections with ceftriaxone should be used with special caution in patients with allergic diathesis, because hypersensitivity reactions emerge faster and proceed more severely after intravenous injection (see section 4.8).

Hypersensitivity reactions may occur in all degrees of severity up to anaphylactic shock (see section 4.8).
In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined in section 4.2.
In case of simultaneous impairment of renal and liver function, serum-level of ceftriaxone should be monitored in regular intervals. Monitoring of renal and hepatic function and haematological parameters at regular intervals are indicated during long-term treatment (see section 4.8).

Each administration of antibiotics can lead to multiplication of pathogens resistant to the active substance used. Signs of consecutive secondary infections with such pathogens (including candida and fungi) are to be heeded. Secondary infections are to be treated accordingly (see section 5.1).

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. Drugs that inhibit peristalsis must not be given.

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

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 80 mg/kg body weight should be avoided – except for meningitis – because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of ceftriaxone precipitate in the gallbladder is recommended.

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

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the medicinal product to produce a positive Coombs’ test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins. 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.

As with other antibiotics, incidental occurrences of vitamin K –deficiency should be considered. High intravenous doses (≥1 g or ≥50 mg/kg body weight) of ceftriaxone should be administered slowly (over a minimum period of 30 minutes) in order to avoid high concentrations in the bile. This medicinal product contains 7.2 mmol (165.6 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Aminoglycosides:
In case of concomitant administration of cephalosporins and aminoglycosides there has been reported an increased risk of oto- and nephrotoxicity. Dose adjustment may be necessary. Furthermore, these medicinal products must be administered separately to avoid physicochemical incompatibility between ceftriaxone and the aminoglycoside.

Bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may antagonise the activity of ceftriaxone, especially in acute infections accompanied by rapid proliferation of micro-organisms. Simultaneous use of ceftriaxone and bacteriostatic antibiotics is, therefore, not recommended.
Probenecid:
Contrary to other cephalosporins, probenecid does not impede tubular secretion of ceftriaxone.

Oral contraceptives:
Ceftriaxone may adversely affect the efficacy of hormonal contraceptives. Consequently, it is advisable to use supplementary non-hormonal contraceptive measures.

Other:
Laboratory-diagnostic tests
The Coombs test may be false-positive in rare cases during treatment with ceftriaxone (see section 4.4). Non-enzymatic methods for glucose determinations in urine may yield false-positive results. For this reason, urine glucose determination during therapy with ceftriaxone should be carried out enzymatically.
Ceftriaxone may lead to false-positive results of galactose determination in blood.
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.

4.6 PREGNANCY AND LACTATION
There are no data on use of ceftriaxone in pregnant women. Ceftriaxone crosses the placenta.
Animal studies indicate no reproductive toxicity (see section 5.3). As a precautionary measure, ceftriaxone should only be used during pregnancy after benefit/risk assessment by the physician in charge, especially during the first trimester.
Ceftriaxone is excreted in low concentrations in breast milk. Caution should be exercised when prescribing to breast-feeding women. Diarrhoea and fungal infection of the mucous membrane could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Usually, Ceftriaxone has no or negligible influence on the ability to drive and use machines. However, undesirable effects such as hypotension, dizziness or vertigo (see section 4.8) should be taken into account.

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 is due to the low blood volume of the newborns. Moreover half life is longer than in adults. The following adverse reactions, reversible spontaneously or after treatment discontinuation, have been observed in association with ceftriaxone use:

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>&gt; 1/10</td>
<td>&gt; 1/100 to &lt; 1/10</td>
<td>&gt; 1/1000 to &lt; 1/100</td>
<td>&gt; 1/10,000 to &lt; 1/1000</td>
<td>&lt; 1/10,000</td>
</tr>
<tr>
<td></td>
<td>Eosinophilia, leucopenia, granulocytopenia</td>
<td>Agranulocytosis (&lt;500/mm³), mostly after 10 day treatment and a total dose of 20g ceftriaxone and more; Coagulation disorders. Thrombocytopenia. Minor prolongation in the prothrombin time has been described.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness, vertigo.</td>
<td>Anaemia (including haemolytic anaemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Stomatitis, glossitis, anorexia, nausea, emesis, abdominal pain, loose stool or diarrhoea. These undesirable effects are mostly mild and frequently subside during, otherwise after discontinuation of therapy</td>
<td>Pseudomembranous enterocolitis (see section 4.4). If severe, persistent diarrhoea occurs during or after treatment, pseudomembranous colitis which is a serious, even life-threatening complication mostly caused by <em>Clostridium difficile</em>, should be considered. Discontinuation of therapy with ceftriaxone depending on the indication should be considered and appropriate treatment measures should be initiated: e.g. intake of specific antibiotics/chemotherapeutics with clinically proven efficacy. Antiperistalsics are contraindicated.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Renal and urinary disorders | Oliguria, increase in serum creatinine | Precipitates of ceftriaxone in the kidneys in paediatric patients, mostly in children older than 3 years treated either with high daily doses (e.g. 80 mg/kg BW per day and more) or with total doses above 10 g ceftriaxone and who presented several risk factors (e.g. restricted fluid supply). However,
<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td>Mycosis of the genital tract. Superinfections with non-susceptible micro-organisms.</td>
<td>this symptomatology is reversible after discontinuation of ceftriaxone. Haematuria</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Phlebitis following intravenous administration. This can be minimised by slow injection (over 2-4 minutes). Pain at the site of injection. In rapid intravenous injection intolerability reactions in the form of sensation of heat or nausea may occur. This can be avoided by slow injection (2-4 minutes).</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic skin reactions (e.g. dermatitis, urticaria, exanthema), pruritus, oedematous swelling of skin and joints</td>
<td>Severe acute hypersensitivity reactions up to anaphylactic shock. Lyell syndrome/toxic epidermolysis, Stevens-Johnson syndrome or Erythema multiforme. Severe acute hypersensitivity reactions and anaphylactic</td>
</tr>
<tr>
<td>Hepatobilary disorders</td>
<td>Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of children/reversible cholelithiasis in children. This disorder is rare in adults (see below).</td>
<td>Elevated liver enzymes in serum (AST, ALT, alkaline phosphatase).</td>
</tr>
</tbody>
</table>

4.9 OVERDOSE
No case of overdose has been reported.

**Symptoms of intoxication**
Typical signs of overdose can be expected to correspond to the adverse reaction profile. Colics occurred very rarely in the presence of nephropathy or cholelithiasis when using high doses administered more frequently and more rapidly than recommended.

**Therapy of intoxication**
Excessive serum concentration of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Symptomatic therapeutic measures are indicated.
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group
Cephalosporins and related substances, ATC code: J01DD04

Mechanism of action
Ceftriaxone has bactericidal activity that results from the inhibition of bacterial cell wall synthesis.
Ceftriaxone has a high degree of stability in the presence of β-lactamases produced by Gram-negative and Gram-positive bacteria.
Synergistic effects of ceftriaxone and aminoglycosides on certain Gram-negative bacteria have been noted in vitro.

Mechanism of resistance
Ceftriaxone is active against organisms producing some types of beta-lactamase, for example TEM-1. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes. Ceftriaxone cannot be expected to be active against the majority of bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam medicinal products. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

Breakpoints

**Ceftriaxone – EUCAST clinical MIC breakpoints**

Enterobacteriaceae: S\(\leq\)1 mg/L/R\(>\)2 mg/L

Staphylococcus: Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility.

Streptococcus A, B, C, G: S\(\leq\)0.5 mg/L/R\(>\)0.5 mg/L

S. pneumoniae: S\(\leq\)0.5 mg/L/R\(>\)2 mg/L

H. influenzae, M. catarrhalis: S\(\leq\)0.12 mg/L/R\(>\)0.12 mg/L

N. gonorrhoeae: S\(\leq\)0.12 mg/L/R\(>\)0.12 mg/L

N. meningitides: S\(\leq\)0.12 mg/L/R\(>\)0.12 mg/L

Non-species related breakpoints: S\(\leq\)1 mg/L/R\(>\)2 mg/L

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

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

3 Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species.

Microbiology
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.

Commonly susceptible species

**Gram-Positive aerobes**

*Staphylococcus aureus (MSSA)*

*Staphylococcus epidermidis (MSSA)*

*Streptococcus pyogenes*
Streptococcus pneumoniae  
Viridans group streptococci

**Gram-negative aerobes**
- Escherichia coli 1
- Haemophilus influenzae
- Haemophilus parainfluenzae
- Klebsiella pneumoniae 1
- Klebsiella oxytoca 1
- Moraxella catarrhalis
- Neisseria meningitidis
- Proteus mirabilis 1

**Anaerobes**
- Bacteroides fragilis
- Clostridium species
- Peptostreptococcus spp.

Species for which acquired resistance may be a problem
- Acinetobacter spp
- Citrobacter freundii 1
- Enterobacter spp. 1,2
- Morganella morganii
- Serratia marcescens

**Inherently resistant organisms**
- Clostridium difficile
- Enterococci
- Listeria monocytogenes
- Proteus vulgaris
- Pseudomonas spp.

