Public Assessment Report

Decentralised Procedure

Ceftriaxone 500mg Powder for Solution for Injection/Infusion

Ceftriaxone 1g Powder for Solution for Injection/Infusion

Ceftriaxone 2g Powder for Solution for Injection/Infusion

PL 25975/0032
PL 25975/0033
PL 25975/0037

UK/H/1246/01-03/DC

Cardinal Health
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Cardinal Health Marketing Authorisations (licences) for the medicinal products Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion (Product Licence numbers: PL 25975/0032-3 and 0037). These medicines are available on prescription only.

Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion belongs to a group of antibiotics called cephalosporins. Antibiotics are used to kill the bacteria or ‘germs’ that cause infections. Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion is used to treat infections, including: infections of the lungs, bones, joints, flesh, skin, soft tissue and brain (meningitis). It can also be used to treat gonorrhoea and to prevent infections that may occur before or after some surgical operations.

The data submitted in support of these applications for Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

### Information about decentralised procedure

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion</th>
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<td>Level 2 Initial</td>
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<td>Level 3 10.1</td>
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</table>
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 500mg Powder for Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial of powder for solution for injection/infusion contains 0.5964g Ceftriaxone Sodium equivalent to 0.5g Ceftriaxone
Sodium content 42mg (equivalent to approx 1.8 mMol)
The product contains no excipients or preservatives

3 PHARMACEUTICAL FORM
Powder for solution for injection/infusion.
White to yellowish powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ceftriaxone is indicated for the treatment of the following bacterial infections when caused by micro-organisms that are susceptible to Ceftriaxone and if parenteral treatment is necessary (see section 5.1).
Bacterial Meningitis.
Infection of bones or joints
Infections of skin or soft tissue pneumonia.
Gonorrhoea
Peri-operative prophylaxis of infections associated with surgery
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
Ceftriaxone for injection/Infusion may be administered by intravenous bolus injection, by intravenous infusion or by deep intramuscular injection after reconstitution of the solution according to the directions given below (see section 6.6).
Diluents containing calcium, (e.g. Ringer’s solution or Hartmann’s solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form.
Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line.
Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously (see sections 4.3, 4.4 and 6.2).
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.

The intramuscular method of administration should only be used in exceptional clinical situations (see section 4.3) and should undergo a risk-benefit assessment.

For intramuscular injection the special advice below and also in section 6.6 must be followed.

For intramuscular administration ceftriaxone is dissolved in lidocaine hydrochloride solution and injected deep into the gluteus maximus muscle. Not more than 1 g of ceftriaxone should be injected on either side of the body. The maximum daily dose by intramuscular administration should not exceed 2 g. The summary of product characteristics of lidocaine hydrochloride solution 1% has to be taken into account.

Normal dosage

Adults and adolescents aged over 12 years with a body weight ≥50 kg:
The usual dose is 1 to 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 4g, administered once a day intravenously.

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:
20-50 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).

Elderly:
For elderly patients the dosage recommendations are the same as for adults - without modification.

Special dosage recommendations

Meningitis:
Treatment is initiated with 100 mg per kg bodyweight once daily – not exceeding 4 g daily. After determining the sensitivity of the pathogen the dose may be reduced accordingly.

In newborns 0 – 14 days of age the dose should not exceed 50 mg/kg/24 h.

Perioperative prophylaxis:
The normal daily dose of ceftriaxone should be administered 30-90 minutes prior to surgery. One single administration is usually sufficient.

Renal insufficiency:
In patients with impaired renal function, adjustment of the ceftriaxone dose is not necessary if the hepatic function is normal. In renal insufficiency with a
reduced creatinine clearance of < 10 ml/min the daily dose of ceftriaxone should not exceed 2 g in adult patients.

Hepatic insufficiency:
The dose does not need to be altered in patients with a liver disease provided that the renal function is normal (see section 4.8).
In simultaneous severe renal and hepatic insufficiency the serum ceftriaxone concentrations should be monitored regularly and the dosage adjusted appropriately for children and adults (see sections 4.4 and 5.2).

Haemodialysis or peritoneal dialysis
As ceftriaxone is dialysable only to a very minor extent there is no need for 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. In patients on continuous ambulatory peritoneal dialysis (CAPD), ceftriaxone may be administered either intravenously or in case of CAPD associated infections may be added directly to the dialysis solution (e.g. 1-2 g ceftriaxone in the first dialysis fluid of the respective day of treatment) (see section 6.6).

Adult Uncomplicated Gonnorhoea
A single dose of 250mg intramuscularly should be administered.

Duration of therapy
The normal duration of therapy depends on the characteristics of the infection. Generally the administration of ceftriaxone should be continued for at least 48 to 72 hours beyond the normalisation of body temperature and evidence of bacterial eradication has been obtained. Dosage recommendations for special indications should be taken into account.

4.3 Contraindications
Hypersensitivity to Ceftriaxone or to any of the cephalosporins.
Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam drug.
Ceftriaxone is contraindicated in:
- premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),
- full-term newborns (up to 28 days of age) with
  - jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired
  - if they require (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium (see sections 4.4, 4.8 and 6.2).

4.4 Special warnings and precautions for use
Anaphylactic shock cannot be ruled out even if a thorough patient history is taken.
Before therapy with Ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to Ceftriaxone, any other cephalosporin, or to any penicillin or other beta-lactam drug. Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. It is also contraindicated in patients who have had a previous immediate and/or any
severe hypersensitivity reaction to any penicillin or to any other beta-lactam
drug. Ceftriaxone should be given with caution to patients who have had any
other type of hypersensitivity reaction to a penicillin or any other beta-lactam
drug.
Ceftriaxone should be given with caution to patients who have other allergic
diatheses.
In severe renal impairment accompanied by hepatic insufficiency, dosage
reduction is required as outlined under section 4.2, Posology and method of
administration.
Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all
been reported with the use of Ceftriaxone. These diagnoses should be
considered in any patient who develops diarrhoea during or shortly after
treatment. Ceftriaxone should be discontinued if severe and/or bloody
diarrhoea occurs during treatment and appropriate therapy instituted.
Ceftriaxone should be used with caution in individuals with a previous history
of gastro-intestinal disease, particularly colitis.
Prolonged use of Ceftriaxone may result in the overgrowth of non-susceptible
organisms, such as Enterococci and Candida spp.

Interaction with Calcium-Containing Products
Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and
kidneys in premature and full-term newborns aged less than 1 month have
been described. At least one of them had received ceftriaxone and calcium at
different times and through different intravenous lines. In the available
scientific data, there are no reports of confirmed intravascular precipitations in
patients, other than newborns, treated with ceftriaxone and calcium-containing
solutions or any other calcium-containing products. In vitro studies
demonstrated that newborns have an increased risk of precipitation of
ceftriaxone-calcium compared to other age groups.
In patients of any age ceftriaxone must not be mixed or administered
simultaneously with any calcium-containing IV solutions, even via different
infusion lines or at different infusion sites. However, in patients older than 28
days of age ceftriaxone and calcium-containing solutions may be administered
sequentially one after another if infusion lines at different sites are used, or if
the infusion lines are replaced or thoroughly flushed between infusions with
physiological salt-solution to avoid precipitation. In patients requiring
continuous infusion with calcium-containing TPN solutions, healthcare
professionals may wish to consider the use of alternative antibacterial
treatments which do not carry a similar risk of precipitation. If use of
ceftriaxone is considered necessary in patients requiring continuous nutrition,
TPN solutions and ceftriaxone can be administered simultaneously, albeit via
different infusion lines at different sites. Alternatively, infusion of TPN
solution could be stopped for the period of ceftriaxone infusion, considering
the advice to flush infusion lines between solutions. (see sections 4.3, 4.8, 5.2
and 6.2).
In vivo and in vitro studies have shown that Ceftriaxone, like some other
cephalosporins, can displace bilirubin from serum albumin. Clinical data
obtained in neonates have confirmed this finding. Ceftriaxone for
Injection/Infusion should therefore not be used in jaundiced newborns or in
those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is
likely to be impaired. Ceftriaxone for Injection/Infusion 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
for Injection/Infusion on a body weight basis. In children, doses greater than
80mg/kg body weight should be avoided (except for meningitis) because of
the increased risk of biliary precipitates. There is no clear evidence of
gallstones or of acute cholecystitis developing in children or infants treated
with Ceftriaxone for Injection/Infusion and conservative management of
Ceftriaxone precipitate in the gallbladder is recommended.
Cephalosporins as a class tend to be absorbed onto the surface of the red cell
membranes and react with antibodies directed against the drug to produce a
positive Coombs' test and occasionally a rather mild haemolytic anaemia. In
this respect, there may be some cross-reactivity with penicillins.
Cases of pancreatitis, possible of biliary obstruction aetiology, have been
rarely reported in patients treated with Ceftriaxone for Injection/Infusion.
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 for Injection/Infusion related biliary
precipitation can not be ruled out.
The intramuscular method of administration is reserved to single interventions
and exceptional clinical situations and should undergo a risk-benefit
assessment. It is not indicated in severe conditions such as sepsis or meningitis
and in children younger than 12 years of age (see also 4.3).Because of the
need for reconstitution with lidocaine intramuscular injection of ceftriaxone is
not indicated during pregnancy and lactation.(See also section 4.6) Intravasal
injection must be strictly avoided because intravasally administered lidocaine
can lead to severe undesirable effects. The Summary of Product
Characteristics of the chosen lidocaine hydrochloride solution 1% has to be
regarded.
The stated dosage should not be exceeded.
During treatment, the blood cell count should be checked regularly.
Each gram of Ceftriaxone for Injection/Infusion contains approximately
3.6mmol sodium. To be taken into consideration by patients on a controlled
sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
In vitro, chloramphenicol has been reported to be antagonistic with respect to
Ceftriaxone and other cephalosporins. The clinical relevance of this finding is
unknown, but caution is advised if concurrent administration of Ceftriaxone
with chloramphenicol is proposed.
In patients treated with Ceftriaxone for Injection/Infusion, the Coombs' test
may rarely become false positive. Ceftriaxone for Injection/Infusion, like other
antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-
 enzymatic methods for glucose determination in urine may give false-positive
results. For this reason, urine-glucose determination during therapy with
Ceftriaxone for Injection/Infusion should be done enzymatically.
Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives.
Consequently, it is advisable to use supplementary (non-hormonal)
contraceptive measures during treatment and in the month following treatment.
In case of intramuscular administration of ceftriaxone the Summary of Product Characteristics of the lidocaine-containing product chosen for reconstitution must be regarded

