SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ceftriaxone 1g powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1.19g Ceftriaxone sodium equivalent to 1g Ceftriaxone

Also contains 3.6mmol sodium.

3 PHARMACEUTICAL FORM

Powder for solution for injection

A white or almost white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Treatment may be started before the results of susceptibility tests are known.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Ceftriaxone is for parenteral use only and may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous

infusion, after reconstitution of the solution (see section 6.6). Following reconstitution, a colourless solution is produced.

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

Adults and children over 12 years of age

Standard therapeutic dosage: 1g once a day.

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

The duration of therapy should be varied according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or as soon as there is evidence of bacterial eradication.

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

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

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

Neonates, infants and children up to 12 years
The following dosage schedules are recommended for once daily administration:

Neonates
A daily dose of 20 - 50mg/kg body weight, not to exceed 50mg/kg. In the neonate, the intravenous dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy (see section 4.4).

Infants and children of up to 12 years
Standard therapeutic dosage: 20 - 50mg/kg body weight once daily.
In severe infections up to 80mg/kg body weight daily may be given. For children with bodyweights of 50kg or more, the usual adult dosage should be given. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. Doses greater than 80mg/kg body weight should be avoided except in meningitis (see Special dosage recommendations).

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

Renal and hepatic impairment
In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is normal. Only in cases of pre-terminal renal failure (creatinine clearance < 10ml per minute) should the daily dosage be limited to 2g or less.

In patients with liver damage there is no need for the dosage to be reduced provided renal function is normal.

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

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

4.3. Contraindications

Known hypersensitivity to ceftriaxone or to any of the cephalosporins.

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

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

Calcium treatment because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

4.4. Special warnings and precautions for Use

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

other type of hypersensitivity reaction to a penicillin or any other beta-lactam drug.

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

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

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

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

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

In vivo and *in vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Clinical data obtained in neonates have confirmed this finding. ceftriaxone should therefore not be used in jaundiced new-borns or in those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is likely to be impaired. Particular caution should be exercised in babies born prematurely

Ceftriaxone may precipitate in the gallbladder and kidneys and then be detectable as shadows on ultrasound (see section 4.8). This can happen in patients of any age but is more likely in infants and small children who are usually given a larger dose of ceftriaxone on a body weight basis. In children, doses greater than 80mg/kg body weight should be avoided (except in meningitis) because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone. As the condition appears to be transient and reversible upon discontinuation, therapeutic procedures are not normally indicated

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

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

4.5. Interactions with other medicinal products and other forms of interaction

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

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

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

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

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

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

4.6. Pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Rarely, severe adverse reactions have been reported in preterm and full-term newborns. These reactions have caused death in some cases. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone-calcium salt have been

observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation was due to the low blood volume of the newborns. Moreover the half life is longer than in adults.

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

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

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

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

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

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

Hepato-biliary disorders
Rare (≥ 0.01% - < 0.1%): Increase in serum liver enzymes (AST, ALT, alkaline phosphatase).
Precipitation of ceftriaxone calcium salt in the gallbladder has been observed (see section 4.4), mostly in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application, in some studies to above 30 %. The incidence seems to be lower with slow infusion (20-30 minutes). This effect is usually asymptomatic, but in rare cases, the precipitations have been accompanied by clinical symptoms such as pain,

nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

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

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

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

An intramuscular injection without lidocaine is painful.

4.9. Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Cephalosporins and related substances
ATC code : J01D A13

Mode of action
Ceftriaxone has bactericidal activity resulting from the inhibition of bacterial cell wall synthesis ultimately leading to cell death. Ceftriaxone is stable to a broad range of bacterial β-lactamases and is active against a broad spectrum of bacterial pathogens including both Gram-positive and Gram-negative species.

Mechanism of resistance
Ceftriaxone is stable to a wide range of both Gram-positive and Gram-negative beta-lactamases, including those which are able to hydrolyse advanced generation penicillin derivatives and other cephalosporins. Resistance to ceftriaxone is encoded mainly by the production of some beta-

lactam hydrolysing enzymes (including carbapenemases and some ESBLs) especially in Gram-negative organisms. For Gram-positive organisms such as *S. aureus* and *S. pneumoniae*, acquired resistance is mainly encoded by cell wall target site alterations. Outside of the advanced generation parenteral cephalosporins, cross-resistance to other drug classes is generally not encountered.

