

**CEFTRIAXONE SODIUM 1G POWDER FOR SOLUTION FOR
INJECTION**

PL 14894/0342

**CEFTRIAXONE SODIUM 2G POWDER FOR SOLUTION FOR
INJECTION**

PL 14894/0343

RANBAXY (UK) LIMITED

UKPAR

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**CEFTRIAXONE SODIUM 1G POWDER FOR SOLUTION FOR
INJECTION****PL 14894/0342****CEFTRIAXONE SODIUM 2G POWDER FOR SOLUTION FOR
INJECTION****PL 14894/0343****LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal product Ceftriaxone Sodium 1g Powder for Solution for Injection (PL 14894/0342) and Ceftriaxone Sodium 2g Powder for Solution for Injection (PL 14894/0343) on 26th March 2009. These are prescription-only medicines (POM).

Ceftriaxone is an antibiotic used to treat bacterial infections including infections of the chest (pneumonia) the brain or spinal cord (meningitis), blood infections (septicaemia), sexual organs (gonorrhoea), bones, skin or soft tissues and those patients susceptible to infections due to low numbers of white blood cells in their circulation.

Ceftriaxone Powder for Solution for Injection contains the active ingredient ceftriaxone, which is an antibacterial medicine.

The test product was considered the same as the original products Rocephin® 1g injection and Rocephin® 2g injection (Roche Products Limited) based on the data submitted and no new safety issues arose as a result of this data. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Ceftriaxone 1g Powder for Solution for injection and Ceftriaxone 2g Powder Solution for Injection outweigh the risks, hence marketing Authorisations have been granted.

**CEFTRIAZONE SODIUM 1G POWDER FOR SOLUTION FOR
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INJECTION**

PL 14894/0343

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Ranbaxy (UK) Limited Marketing Authorisations for the medicinal products Ceftriaxone 1g Powder for Solution for Injection (PL 14894/0342) and Ceftriaxone powder for Solution for Injection (PL 14894/0343) on 26th March 2009. The products are prescription-only medicine (POM).

These two strengths of Ceftriaxone, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, and have been shown to be generic medicinal products of the original, Rocephin® 1g injection and Rocephin® 2g injection (Roche products limited). The reference products have been authorised in the UK since September 1988 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient ceftriaxone, like other beta-lactam drugs, ceftriaxone exerts antibacterial activity by binding to and inhibiting the action of certain bacterial cell wall synthetic enzymes, namely the penicillin binding proteins. This results in the interruption of cell wall (peptidoglycan) biosynthesis, which can lead to bacterial cell lysis and death.

Ceftriaxone 1g and 2g Powder for Solution for Injection are indicated for the treatment of bacterial infections. Like other third-generation cephalosporins, it has broad spectrum activity against Gram positive and Gram negative bacteria

PHARMACEUTICAL ASSESSMENT

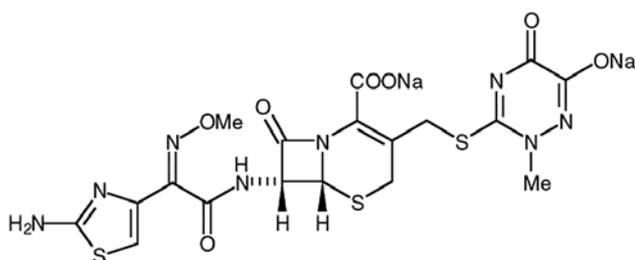
DRUG SUBSTANCE

Ceftriaxone Sodium

INN: Ceftriaxone Sodium

Chemical Name: Disodium (6*R*,7*R*)-7-[[*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[[2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulphonyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Structure:



Molecular formula: $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3\frac{1}{2}H_2O$

Molecular weight: 662

Physical form: Ceftriaxone is an almost white or yellowish, crystalline powder that is slightly hygroscopic.

Solubility: It is freely soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol.