4.6 Pregnancy and lactation

Pregnancy
Ceftriaxone reaches the embryo/fetus via the placenta. There is not sufficient experience in the human use of ceftriaxone: Animal data reveal no undesirable effects on reproduction (see section 5.3).
As a precautionary measure, ceftriaxone should only be used during pregnancy after careful benefit/risk assessment by the physician in charge, especially during the first trimester.

Lactation
Ceftriaxone is excreted in maternal milk at low concentrations. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.
Ceftriaxone should only be used after careful benefit/risk assessment by the physician in charge.
Additionally - intramuscular administration:
Ceftriaxone and lidocaine must not be used during pregnancy. Controlled clinical trials and data in pregnant women are not available. Animal data of ceftriaxone reveal no undesirable effects on reproduction. In animal studies treated with lidocaine some evidence on neurobehavioral changes but no embryotoxic or teratogenic effects were observed.
Lidocaine passes into breast milk in small amounts. Ceftriaxone with lidocaine must not be used during lactation.

4.7 Effects on ability to drive and use machines
Ceftriaxone has no or negligible influence on the ability to drive and use machines. However, undesirable effects such as hypotension or vertigo (see section 4.8) should be taken into account.

4.8 Undesirable effects
The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts.
Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full-term newborns (aged <28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem.
The high risk of precipitation in newborns is due to the low blood volume and the longer half life than in adults (see sections 4.3, 4.4, 4.8 and 5.2).
The following convention has been used for the classification of frequency:
very common \(\geq 1/10\)
common \(1/100 \) and \(<1/10\)
uncommon 1/1000 and <1/100
rare 1/10,000 and <1/1000
very rare <1/10,000.
Not known (cannot be estimated from the available data).

Infections and infestations

Rare: Mycosis of the genital tract.

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

Blood and lymphatic system disorders

Rare: Neutropenia, leucopenia, eosinophilia, thrombocytopenia, anaemia (including haemolytic anaemia), slight prolongation of prothrombin time.

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

Immune system disorders

Rare: Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions (see section 4.4

Nervous system disorders

Rare: Headache, dizziness.

Gastrointestinal disorders

Common: Loose stools or diarrhoea, nausea, vomiting.

Rare: Stomatitis, glossitis. These side effects are usually mild and commonly disappear during treatment or after discontinuation of treatment.

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

Hepato-biliary disorders

Rare: Increase in serum liver enzymes (AST, ALT, alkaline phosphatase).

Jaundice

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed (see section 4.4), mostly in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application, in some studies to above 30%. The incidence seems to be lower with slow infusion (20-30 minutes). This effect is usually asymptomatic, but in rare cases, the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

Skin and subcutaneous tissue disorders

Uncommon: Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritis, oedema.

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

Renal and urinary disorders

Rare: Increase in serum creatinine, oliguria, glycosuria, haematuria.

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

**General disorders and administration site conditions**

*Rare*: Phlebitis and injection site pain following intravenous administration. This can be minimised by slow injection over at least 2-4 minutes. Rigors, pyrexia.

An intramuscular injection without lidocaine is painful.

**4.9 Overdose**

In the case of overdosage, drug concentrations would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment should be symptomatic.

**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 \( \beta \)-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.

**Susceptibility**

*Breakpoints*

**EUCAST (2009-05-25)**

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<td><em>Enterobacteriaceae</em></td>
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<tr>
<td><em>H.influenza</em></td>
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<tr>
<td><em>M.catarrhalis</em></td>
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<tr>
<td><em>Neisseria spp.</em></td>
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<tr>
<td><em>S.pneumoniae</em></td>
<td>0.5/2</td>
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<tr>
<td>Other <em>streptococci</em></td>
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<td>----------------------</td>
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<tr>
<td>Non-species related breakpoints</td>
<td>1/2</td>
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</tbody>
</table>

* Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility.
** The susceptibility of streptococcus groups A, B, C and G can be inferred from their susceptibility to benzylpenicillin.
*** Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table.

**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)*
- *Streptococcus agalactiae*
- *Streptococcus bovis*
- *Streptococcus pyogenes* *
- *Streptococcus pneumoniae* *

**Gram-positive anaerobes**

- *Peptococcus niger*
- *Peptostreptococcus spp.*

**Gram-negative aerobes**

- *Citrobacter koseri*  
- *Escherichia coli* *
- *Haemophilus influenzae* *
- *Haemophilus parainfluenzae* *
- *Klebsiella pneumoniae* *
- *Klebsiella oxytoca* *
- *Moraxella catarrhalis* *
- *Morganella morganii* *
- *Neisseria meningitidis* *
- *Proteus mirabilis* *
- *Proteus vulgaris* *
- *Providencia spp.* *
- *Salmonella spp.* *
- *Serratia spp.*
**Species for which acquired resistance may be a problem**

**Gram-positive aerobes**

*Staphylococcus epidermidis*<sup>*</sup> (MSSE)

**Gram-negative aerobes**

*Citrobacter freundii*<sup>1</sup>
*Enterobacter spp.*<sup>1,3</sup>
*Pseudomonas aeruginosa*<sup>2</sup>

**Inherently resistant species**

**Gram-positive aerobes**

*Enterococcus faecalis*
*Enterococcus faecium*
*Listeria monocytogenes*
*Staphylococcus aureus MRSA*
*Staphylococcus epidermidis MRSE*

**Gram-positive anaerobes**

*Clostridium difficile*

**Gram-negative aerobes**

*Acinetobacter spp.*
*Achromobacter spp.*
*Aeromonas spp.*
*Alcaligenes spp.*
*Flavobacterium spp.*
*Legionella gormanii*

**Gram-negative anaerobes**

*Bacteroides spp.*

**Others**

*Chlamydia spp.*
*Chlamydophila spp.*
*Mycobacterium spp.*
*Mycoplasma spp.*
*Rickettsia spp.*
*Ureaplasma urealyticum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
$ Species with natural intermediate susceptibility

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 In suspected or proven *Pseudomonas* infection combination with an aminoglycoside is necessary.
3 Clinical efficacy has been demonstrated for susceptible isolates of *Enterobacter cloacae* and *Enterobacter aerogenes* in approved clinical indications.

5.2 Pharmacokinetic properties
Mean peak concentrations after bolus intravenous injection are about 120mg/l following a 500mg dose. Intramuscular injection of 500mg Ceftriaxone in 1% lignocaine produces mean peak plasma concentrations of 40-70 mg/l within one hour. Ceftriaxone is a cephalosporin for parenteral administration. Ceftriaxone is not absorbed after oral application.

**Absorption**
Ceftriaxone is completely absorbed following intramuscular administration with peak plasma concentrations (about 80 mg/l) occurring between 2 and 3 hours after dosing.

**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).

**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 are 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.

*Newborn infants*

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

*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.