1) Some strains produce inducible or stably derepressed chromosomally-encoded cephalosporinases and ESBLs (extended spectrum beta-lactamases) and thus are clinically resistant to cephalosporins.

2) Clinical efficacy has been demonstrated for susceptible isolates of Enterobacter cloacae and Enterobacter aerogenes in approved clinical indications.

**5.2 PHARMACOKINETIC PROPERTIES**
Ceftriaxone is a cephalosporin for parenteral administration. Ceftriaxone is not absorbed after oral application.

After a dose of 1 – 2 g, concentrations have been shown to remain above the MIC values for most infection-causing pathogens for over 24 hours in over 60 different tissues (including lungs, heart, bile ducts, liver, tonsils, middle ear, nasal mucosa, bones) and in many tissue fluids (including cerebrospinal fluid, pleural fluid as well as prostatic and synovial fluid).

**Distribution**
Ceftriaxone distributes well in various compartments and also passes the placental barrier. The mean volume of distribution in healthy adults is 0.13 L/kg.

Ceftriaxone is reversibly bound to albumin. The binding is 95 % at plasma concentrations less than 100 μg/ml with the binding percentage decreasing as the concentration increases (to 85 % at ceftriaxone plasma concentrations of 300 μg/ml).

**Serum levels**
Following an intravenous infusion of 1 g ceftriaxone for 30 minutes, serum levels immediately after cessation of the infusion process were at 123.2 μg/ml, and at 94.81, 57.8, 20.2 and 4.6 μg/ml, respectively, 1.5, 4, 12 and 24 hours after the onset of infusion.

Ceftriaxone penetrates the inflamed meninges of newborn, infants and children. In CSF the peak concentrations of 18 mg/l are achieved, after a 50-100 mg/kg intravenous dose, in about four hours. In
adult patients with meningitis, therapeutic concentrations are achieved within 2-24 hours with the dose of 50 mg/kg.

Ceftriaxone crosses the placenta and is excreted in human milk at low concentrations.

Biotransformation
Ceftriaxone does not undergo systemic metabolism but it is broken down in the small intestine by bacterial action.

Elimination
Over a 0.15 to 3 g dose range, the values of elimination half-life range from 6 to 9 hours, total plasma clearance from 0.6-1.4 l/h and renal clearance from 0.3-0.7 l/h.
50-60 % of ceftriaxone is eliminated as an unchanged active substance in the urine whilst the remainder is excreted via the bile into the faeces as microbiologically inactive metabolites.
Ceftriaxone concentrates in the urine. The urine concentrations are 5-10 times higher than those found in the plasma.

Ceftriaxone cannot be removed by dialysis. This applies to both haemodialysis and peritoneal dialysis. Urinary excretion is via glomerular filtration. No tubular secretion takes place. For this reason, no increase in the serum levels is to be expected in coincident administration of probenecid and is actually – even at higher dosage e.g. with 1-2 g probenecid – not found.

Non-Linearity
The pharmacokinetics of ceftriaxone is non-linear with respect to the dose. This non-linearity is explained by a concentration dependent decrease of binding to plasma proteins which leads to a respective increase in distribution and elimination.
With the exception of elimination half-life, all pharmacokinetic parameters are dose-dependent. Repeat dosing of 0.5 to 2 g results in 15 % - 36 % accumulation above single dose values.

Special patient groups
Elderly above 75 years: the plasma elimination half-life of ceftriaxone is about 2 – 3 fold increased compared to young adults.
In newborn infants of 3 days of age, the half-life of ceftriaxone in the serum amounts to approximately 16 hours, and approximately 9 hours in newborn infants aged from 9 to 30 days.
Patients with impaired renal and/or liver function:
Patients with an impaired renal function have an increased excretion of ceftriaxone into the bile. Patients with an impaired liver function have an increased renal excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is almost not increased in these patient groups. Patients with an impaired renal function, as well as an impaired liver function, may have an increased ceftriaxone plasma elimination half-life. In case of terminal renal insufficiency, the half-life is distinctively higher and reaches approximately 14 hours.

5.3 PRECLINICAL SAFETY DATA
The adverse reactions (e.g. gastrointestinal disturbances and nephrotoxicity) associated with high parenteral doses of cephalosporins have been shown to be reversible in animals during repeat dosing.
After high doses of ceftriaxone diarrhoea, formation of biliary calculi in the gall bladder and nephropathy were observed in monkeys and dogs.
Ceftriaxone has no effect on fertility or reproduction. It has not been shown to possess any mutagenic activity.

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 such as Hartmann's solution and Ringer's solution. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.
6.3 SHELF LIFE

Unopened: 24 months

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

This medicinal product does not require any special storage conditions.
Keep vial(s) in the outer carton to protect from light.
For storage conditions of the reconstituted/diluted product see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Ceftriaxone 2g vial: Filled in 20 mL clear glass molded Type I vial, sealed with gray bromobutyl rubber stopper and white coloured flip off seal.
Ceftriaxone 2 g (infusion) vial: Filled in 100 mL clear glass molded Type I vial, sealed with gray bromobutyl rubber stopper and white coloured flip off seal.
Pack sizes: 1 or 5 vials per carton.
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Preparation of solutions for injection and infusion
The use of freshly prepared solutions is recommended. These maintain potency for at least 6 hours at or below 25°C in daylight, or 24 hours at 2 – 8°C.
When reconstituted in water for injections, ceftriaxone powder gives a light yellow to amber coloured clear solution.
Ceftriaxone for Injection should not be mixed in the same syringe with any drug other than 1.0% Lidocaine Hydrochloride BP solution (for intramuscular injection only).

Intramuscular injection: Ceftriaxone 2g Powder for Solution for Injection should be dissolved in 7ml of 1.0% 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 in Lidocaine should not be administered intravenously.

Intravenous injection: Ceftriaxone 2g Powder for Solution for Injection should be dissolved in 20ml 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: Ceftriaxone 2g Powder for Solution for Injection/Infusion should be dissolved in 40ml of one of the following calcium-free solutions: Glucose Injection BP 5% or 10%, Sodium Chloride Injection BP, Sodium Chloride and Glucose Injection BP (0.45% sodium chloride and 2.5% glucose), dextran 6% in Glucose Injection BP 5%, hydroxyethyl starch 6 - 10% infusions. The infusion should be administered over at least 30 minutes.

Add the recommended volume of reconstitution solution and shake well until the contents of the vial have dissolved completely. The solution should be visually inspected prior to use. Only clear solutions practically free from particles should be used.
For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER

Orchid Europe Limited,
Building 3, Chiswick Park, 566, Chiswick High Road,
Chiswick, London, W4 5YA, United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
   PL 22805/0005

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
   09/10/2009

10 DATE OF REVISION OF THE TEXT
    09/10/2009
Ceftriaxone 250 mg powder for solution for injection (Ceftriaxone)

The name of your medicine is Ceftriaxone 250mg powder for solution for injection, which will be referred to as Ceftriaxone throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ceftriaxone is and what it is used for
2. Before you use Ceftriaxone
3. How to use Ceftriaxone
4. Possible side effects
5. How to store Ceftriaxone
6. Further information

1. What Ceftriaxone is and what it is used for

Ceftriaxone belongs to a group of antibacterial agents called cephalosporins, which act by killing the bacteria.

Ceftriaxone is used when an infection is known to be or likely to be caused by bacteria that are sensitive to Ceftriaxone. It is used for the treatment of the following conditions:
- Infection of the bloodstream by bacteria (septicaemia)
- Infection of the membranes and fluid surrounding the brain and spinal cord (meningitis)
- Chest infections such as pneumonia

The treatment may sometimes need to be started before knowing if the bacteria are sensitive to Ceftriaxone or not.

If you have been on Ceftriaxone treatment for a prolonged period, it may result in the overgrowth of organisms on which Ceftriaxone does not act. This may need to be treated by other antimicrobial agents.

When Ceftriaxone is given in larger doses, especially to children, it may precipitate in the gallbladder and kidneys and then be seen as shadows on ultrasound. The condition is usually reversible and your doctor will normally not recommend a separate treatment.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is especially important if:
- you are taking antibiotics called aminoglycosides (e.g. gentamicin). The use of Ceftriaxone with such drugs can cause damage both to kidneys and hearing.
- you are taking antibiotics like chloramphenicol and tetracycline. These drugs should not be used together with Ceftriaxone as they are known to weaken the effects of Ceftriaxone and other cephalosporins.
- you are taking birth control pills (Ceftriaxone may reduce their effectiveness). You should use additional contraceptive measures like the barrier method (condom or diaphragm with spermicide) during treatment to avoid pregnancy.

Laboratory tests
Ceftriaxone can alter the results of some blood tests (such as cross-matching blood and the Coombs' test). It is important to tell the doctor that you are taking this medicine if you have to have any of these tests.

Ceftriaxone can also alter the results of some urine tests for glucose (a type of sugar). If you have diabetes and routinely test your urine, tell your doctor. This is because other tests may have to be used to monitor your diabetes
2. Before you use Ceftriaxone

Do not use Ceftriaxone if you:

- are allergic (hypersensitive) to Ceftriaxone or any other cephalosporin type of antibiotics.
- ever had a severe allergic reaction to any penicillin or any other beta-lactam antibiotics.