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

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

	Susceptible	**Intermediate**	**Resistant**
Enterobacteriaceae , P. aeruginosa and other non-Enterobacteriaceae, Staphylococcus spp.	≤ 8 Disk: ≤ 13	16-32 Disk: 14 – 20	≥ 64 Disk: ≥ 21
Haemophilus spp.	≤ 2 Disk: ≥ 26	-	-
Neisseria spp.	≤ 0.25 Disk: ≥ 35	-	-
Streptococcus pneumoniae *	≤ 0.5	1	≥ 2
Other *Streptococcus* spp.**	Beta strep ≤ 0.5 Disk: ≥ 24 Viridans group: ≤ 0.5 Disk: ≥ 27	- Viridans group: 1 Disk: 25-26	- Viridans group: ≥ 2 Disk: ≤ 24

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

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Ceftriaxone susceptibility among Gram-positive and Gram-negative bacterial species in Europe from January 1999-December 2001:

Commonly susceptible species (i.e. resistance < 10% in all EU Member States)
Gram-Positive aerobes : MS[a] coagulase negative *Staphylococcus* spp. (including *S. epidermis*)* MS[b]*Staphylococcus aureus** Group B (*Streptococcus agalactiae*) *Streptococcus bovis* *Streptococcus pneumoniae** Group A *Streptococcus (Streptococcus pyogenes)** *Streptococcus viridans** Gram-Negative aerobes : *Citrobacter* spp. (including *C.freundii*) *Escherichia coli** *Haemophilus influenzae* (including beta-lactamase positive isolates)[c*] *Haemophilus para-influenzae** *Klebsiella* spp. (including *K. pneumoniae* and *K. oxytoca*)* *Moraxella catarrhalis** *Morganella morganii** *Neisseria gonorrhoea* (including penicillin-resistant isolates)* *Neisseria meningitidis** *Proteus* spp. (including *P. mirabilis* and *P. vulgaris*)* *Salmonella* spp. (including *S. typhimurium*) *Serratia* spp. (including *Serratia marsescens*)* *Shigella* spp. Anaerobes: *Clostridium* spp.*
Species for which acquired resistance may be a problem (i.e. resistance ≥ 10% in at least one EU Member State)
Gram-Negative aerobes: *Pseudomonas aeruginosa* + *Enterobacter* spp. (including *E. aerogenes and E. cloacae*)*+ *Acinetobacter* spp. (including *A. baumanii* and *A. calcoaceticus*)*+ Anaerobes: *Bacteroides* spp.* *Peptostreptococcus* spp.*
Inherently resistant organisms
Gram-Positive aerobes: MR[d] coagulase negative *Staphylococcus* spp. (including *S. epidermidis*) MR[e]*Staphylococcus aureus* *Enterococcus* spp.

Gram-Negative aerobes: *Listeria monocytogenes* *Mycoplasma* spp. *Stenotrophomonas maltophilia* *Ureaplasma urealyticum* Others: *Chlamydia* spp.

[a]Methicillin-susceptible Coagulase-Negative *Staphylococcus*
[b]Methicillin-susceptible *Staphylococcus aureus*
[c]Non-susceptible range (no resistant breakpoints defined)
[d]Methicillin-resistant Coagulase-Negative *Staphylococcus*
[e]Methicillin-resistant *Staphylococcus aureus*
* Species for which the efficacy of ceftriaxone has been demonstrated both *in vitro* and *in vivo*
+ Species for which high rates of resistance have been observed in one or more regions within the EU

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

5.2. Pharmacokinetic properties

The pharmacokinetics of ceftriaxone are largely determined by its concentration-dependent binding to serum albumin. The plasma free (unbound) fraction of the drug in man is approximately 5% over most of the therapeutic concentration range, increasing to 15% at concentration of 300mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

Plasma concentrations: Mean peak concentrations after bolus intravenous injection are about 120mg/l following a 500mg dose and about 200mg/l following a 1g dose; mean levels of 250mg/l are achieved after infusion of 2g over 30 minutes. Intramuscular injection of 500mg ceftriaxone in 1.06% Lidocaine produces mean peak plasma concentrations of 40 - 70mg/l within 1 hour. Bioavailability after intramuscular injection is 100%

Excretion: The drug is eliminated mainly as unchanged ceftriaxone, approximately 60% of the dose being excreted in the urine (almost exclusively by glomerular filtration) and the remainder via the biliary and intestinal tracts.

The total plasma clearance is 10 - 22ml/min. The renal clearance is 5 - 12ml/min. The elimination half-life in adults is about 8 hours. The half-life is not significantly affected by the dose, the route of administration or by repeated administration

Pharmacokinetics in special clinical situations
In the first week of life, 80% of the dose is excreted in the urine; over the first month, this falls to levels similar to those in the adult.

In elderly person aged over 75 years, the average elimination half-life is usually 2 to 3 times longer than in the young adult group. As with all cephalosporins, a decrease in renal function in the elderly may lead to an increase in half-life. Evidence gathered to date with ceftriaxone however, suggests that no modification of the dosage regimen is needed.