**Special clinical situations**

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

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 gallbladder 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 other agents. In particular diluents containing calcium, (e.g. Ringer’s solution, Hartmann’s solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate
can form. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions (see section 4.2, 4.3, 4.4 and 4.8). This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 **Shelf life**
Unopened - 2 years
For reconstituted solution, chemical and physical in-use stability has been demonstrated for 6 hours at 25°C and 24 hrs at 2-8°C. From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 **Special precautions for storage**
Unopened: Do not store above 25°C. Store in the outer carton to protect from light.
After reconstitution: The reconstituted solution should be used immediately from microbiological point of view. See section 6.3 for complete storage instructions.

6.5 **Nature and contents of container**
10ml tubular (EP Type 1) glass vial with 20mm grey bromo butyl rubber plugs and aluminium flip off seal, containing a sterile white to yellowish crystalline powder. Pack of 1 vial.

6.6 **Special precautions for disposal**
Ceftriaxone injection and infusions should be reconstituted before administration to the patient. The volume of diluent to be used for the reconstitution is dependent upon the method of administration.

**Intramuscular injection:**
Ceftriaxone for Injection/Infusion 500 mg should be dissolved in 1.8ml of 1% Lidocaine Hydrochloride solution. The solution should be administered by deep intramuscular injection.

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Diluent to be added</th>
<th>Approx. available volume*</th>
</tr>
</thead>
<tbody>
<tr>
<td>500mg</td>
<td>1.8ml</td>
<td>2.1ml</td>
</tr>
</tbody>
</table>

*S* calculated from displacement value

*Solutions in Lidocaine must not be administered intravenously.*

**Intravenous injection:**
Ceftriaxone for Injection/Infusion should be dissolved in 5ml of Water for Injections. The injection should be administered over at least 1 - 2 minutes, directly into the vein.

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Diluent to be added</th>
<th>Approx. available volume*</th>
</tr>
</thead>
<tbody>
<tr>
<td>500mg</td>
<td>5ml</td>
<td>5.4ml</td>
</tr>
</tbody>
</table>

*S* calculated from displacement value

**Intravenous infusion:**
Ceftriaxone for Injection/Infusion can be added to one of the following calcium-free solutions (Concentration between 10mg/ml and 50mg/ml are recommended, the minimum concentration for infusion should be 10mg/ml): Dextrose Injection 5% or 10%, Sodium Chloride Injection, Sodium Chloride and Dextrose Injection (0.45% Sodium Chloride and 2.5% Dextrose), Dextran 6% in Dextrose Injection 5%, Hydroxyethyl Starch 6 - 10% infusions. The infusion should be administered over at least 30 minutes. Solutions to be administered intravenously must not be administered using tubing that contains, or has contained, calcium-containing fluids. The reconstituted solution should be shaken up to 60 seconds to ensure complete dissolution of ceftriaxone. When reconstituted for intravenous infusion, the white to yellowish crystalline powder gives a pale yellow to amber solution. For single use only. Discard any unused solution. The reconstitution/dilution is to be made under aseptic conditions. The reconstituted solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Cardinal Health Bampton Road Harold Hill Essex RM3 8UG

8 MARKETING AUTHORISATION NUMBER(S)
PL 25975/0032

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/10/2009

10 DATE OF REVISION OF THE TEXT
28/10/2009

1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 1g Powder for Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1g vial contains 1g ceftriaxone as 1.19g hydrated disodium ceftriaxone. Sodium content 84mg (equivalent to approx 3.6 mMol) The product contains no excipients or preservatives
3 PHARMACEUTICAL FORM
Powder for solution for injection/infusion.
White to yellowish powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ceftriaxone is indicated for the treatment of the following bacterial infections when caused by micro-organisms that are susceptible to Ceftriaxone and if paranteral treatment is nescessary(see section 5.1).
Bacterial Meningitis.
Infection of bones or joints
Infections of skin or soft tissue
pneumonia.
Gonorrhoea
Peri-operative prophylaxis of infections associated with surgery
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
Ceftriaxone for injection/Infusion may be administered by intravenous bolus injection, by intravenous infusion or by deep intramuscular injection after reconstitution of the solution according to the directions given below (see section 6.6).
Diluents containing calcium, (e.g. Ringer’s solution or Hartmann’s solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form.
Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line.
Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously (see sections 4.3, 4.4 and 6.2).

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.

The intramuscular method of administration should only be used in exceptional clinical situations (see section 4.3) and should undergo a risk-benefit assessment.
For intramuscular injection the special advice below and also in section 6.6 must be followed.
For intramuscular administration ceftriaxone is dissolved in lidocaine hydrochloride solution and injected deep into the gluteus maximus muscle.
Not more than 1 g of ceftriaxone should be injected on either side of the body.
The maximum daily dose by intramuscular administration should not exceed 2
g. The summary of product characteristics of lidocaine hydrochloride solution 1% has to be taken into account.

Normal dosage

Adults and adolescents aged over 12 years with a body weight ≥50 kg:
The usual dose is 1 to 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 4g, administered once a day intravenously.

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:
20-50 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).

Elderly:
For elderly patients the dosage recommendations are the same as for adults - without modification.

Special dosage recommendations

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

Perioperative prophylaxis:
The normal daily dose of ceftriaxone should be administered 30-90 minutes prior to surgery. One single administration is usually sufficient.

Renal insufficiency:
In patients with impaired renal function, adjustment of the ceftriaxone dose is not necessary if the hepatic function is normal. In renal insufficiency with a reduced creatinine clearance of < 10 ml/min the daily dose of ceftriaxone should not exceed 2 g in adult patients.

Hepatic insufficiency:
The dose does not need to be altered in patients with a liver disease provided that the renal function is normal (see section 4.8).
In simultaneous severe renal and hepatic insufficiency the serum ceftriaxone concentrations should be monitored regularly and the dosage adjusted appropriately for children and adults (see sections 4.4 and 5.2).

Haemodialysis or peritoneal dialysis
As ceftriaxone is dialysable only to a very minor extent there is no need for 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. In patients on continuous ambulatory peritoneal dialysis (CAPD), ceftriaxone may be administered either intravenously or in case of CAPD associated infections may be added directly to the dialysis solution (e.g. 1-2 g ceftriaxone in the first dialysis fluid of the respective day of treatment) (see section 6.6).
**Adult Uncomplicated Gonorrhoea**
A single dose of 250mg intramuscularly should be administered.

**Duration of therapy**
The normal duration of therapy depends on the characteristics of the infection. Generally the administration of ceftriaxone should be continued for at least 48 to 72 hours beyond the normalisation of body temperature and evidence of bacterial eradication has been obtained. Dosage recommendations for special indications should be taken into account.

4.3 **Contraindications**
Hypersensitivity to Ceftriaxone or to any of the cephalosporins.
Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam drug.

Ceftriaxone is contraindicated in:
- premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),
- full-term newborns (up to 28 days of age) with
  - jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired
  - if they require (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium (see sections 4.4, 4.8 and 6.2).

4.4 **Special warnings and precautions for use**
Anaphylactic shock cannot be ruled out even if a thorough patient history is taken.

Before therapy with Ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to Ceftriaxone, any other cephalosporin, or to any penicillin or other beta-lactam drug. Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. It is also contraindicated in patients who have had a previous immediate and/or any severe hypersensitivity reaction to any penicillin or to any other beta-lactam drug. Ceftriaxone should be given with caution to patients who have had any other type of hypersensitivity reaction to a penicillin or any other beta-lactam drug.

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

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined under section 4.2, Posology and method of administration.

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of Ceftriaxone. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Ceftriaxone should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.

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

Prolonged use of Ceftriaxone may result in the overgrowth of non-susceptible organisms, such as *Enterococci* and *Candida spp.*
Interaction with Calcium-Containing Products

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. In vitro studies demonstrated that newborns have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups. In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used, or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions. (see sections 4.3, 4.8, 5.2 and 6.2).

In vivo and in vitro studies have shown that Ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Clinical data obtained in neonates have confirmed this finding. Ceftriaxone for Injection/Infusion should therefore not be used in jaundiced newborns or in those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is likely to be impaired. Ceftriaxone for Injection/Infusion 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 for Injection/Infusion on a body weight basis. In children, doses greater than 80mg/kg body weight should be avoided (except for meningitis) because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with Ceftriaxone for Injection/Infusion and conservative management of Ceftriaxone precipitate in the gallbladder is recommended.