Ceftriaxone will not be given to your newborn baby if any of the following conditions are present:

- jaundice (yellowing of the skin or whites of the eyes caused by liver or blood problems)
- low level of protein in the blood
- excessive acid in the body fluids
- premature birth
- calcium treatment (this is because Ceftriaxone and calcium-containing products can interact with each other)

Take special care with Ceftriaxone

Ceftriaxone is not suitable for everyone. Before treatment with Ceftriaxone, make sure your doctor knows if you:

- have ever had an allergic reaction to any penicillin or any other beta-lactam antibiotic. This is because you may have an increased chance of being allergic to Ceftriaxone if you are allergic to penicillins.
- suffer from allergies or have asthma (a condition that affects the airways).
- have ever been told that your kidneys and liver do not work very well. You will then need to have regular blood tests during your treatment to monitor your condition.
- have an infection caused by a bacterium called *Pseudomonas aeruginosa*. Your doctor may sometimes need to use some other antibiotic or use Ceftriaxone at the same time as other antibiotics (such as aminoglycosides) to help treat the infection.
- have ever had gallbladder, or gastrointestinal disease (especially inflammation of the large bowel called as colitis).
- have recently been very ill or if you are being fed through a vein.
- are on a low sodium diet.
- develop loose and/or frequent motions (diarrhoea) during or shortly after treatment. If your diarrhoea is severe or there is presence of blood in the stools, contact your doctor immediately. You might have developed an infection of the large bowel, which needs special treatment. Medicines which may slow or stop bowel movements must not be taken.

while you are having this medicine.

Ceftriaxone can also alter the results of some blood tests for galactose (a type of sugar).

Taking Ceftriaxone with food and drink

Ceftriaxone can be administered intravenously (into a vein) regardless of meals. Alcohol can interact with certain medicines. However, there are no known interactions (such as unpleasant physical reactions) between alcohol and Ceftriaxone.

Pregnancy and breast-feeding

Before starting treatment, you must tell your doctor if you are pregnant or if you intend to become pregnant. Ceftriaxone will be given to a pregnant woman only if it is really needed.

Mothers who wish to breast-feed should discuss with their doctor. Small amounts of Ceftriaxone enter the milk. Inform your doctor if your baby develops diarrhoea or any other unusual symptom. Some babies may be sensitised to Ceftriaxone and can develop allergic reactions.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Ceftriaxone may affect your ability to drive or operate machinery as dizziness has been reported during treatment with Ceftriaxone. If affected, do not drive or use machines.

Important information about some of the ingredients of Ceftriaxone

This medicinal product contains 0.9 mmol (20.7 mg) sodium per 250 mg dose. This should be taken into consideration by patients under controlled sodium diet.

3. How to use Ceftriaxone

Dosage

A doctor or nurse will usually give you this medicine. Your doctor will decide the dose (amount) and route of administration of your medicine. This will depend on your age, the nature of your illness and any underlying conditions eg. kidney/liver problems.

Always use Ceftriaxone exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How Ceftriaxone injection is given

Ceftriaxone is supplied as a powder, so it must be made into a solution before it can be given. Your doctor or nurse will prepare a freshly prepared solution of Ceftriaxone.
Ceftriaxone will usually be given by a doctor or nurse intravenously (into a vein) either by a slow injection over at least 2 to 4 minutes or by a slow infusion (drip) over at least 30 minutes.

The usual dose is:

**Adults and children over 12 years old:**
The usual dosage range for Ceftriaxone is 1 to 2g given once each day. In some cases, where infections are severe, the doctor may administer a higher dose up to 4g each day.
The doses are the same for elderly patients, provided the liver and kidneys are normal.

**Newborn and very young babies (neonates) aged up to 14 days:**
The daily dose is worked out according to the weight of the child. The usual daily dose is 20 to 50 mg of Ceftriaxone per kg of bodyweight given once each day. The maximum dose for the treatment of severe infections including meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) in this age group is 50 mg per kg of bodyweight.

**Infants and children aged up to 12 years:**
The usual daily dose is 20 to 80 mg of Ceftriaxone per kg of bodyweight given once daily. In severe infections, a daily dose of 80 mg per kg of bodyweight may be given by intravenous injection.
For children with body weights of 50 kg or more, the usual adult dosages are used.
The usual starting dose for children in the treatment of meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) is 100 mg per kg of bodyweight once each day. In some patients where infections are severe, the doctor may give a higher dose up to 4g every day.

**Persons with kidney and/or liver problems:**
Patients in whom the kidneys are not working properly but the liver is normal, the dosage of Ceftriaxone is usually not reduced.
However, in patients with extremely reduced working of the kidneys, the dose of Ceftriaxone may be limited to 2g or less.
If you are on dialysis, no additional dose will be required after dialysis. You may need to have blood tests so your doctor can work out the right dose for you.
In patients with liver disease but with normal kidneys, the dosage of Ceftriaxone is usually not reduced.
In patients with both severe kidney and liver problems, blood tests may be required to adjust dosage.

The following side effects have also been reported:

Very common side effects (affects more than one in ten persons):
- deposits of Ceftriaxone in the gall bladder are very common in children and may cause symptoms such as abdominal discomfort. These deposits usually disappear once treatment has been stopped.

Common side effects (affects less than one in ten but more than one in a hundred persons):
- allergic reactions such as hives, skin itching and swollen joints.
- changes in blood tests that check how your liver is working.
- pain or inflammation at the site of injection.

Uncommon side effects (affects less than one in a hundred but more than one in a thousand persons):
- inflammation of the mouth or tongue
- loss of appetite
- feeling sick (nausea)
- being sick (vomiting)
- abdominal (tummy) pain
- diarrhoea

(The above digestive problems are usually mild and commonly disappear during treatment or after stoppage of treatment)

- infections: having a course of Ceftriaxone can temporarily increase the chance that you can get infections caused by other pathogens. For example, thrush may occur
- headache
- a feeling of dizziness and/or “spinning”
- blood tests which show changes in the way the kidney is working. You may pass less urine than is normal for you.

Rare side effects (affects less than one in thousand but more than one in ten thousand persons):
- reduction in the number of white blood cells, which makes infections more likely. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are taking this medicine as it may affect your result.
- inflammation of the pancreas, which causes severe pain in the abdomen and back
- gall stones in adults
- kidney stones in children

Very rare side effects (affects less than one in ten thousand persons):
Duration of treatment
Your doctor will advise you on how long your treatment should last. The duration of treatment depends according to the course of the disease. Ceftriaxone would generally be continued for a minimum of 48 to 72 hours after you have been without fever or after a laboratory evidence of bacterial removal is obtained.

If you use more Ceftriaxone than you should
Since a doctor or nurse will give you Ceftriaxone, it is very unlikely that you will be given too much Ceftriaxone. If you think you or someone you know has received too much medicine please tell your doctor or nurse or contact the nearest hospital-accident and emergency department.

If you forget to use Ceftriaxone
Since a doctor or nurse will give you Ceftriaxone, it is very unlikely that you will miss a dose. If you think you may have missed a dose please tell your doctor or nurse.

If you stop using Ceftriaxone
You must use your medication exactly as directed. Do not stop your treatment on your own for any reason because, your infection may return.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

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

The following side effects are important and will require immediate action if you experience them. You should stop taking Ceftriaxone and see your doctor immediately if the following symptoms occur:

Rare side effects (affects less than one in thousand but more than one in ten thousand persons):
- watery and severe diarrhoea that may also be bloody

Very rare side effects (affects less than one in ten thousand persons):
- a sudden allergic reaction with shortness of breath, rash, wheezing and drop of blood pressure
- severe, extensive, blistering skin rash

- easy bruising or bleeding
- reduction in red blood cells (anaemia) which can make the skin pale and cause weakness or breathlessness

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

5. How to store Ceftriaxone
Keep out of the reach and sight of children.

Do not use Ceftriaxone after the expiry date, which is stated on the label or carton.

This medicinal product does not require any special storage conditions.

Keep vial(s) in the outer carton to protect from light.

Your doctor, pharmacist or nurse will know how to store Ceftriaxone injection properly.

6. Further information

What Ceftriaxone contains
The active substance is Ceftriaxone. There are no other ingredients.

What Ceftriaxone looks like and contents of the pack
Ceftriaxone is an almost white to yellowish powder, packaged in a clear glass vial with blue coloured flip off seal.

Pack of 1 or 5 vials in a carton.

Not all pack sizes may be marketed.

When reconstituted in water for injections, Ceftriaxone powder gives a light yellow to amber coloured clear solution.

Marketing Authorisation Holder
Orchid Europe Ltd
Building 3, Chiswick Park, 566, Chiswick High Road, Chiswick, London, W4 5YA
United Kingdom

This leaflet was last approved in August 2009
Technical Leaflet

The following information is intended for medical or healthcare professionals only:

Ceftriaxone 250mg Powder for Solution for Injection

Method and route of administration:
Ceftriaxone 250mg powder for solution for injection is injected into a vein (intravenous injection into vein); however, it can also be injected into a muscle (intramuscular administration).