All aspects of the manufacture and control of ceftriaxone sodium are supported by a European Directorate for the Quality of medicines and Healthcare (EDQM) Certificate of Suitability. This certificate is accepted as confirmation of the suitability of ceftriaxone sodium for inclusion in the medicinal product.

Ceftriaxone sodium is stored in appropriate packaging that has been evaluated in relation to the grant of the EDQM Certificate of Suitability.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a re-test period of 3 years when stored in the appropriate packaging.

DRUG PRODUCT

Other ingredients

No other ingredients or pharmaceutical excipients are used in the final drug product.

None of the starting materials or any part of the drug product contains material of animal or human origin.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation data have been provided on ten consecutive manufacturing batches for both 1g and 2g pack sizes, which are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The product is filled in 10ml (for 1g size) and 50ml (for 2g size), Type II clear and colourless glass vials with a bromobutyl stopper and aluminium and propylene flip-off cap. The vials are packed in boxes of 1 or 5 vials (for 1g size) and 1 vial (for 2g size). A certificate of analysis from the supplier confirmed that the glass was Ph Eur Type II glass.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory with storage directions of 'Do not store above 25°C' and 'keep the container in the outer carton in order to protect from light'. The reconstituted product is to be kept for 6 hours at 25°C or for 24 hours at 2-8°C. 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 or 6 hours at 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Conclusion

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

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

I. INTRODUCTION

Background

The first agents of the cephalosporin class to be developed possessed antibacterial activity against aerobic gram-positive cocci, including penicillinase-producing staphylococci, and against certain fastidious aerobic gram-negative organisms of the genera *Neisseria* and *Haemophilus*. Activity of these early, injectable compounds (eg. cephaloridine and cephalothin) against gram-negative bacilli was limited to some of the enterobacterial species.

Further modifications of the side chains to the cephalosporin "nucleus" have given rise to a large series of molecules that are more active (w/w) against gram-negative aerobes and show greater stability in the presence of some of the commonest beta-lactamase enzymes. Some of these have also been modified so as to be orally available.

Ceftriaxone was developed to include at least some of the non-fermenting aerobic gram-negative pathogens within its spectrum of activity and to allow for once daily dosing by the parenteral route (IV or IM). Ceftriaxone is active *in vitro* and *in vivo* against the gram-negative respiratory pathogens *H. influenzae* and *M. catarrhalis* and the enterobacteriaceae (such as *Enterobacter spp.*) but is generally not considered to be sufficiently active against some of the non-fermenting gram-negative rods (such as *Pseudomonas aeruginosa*) to be relied upon as monotherapy.

In contrast to ceftazidime, whose spectrum does extend to the non-fermenters, ceftriaxone possesses considerable activity against gram-positive bacterial species such that it can be relied upon as a sole agent to treat many infections due to mixtures of gram-positive and negative species in the absence of acquired mechanisms of resistance. However, like all cephalosporins, ceftriaxone is not active against enterococci. Activity against anaerobic species is variable and the need for addition of an anti-anaerobic agent has to be judged on an individual basis.

Ceftriaxone is very stable in the presence of common beta-lactamases (such as TEM-1), but it is efficiently hydrolysed by some (but by no means all) of the known extended-spectrum beta-lactamases (ESBLs) and also by the *AmpC* chromosomal cephalosporinases that may be induced or become stably derepressed in certain non-fermenters. Resistance or at least reduced susceptibility to ceftriaxone may also be mediated by alterations in the penicillin-binding proteins, by impermeability of the outer membrane in gram-negative organisms and/or by drug efflux pumps. More than one such mechanism of resistance may occur in a single bacterial cell.

Regulatory Status

Ceftriaxone for intravenous use was first approved on 2/09/1988 in the UK. MA was granted to Roche Products Ltd, for the 1gr formulation (PL 00031/0171), renewal was obtained on 23/10/1998. There is also another MA granted to Roche for the 2 gr formulation (PL 00031/0172).