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the drug to produce a positive Coombs’ test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins. Cases of pancreatitis, possible of biliary obstruction aetiology, have been rarely reported in patients treated with Ceftriaxone for Injection/Infusion. 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 for Injection/Infusion related biliary precipitation can not be ruled out.
The intramuscular method of administration is reserved to single interventions and exceptional clinical situations and should undergo a risk-benefit assessment. It is not indicated in severe conditions such as sepsis or meningitis and in children younger than 12 years of age (see also 4.3). Because of the need for reconstitution with lidocaine intramuscular injection of ceftriaxone is not indicated during pregnancy and lactation. (See also section 4.6) Intravasal injection must be strictly avoided because intravasally administered lidocaine can lead to severe undesirable effects. The Summary of Product Characteristics of the chosen lidocaine hydrochloride solution 1% has to be regarded.
The stated dosage should not be exceeded.
During treatment, the blood cell count should be checked regularly.
Each gram of Ceftriaxone for Injection/Infusion contains approximately 3.6mmol sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
In vitro, chloramphenicol has been reported to be antagonistic with respect to Ceftriaxone and other cephalosporins. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of Ceftriaxone with chloramphenicol is proposed.
In patients treated with Ceftriaxone for Injection/Infusion, the Coombs' test may rarely become false positive. Ceftriaxone for Injection/Infusion, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with Ceftriaxone for Injection/Infusion should be done enzymatically. Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.
In case of intramuscular administration of ceftriaxone the Summary of Product Characteristics of the lidocaine-containing product chosen for reconstitution must be regarded.

4.6 Pregnancy and lactation

Pregnancy
Ceftriaxone reaches the embryo/fetus via the placenta. There is not sufficient experience in the human use of ceftriaxone: Animal data reveal no undesirable effects on reproduction (see section 5.3). As a precautionary measure, ceftriaxone should only be used during pregnancy after careful benefit/risk assessment by the physician in charge, especially during the first trimester.

Lactation
Ceftriaxone is excreted in maternal milk at low concentrations. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.
Ceftriaxone should only be used after careful benefit/risk assessment by the physician in charge.

**Additionally - intramuscular administration:**
Ceftriaxone and lidocaine must not be used during pregnancy. Controlled clinical trials and data in pregnant women are not available. Animal data of ceftriaxone reveal no undesirable effects on reproduction. In animal studies treated with lidocaine some evidence on neurobehavioral changes but no embryotoxic or teratogenic effects were observed.

Lidocaine passes into breast milk in small amounts. Ceftriaxone with lidocaine must not be used during lactation.

### 4.7 Effects on ability to drive and use machines
Ceftriaxone has no or negligible influence on the ability to drive and use machines. However, undesirable effects such as hypotension or vertigo (see section 4.8) should be taken into account.

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

Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full-term newborns (aged <28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem.

The high risk of precipitation in newborns is due to the low blood volume and the longer half life than in adults (see sections 4.3, 4.4, 4.8 and 5.2).

The following convention has been used for the classification of frequency:

- very common ≥1/10
- common ≥1/100 and <1/10
- uncommon ≥1/1000 and <1/100
- rare ≥1/10,000 and <1/1000
- very rare <1/10,000.

Not known (cannot be estimated from the available data).

**Infections and infestations**

*Rare*: Mycosis of the genital tract.
Superinfections of various sites with yeasts, fungi or other resistant organisms are possible.

**Blood and lymphatic system disorders**

*Rare*: Neutropenia, leucopenia, eosinophilia, thrombocytopenia, anaemia (including haemolytic anaemia), slight prolongation of prothrombin time.

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

**Immune system disorders**

*Rare*: Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions (see section 4.4)

**Nervous system disorders**

*Rare*: Headache, dizziness.
Gastrointestinal disorders
 Common: Loose stools or diarrhoea, nausea, vomiting.
 Rare: Stomatitis, glossitis. These side effects are usually mild and commonly
 disappear during treatment or after discontinuation of treatment.
 Very rare: including isolated reports: Pseudomembranous colitis (mostly
 caused by Clostridium difficile), pancreatitis (possibly caused by obstruction
 of bile ducts).
 Hepato-biliary disorders
 Rare: Increase in serum liver enzymes (AST, ALT, alkaline phosphatase).
 Jaundice
 Precipitation of ceftriaxone calcium salt in the gallbladder has been observed
 (see section 4.4), mostly in patients treated with doses higher than the
 recommended standard dose. In children, prospective studies have shown a
 variable incidence of precipitation with intravenous application, in some
 studies to above 30 %. The incidence seems to be lower with slow infusion
 (20-30 minutes). This effect is usually asymptomatic, but in rare cases, the
 precipitations have been accompanied by clinical symptoms such as pain,
 nausea and vomiting. Symptomatic treatment is recommended in these cases.
 Precipitation is usually reversible upon discontinuation of ceftriaxone.
 Skin and subcutaneous tissue disorders
 Uncommon: Allergic skin reactions such as maculopapular rash or exanthema,
 urticaria, dermatitis, pruritis, oedema.
 Very rare: including isolated reports: Erythema multiforme, Stevens Johnson
 Syndrome, Lyell's Syndrome/toxic epidermal necrolysis.
 Renal and urinary disorders
 Rare: Increase in serum creatinine, oliguria, glycosuria, haematuria.
 Very rare: including isolated reports: Renal precipitation, mostly in children
 older than 3 years who have been treated with either high daily doses (80
 mg/kg/day and more) or total doses exceeding 10g and with other risk factors
 such as dehydration or immobilisation. Renal precipitation is reversible upon
 discontinuation of ceftriaxone. Anuria and renal impairment have been
 reported in association.
 General disorders and administration site conditions
 Rare: Phlebitis and injection site pain following intravenous administration.
 This can be minimised by slow injection over at least 2-4 minutes. Rigors,
 pyrexia.
 An intramuscular injection without lidocaine is painful.

4.9 Overdose
In the case of overdosage, drug concentrations would not be reduced by
haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment
should be symptomatic.

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.

**Susceptibility**

**Breakpoints**

EUCAST (2009-05-25)

<table>
<thead>
<tr>
<th>Species-related breakpoints</th>
<th>Susceptible/Resistant (S/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>1/2</td>
</tr>
<tr>
<td>H.influenza</td>
<td>0.12/0.12</td>
</tr>
<tr>
<td>M.catarrhalis</td>
<td>1/2</td>
</tr>
<tr>
<td>Neisseria spp.</td>
<td>0.12/0.12</td>
</tr>
<tr>
<td>S.pneumoniae</td>
<td>0.5/2</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>0.5/0.5</td>
</tr>
<tr>
<td>Non-species related breakpoints</td>
<td>1/2</td>
</tr>
</tbody>
</table>

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

** The susceptibility of streptococcus groups A, B, C and G can be inferred from their susceptibility to benzylpenicillin.

*** Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table.

**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)
*Streptococcus agalactiae*
*Streptococcus bovis*
*Streptococcus pyogenes*
*Streptococcus pneumoniae*

Gram-positive anaerobes

*Peptococcus niger*
*Peptostreptococcus spp.*

Gram-negative aerobes

*Citrobacter koseri*
*Escherichia coli*
*Haemophilus influenzae*
*Haemophilus parainfluenzae*
*Klebsiella pneumoniae*
*Klebsiella oxytoca*
*Moraxella catarrhalis*
*Morganella morganii*
*Neisseria meningitidis*
*Proteus mirabilis*
*Proteus vulgaris*
*Providencia spp.*
*Salmonella spp.*
*Serratia spp.*
*Shigella spp.*

Species for which acquired resistance may be a problem

Gram-positive aerobes

*Staphylococcus epidermidis*(MSSE)

Gram-negative aerobes

*Citrobacter freundii*
*Enterobacter spp.*
*Pseudomonas aeruginosa*

Inherently resistant species

Gram-positive aerobes

*Enterococcus faecalis*
Enterococcus faecium
Listeria monocytogenes
Staphylococcus aureus MRSA
Staphylococcus epidermidis MRSE

**Gram-positive anaerobes**

Clostridium difficile

**Gram-negative aerobes**

Acinetobacter spp.
Achromobacter spp.
Aeromonas spp.
Alcaligenes spp.
Flavobacterium spp.
Legionella gormanii

**Gram-negative anaerobes**

Bacteroides spp.

**Others**

Chlamydia spp.
Chlamyphila spp.
Mycobacterium spp.
Mycoplasma spp.
Rickettsia spp.
Ureaplasma urealyticum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
$ Species with natural intermediate susceptibility

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 In suspected or proven *Pseudomonas* infection combination with an aminoglycoside is necessary.
3 Clinical efficacy has been demonstrated for susceptible isolates of *Enterobacter cloacae* and *Enterobacter aerogenes* in approved clinical indications.

### 5.2 Pharmacokinetic properties

Mean peak concentrations after bolus intravenous injection are about 200mg/l following a 1g dose. Intramuscular injection of 500mg Ceftriaxone in 1% lignocaine produces mean peak plasma concentrations of 40-70 mg/l within one hour.
Ceftriaxone is a cephalosporin for parenteral administration. Ceftriaxone is not absorbed after oral application.