*Intramuscular injection (injection into a muscle)*
Ceftriaxone 250mg powder for solution for injection should be dissolved in 1ml of 1.0% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection.

*Intravenous injection (injection into a vein)*
Ceftriaxone 250mg powder for solution for injection should be dissolved in 5ml 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.

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 such as Hartmann’s solution and Ringer’s solution. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

Reconstituted solutions should be inspected visually. Only clear solutions free of visible particles should be used. The reconstituted product is for single use only and any unused solution must be discarded. Ceftriaxone should not be mixed in the same syringe with any medicinal product other than 1% lidocaine hydrochloride solution (for intramuscular injection only).

Special precautions for storage
This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light.

After reconstitution, chemical and physical in-use stability has been demonstrated for at least 6 hours at or below 25°C or 24 hours at 2-8°C. Protect from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at or below 25°C or 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. Unused solution should be discarded.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Ceftriaxone 500 mg powder for solution for injection (Ceftriaxone)

The name of your medicine is Ceftriaxone 500mg powder for solution for injection, which will be referred to as Ceftriaxone throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ceftriaxone is and what it is used for
2. Before you use Ceftriaxone
3. How to use Ceftriaxone
4. Possible side effects
5. How to store Ceftriaxone
6. Further information

1. What Ceftriaxone is and what it is used for

Ceftriaxone belongs to a group of antibacterial agents called cephalosporins, which act by killing the bacteria.

Ceftriaxone is used when an infection is known to be or likely to be caused by bacteria that are sensitive to Ceftriaxone. It is used for the treatment of the following conditions:
- Infection of the bloodstream by bacteria (septicaemia)
- Infection of the membranes and fluid surrounding the brain and spinal cord (meningitis)
- Chest infections such as pneumonia

The treatment may sometimes need to be started before knowing if the bacteria are sensitive to Ceftriaxone or not.

2. Before you use Ceftriaxone

Do not use Ceftriaxone if you:
- are allergic (hypersensitive) to Ceftriaxone or any other cephalosporin type of antibiotics.
- ever had a severe allergic reaction to any penicillin or any other beta-lactam antibiotics.

If you have been on Ceftriaxone treatment for a prolonged period, it may result in the overgrowth of organisms on which Ceftriaxone does not act. This may need to be treated by other antimicrobial agents.

When Ceftriaxone is given in larger doses, especially to children, it may precipitate in the gallbladder and kidneys and then be seen as shadows on ultrasound. The condition is usually reversible and your doctor will normally not recommend a separate treatment.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is especially important if:
- you are taking antibiotics called aminoglycosides (eg. gentamicin). The use of Ceftriaxone with such drugs can cause damage both to kidneys and hearing.
- you are taking antibiotics like chloramphenicol and tetracycline. These drugs should not be used together with Ceftriaxone as they are known to weaken the effects of Ceftriaxone and other cephalosporins.
- you are taking birth control pills (Ceftriaxone may reduce their effectiveness). You should use additional contraceptive measures like the barrier method (condom or diaphragm with spermicide) during treatment to avoid pregnancy.

Laboratory tests

Ceftriaxone can alter the results of some blood tests (such as cross-matching blood and the Coombs’ test). It is important to tell the doctor that you are taking this medicine if you have to have any of these tests.

Ceftriaxone can also alter the results of some urine tests for glucose (a type of sugar). If you have diabetes and routinely test your urine, tell your doctor. This is because other tests may have to be used to monitor your diabetes while you are having this medicine.

Ceftriaxone can also alter the results of some blood tests for galactose (a type of sugar).

Taking Ceftriaxone with food and drink

Ceftriaxone can be administered intravenously (into a vein) regardless of meals.
Ceftriaxone will not be given to your newborn baby if any of the following conditions are present:

- jaundice (yellowing of the skin or whites of the eyes caused by liver or blood problems)
- low level of protein in the blood
- excessive acid in the body fluids
- premature birth
- calcium treatment (this is because Ceftriaxone and calcium-containing products can interact with each other)

Take special care with Ceftriaxone

Ceftriaxone is not suitable for everyone. Before treatment with Ceftriaxone, make sure your doctor knows if you:

- have ever had an allergic reaction to any penicillin or any other beta-lactam antibiotic. This is because you may have an increased chance of being allergic to Ceftriaxone if you are allergic to penicillins.
- suffer from allergies or have asthma (a condition that affects the airways).
- have ever been told that your kidneys and liver do not work very well. You will then need to have regular blood tests during your treatment to monitor your condition.
- have an infection caused by a bacterium called *Pseudomonas aeruginosa*. Your doctor may sometimes need to use some other antibiotic or use Ceftriaxone at the same time as other antibiotics (such as aminoglycosides) to help treat the infection.
- have ever had gallbladder, or gastrointestinal disease (especially inflammation of the large bowel called as colitis).
- have recently been very ill or if you are being fed through a vein.
- are on a low sodium diet.
- develop loose and/or frequent motions (diarrhoea) during or shortly after treatment. If your diarrhoea is severe or there is presence of blood in the stools, contact your doctor immediately. You might have developed an infection of the large bowel, which needs special treatment. Medicines which may slow or stop bowel movements must not be taken.

Alcohol can interact with certain medicines. However, there are no known interactions (such as unpleasant physical reactions) between alcohol and Ceftriaxone.

**Pregnancy and breast-feeding**

Before starting treatment, you must tell your doctor if you are pregnant or if you intend to become pregnant. Ceftriaxone will be given to a pregnant woman only if it is really needed.

Mothers who wish to breast-feed should discuss with their doctor. Small amounts of Ceftriaxone enter the milk. Inform your doctor if your baby develops diarrhoea or any other unusual symptom. Some babies may be sensitised to Ceftriaxone and can develop allergic reactions.

Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**

Ceftriaxone may affect your ability to drive or operate machinery as dizziness has been reported during treatment with Ceftriaxone. If affected, do not drive or use machines.

**Important information about some of the ingredients of Ceftriaxone**

This medicinal product contains 1.8 mmol (41.4 mg) sodium per 500 mg dose. This should be taken into consideration by patients under controlled sodium diet.

### 3. How to use Ceftriaxone

**Dosage**

A doctor or nurse will usually give you this medicine. Your doctor will decide the dose (amount) and route of administration of your medicine. This will depend on your age, the nature of your illness and any underlying conditions eg. kidney/liver problems.

Always use Ceftriaxone exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**How Ceftriaxone injection is given**

Ceftriaxone is supplied as a powder, so it must be made into a solution before it can be given. Your doctor or nurse will prepare a freshly prepared solution of Ceftriaxone.
Ceftriaxone will usually be given by a doctor or nurse intravenously (into a vein) either by a slow injection over at least 2 to 4 minutes or by a slow infusion (drip) over at least 30 minutes.

The usual dose is:

**Adults and children over 12 years old:**
The usual dosage range for Ceftriaxone is 1 to 2g given once each day. In some patients, where infections are severe, the doctor may administer a higher dose up to 4g each day.
The doses are the same for elderly patients, provided the liver and kidneys are normal.

**Newborn and very young babies (neonates) aged up to 14 days:**
The daily dose is worked out according to the weight of the child. The usual daily dose is 20 to 50 mg of Ceftriaxone per kg of bodyweight given once each day.
The maximum dose for the treatment of severe infections including meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) in this age group is 50 mg per kg of bodyweight.

**Infants and children aged up to 12 years:**
The usual daily dose is 20 to 80 mg of Ceftriaxone per kg of bodyweight given once daily. In severe infections, a daily dose of 80 mg per kg of bodyweight may be given by intravenous injection.
For children with body weights of 50 kg or more, the usual adult dosages are used.
The usual starting dose for children in the treatment of meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) is 100 mg per kg of bodyweight once each day. In some patients where infections are severe, the doctor may give a higher dose up to 4g every day.

**Persons with kidney and/or liver problems:**
Patients in whom the kidneys are not working properly but the liver is normal, the dosage of Ceftriaxone is usually not reduced.
However, in patients with extremely reduced working of the kidneys, the dose of Ceftriaxone may be limited to 2g or less.
If you are on dialysis, no additional dose will be required after dialysis. You may need to have blood tests so your doctor can work out the right dose for you.
In patients with liver disease but with normal kidneys, the dosage of Ceftriaxone is usually not reduced.
In patients with both severe kidney and liver problems, blood tests may be required to adjust dosage.

The following side effects have also been reported:

**Very common side effects (affects more than one in ten persons):**
- deposits of Ceftriaxone in the gall bladder are very common in children and may cause symptoms such as abdominal discomfort. These deposits usually disappear once treatment has been stopped.

**Common side effects (affects less than one in ten but more than one in a hundred persons):**
- allergic reactions such as hives, skin itching and swollen joints.
- changes in blood tests that check how your liver is working.
- pain or inflammation at the site of injection.