According to the application forms, the applicant's formulation of ceftriaxone is not approved anywhere in the EU.

Indications

These are the same as in the reference product.

Dose and Dose Regimen

These are the same as in the reference product..

ASSESSOR'S COMMENT

The applicant has not presented any bioequivalence study for the intramuscular formulation/s. It should be noted that under current regulations this is acceptable as long as the product is of the same type of solution, and contains the same active substance and the same or comparable excipients as the reference product already approved.

II. CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics have been well described in the relevant section of the SPC. The applicant does not present any new data based on the “essentially similar” claim and the fact that the applicant’s formulation is said to be similar to the innovator and contains no inactive ingredients.

Pharmacodynamics

Effectively, the pharmacodynamics of ceftriaxone relate to its antibacterial activity. There are no new data presented by the applicant.

III CLINICAL EFFICACY

The applicant does not present any new data in the clinical expert report with regards to efficacy.

IV. CLINICAL SAFETY

The dossier does not contain any new information on safety of this product.

V. CLINICAL EXPERT REPORT

A suitably qualified person has written the clinical expert report and this is satisfactory.

VI.1.1 SPC

The SPC is satisfactory.

VI.1.2 PIL

The Patient Information Leaflet is medically satisfactory.

VI.1.3 Labels

The labels are satisfactory.

VII. CONCLUSIONS

Marketing Authorisations should be granted for these products

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ceftriaxone 1g Powder for Solution for Injection and Ceftriaxone 2g Powder for Solution for are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

No bioequivalence study was required for this type of product. No new to unexpected safety concerns arise from these applications.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SPC, PIL, technical leaflet, and labelling are satisfactory and consistent with that for the innovator product.

The Marketing Authorisation Holder (MAH) currently has no plans to market the product and therefore has not carried out a PIL User Test to show compliance with current guidelines. The MAH has committed to submitting a PIL User Test by means of a variation before the product is placed on the market.

The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ceftriaxone sodium is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**CEFTRIAZONE SODIUM 1G POWDER FOR SOLUTION FOR
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INJECTION****PL 14894/0343****STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation applications on 23 rd December 2004.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 24 th January 2005.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 23 rd May 2007, 14 th November 2008 and 28 th January 2009 and further information relating to the clinical dossiers on 13 th July 2005 and 6 th March 2006.
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 14 th November 2008, 17 th February 2009 for the clinical section on 15 th February 2006 and 11 th July 2006.
5	The application was determined on 26 th March 2009.

**CEFTRIAZONE SODIUM 1G POWDER FOR SOLUTION FOR
INJECTION****PL 14894/0342****CEFTRIAZONE SODIUM 2G POWDER FOR SOLUTION FOR
INJECTION****PL 14894/0343****STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

Date submitted	Application type	Scope	Outcome

CEFTRIAXONE SODIUM 1G POWDER FOR SOLUTION FOR INJECTION

PL 14894/0342

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ceftriaxone 1 g Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 g vial contains 1 g ceftriaxone (as hydrated disodium).

Also contains 3.6 mmol sodium (see section 4.4)

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

Almost white to yellowish crystalline powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ceftriaxone is indicated for the treatment of the following infections when caused by micro-organisms that are susceptible to ceftriaxone and if parenteral treatment is necessary (see section 5.1):

- Bacterial meningitis
- Infections of bones or joints
- Infections of skin or soft tissues
- Pneumonia

Ceftriaxone is indicated for perioperative prophylaxis in patients with a certain risk of severe postoperative infections (see section 4.4). Depending on the mode of surgery and the expected spectrum of pathogens ceftriaxone should be combined with an appropriate antimicrobial agent with additional anaerobic coverage.

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Route and method of administration

Ceftriaxone may be administered by intravenous bolus injection, by intravenous infusion or by intramuscular injection after reconstitution of the solution according to the directions given below (see section 6.6).