**Absorption**
Ceftriaxone is completely absorbed following intramuscular administration with peak plasma concentrations (about 80 mg/l) occurring between 2 and 3 hours after dosing.

**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).

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

**Special clinical situations**

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

**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 gallbladder 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 other agents. In particular diluents containing calcium, (e.g. Ringer’s solution, Hartmann’s solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions (see section 4.2, 4.3, 4.4 and 4.8). This medicinal product must not be mixed with other medicinal product except those mentioned in 6.6

**6.3 Shelf life**

Unopened: 2 years

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

**6.4 Special precautions for storage**

Unopened: Do not store above 25°C. Store in the outer carton to protect from light.
After reconstitution: The reconstituted solution should be used immediately from microbiological point of view. See section 6.3 for complete storage instructions

6.5 Nature and contents of container
10ml tubular (EP Type 1) glass vial with 20mm grey bromo butyl rubber plugs and aluminium flip off seal, containing a sterile white to yellowish crystalline powder. Pack of 1 vial.

6.6 Special precautions for disposal
Ceftriaxone injection and infusions should be reconstituted before administration to the patient. The volume of diluent to be used for the reconstitution is dependent upon the method of administration.

**Intramuscular injection:**
Ceftriaxone for Injection/Infusion 1g should be dissolved in 3.5ml of 1% Lidocaine Hydrochloride solution. The solution should be administered by deep intramuscular injection.

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Diluent to be added</th>
<th>Approx. available volume*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g</td>
<td>3.5ml</td>
<td>4.2ml</td>
</tr>
</tbody>
</table>

*calculated from displacement value

*Solutions in Lidocaine must not be administered intravenously.*

**Intravenous injection:**
Ceftriaxone for Injection/Infusion should be dissolved in 10 ml of Water for Injections. The injection should be administered over at least 2 - 4 minutes, directly into the vein.

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Diluent to be added</th>
<th>Approx. available volume*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g</td>
<td>10ml</td>
<td>10.8ml</td>
</tr>
</tbody>
</table>

*calculated from displacement value

**Intravenous infusion:**
Ceftriaxone for Injection/Infusion can be added to one of the following calcium-free solutions (Concentration between 10mg/ml and 50mg/ml are recommended, the minimum concentration for infusion should be 10mg/ml): Dextrose Injection 5% or 10%, Sodium Chloride Injection, Sodium Chloride and Dextrose Injection (0.45% Sodium Chloride and 2.5% Dextrose), Dextran 6% in Dextrose Injection 5%, Hydroxyethyl Starch 6 - 10% infusions. The infusion should be administered over at least 30 minutes.

Solutions to be administered intravenously must not be administered using tubing that contains, or has contained, calcium-containing fluids.

The reconstituted solution should be shaken up to 60 seconds to ensure complete dissolution of ceftriaxone.

When reconstituted for intravenous infusion, the white to yellowish crystalline powder gives a pale yellow to amber solution.

For single use only. Discard any unused solution.

The reconstitution/dilution is to be made under aseptic conditions.

The reconstituted solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Cardinal Health Bampton Road Harold Hill Essex RM3 8UG

8 MARKETING AUTHORISATION NUMBER(S)
PL 25975/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
28/10/2009

10 DATE OF REVISION OF THE TEXT
28/10/2009

1 NAME OF THE MEDICINAL PRODUCT
Ceftriaxone 2g Powder for Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 2g vial contains 2g ceftriaxone as 2.39g hydrated disodium ceftriaxone

Sodium content 168mg (equivalent to approx 7.2 mMol)
The product contains no excipients or preservatives

3 PHARMACEUTICAL FORM
Powder for solution for injection/infusion.
White to yellowish powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ceftriaxone is indicated for the treatment of the following bacterial infections when caused by micro-organisms that are susceptible to Ceftriaxone and if paranteral treatment is necessary (see section 5.1).
Bacterial Meningitis.
Infection of bones or joints
Infections of skin or soft tissue
Pneumonia.
Gonorrhoea
Peri-operative prophylaxis of infections associated with surgery
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
Ceftriaxone for injection/Infusion may be administered by intravenous bolus injection or by intravenous infusion.

Diluents containing calcium, (e.g. Ringer’s solution or Hartmann’s solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously (see sections 4.3, 4.4 and 6.2).

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.

Normal dosage

**Adults and adolescents aged over 12 years with a body weight ≥50 kg:**
The usual dose is 1 to 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 4g, administered once a day intravenously.

**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:**
20-50 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).

**Elderly:**
For elderly patients the dosage recommendations are the same as for adults - without modification.

Special dosage recommendations

**Meningitis:**
Treatment is initiated with 100 mg per kg bodyweight once daily – not exceeding 4 g daily. After determining the sensitivity of the pathogen the dose may be reduced accordingly.

In newborns 0 – 14 days of age the dose should not exceed 50 mg/kg/24 h.

**Perioperative prophylaxis:**
The normal daily dose of ceftriaxone should be administered 30-90 minutes prior to surgery. One single administration is usually sufficient.

**Renal insufficiency:**
In patients with impaired renal function, adjustment of the ceftriaxone dose is not necessary if the hepatic function is normal. In renal insufficiency with a
reduced creatinine clearance of < 10 ml/min the daily dose of ceftriaxone should not exceed 2 g in adult patients.

Hepatic insufficiency:
The dose does not need to be altered in patients with a liver disease provided that the renal function is normal (see section 4.8).
In simultaneous severe renal and hepatic insufficiency the serum ceftriaxone concentrations should be monitored regularly and the dosage adjusted appropriately for children and adults (see sections 4.4 and 5.2).

Haemodialysis or peritoneal dialysis
As ceftriaxone is dialysable only to a very minor extent there is no need for 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. In patients on continuous ambulatory peritoneal dialysis (CAPD), ceftriaxone may be administered either intravenously or in case of CAPD associated infections may be added directly to the dialysis solution (e.g. 1-2 g ceftriaxone in the first dialysis fluid of the respective day of treatment) (see section 6.6).

Duration of therapy
The normal duration of therapy depends on the characteristics of the infection. Generally the administration of ceftriaxone should be continued for at least 48 to 72 hours beyond the normalisation of body temperature and evidence of bacterial eradication has been obtained. Dosage recommendations for special indications should be taken into account.

4.3 Contraindications
Hypersensitivity to Ceftriaxone or to any of the cephalosporins.
Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam drug.
Ceftriaxone is contraindicated in:
- premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),
- full-term newborns (up to 28 days of age) with
  - jaundice, or who are hypoalbuminaemic or acidic because these are conditions in which bilirubin binding is likely to be impaired
  - if they require (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium (see sections 4.4, 4.8 and 6.2).

4.4 Special warnings and precautions for use
Anaphylactic shock cannot be ruled out even if a thorough patient history is taken.
Before therapy with Ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to Ceftriaxone, any other cephalosporin, or to any penicillin or other beta-lactam drug. Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. It is also contraindicated in patients who have had a previous immediate and/or any severe hypersensitivity reaction to any penicillin or to any other beta-lactam drug. Ceftriaxone should be given with caution to patients who have had any
other type of hypersensitivity reaction to a penicillin or any other beta-lactam drug.
Ceftriaxone should be given with caution to patients who have other allergic diatheses.
In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined under section 4.2, Posology and method of administration.
Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of Ceftriaxone. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Ceftriaxone should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.
Ceftriaxone should be used with caution in individuals with a previous history of gastro-intestinal disease, particularly colitis.
Prolonged use of Ceftriaxone may result in the overgrowth of non-susceptible organisms, such as Enterococci and Candida spp.

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

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used, or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions. (see sections 4.3, 4.8, 5.2 and 6.2).

In vivo and in vitro studies have shown that Ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Clinical data obtained in neonates have confirmed this finding. Ceftriaxone for Injection/Infusion should therefore not be used in jaundiced newborns or in those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is likely to be impaired. Ceftriaxone for Injection/Infusion 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 for Injection/Infusion on a body weight basis. In children, doses greater than 80mg/kg body weight should be avoided (except for meningitis) because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with Ceftriaxone for Injection/Infusion and conservative management of Ceftriaxone precipitate in the gallbladder is recommended.

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

Cases of pancreatitis, possible of biliary obstruction aetiology, have been rarely reported in patients treated with Ceftriaxone for Injection/Infusion. 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 for Injection/Infusion related biliary precipitation can not be ruled out.

Intravasal injection must be strictly avoided because intravasally administered lidocaine can lead to severe undesirable effects. The Summary of Product Characteristics of the chosen lidocaine hydrochloride solution 1% has to be regarded.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.

4.6 Pregnancy and lactation

Pregnancy

Ceftriaxone reaches the embryo/fetus via the placenta. There is not sufficient experience in the human use of ceftriaxone: Animal data reveal no undesirable effects on reproduction (see section 5.3).
As a precautionary measure, ceftriaxone should only be used during pregnancy after careful benefit/risk assessment by the physician in charge, especially during the first trimester.