**Uncommon side effects (affects less than one in a hundred but more than one in a thousand persons):**
- inflammation of the mouth or tongue
- loss of appetite
- feeling sick (nausea)
- being sick (vomiting)
- abdominal (tummy) pain
- diarrhoea

(The above digestive problems are usually mild and commonly disappear during treatment or after stoppage of treatment)
- infections: having a course of Ceftriaxone can temporarily increase the chance that you can get infections caused by other pathogens. For example, thrush may occur
- headache
- a feeling of dizziness and/or "spinning"
- blood tests which show changes in the way the kidney is working. You may pass less urine than is normal for you.

**Rare side effects (affects less than one in thousand but more than one in ten thousand persons):**
- reduction in the number of white blood cells, which makes infections more likely. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are taking this medicine as it may affect your result.
- inflammation of the pancreas, which causes severe pain in the abdomen and back
- gall stones in adults
- kidney stones in children

**Very rare side effects (affects less than one in ten thousand persons):**
Duration of treatment
Your doctor will advise you on how long your treatment should last. The duration of treatment depends according to the course of the disease. Ceftriaxone would generally be continued for a minimum of 48 to 72 hours after you have been without fever or after a laboratory evidence of bacterial removal is obtained.

If you use more Ceftriaxone than you should
Since a doctor or nurse will give you Ceftriaxone, it is very unlikely that you will be given too much Ceftriaxone. If you think you or someone you know has received too much medicine please tell your doctor or nurse or contact the nearest hospital-accident and emergency department.

If you forget to use Ceftriaxone
Since a doctor or nurse will give you Ceftriaxone, it is very unlikely that you will miss a dose. If you think you may have missed a dose please tell your doctor or nurse.

If you stop using Ceftriaxone
You must use your medication exactly as directed. Do not stop your treatment on your own for any reason because, your infection may return.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

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

The following side effects are important and will require immediate action if you experience them. You should stop taking Ceftriaxone and see your doctor immediately if the following symptoms occur:

Rare side effects (affects less than one in thousand but more than one in ten thousand persons):
- watery and severe diarrhoea that may also be bloody

Very rare side effects (affects less than one in ten thousand persons):
- a sudden allergic reaction with shortness of breath, rash, wheezing and drop of blood pressure
- severe, extensive, blistering skin rash
- easy bruising or bleeding
- reduction in red blood cells (anaemia) which can make the skin pale and cause weakness or breathlessness

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

5. How to store Ceftriaxone
Keep out of the reach and sight of children.

Do not use Ceftriaxone after the expiry date, which is stated on the label or carton.

This medicinal product does not require any special storage conditions.
Keep vial(s) in the outer carton to protect from light.

Your doctor, pharmacist or nurse will know how to store Ceftriaxone injection properly.

6. Further information
What Ceftriaxone contains
The active substance is Ceftriaxone. There are no other ingredients.

What Ceftriaxone looks like and contents of the pack
Ceftriaxone is an almost white to yellowish powder, packaged in a clear glass vial with white coloured flip off seal.
Pack of 1 or 5 vials in a carton.
Not all pack sizes may be marketed.

When reconstituted in water for injections, Ceftriaxone powder gives a light yellow to amber coloured clear solution.

Marketing Authorisation Holder
Orchid Europe Ltd
Building 3, Chiswick Park, 566, Chiswick High Road, Chiswick, London, W4 5YA
United Kingdom

This leaflet was last approved in August 2009
Technical Leaflet
The following information is intended for medical or healthcare professionals only:
Ceftriaxone 500mg Powder for Solution for Injection

Method and route of administration:
Ceftriaxone 500mg powder for solution for injection is injected in to a vein (intravenous injection into vein); however, it can also be injected into a muscle (intramuscular administration).

Intramuscular injection (injection into a muscle)
Ceftriaxone 500mg powder for solution for injection should be dissolved in 2ml of 1.0% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection.

Intravenous injection (injection into a vein)
Ceftriaxone 500mg powder for solution for injection should be dissolved in 5ml 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.

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 such as Hartmann’s solution and Ringer’s solution. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

Reconstituted solutions should be inspected visually. Only clear solutions free of visible particles should be used. The reconstituted product is for single use only and any unused solution must be discarded. Ceftriaxone should not be mixed in the same syringe with any medicinal product other than 1% lidocaine hydrochloride solution (for intramuscular injection only).

Special precautions for storage
This medicinal product does not require any special storage conditions.
Keep vial(s) in the outer carton to protect from light.

After reconstitution, chemical and physical in-use stability has been demonstrated for atleast 6 hours at or below 25°C or 24 hours at 2-8°C. Protect from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at or below 25°C or 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. Unused solution should be discarded.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Ceftriaxone 1 g powder for solution for injection (Ceftriaxone)

The name of your medicine is Ceftriaxone 1g powder for solution for injection, which will be referred to as Ceftriaxone throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ceftriaxone is and what it is used for
2. Before you use Ceftriaxone
3. How to use Ceftriaxone
4. Possible side effects
5. How to store Ceftriaxone
6. Further information

1. What Ceftriaxone is and what it is used for

Ceftriaxone belongs to a group of antibacterial agents called cephalosporins, which act by killing the bacteria.

Ceftriaxone is used when an infection is known to be or likely to be caused by bacteria that are sensitive to Ceftriaxone. It is used for the treatment of the following conditions:
- Infection of the bloodstream by bacteria (septicaemia)
- Infection of the membranes and fluid surrounding the brain and spinal cord (meningitis)
- Chest infections such as pneumonia

The treatment may sometimes need to be started before knowing if the bacteria are sensitive to Ceftriaxone or not.

2. Before you use Ceftriaxone

Do not use Ceftriaxone if you:
- are allergic (hypersensitive) to Ceftriaxone or any other cephalosporin type of antibiotics.
- ever had a severe allergic reaction to any penicillin or any other beta-lactam antibiotics.

If you have been on Ceftriaxone treatment for a prolonged period, it may result in the overgrowth of organisms on which Ceftriaxone does not act. This may need to be treated by other antimicrobial agents.

When Ceftriaxone is given in larger doses, especially to children, it may precipitate in the gallbladder and kidneys and then be seen as shadows on ultrasound. The condition is usually reversible and your doctor will normally not recommend a separate treatment.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is especially important if:
- you are taking antibiotics called aminoglycosides (eg. gentamicin). The use of Ceftriaxone with such drugs can cause damage both to kidneys and hearing.
- you are taking antibiotics like chloramphenicol and tetracycline. These drugs should not be used together with Ceftriaxone as they are known to weaken the effects of Ceftriaxone and other cephalosporins.
- you are taking birth control pills (Ceftriaxone may reduce their effectiveness). You should use additional contraceptive measures like the barrier method (condom or diaphragm with spermicide) during treatment to avoid pregnancy.

Laboratory tests
Ceftriaxone can alter the results of some blood tests (such as cross-matching blood and the Coombs’ test). It is important to tell the doctor that you are taking this medicine if you have to have any of these tests.

Ceftriaxone can also alter the results of some urine tests for glucose (a type of sugar). If you have diabetes and routinely test your urine, tell your doctor. This is because other tests may have to be used to monitor your diabetes while you are having this medicine.

Ceftriaxone can also alter the results of some blood tests for galactose (a type of sugar).

Taking Ceftriaxone with food and drink
Ceftriaxone can be administered intravenously (into a vein) regardless of meals.
Ceftriaxone will not be given to your newborn baby if any of the following conditions are present:
- jaundice (yellowing of the skin or whites of the eyes caused by liver or blood problems)
- low level of protein in the blood
- excessive acid in the body fluids
- premature birth
- calcium treatment (this is because Ceftriaxone and calcium-containing products can interact with each other)

Take special care with Ceftriaxone
Ceftriaxone is not suitable for everyone. Before treatment with Ceftriaxone, make sure your doctor knows if you:
- have ever had an allergic reaction to any penicillin or any other beta-lactam antibiotic. This is because you may have an increased chance of being allergic to Ceftriaxone if you are allergic to penicillins.
- suffer from allergies or have asthma (a condition that affects the airways).
- have ever been told that your kidneys and liver do not work very well. You will then need to have regular blood tests during your treatment to monitor your condition.
- have an infection caused by a bacterium called *Pseudomonas aeruginosa*. Your doctor may sometimes need to use some other antibiotic or use Ceftriaxone at the same time as other antibiotics (such as aminoglycosides) to help treat the infection.
- have ever had gallbladder, or gastrointestinal disease (especially inflammation of the large bowel called as colitis).
- have recently been very ill or if you are being fed through a vein.
- are on a low sodium diet.
- develop loose and/or frequent motions (diarrhoea) during or shortly after treatment. If your diarrhoea is severe or there is presence of blood in the stools, contact your doctor immediately. You might have developed an infection of the large bowel, which needs special treatment. Medicines which may slow or stop bowel movements must not be taken.

Alcohol can interact with certain medicines. However, there are no known interactions (such as unpleasant physical reactions) between alcohol and Ceftriaxone.

Pregnancy and breast-feeding
Before starting treatment, you must tell your doctor if you are pregnant or if you intend to become pregnant. Ceftriaxone will be given to a pregnant woman only if it is really needed.