Dosage and mode of administration should be determined by the severity and site of infection, susceptibility of the causative micro-organism and the patient's age and condition.

An intravenous injection should be administered over at least 2-4 minutes directly into the vein or via the tubing of an intravenous infusion

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 dissolved in lidocaine hydrochloride solution is 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 \geq 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 4 g, 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:

20-80 mg per kg bodyweight intravenously once daily (24-hour intervals).

In severe infections the daily dose of 80 mg per kg bodyweight must not be exceeded, except in meningitis (see section 4.2).

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.

Age group	Normal dosage	Frequency
Newborn infants (age 0-14 days)	20-50 mg/kg Maximum: 50 mg/kg	Once daily
Children 15 days-12 years of age $<$ 50 kg	20-80 mg/kg Maximum: 80 mg/kg	Once daily
Adolescents over 12-17 years \geq 50 kg	1-2 g Maximum: 4 g	Once daily
Adults \geq 17 years	1-2 g Maximum: 4 g	Once daily
Elderly	1-2 g Maximum: 4 g	Once daily

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 helatic function is normal. In renal insufficiency with a reduced creatinine clearance $<$ 10ml/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 section 4.4 and 5.2).

Haemodialysis or peritoneal dialysis

As ceftriaxone is dialyzable 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 the active substance, to other cephalosporins or to any of the excipients.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products (see section 4.4).

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

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

Intramuscular injection of the medicinal product is contraindicated:

- in infants < 2 years of age
- during pregnancy and lactation

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

In infections caused by other bacteria in patients with neutropenic fever interventional treatment with ceftriaxone should be combined with an aminoglycoside.

Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-lactam-medicinal products because patients hypersensitive to these medicines may be hypersensitive to ceftriaxone as well (cross-allergy).

Hypersensitivity reactions against ceftriaxone are more likely in patients with any other type of hypersensitivity reaction or asthma bronchiale.

Injections with ceftriaxone should be used with special caution in patients with allergic diathesis, because hypersensitivity reactions emerge faster and proceed more severely after intravenous injection (see section 4.8).

Hypersensitivity reactions may occur in all degrees of severity up to anaphylactic shock (see section 4.8).

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

In case of simultaneous impairment of renal and liver function, serum-level of ceftriaxone should be monitored in regular intervals.

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

Pseudomembranous colitis has been reported with almost all antibiotics, including ceftriaxone. This diagnosis should be considered in patients who develop diarrhoea during or following treatment with ceftriaxone (see section 4.8).

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

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 for meningitis – because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of ceftriaxone precipitate in the gallbladder is recommended.

Patients with risk factors for biliary stasis/sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition, have increased risk of pancreatitis (see section 4.8). Trigger role of ceftriaxone-related biliary precipitation cannot be ruled-out.

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the 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.

This medicinal product contains approximately 3.6 mmol (or 83 mg) sodium per dose which should be taken into consideration by patients on a controlled sodium diet.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Aminoglycosides:

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

Bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may antagonise the activity of ceftriaxone, especially in acute infections accompanied by rapid proliferation of micro-organisms. Simultaneous use of ceftriaxone and bacteriostatic antibiotics is, therefore not recommended.

Ceftriaxone / probenacid:

Contrary to other cephalosporins, probenacid does not impede tubular secretion of ceftriaxone.

Oral contraceptives:

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.

Other:*Laboratory-diagnostic tests*

The Coombs test may be false-positive in rare cases during treatment with ceftriaxone (see section 4.4).

Non-enzymatic methods for glucose determinations in urine may yield false-positive results. For this reason, urine glucose determination during therapy with ceftriaxone should be carried out enzymatically.

Ceftriaxone may lead to false-positive results of galactose determination in blood.

4.6 PREGNANCY AND LACTATION

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

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

Powder for solution for injection – intramuscular administration:

The use of ceftriaxone and lidocaine is contraindicated during pregnancy and lactation (see section 4.3).