**Lactation**
Ceftriaxone is excreted in maternal milk at low concentrations. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.
Ceftriaxone should only be used after careful benefit/risk assessment by the physician in charge.

**4.7 Effects on ability to drive and use machines**
Ceftriaxone has no or negligible influence on the ability to drive and use machines. However, undesirable effects such as hypotension or vertigo (see section 4.8) should be taken into account.

**4.8 Undesirable effects**
The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts.
Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full-term newborns (aged <28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem.
The high risk of precipitation in newborns is due to the low blood volume and the longer half life than in adults (see sections 4.3, 4.4, 4.8 and 5.2).
The following convention has been used for the classification of frequency:
very common ≥1/10
common ≥1/100 and <1/10
uncommon ≥1/1000 and <1/100
rare ≥1/10,000 and <1/1000
very rare <1/10,000.
Not known (cannot be estimated from the available data).

**Infections and infestations**
*Rare*: Mycosis of the genital tract.
Superinfections of various sites with yeasts, fungi or other resistant organisms are possible.

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

**Immune system disorders**
*Rare*: Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions (see section 4.4)

**Nervous system disorders**
*Rare*: Headache, dizziness.
Gastrointestinal disorders
*Common:* Loose stools or diarrhoea, nausea, vomiting.
*Rare:* Stomatitis, glossitis. These side effects are usually mild and commonly disappear during treatment or after discontinuation of treatment.
*Very rare:* including isolated reports: Pseudomembranous colitis (mostly caused by *Clostridium difficile*), pancreatitis (possibly caused by obstruction of bile ducts).

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

Jaundice
Precipitation of ceftriaxone calcium salt in the gallbladder has been observed (see section 4.4), mostly in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application, in some studies to above 30%. The incidence seems to be lower with slow infusion (20-30 minutes). This effect is usually asymptomatic, but in rare cases, the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

Skin and subcutaneous tissue disorders
*Uncommon:* Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritis, oedema.
*Very rare:* including isolated reports: Erythema multiforme, Stevens Johnson Syndrome, Lyell's Syndrome/toxic epidermal necrolysis.

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

General disorders and administration site conditions
*Rare:* Phlebitis and injection site pain following intravenous administration. This can be minimised by slow injection over at least 2-4 minutes. Rigors, pyrexia.

4.9 Overdose
In the case of overdosage, drug concentrations would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment should be symptomatic.

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.

**Susceptibility**

**Breakpoints**

EUCAST (2009-05-25)

<table>
<thead>
<tr>
<th>Species-related breakpoints</th>
<th>Susceptible/Resistant (S≤/R&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>1/2</td>
</tr>
<tr>
<td><em>H.influenza</em></td>
<td>0.12/0.12</td>
</tr>
<tr>
<td><em>M.catarrhalis</em></td>
<td>1/2</td>
</tr>
<tr>
<td><em>Neisseria spp.</em></td>
<td>0.12/0.12</td>
</tr>
<tr>
<td><em>S.pneumoniae</em></td>
<td>0.5/2</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>0.5/0.5</td>
</tr>
<tr>
<td>Non-species related breakpoints</td>
<td>1/2</td>
</tr>
</tbody>
</table>

* Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility.
** The susceptibility of streptococcus groups A, B, C and G can be inferred from their susceptibility to benzylpenicillin.
*** Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table.

**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)
Streptococcus agalactiae
Streptococcus bovis
Streptococcus pyogenes*
Streptococcus pneumoniae*

Gram-positive anaerobes

Peptococcus niger
Peptostreptococcus spp.

Gram-negative aerobes

Citrobacter koseri
Escherichia coli*1
Haemophilus influenzae*
Haemophilus parainfluenzae*
Klebsiella pneumoniae*1
Klebsiella oxytoca*1
Moraxella catarrhalis*
Morganella morganii1
Neisseria meningitidis*
Proteus mirabilis*
Proteus vulgaris1
Providencia spp.1
Salmonella spp.1
Serratia spp.1
Shigella spp.

Species for which acquired resistance may be a problem

Gram-positive aerobes

Staphylococcus epidermidis*5 (MSSE)

Gram-negative aerobes

Citrobacter freundii1
Enterobacter spp.1,3
Pseudomonas aeruginosa5,2

Inherently resistant species

Gram-positive aerobes

Enterococcus faecalis
Enterococcus faecium
Listeria monocytogenes
Staphylococcus aureus MRSA
Staphylococcus epidermidis MRSE

Gram-positive anaerobes

Clostridium difficile

Gram-negative aerobes

Acinetobacter spp.
Achromobacter spp.
Aeromonas spp.
Alcaligenes spp.
Flavobacterium spp.
Legionella gormanii

Gram-negative anaerobes

Bacteroides spp.

Others

Chlamydia spp.
Chlamydophila spp.
Mycobacterium spp.
Mycoplasma spp.
Rickettsia spp.
Ureaplasma urealyticum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
$ Species with natural intermediate susceptibility

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 In suspected or proven Pseudomonas infection combination with an aminoglycoside is necessary.
3 Clinical efficacy has been demonstrated for susceptible isolates of Enterobacter cloacae and Enterobacter aerogenes in approved clinical indications.

5.2 Pharmacokinetic properties
Mean levels of 250mg/l are achieved after infusion of 2g over 30 minutes. Ceftriaxone is a cephalosporin for parenteral administration. Ceftriaxone is not absorbed after oral application.

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).

**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 are 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.

*Newborn infants*

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

*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.

**Special clinical situations**

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

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 gallbladder 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 other agents. In particular diluents containing calcium, (e.g. Ringer’s solution, Hartmann’s solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions (see section 4.2, 4.3, 4.4 and 4.8). This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 **Shelf life**

Unopened - 2 years

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

6.4 **Special precautions for storage**

Unopened: Do not store above 25°C. Store in the outer carton to protect from light.

After reconstitution: The reconstituted solution should be used immediately from microbiological point of view. See section 6.3 for complete storage instructions.

6.5 **Nature and contents of container**

10ml tubular (EP Type 1) glass vial with 20mm grey bromo butyl rubber plugs and aluminium flip off seal, containing a sterile white to yellowish crystalline powder. Pack of 1 vial.
6.6 Special precautions for disposal
Ceftriaxone injection and infusions should be reconstituted before administration to the patient. The volume of diluent to be used for the reconstitution is dependent upon the method of administration.

Intravenous injection:
Ceftriaxone for Injection/Infusion should be dissolved in 20ml of Water for Injections. The injection should be administered over at least 4 - 8 minutes, directly into the vein.

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Diluent to be added</th>
<th>Approx. available volume*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2g</td>
<td>20ml</td>
<td>21.6ml</td>
</tr>
</tbody>
</table>

*calculated from displacement value

Intravenous infusion:
Ceftriaxone for Injection/Infusion can be added to one of the following calcium-free solutions (Concentration between 10mg/ml and 50mg/ml are recommended, the minimum concentration for infusion should be 10mg/ml): Dextrose Injection 5% or 10%, Sodium Chloride Injection, Sodium Chloride and Dextrose Injection (0.45% Sodium Chloride and 2.5% Dextrose), Dextran 6% in Dextrose Injection 5%, Hydroxyethyl Starch 6 - 10% infusions. The infusion should be administered over at least 30 minutes. Solutions to be administered intravenously must not be administered using tubing that contains, or has contained, calcium-containing fluids. The reconstituted solution should be shaken up to 60 seconds to ensure complete dissolution of ceftriaxone. When reconstituted for intravenous infusion, the white to yellowish crystalline powder gives a pale yellow to amber solution. For single use only. Discard any unused solution. The reconstitution/dilution is to be made under aseptic conditions. The reconstituted solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Cardinal Health Bampton Road Harold Hill Essex RM3 8UG

8 MARKETING AUTHORISATION NUMBER(S)
PL 25975/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/10/2009

10 DATE OF REVISION OF THE TEXT
28/10/2009
Module 3

Product Information Leaflet
MHRA PAR; CEFTRIAXONE 500MG, 1G AND 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 25975/0032-3 AND 0037

TECHNICAL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT

Ceftriaxone 250mg Powder for Solution for Injection/Infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for injection/concentration contains 0.25g of ceftriaxone. Sodium chloride equivalent to 50mg/ml.

Sodium content 42.4 mg per 1ml (12.6mM)

The amount exceeds requirements for prescription purposes.

PHARMACEUTICAL FORM

Powder for injection/concentration.

White to yellowish powder.

CLINICAL PARTICULARS

Therapeutic Indications

Ceftriaxone is indicated for the treatment of the following infectious infections caused by microorganisms that are susceptible to Ceftriaxone and Empirical treatment is necessary.