Mothers who wish to breast-feed should discuss with their doctor. Small amounts of Ceftriaxone enter the milk. Inform your doctor if your baby develops diarrhoea or any other unusual symptom. Some babies may be sensitised to Ceftriaxone and can develop allergic reactions.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Ceftriaxone may affect your ability to drive or operate machinery as dizziness has been reported during treatment with Ceftriaxone. If affected, do not drive or use machines.

Important information about some of the ingredients of Ceftriaxone
This medicinal product contains 3.6 mmol (82.8 mg) sodium per 1 g dose. This should be taken into consideration by patients under controlled sodium diet.

### 3. How to use Ceftriaxone

#### Dosage
A doctor or nurse will usually give you this medicine. Your doctor will decide the dose (amount) and route of administration of your medicine. This will depend on your age, the nature of your illness and any underlying conditions eg. kidney/liver problems.

Always use Ceftriaxone exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

#### How Ceftriaxone injection is given
Ceftriaxone is supplied as a powder, so it must be made into a solution before it can be given. Your doctor or nurse will prepare a freshly prepared solution of Ceftriaxone.
Ceftriaxone will usually be given by a doctor or nurse intravenously (into a vein) either by a slow injection over at least 2 to 4 minutes or by a slow infusion (drip) over at least 30 minutes.

The usual dose is:

**Adults and children over 12 years old:**
The usual dosage range for Ceftriaxone is 1 to 2g given once each day. In some patients, where infections are severe, the doctor may administer a higher dose up to 4g each day.
The doses are the same for elderly patients, provided the liver and kidneys are normal.

**Newborn and very young babies (neonates) aged up to 14 days:**
The daily dose is worked out according to the weight of the child. The usual daily dose is 20 to 50 mg of Ceftriaxone per kg of bodyweight given once each day. The maximum dose for the treatment of severe infections including meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) in this age group is 50 mg per kg of bodyweight.

**Infants and children aged up to 12 years:**
The usual daily dose is 20 to 80 mg of Ceftriaxone per kg of bodyweight given once daily. In severe infections, a daily dose of 80 mg per kg of bodyweight may be given by intravenous injection.
For children with body weights of 50 kg or more, the usual adult dosages are used.
The usual starting dose for children in the treatment of meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) is 100 mg per kg of bodyweight once each day. In some patients where infections are severe, the doctor may give a higher dose up to 4g every day.

**Persons with kidney and/or liver problems:**
Patients in whom the kidneys are not working properly but the liver is normal, the dosage of Ceftriaxone is usually not reduced.
However, in patients with extremely reduced working of the kidneys, the dose of Ceftriaxone may be limited to 2g or less.
If you are on dialysis, no additional dose will be required after dialysis. You may need to have blood tests so your doctor can work out the right dose for you.
In patients with liver disease but with normal kidneys, the dosage of Ceftriaxone is usually not reduced.
In patients with both severe kidney and liver problems, blood tests may be required to adjust dosage.

The following side effects have also been reported:

**Very common side effects (affects more than one in ten persons):**
- deposits of Ceftriaxone in the gall bladder are very common in children and may cause symptoms such as abdominal discomfort. These deposits usually disappear once treatment has been stopped.

**Common side effects (affects less than one in ten but more than one in a hundred persons):**
- allergic reactions such as hives, skin itching and swollen joints.
- changes in blood tests that check how your liver is working.
- pain or inflammation at the site of injection.

**Uncommon side effects (affects less than one in a hundred but more than one in a thousand persons):**
- inflammation of the mouth or tongue
- loss of appetite
- feeling sick (nausea)
- being sick (vomiting)
- abdominal (tummy) pain
- diarrhoea

(The above digestive problems are usually mild and commonly disappear during treatment or after stoppage of treatment)
- infections: having a course of Ceftriaxone can temporarily increase the chance that you can get infections caused by other pathogens. For example, thrush may occur
- headache
- a feeling of dizziness and/or "spinning"
- blood tests which show changes in the way the kidney is working. You may pass less urine than is normal for you.

**Rare side effects (affects less than one in thousand but more than one in ten thousand persons):**
- reduction in the number of white blood cells, which makes infections more likely. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are taking this medicine as it may affect your result.
- inflammation of the pancreas, which causes severe pain in the abdomen and back
- gall stones in adults
- kidney stones in children

**Very rare side effects (affects less than one in ten thousand persons):**
Duration of treatment
Your doctor will advise you on how long your treatment should last. The duration of treatment depends according to the course of the disease. Ceftriaxone would generally be continued for a minimum of 48 to 72 hours after you have been without fever or after a laboratory evidence of bacterial removal is obtained.

If you use more Ceftriaxone than you should
Since a doctor or nurse will give you Ceftriaxone, it is very unlikely that you will be given too much Ceftriaxone. If you think you or someone you know has received too much medicine please tell your doctor or nurse or contact the nearest hospital-accident and emergency department.

If you forget to use Ceftriaxone
Since a doctor or nurse will give you Ceftriaxone, it is very unlikely that you will miss a dose. If you think you may have missed a dose please tell your doctor or nurse.

If you stop using Ceftriaxone
You must use your medication exactly as directed. Do not stop your treatment on your own for any reason because, your infection may return.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

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

The following side effects are important and will require immediate action if you experience them. You should stop taking Ceftriaxone and see your doctor immediately if the following symptoms occur:

Rare side effects (affects less than one in thousand but more than one in ten thousand persons):
- watery and severe diarrhoea that may also be bloody

Very rare side effects (affects less than one in ten thousand persons):
- a sudden allergic reaction with shortness of breath, rash, wheezing and drop of blood pressure
- severe, extensive, blistering skin rash
- easy bruising or bleeding
- reduction in red blood cells (anaemia) which can make the skin pale and cause weakness or breathlessness

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

5. How to store Ceftriaxone
Keep out of the reach and sight of children.

Do not use Ceftriaxone after the expiry date, which is stated on the label or carton.

This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light.

Your doctor, pharmacist or nurse will know how to store Ceftriaxone injection properly.

6. Further information
What Ceftriaxone contains
The active substance is Ceftriaxone. There are no other ingredients.

What Ceftriaxone looks like and contents of the pack
Ceftriaxone is an almost white to yellowish powder, packaged in a clear glass vial with blue coloured flip off seal. Pack of 1 or 5 vials in a carton. Not all pack sizes may be marketed.

When reconstituted in water for injections, Ceftriaxone powder gives a light yellow to amber coloured clear solution.

Marketing Authorisation Holder
Orchid Europe Ltd
Building 3, Chiswick Park,
566, Chiswick High Road,
Chiswick, London, W4 5YA
United Kingdom

This leaflet was last approved in August 2009
Technical Leaflet
The following information is intended for medical or healthcare professionals only:

Ceftriaxone 1 g Powder for Solution for Injection

Method and route of administration:
Ceftriaxone 1g powder for solution for injection is injected in to a vein (intravenous injection into vein); however, it can also be injected into a muscle (intramuscular administration).

Intramuscular injection (injection into a muscle)
Ceftriaxone 1g powder for solution for injection should be dissolved in 3.5ml of 1.0% Lidocaine Hydrochloride BP solution. The solution should be administered by deep intramuscular injection.

Intravenous injection (injection into a vein)
Ceftriaxone 1g powder for solution for injection should be dissolved 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.

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 such as Hartmann’s solution and Ringer’s solution. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

Reconstituted solutions should be inspected visually. Only clear solutions free of visible particles should be used. The reconstituted product is for single use only and any unused solution must be discarded. Ceftriaxone should not be mixed in the same syringe with any medicinal product other than 1% lidocaine hydrochloride solution (for intramuscular injection only).

Special precautions for storage
This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light.

After reconstitution, chemical and physical in-use stability has been demonstrated for atleast 6 hours at or below 25°C or 24 hours at 2-8°C. Protect from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at or below 25°C or 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. Unused solution should be discarded.
Ceftriaxone 2g 
powder for solution for injection or infusion 
(Ceftriaxone)

The name of your medicine is Ceftriaxone 2g powder for solution for injection or infusion, which will be referred to as Ceftriaxone throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ceftriaxone is and what it is used for
2. Before you use Ceftriaxone
3. How to use Ceftriaxone
4. Possible side effects
5. How to store Ceftriaxone
6. Further information

1. What Ceftriaxone is and what it is used for

Ceftriaxone belongs to a group of antibacterial agents called cephalosporins, which act by killing the bacteria.

Ceftriaxone is used when an infection is known to be or likely to be caused by bacteria that are sensitive to Ceftriaxone. It is used for the treatment of the following conditions:
- Infection of the bloodstream by bacteria (septicaemia)
- Infection of the membranes and fluid surrounding the brain and spinal cord (meningitis)
- Chest infections such as pneumonia

The treatment may sometimes need to be started before knowing if the bacteria are sensitive to Ceftriaxone or not.

2. Before you use Ceftriaxone

Do not use Ceftriaxone if you:
- are allergic (hypersensitive) to Ceftriaxone or any other cephalosporin type of antibiotics.
- ever had a severe allergic reaction to any penicillin or any other beta-lactam antibiotics.