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

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

The following adverse reactions, that reverse spontaneously or after treatment discontinuation, have been observed in association with ceftriaxone use.

In this section, undesirable effects are defined as follows:

Very common	>1/10
Common	>1/100, </10
Uncommon	>1/1000, </100
Rare	>1/10000, </1000
Very rare, including isolated reports	</10000

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and Infestations

Uncommon:

Mycosis of the genital tract.

Superinfections with non-susceptible micro-organisms.

Blood and lymphatic system disorders*Rare:*

Eosinophilia, leucopenia, granulocytopenia.

Very rare including isolated reports:

Agranulocytosis (<500/mm³), mostly after 10-day treatment and a total dose of 20 g ceftriaxone and more; Coagulation disorders, Thrombocytopenia. Minor prolongation in the prothrombin time has been described.

Anaemia (including haemolytic anaemia)

Immune system disorders*Common:*

Allergic skin reactions (e.g. dermatitis, urticaria, exanthema), pruritus, oedematous swelling of skin and joints

Rare:

Severe acute hypersensitivity reactions up to anaphylactic shock.

Lyell syndrome/toxic epidermolysis, Stevens-Johnson syndrome or Erythema multiforme.

Severe acute hypersensitivity reactions and anaphylactic shock require immediate discontinuation of the administration of ceftriaxone and the initiation of appropriate emergency measures.

Nervous system disorders*Uncommon:*

Headache, dizziness, vertigo.

Gastrointestinal disorders*Uncommon:*

Stomatitis, glossitis, anorexia, nausea, emesis, abdominal pain, loose stool or diarrhoea. These undesirable effects are mostly mild and frequently subside during, otherwise after discontinuation of therapy.

Very rare:

Pseudomembranous enterocolitis (see section 4.4).

If severe, persistent diarrhoea occurs during or after treatment, pseudomembranous colitis which is a serious, even life-threatening complication mostly caused by *clostridium difficile*, should be considered. Discontinuation of therapy with ceftriaxone depending on the indication should be considered and appropriate treatment measures should be initiated: e.g. intake of specific antibiotics/chemotherapeutics with clinically proven efficacy.

Antiperistaltics are contraindicated.

Hepato-biliary disorders*Very common:*

Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of children/reversible cholelithiasis in children. This disorder is rare in adults (see below).

Common:

Elevated liver enzymes in serum (AST, ALT, alkaline phosphatase).

Rare:

Pancreatitis (see section 4.4). Increase in liver enzymes.

Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of adults, which disappeared after discontinuation or cessation of therapy with ceftriaxone. These opacities

usually occurred only after administration of higher doses than the recommended standard doses. In the rare cases in which the precipitates are accompanied by clinical symptoms such as pain, symptomatic measures are recommended. Discontinuation of treatment should be considered too (see section 4.4).

Renal and urinary disorders

Uncommon:

Oliguria, increase in serum creatinine.

Rare:

Precipitates of ceftriaxone in the kidneys in paediatric patients, mostly in children older than 3 years treated either with high daily doses (e.g. 80 mg/kg BW per day and more) or with total doses above 10g ceftriaxone and who presented several risk factors (e.g. restricted fluid supply). However, this symptomatology is reversible after discontinuation of ceftriaxone.

General disorders and administration site conditions

Common:

Phlebitis following intravenous administration. This can be minimised by slow injection (over 2-4 minutes).

Pain at the site of injection.

In rapid intravenous injection intolerance reactions in the form of sensation of heat or nausea may occur. This can be avoided by slow injection (2-4 minutes).

4.9 OVERDOSE

No case of overdose has been reported.

Symptoms of intoxication

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

Therapy of intoxication

Excessive serum concentration of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. There is specific antidote. Symptomatic therapeutic measures are indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Cephalosporins and related substances, ATC code: J01DD04

Mechanism of action

Ceftriaxone has bactericidal activity that results from the inhibition of bacterial cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of β -lactamases produced by Gram-negative and Gram-positive bacteria.