In patients with *renal* or *hepatic dysfunction*, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

Cerebrospinal fluid: Ceftriaxone crosses non-inflamed and inflamed meninges, attaining concentrations 4 - 17% of the simultaneous plasma concentration

5.3. Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC

6 PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None

6.2. Incompatibilities

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

Ceftriaxone is not compatible with amsacrine, vancomycin, fluconozole, aminoglycosides and labetalol.

6.3. Shelf life

36 months unopened.

Reconstituted solutions: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours below 25°C. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

Do not store above 25°C.
For shelf-life of reconstituted solutions, see section 6.3.

6.5. Nature and contents of container

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

6.6. Special precautions for disposal

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

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

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

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

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

7 MARKETING AUTHORISATION HOLDER

Villerton Invest SA
8-10, Rue Jean Monnet
L-2180 Luxembourg

8 MARKETING AUTHORISATION NUMBER

PL 24780/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/01/2008

10 DATE OF REVISION OF THE TEXT

10/10/2008

4.8. Undesirable effects

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

The following convention has been used for the classification of frequency:
Very common (≥ 1/10)
Common (≥ 1/100 - < 1/10)
Uncommon (≥ 1/1000 - < 1/100)
Rare (≥ 1/10000 - < 1/1000)
Not known (cannot be estimated from the available data)

System Organ Class	**Common**	**Uncommon**	**Rare**	**Not Known**[a]
Infections and infestations		Genital fungal infection	Pseudo-membranous colitis[b]	Superinfection[b]
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia[b] Agranulocytosis

Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity[b] Jarisch-Herxheimer reaction[b].
Nervous system disorders		Headache Dizziness	Encephalopathy	Convulsion
Ear and labyrinth disorders				Vertigo
Cardiac disorders				Kounis syndrome
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b] Loose stools	Nausea Vomiting		Pancreatitis[b] Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation[b] Kernicterus Hepatitis[c] Hepatitis cholestatic[b,c]
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome[b] Toxic epidermal necrolysis[b] Erythema multiforme Acute generalised exanthematous pustulosis; Drug reaction with eosinophilia and systemic symptoms (DRESS)[b].
Renal and			Haematuria	Oliguria

urinary disorders			Glycosuria	Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		Coombs test false positive[b] Galactosaemia test false positive[b] Non enzymatic methods for glucose determination false positive[b]

a. Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.
b. See section 4.4
c. Usually reversible upon discontinuation of ceftriaxone

Description of selected adverse reactions

Infections and infestations
Reports of diarrhoea following the use of ceftriaxone may be associated with *Clostridium difficile*. Appropriate fluid and electrolyte management should be instituted (see section 4.4).

Ceftriaxone-calcium salt precipitation
Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (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 neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4, and 5.2).

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day) or total doses exceeding 10 grams and who have with other risk factors (e.g. fluid restrictions or confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily 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 - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Ceftriaxone concentrations cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdose should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins.
ATC code: J01D D04

Mode of action
Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Resistance
Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs), carbapenemases and Amp C enzymes that may be induced or stably depressed in certain aerobic Gram-negative bacterial species.
- reduced affinity of penicillin-binding proteins for ceftriaxone.
- outer membrane impermeability in Gram-negative organisms.
- bacterial efflux pumps.

Susceptibility testing breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Pathogen	**Dilution Test (MIC, mg/L)**	
	Susceptible	**Resistant**
Enterobacteriaceae	≤ 1	>2
Staphylococcus spp.	a	a
Streptococcus spp. (Groups A, B, C and G)	b	b
Streptococcus pneumoniae	≤ 0.5c	>2
Viridans group *Streptococci*	≤ 0.5	>0.5
Haemophilus influenzae	≤ 0.12c	>0.12
Moraxella catarrhalis	≤ 1	>2
Neisseria gonorrhoeae	≤ 0.12	>0.12
Neisseria meningitidis	≤ 0.12c	>0.12
Non-species related	≤ 1d	>2

a. Susceptibility inferred from cefoxitin susceptibility.
b. Susceptibility inferred from penicillin susceptibility.
c. Isolates with a ceftriaxone MIC above the susceptible breakpoint are rare and, if found, should be re-tested and, if confirmed, should be sent to a reference laboratory.
d. Breakpoints apply to a daily intravenous dose of 1 g x 1 and a high dose of at least 2 g x 1.

Clinical efficacy against specific pathogens

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 ceftriaxone in at least some types of infections is questionable.