Bacterial meningitis

Infection of bone or joints

Infections of the skin or soft tissues

Pneumonia

Gastroenteritis

Peptic ulcer disease associated with infection.

PRECAUTIONS TO BE TAKEN IN SELECTED POPULATIONS

Pregnancy and lactation

Ceftriaxone is not recommended for use during pregnancy unless the potential benefit justifies the potential risk to the fetus.

There is no experience with ceftriaxone use in breastfeeding women. If ceftriaxone is used in pregnant women, it should be used with caution.

Pediatric use

Ceftriaxone is not recommended for use in children under 18 years of age.

Contraindications

Ceftriaxone is contraindicated in:

- Pseudomembranous colitis caused by Clostridium difficile or other Clostridium species

- Ceftriaxone hypersensitivity reaction

- Hypersensitivity to any component of the medicinal product

- Ceftriaxone is not recommended for use in patients with known or suspected penicillin allergy.

ADVERSE REACTIONS

The most common adverse reactions are:

- Nausea
- Vomiting
- Diarrhea
- Abdominal pain
- Rash
- Pruritus
- Urticaria

These reactions are generally mild and are usually self-limiting.

INTERACTIONS

No significant interactions are expected with ceftriaxone.

DOSE AND ADMINISTRATION

The dose and frequency of administration should be determined by the severity of the infection and the susceptibility of the causative organism.

ADDITIONAL INFORMATION

Ceftriaxone is a third-generation cephalosporin with broad-spectrum activity against Gram-negative and Gram-positive bacteria.

REFERENCES

For further information, please refer to the full summary of product characteristics (SmPC).

MHRA PAR; CEFTRIAXONE 500MG, 1G AND 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 25975/0032-3 AND 0037

TECHNICAL PRESCRIBING INFORMATION

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Ceftriaxone is not recommended for use during pregnancy unless the potential benefit justifies the potential risk to the fetus.

There is no experience with ceftriaxone use in breastfeeding women. If ceftriaxone is used in pregnant women, it should be used with caution.

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Ceftriaxone is not recommended for use in children under 18 years of age.

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ADDITIONAL INFORMATION

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REFERENCES

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Continued...
MHRA PAR; CEFTRIAXONE 500MG, 1G AND 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 25975/0032-3 AND 0037
For people with kidney problems, the dose does not need to be reduced. If you have kidney problems, your doctor will tell you how long your injection should be continued. This will depend on the infection being treated and your response to the treatment.

If you stop taking Ceftriaxone for Injection/Infusion:

Your doctor knows how to prescribe and use medicines. If you are concerned about your treatment, please talk to your doctor.

If you stop taking Ceftriaxone for Injection/Infusion:

It is important that you take the full course of your medicine, which should not be interrupted even if you feel well within 2-3 days after the last treatment. If you do not finish all of the prescribed treatment course or even stop during treatment you should talk to your doctor.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ceftriaxone for Injection/Infusion can cause side effects, although not everybody gets them.

Some side effects:

if any of the following side effects occur, consult your doctor immediately. These are symptoms of a serious allergic reaction (anaphylaxis):

- difficulty in breathing, skin rash, or hives
- swelling of the face, lips, tongue, or mouth
- severe pain or tenderness in the abdomen
- numbness, tingling, or loss of feeling
- faintness or dizziness
- fever, chills, or illness

Other side effects:

If any of the following side effects occur, consult your doctor immediately.

- vomiting, diarrhea, fever, shaking, or chills.
- excessive thirst or urination.
- severe pain or tenderness in the abdomen.
- malaise, weakness, or fatigue.
- severe allergic reaction (anaphylaxis).

If you experience any of these side effects, or if you notice any side effects not listed in this leaflet, please refer to your doctor or nurse.

5. STORING CEFTRIAXONE FOR INJECTION/INFUSION

Store out of the reach and sight of children.

You should not give G/M for Injection/Infusion after its expiry date (EDP), which is stated on the outer container and label. If a container does not have this expiry date, you are given the medicine.

Your expiry date (EDP) will be the last day of that month.

This medicine will be stored below 25°C and in the outer container in a place from light.

Any unused container should be discarded by a doctor.

6. FURTHER INFORMATION

Withdrawal from the injection/infusion contains:

Ceftriaxone sodium and Ceftriaxone sodium are equivalent to 500mg of Ceftriaxone, as a powder for solution for injection or infusion. The injection contains 25mg per 10ml injection.

For more information about the withdrawal from the injection/infusion, please contact the manufacturer's customer service department.

Product Licence No. PL 25975/0032-3 and 0037

If this leaflet is difficult to read, please contact the marketing authorization holder for help.
MHRA PAR; CEFTRIAXONE 500MG, 1G AND 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 25975/0032-3 AND 0037
Continued overleaf
During treatment, the blood count should be checked regularly.

Intravenous or oral administration and other relevant information

In vitro, ceftriaxone has been reported to be inactive against staphylococci, enterococci and some Haemophilus influenzae strains. Ceftriaxone may cause anaphylaxis. The use of ceftriaxone should be limited to infections in which no effective alternatives are available.

Pregnancy and lactation

Ceftriaxone is excreted in breast milk. The possible risk to the infant depends on the importance of the drug to the mother and the need for the drug in the mother.

In the absence of evidence to the contrary, ceftriaxone is generally not considered to be teratogenic in humans. However, the use of ceftriaxone in pregnant women should be restricted to those cases where, in the opinion of the physician, the benefit outweighs the possible risk to the foetus. There is no evidence from animal studies to suggest that ceftriaxone causes harm to the foetus.

Side effects and interactions

Ceftriaxone may cause adverse reactions similar to those caused by other cephalosporins. These may include skin rash, urticaria, fever, eosinophilia, maculopapular rash, pseudomembranous colitis, extraintestinal pseudomembranous colitis, neutropenia, eosinophilia, and thrombocytopenia. Rare cases of severe anaphylactoid reactions have been reported with ceftriaxone. Ceftriaxone should be used cautiously in patients with a history of previous reactions to cephalosporins.

Interactions

Ceftriaxone is not extensively metabolized and, therefore, does not interfere with the metabolism of drugs that are cleared by the liver.

Other aspects

Ceftriaxone is supplied as a sterile, aqueous, freeze-dried powder for injection. For reconstitution, the powder is added to a solution of 0.9% sodium chloride injection or 5% dextrose injection. The solution is then administered by intravenous infusion over 15 to 20 minutes.

Intramuscular administration

Ceftriaxone is supplied as a sterile, aqueous, freeze-dried powder for injection. For reconstitution, the powder is added to a solution of 0.9% sodium chloride injection or 5% dextrose injection. The solution is then administered by intramuscular injection as a single dose for a minimum of 20 minutes.

Intravenous administration

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For people with sober minds, the drug is usually released. If the condition is normal, the patient will be treated. The daily dose of Ceftriaxone for injection should be 2 g in adults.

- Use in elderly patients:
  - The daily dose is the same as for adults.
  - The treatment duration is the same as for adults.
  - For severe cases or complications, a higher dose may be required.

- For the treatment of infections, a single dose of Ceftriaxone should be administered into a vein.
- If Ceftriaxone for injection is being given as a child under 12 years old or in a greater or breastfeeding person, it will be given as a mini dose.

Ceftriaxone for dermal injury is usually given once a day.

- The length of treatment is usually at least 7 days after the injury has been treated, or until the patient is well.
- For dermal injuries or wounds, treatment should continue for 1-2 days if the injury is severe or is a burn.

4. POSSIBLE SIDE EFFECTS

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

### Side effects

If any of the following side effects occur, please consult your doctor immediately. These are symptoms of a serious allergic reaction (anaphylaxis):
- Swelling of the face, lips, mouth or throat
- Difficulty breathing, hoarseness, or swelling of the tongue
- Wheezing or tightness of the chest
- Fainting
- Shock
- Any other symptoms of anaphylaxis

If diabetes or any side effects occur, please consult your doctor immediately. These are symptoms of a serious infection:
- Fever, chills, or signs of bacterial infection
- Rash or redness
- Swelling of the hands
- Headache
- Any other symptoms of a serious infection

### Treatment

- If you experience any of these side effects, or if you notice any side effects not listed in this leaflet, please consult your doctor.

5. STORAGE OF CEFTRIAXONE FOR INJECTION/INFUSION

Store in a cool and dry place.

6. FURTHER INFORMATION

For more information, please contact the manufacturer or the national regulatory body.