If you have been on Ceftriaxone treatment for a prolonged period, it may result in the overgrowth of organisms on which Ceftriaxone does not act. This may need to be treated by other antimicrobial agents.

When Ceftriaxone is given in larger doses, especially to children, it may precipitate in the gallbladder and kidneys and then be seen as shadows on ultrasound. The condition is usually reversible and your doctor will normally not recommend a separate treatment.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is especially important if:
- you are taking antibiotics called aminoglycosides (e.g. gentamicin). The use of Ceftriaxone with such drugs can cause damage both to kidneys and hearing.
- you are taking antibiotics like chloramphenicol and tetracycline. These drugs should not be used together with Ceftriaxone as they are known to weaken the effects of Ceftriaxone and other cephalosporins.
- you are taking birth control pills (Ceftriaxone may reduce their effectiveness). You should use additional contraceptive measures like the barrier method (condom or diaphragm with spermicide) during treatment to avoid pregnancy.

Laboratory tests
Ceftriaxone can alter the results of some blood tests (such as cross-matching blood and the Coombs’ test). It is important to tell the doctor that you are taking this medicine if you have to have any of these tests.

Ceftriaxone can also alter the results of some urine tests for glucose (a type of sugar). If you have diabetes and routinely test your urine, tell your doctor. This is because other tests may have to be used to monitor your diabetes while you are having this medicine.

Ceftriaxone can also alter the results of some blood tests for galactose (a type of sugar).

Taking Ceftriaxone with food and drink
Ceftriaxone can be administered intravenously (into a vein) regardless of meals.
Ceftriaxone will not be given to your newborn baby if any of the following conditions are present:

- jaundice (yellowing of the skin or whites of the eyes caused by liver or blood problems)
- low level of protein in the blood
- excessive acid in the body fluids
- premature birth
- calcium treatment (this is because Ceftriaxone and calcium-containing products can interact with each other)

Take special care with Ceftriaxone

Ceftriaxone is not suitable for everyone. Before treatment with Ceftriaxone, make sure your doctor knows if you:

- have ever had an allergic reaction to any penicillin or any other beta-lactam antibiotic. This is because you may have an increased chance of being allergic to Ceftriaxone if you are allergic to penicillins.
- suffer from allergies or have asthma (a condition that affects the airways).
- have ever been told that your kidneys and liver do not work very well. You will then need to have regular blood tests during your treatment to monitor your condition.
- have an infection caused by a bacterium called *Pseudomonas aeruginosa*. Your doctor may sometimes need to use some other antibiotic or use Ceftriaxone at the same time as other antibiotics (such as aminoglycosides) to help treat the infection.
- have ever had gallbladder, or gastrointestinal disease (especially inflammation of the large bowel called as colitis).
- have recently been very ill or if you are being fed through a vein.
- are on a low sodium diet.
- develop loose and/or frequent motions (diarrhoea) during or shortly after treatment. If your diarrhoea is severe or there is presence of blood in the stools, contact your doctor immediately. You might have developed an infection of the large bowel, which needs special treatment. Medicines which may slow or stop bowel movements must not be taken.

Alcohol can interact with certain medicines. However, there are no known interactions (such as unpleasant physical reactions) between alcohol and Ceftriaxone.

**Pregnancy and breast-feeding**

Before starting treatment, you must tell your doctor if you are pregnant or if you intend to become pregnant. Ceftriaxone will be given to a pregnant woman only if it is really needed.

Mothers who wish to breast-feed should discuss with their doctor. Small amounts of Ceftriaxone enter the milk. Inform your doctor if your baby develops diarrhoea or any other unusual symptom. Some babies may be sensitised to Ceftriaxone and can develop allergic reactions.

Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**

Ceftriaxone may affect your ability to drive or operate machinery as dizziness has been reported during treatment with Ceftriaxone. If affected, do not drive or use machines.

**Important information about some of the ingredients of Ceftriaxone**

This medicinal product contains 7.2 mmol (165.6 mg) sodium per 2 g dose. This should be taken into consideration by patients under controlled sodium diet.

### 3. How to use Ceftriaxone

**Dosage**

A doctor or nurse will usually give you this medicine. Your doctor will decide the dose (amount) and route of administration of your medicine. This will depend on your age, the nature of your illness and any underlying conditions eg. kidney/liver problems.

Always use Ceftriaxone exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**How Ceftriaxone injection is given**

Ceftriaxone is supplied as a powder, so it must be made into a solution before it can be given. Your doctor or nurse will prepare a freshly prepared solution of Ceftriaxone.
Ceftriaxone will usually be given by a doctor or nurse intravenously (into a vein) either by a slow injection over at least 2 to 4 minutes or by a slow infusion (drip) over at least 30 minutes.

The usual dose is:

**Adults and children over 12 years old:**
The usual dosage range for Ceftriaxone is 1 to 2g given once each day. In some patients, where infections are severe, the doctor may administer a higher dose up to 4g each day.
The doses are the same for elderly patients, provided the liver and kidneys are normal.

**Newborn and very young babies (neonates) aged up to 14 days:**
The daily dose is worked out according to the weight of the child. The usual daily dose is 20 to 50 mg of Ceftriaxone per kg of bodyweight given once daily. The maximum dose for the treatment of severe infections including meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) in this age group is 50 mg per kg of bodyweight.

**Infants and children aged up to 12 years:**
The usual daily dose is 20 to 80 mg of Ceftriaxone per kg of bodyweight given once daily. In severe infections, a daily dose of 80 mg per kg of bodyweight may be given by intravenous injection.

For children with body weights of 50 kg or more, the usual adult dosages are used.
The usual starting dose for children in the treatment of meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) is 100 mg per kg of bodyweight once each day. In some patients where infections are severe, the doctor may give a higher dose up to 4g every day.

**Persons with kidney and/or liver problems:**
Patients in whom the kidneys are not working properly but the liver is normal, the dosage of Ceftriaxone is usually not reduced.
However, in patients with extremely reduced working of the kidneys, the dose of Ceftriaxone may be limited to 2g or less.
If you are on dialysis, no additional dose will be required after dialysis. You may need to have blood tests so your doctor can work out the right dose for you.
In patients with liver disease but with normal kidneys, the dosage of Ceftriaxone is usually not reduced.
In patients with both severe kidney and liver problems, blood tests may be required to adjust dosage.

The following side effects have also been reported:

**Very common side effects (affects more than one in ten persons):**
- deposits of Ceftriaxone in the gall bladder are very common in children and may cause symptoms such as abdominal discomfort. These deposits usually disappear once treatment has been stopped.

**Common side effects (affects less than one in ten but more than one in a hundred persons):**
- allergic reactions such as hives, skin itching and swollen joints.
- changes in blood tests that check how your liver is working.
- pain or inflammation at the site of injection.

**Uncommon side effects (affects less than one in a hundred but more than one in a thousand persons):**
- inflammation of the mouth or tongue
- loss of appetite
- feeling sick (nausea)
- being sick (vomiting)
- abdominal (tummy) pain
- diarrhoea

(The above digestive problems are usually mild and commonly disappear during treatment or after stoppage of treatment)

- infections: having a course of Ceftriaxone can temporarily increase the chance that you can get infections caused by other pathogens. For example, thrush may occur
- headache
- a feeling of dizziness and/or “spinning”
- blood tests which show changes in the way the kidney is working. You may pass less urine than is normal for you.

**Rare side effects (affects less than one in thousand but more than one in ten thousand persons):**
- reduction in the number of white blood cells, which makes infections more likely. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are taking this medicine as it may affect your result.
- inflammation of the pancreas, which causes severe pain in the abdomen and back
- gall stones in adults
- kidney stones in children

**Very rare side effects (affects less than one in ten thousand persons):**
Duration of treatment
Your doctor will advise you on how long your treatment should last. The duration of treatment depends according to the course of the disease. Ceftriaxone would generally be continued for a minimum of 48 to 72 hours after you have been without fever or after a laboratory evidence of bacterial removal is obtained.

If you use more Ceftriaxone than you should
Since a doctor or nurse will give you Ceftriaxone, it is very unlikely that you will be given too much Ceftriaxone. If you think you or someone you know has received too much medicine please tell your doctor or nurse or contact the nearest hospital-accident and emergency department.

If you forget to use Ceftriaxone
Since a doctor or nurse will give you Ceftriaxone, it is very unlikely that you will miss a dose. If you think you may have missed a dose please tell your doctor or nurse.

If you stop using Ceftriaxone
You must use your medication exactly as directed. Do not stop your treatment on your own for any reason because, your infection may return.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

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

The following side effects are important and will require immediate action if you experience them. You should stop taking Ceftriaxone and see your doctor immediately if the following symptoms occur:

- easy bruising or bleeding
- reduction in red blood cells (anaemia) which can make the skin pale and cause weakness or breathlessness

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

5. How to store Ceftriaxone
Keep out of the reach and sight of children.

Do not use Ceftriaxone after the expiry date, which is stated on the label or carton.