Commonly susceptible species
Gram-positive aerobes *Staphylococcus aureus* (methicillin-susceptible)[£] Staphylococci coagulase-negative (methicillin-susceptible)[£] *Streptococcus pyogenes* (Group A) *Streptococcus agalactiae* (Group B) *Streptococcus pneumoniae* Viridans Group *Streptococci*

Gram-negative aerobes
Borrelia burgdorferi
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoea
Neisseria meningitidis
Proteus mirabilis
Providencia spp.
Treponema pallidum

Species for which acquired resistance may be a problem

Gram-positive aerobes
Staphylococcus epidermidis[+]
Staphylococcus haemolyticus[+]
Staphylococcus hominis[+]

Gram-negative aerobes:
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli[%]
Klebsiella pneumoniae[%]
Klebsiella oxytoca[%]
Morganella morganii
Proteus vulgaris
Serratia marcescens

Anaerobes:
Bacteroides spp.
Fusobacterium spp.
Peptostreptococcus spp.
Clostridium perfringens

Inherently resistant organisms

Gram-positive aerobes:
Enterococcus spp.
Listeria monocytogenes

Gram-negative aerobes:
Acinetobacter baumannii
Pseudomonas aeruginosa Stenotrophomonas maltophilia

Anaerobes
Clostridium difficile

Others: *Chlamydia* spp. *Chlamydophila* spp. *Mycoplasma* spp. *Legionella* spp. *Ureaplasma urealyticum*

£ All methicillin-resistant staphylococci are resistant to ceftriaxone.

+ Resistance rates >50% in at least one region

% ESBL producing strains are always resistant

5.2 Pharmacokinetic properties

Absorption

Intramuscular administration

Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dose of 1 g is about 81 mg/l and is reached in 2 - 3 hours after administration.

The area under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

Intravenous administration

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively.

Distribution

The volume of distribution of ceftriaxone is 7 – 12 l. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An 8 - 15 % increase in mean peak plasma concentration (Cmax) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed

meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (see section 4.6).

Protein binding
Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85 % at a plasma concentration of 300 mg/l).

Biotransformation
Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora.

Elimination
Plasma clearance of total ceftriaxone (bound and unbound) is 10 - 22 ml/min. Renal clearance is 5 - 12 ml/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine, primarily by glomerular filtration, while 40 - 50 % is excreted unchanged in the bile. The elimination half-life of total ceftriaxone in adults is about 8 hours.

Patients with renal or hepatic impairment
In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered with the half-life slightly increased (less than two fold), even in patients with severely impaired renal function.

The relatively modest increase in half-life in renal impairment is explained by a compensatory increase in non-renal clearance, resulting from a decrease in protein binding and corresponding increase in non-renal clearance of total ceftriaxone.

In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

Older people
In older people aged over 75 years the average elimination half-life is usually two to three times that of young adults.

Paediatric population
The half-life of ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels of free ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. During childhood, the half-life is lower than in neonates or adults.
The plasma clearance and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults.

Linearity/non-linearity
The pharmacokinetics of ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations, increasing less than proportionally with dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone but not for free (unbound) ceftriaxone.

Pharmacokinetic/pharmacodynamic relationship
As with other beta-lactams, the pharmacokinetic-pharmacodynamic index demonstrating the best correlation with in vivo efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone for individual target species (i.e. %T > MIC).

5.3 Preclinical safety data

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity. Carcinogenicity studies on ceftriaxone were not conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

Solutions containing ceftriaxone should not be mixed with or added to other agents except those mentioned in section 6.6. 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 intravenous administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition (see section 4.2, 4.3, 4.4 and 4.8).

If treatment with a combination of another antibiotic with ceftriaxone is intended, administration should not occur in the same syringe or in the same infusion solution.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials: 36 months.

Reconstituted solutions: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours below 25°C. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.
For shelf-life of reconstituted solutions, see section 6.3.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

Concentrations for the intravenous injection: 100 mg/ml,
Concentrations for the intravenous infusion: 50 mg/ml.
(Please refer to section 4.2 for further information).

Preparation of solutions for injection and infusion:

	Powder	Reconstitution solvent	Volume to be added	Approx. displacement volume
Intravenous injection	250 mg	Water for Injections BP	2.5 ml	0.2 ml
	1 g	Water for Injections BP	10 ml	0.6 ml
Intramuscular injection	250 mg	1.0% Lidocaine Hydrochloride BP	1.0 ml	0.06 ml
	1 g	1.0% Lidocaine Hydrochloride BP	3.5 ml	0.66 ml
Intravenous infusion	2g	Glucose Injection BP 5% or 10%, 0.9% Sodium Chloride Injection BP, Sodium Chloride and Glucose Injection BP (0.45% Sodium Chloride and 2.5% Glucose), Dextran 6% in Glucose Injection BP 5%.	40.0 ml	1.2 ml

The use of freshly prepared solutions is recommended. For storage conditions of the reconstituted medicinal product, see section 6.3.

Ceftriaxone should not be mixed in the same syringe with any drug other than 1% Lidocaine Hydrochloride solution (for intramuscular injection only). The infusion line should be flushed after each administration.

7 MARKETING AUTHORISATION HOLDER

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