### Recommended Reading

- MHRA PAR: Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion, PL 25975/0032-3 and 0037
MHRA PAR; CEFTRIAXONE 500MG, 1G AND 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 25975/0032-3 AND 0037
MHRA PAR; CEFTAXONE 500MG, 1G AND 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 25975/0032-3 AND 0037
Interaction with other medicinal products and other forms of interaction

In vitro, co-administration with ceftriaxone has been reported to be antagonistic with respect to Ceftriaxone and other cephalosporins. Clinical evidence of this finding is unclear and caution is advised in the co-administration of Ceftriaxone with trimethoprim.

In patients treated with Ceftriaxone for intra-abdominal infections, the Clostridium perfringens may become false positive. Ceftriaxone may have a role in the treatment of documented or suspected Clostridial infection, especially in the case of anaerobic mixed infections.

Ceftriaxone may also be administered as a 1.5-hour intravenous infusion. The 1-hour interval between doses of 1.5-hour infusion should be maintained. Ceftriaxone may be given intramuscularly in doses of 250mg 500mg, 1g and 2g, respectively. Use of the intramuscular administration route is the same as that for the intravenous route. Ceftriaxone should be given slowly over 2-3 minutes and the dose should be repeated after the patient has recovered fully.

Undesirable effects

The main adverse reaction associated with Ceftriaxone is aseptic meningitis, nausea and vomiting. Other symptoms include diarrhea, abdominal pain, allergic reactions, skin reactions, and fever.

In rare cases, anaphylactic reactions have been reported, particularly in patients with a history of allergy to cephalosporins. In such cases, treatment should be discontinued immediately.

In patients with liver and kidney function impairment, the dose should be reduced or the interval between doses increased.

Special precautions for storage

Unopened vials must be stored at 2-8°C. If the vials are used, the solution should be protected from light.

For all vials that are opened, the solution must be dispensed immediately into the intravenous infusion set and administered within 24 hours. The solution should be stored at ambient temperature and protected from light.

Skin and subcutaneous tissue disorders

Uncommon: Allergic reactions such as eczema, urticaria, angioedema, angioneurotic oedema, rhinitis, conjunctivitis, bronchial asthma.

Rare: Anaphylactic reactions, angioneurotic oedema.

Possible: Other allergic reactions such as pruritus, rash, erythema, urticaria, angioedema, and anaphylactic reactions.

PHARMACOLOGICAL PARTICULARS

List of ingredients

None.

Incompatibilities

Ceftriaxone should not be mixed with any other medicinal products through the same venous access line, as this may affect the stability of the drug.

Pharmacodynamics

Ceftriaxone is a broad-spectrum antibiotic that is active against a wide range of Gram-positive and Gram-negative bacteria, including some strains of Pseudomonas aeruginosa. It is effective against many Streptococcus pneumoniae strains, including those resistant to penicillin.

Pharmacokinetics

Ceftriaxone is well absorbed after oral administration and is distributed to most body tissues, including the brain, where it maintains therapeutic concentrations. It is eliminated primarily by renal excretion, with a half-life of approximately 5-8 hours in adults.

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MHRA PAR; CEFTRIAXONE 500MG, 1G AND 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 25975/0032-3 AND 0037
Module 4

Labelling
Ceftriaxone 500mg Powder for Solution for Injection/Infusion
Ceftriaxone Sodium
For IV or IM use
Powder for Solution for Injection/Infusion
Each vial contains: 0.5g Ceftriaxone as Ceftriaxone Sodium.

Read the package leaflet before use. Do not mix with calcium-containing solutions. Solutions containing lidocaine must not be given intravenously. Keep out of the reach and sight of children. Store in the outer carton to protect from light. Do not store above 25°C.

Variable data

Ceftriaxone 500mg Powder for Solution for Injection/Infusion
For IV or IM use
Each vial contains: 0.5g Ceftriaxone as Ceftriaxone Sodium
This product contains sodium
To be used as directed by the doctor
Read the package leaflet before use. Do not mix with solutions that contain calcium, including Hartmann’s, Ringers and Total Parenteral Nutrition. Solutions containing lidocaine must not be given intravenously.
Label:

Ceftriaxone 1g Powder for Solution for Injection/Infusion

Each vial contains 1g Ceftriaxone as Ceftriaxone Sodium. Powder for Solution for Injection/Infusion

Do not mix with calcium-containing solutions. Solutions containing lidocaine must not be given intravenously. Read the package leaflet before use. Keep out of the reach and sight of children. Store in the outer carton to protect from light. Do not store above 25°C.

Carton:

Ceftriaxone 1g Powder for Solution for Injection/Infusion

For IV or IM use

Each vial contains 1g Ceftriaxone as Ceftriaxone Sodium. This product contains sodium. To be used as directed by the doctor. Read the package leaflet before use. Do not mix with solutions that contain calcium, including Hartmann’s, Ringer’s and Total Parenteral Nutrition.
Label:

2g Ceftriaxone 2g Powder for Solution for Injection/Infusion

Each vial contains 2g Ceftriaxone as Ceftriaxone Sodium.
Read the package leaflet before use.
Do not mix with calcium-containing solutions.
Solutions containing lidocaine must not be given intravenously. Keep out of the reach and sight of children.
Store in the outer carton to protect from light. Do not store above 25°C.
POM PL 25975/0037
Cardinal Health

Carton:

Ceftriaxone 2g Powder for Solution for Injection/Infusion

For IV use

Each vial contains 2g Ceftriaxone as Ceftriaxone Sodium.
This product contains sodium.
To be used as directed by the doctor.
Read the package leaflet before use.
Do not mix with solutions that contain calcium, including Hartmann’s, Flegers and Total Parenteral Nutrition.
Do not store above 25°C.

MHRA PAR; CEFTRIAXONE 500MG, 1G AND 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 25975/0032-3 AND 0037
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the applications for Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion in the treatment of bacterial infections due to susceptible organisms are approvable.

EXECUTIVE SUMMARY
About the product
Ceftriaxone has bactericidal activity resulting from the inhibition of bacterial cell wall synthesis ultimately leading to cell death. Ceftriaxone is active against a broad spectrum of bacterial pathogens, including both Gram-positive and Gram-negative species.

Ceftriaxone is indicated for the treatment of the following bacterial infections when parenteral treatment is required: pneumonia; septicaemia; meningitis; bone, skin and soft tissue infections; infections in neutropenic patients; gonorrhoea; peri-operative prophylaxis of infections associated with surgery.

The test products and their respective reference products contain the same active substance (ceftriaxone sodium), are in the same pharmaceutical form (powder for injection) and have the same route of administration (intravenous or intramuscular).

General comments on the submitted dossier
This is a Decentralised Procedure with the United Kingdom acting as the Reference Member State. These applications are submitted under article 10.1 of Directive 2001/83/EC, as amended, cross-referring to Rocephin 250mg, 1g and 2g vials (PLs 0031/0169, PL 0031/0171, and PL 0031/0172), first authorised in the UK on 2 September 1988.

With UK as the Reference Member State in this Decentralized Procedure, Cardinal Health is applying for a Marketing Authorisations for Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion in Germany and Ireland.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites located outside the Community, the RMS has accepted a copy of the current GMP certificate of satisfactory inspection issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**QUALITY ASPECTS**

**Drug substance**
The chemical-pharmaceutical documentation and Expert Report in relation to Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion are of sufficient quality in view of the present European regulatory requirements. The active substance, ceftriaxone, which is the subject of a Ph. Eur. monograph, is controlled by current Certificates of Suitability. The drug substance specifications for the drug substances are acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. An adequate re-test period has been defined based on conducted stability studies.

**Drug Product**
The development of the products has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug products are adequately drawn up. The proposed shelf-life of 2 years with the storage precautions “do not store above 25°C” and “store in the outer carton to protect from light” is acceptable for unopened product. The reconstituted solution should be used immediately from microbiological point of view.

**NON CLINICAL ASPECTS**
The pharmacodynamic, pharmacokinetic and toxicological properties of ceftriaxone are well known. Therefore, no further studies are required and the applicant provides none.

The lack of an environmental risk assessment is justified since the products are generic versions of an already approved one and it is not likely to change the total market of ceftriaxone.

**CLINICAL ASPECTS**
The applicant has not conducted any clinical studies with ceftriaxone and all the clinical information provided is literature based. The proposed products are indicated for parenteral use only. No bioequivalence studies are required for this type of product according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) and applicant submitted none.

**Pharmacovigilance system**
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

**Risk Management Plan**
Ceftriaxone 500mg, 1g and 2g Powder for Solution for Injection/Infusion are generic products. As with the reference medicinal product, no special important risks or potential risks have been identified which require additional risk minimization activities other than the global pharmacovigilance system.

**Product literature**
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflets were 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. The results indicate that the package leaflets are 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 they contain.

**BENEFIT RISK ASSESSMENT**
The applications contain an adequate review of published clinical data and, for reasons discussed previously, the demonstration of bioequivalence compared to the originator is unnecessary. Approval is recommended.