This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light.

Your doctor, pharmacist or nurse will know how to store Ceftriaxone injection properly.

6. Further information
What Ceftriaxone contains
The active substance is Ceftriaxone. There are no other ingredients.

What Ceftriaxone looks like and contents of the pack
Ceftriaxone is an almost white to yellowish powder, packaged in a clear glass vial with white coloured flip off seal. Pack of 1 or 5 vials in a carton.
Not all pack sizes may be marketed.

When reconstituted in water for injections, Ceftriaxone powder gives a light yellow to amber coloured clear solution.

Marketing Authorisation Holder
Orchid Europe Ltd
Building 3, Chiswick Park, 566, Chiswick High Road, Chiswick, London, W4 5YA
United Kingdom

This leaflet was last approved in August 2009
**Technical Leaflet**

The following information is intended for medical or healthcare professionals only:  

**Ceftriaxone 2g Powder for Solution for Injection or Infusion**

**Method and route of administration:**
Ceftriaxone 2g powder for solution for injection or infusion is injected into a vein (intravenous injection or infusion into vein); however, it can also be injected into a muscle (intramuscular administration).

*Intramuscular injection (injection into a muscle)*
Ceftriaxone 2g powder for solution for injection should be dissolved in 7ml of 1.0% Lidocaine Hydrochloride solution. The solution should be administered by deep intramuscular injection. Not more than 1g Ceftriaxone should be injected on one side.
An injection into the blood vessels must be strictly avoided.

*Intravenous injection (injection into a vein)*
Ceftriaxone 2g powder for solution for injection should be dissolved in 20ml of water for injections. 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 (infusion into a vein)*
Ceftriaxone 2g powder for solution for injection or infusion should be dissolved in 40ml of one of the following calcium-free solutions: Glucose Injection 5% or 10%, Sodium Chloride Injection, Sodium Chloride and Glucose Injection (0.45% sodium chloride and 2.5% glucose), dextran 6% in Glucose Injection 5%, hydroxyethyl starch 6 - 10% infusions. The time of infusion is at least 30 minutes.

**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 such as Hartmann's solution and Ringer's solution. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

Reconstituted solutions should be inspected visually. Only clear solutions free of visible particles should be used. The reconstituted product is for single use only and any unused solution must be discarded. Ceftriaxone should not be mixed in the same syringe with any medicinal product other than 1% lidocaine hydrochloride solution (for intramuscular injection only).

**Special precautions for storage**
This medicinal product does not require any special storage conditions.
Keep vial(s) in the outer carton to protect from light.

After reconstitution, chemical and physical in-use stability has been demonstrated for at least 6 hours at or below 25°C or 24 hours at 2-8°C. Protect from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at or below 25°C or 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. Unused solution should be discarded.
Ceftriaxone

**250 mg**

Powder for solution for injection

Contains **250 mg** ceftriaxone as 298 mg disodium salt 3.5 H₂O. The sodium content is 0.9 mmol (20.7 mg) per vial.

**FOR I.M. INJECTION:** Dissolve in 1 ml solvent (10% Lidocaine HCl BP).

**FOR SLOW I.V. INJECTION:** Dissolve in 5 ml Water for Injections BP and administer over 2-4 minutes.

Intramuscular doses larger than 3.5 ml should be administered into separate muscles.

**Keep out of the reach and sight of children.**

This medicinal product does not require any special storage conditions. Keep vials(s) in the outer carton to protect from light.

**M.L. No. 763**

PL 22805/0001

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Ceftriaxone

**500 mg**

Powder for solution for injection

Contains **500 mg** ceftriaxone as 596.5 mg disodium salt 3.5 H₂O. The sodium content is 1.8 mmol (41.4 mg) per vial.

**FOR I.M. INJECTION:** Dissolve in 2 ml solvent (10% Lidocaine HCl BP).

**FOR SLOW I.V. INJECTION:** Dissolve in 5 ml Water for Injections BP and administer over 2-4 minutes.

Intramuscular doses larger than 3.5 ml should be administered into separate muscles.

**Keep out of the reach and sight of children.**

This medicinal product does not require any special storage conditions. Keep vials(s) in the outer carton to protect from light.

**M.L. No. 763**

PL 22805/0003
Ceftriaxone 1g

Powder for solution for injection

POM

Contains 1g ceftriaxone as 1.19g disodium salt 3.5H2O. The sodium content is 3.6mmol (92.8mg) per vial.

For I.M. Injection: Dissolve in 3.5ml solvent (1.0% Lidocaine HCl BP).

For SLOW I.V. INJECTION: Dissolve in 10ml Water for Injections BP and administer over 2-4 minutes.

Intramuscular doses larger than 3.5ml should be administered into separate muscles.

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light.

M.L. No. 763

Lot: EXP:

Ceftriaxone 2g

Powder for solution for injection or infusion

POM

Contains 2g ceftriaxone as 2.386g disodium salt 3.5H2O. The sodium content is 7.2mmol (165.6mg) per vial.

For full directions for use: See enclosed leaflet.

Intramuscular doses larger than 3.5ml should be administered into separate muscles.

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light.

M.L. No. 763

Lot: EXP:

82
Ceftriaxone 500 mg
Powder for solution for injection

Each vial contains 500 mg ceftriaxone as 596.5 mg of the disodium salt 3.5 H₂O. The sodium content is 1.8 mmol (41.4 mg) per vial.

FOR I.M. INJECTION: Dissolve the contents of the vial in 2 ml solvent (1.0% Lidocaine HCl BP).

FOR SLOW I.V. INJECTION: Dissolve in 5 ml Water for Injections BP and administer over 2-4 minutes.

Any portion of the contents remaining should be discarded after use.

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light.

After reconstitution or after the container has been opened the maximum in-shelf life is 6 hours at or below 25°C or 24 hours at 2-8°C.
UKPAR Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion

1 x 1 g vial

Ceftriaxone

1 g

Powder for solution for injection

Each vial contains 1 g ceftriaxone as 1.19 g of the disodium salt 3.5 H₂O. The sodium content is 3.8 mmol (82.8 mg) per vial.

FOR I.M. INJECTION:
Dissolve the contents of the vial in 3.5 ml solvent (1.0% Lidocaine HCl BP).

FOR SLOW I.V. INJECTION:
Dissolve in 10 ml Water for Injections BP and administer over 2-4 minutes.

Refer to leaflet for information on reconstitution before use.

Any portion of the contents remaining should be discarded after use.

POM

PL 22805/0004

MA Holder:
Orielde Europe Limited
Building 3, Chiswick Park, 566 Chiswick High Road, Chiswick, London, W4 5YA, United Kingdom.

M.L. No. 763

READ ENCLOSED LEAFLET

Ceftriaxone

1 g

Powder for solution for injection

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions. Keep vial(s) in the outer carton to protect from light.

After reconstitution or after the container has been opened the maximum in-shelf life is 6 hours at or below 25°C or 24 hours at 2-8°C.

Place for Barcode

READ ENCLOSED LEAFLET

85
UKPAR Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion

For full directions for use: See enclosed leaflet.

This medicinal product does not require any special storage conditions.

Keep vial(s) in the outer carton to protect from light.

Any portion of the contents remaining should be discarded after use.

Each vial contains 2g ceftriaxone as 2.386g of the disodium salt 3.5 H₂O. The sodium content is 7.2 mmol (195.6 mg) per vial.

MA Holder: Oronhal Europe Limited
Building 3, Chiswick Park, Chiswick, London, W4 5YA, United Kingdom.

M.L. No. 783

Keep out of the reach and sight of children.

After reconstitution or after the container has been opened the maximum in-shelf life is 6 hours at or below 25°C or 24 hours at 2-8°C.
UKPAR Ceftriaxone 250mg, 500mg, 1g Powder for Solution for Injection and 2g Powder for Solution for Injection or Infusion  
Pl. 22805/0001, 3-5
FOR I.M. OR SLOW I.V. INJECTION ONLY.

Each vial contains 250 mg ceftriaxone as 258 mg of the disodium salt 3,5 H₂O.
The sodium content is 0.9 mmol (20.7 mg) per vial.

Refer to leaflet for information on reconstitution before use.

FOR I.M. INJECTION: Dissolve the contents of the vial in 1 ml solvent (1.0% Lidocaine HCl BP).

FOR SLOW I.V. INJECTION: Dissolve in 5 ml Water for Injections BP and administer over 2-4 minutes.

After reconstitution or after the container has been opened the maximum in-shelf life is 8 hours at or below 25°C or 24 hours at 2-8°C.

Any portion of the contents remaining should be discarded after use.

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Keep vial(s) in the outer carton to protect from light.
Each vial contains 2 g ceftriaxone as 2.500 g of the disodium salt 3.5 H2O.
The sodium content is 7.2 mmol (185.6 mg) per vial.
For full directions for use: See enclosed leaflet.
After reconstitution or after the container has been opened the maximum in-shelf life is
6 hours at or below 25°C or 24 hours at 2-8°C
Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.
Keep vial(s) in the outer carton to protect from light.
Any portion of the contents remaining should be discarded after use.