Synergistic effects of ceftriaxone and aminoglycosides on certain Gram-negative bacteria have been noted in vitro.

Mechanism of resistance

Ceftriaxone is active against organisms producing some types of beta-lactamase, for example TEM-1. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporins, 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 drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

Breakpoints

The minimum inhibitory concentration (MIC, according to the German Institute for Standardization DIN 58940) are 4 mg/l, – (sensitive) and 32 mg/l (resistant).

The MIC breakpoints according to the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards) are 8 µg/ml (sensitive), 16-32 µg/ml (intermediate) and 64 µg/ml (resistant) for Enterobacteriaceae and Staphylococcus spp..

The respective values for *Streptococcus pneumoniae* are 0.5 µg/ml (sensitive), 1 µg/ml (intermediate) and 2 µg/ml (resistant).

The breakpoints for sensitivity are 2 µg/ml for *Haemophilus* spp. and 0.25 µg/ml for *Neisseria gonorrhoea*.

The respective values for anaerobes are 16 µg/ml (sensitive), 32 µg/ml (intermediate) and 64 µg/ml (resistant).

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*¹
Escherichia coli *¹
Haemophilus influenzae *
Haemophilus parainfluenzae *
Klebsiella pneumoniae *¹
Klebsiella oxytoca *¹
Moraxella catarrhalis *
*Morganella morganii*¹
Neisseria meningitidis *
Proteus mirabilis *¹
*Proteus vulgaris*¹
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 *[§] (MSSE)

Gram-negative aerobes

*Citrobacter freundii*¹

Enterobacter spp.^{1 3}

Pseudomonas aeruginosa^{§ 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.

Chlamydoxyla 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 depressed 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

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

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

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).

Serum levels

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

Subsequent to an intramuscular injection of 1 g of ceftriaxone the serum concentration amounted to 79.2 µg/ml after 1.5 hours, and afterwards 58.2, 35.5 and 7.8 µg/ml at the respective time-points 4, 12 and 24 hours after injection.

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

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

Biotransformation

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

Elimination

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

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

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

Ceftriaxone cannot be removed by dialysis. This applies to both haemodialysis and peritoneal dialysis.

Urinary excretion is via glomerular filtration. No tubular secretion takes place. For this reason, no increase in the serum levels is to be expected in coincident administration of probenecid and is actually - even at higher dosage e.g. with 1-2 g probenecid - not found.

Non-Linearity

The pharmacokinetics of ceftriaxone 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 % accumulations above single dose values

Special patient groups

Elderly above 75 years:

The plasma elimination half-life of ceftriaxone is about 2 - 3 fold increased compared to young adults.

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

Patients with impaired renal and/or liver function:

Patients with an impaired renal function have an increased excretion of ceftriaxone into the bile.

Patients with an impaired liver function have an increased renal excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is almost not increased in these patient groups.

Patients with an impaired renal function, as well as an impaired liver function, may have an increased ceftriaxone plasma elimination half-life.

In case of terminal renal insufficiency, the half-life is distinctively higher and reaches approximately 14 hours.

5.3 PRECLINICAL SAFETY DATA

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

After high doses of ceftriaxone diarrhoea, formation of biliary calculi in the 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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. In particular, ceftriaxone is not compatible with calcium-containing solutions such as Hartmann's solution and Ringer's solution.

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

6.3 SHELF LIFE

Unopened:

Powder: 3 years.

Opened and after reconstitution:

For reconstituted solution, chemical and physical in-use stability has been demonstrated for 6 hours at 25°C and for 24 hours 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 or 6 hours at 25°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. Keep the container in the outer carton in order to protect from light.

For storage details of the reconstituted medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Ceftriaxone sodium is supplied in a 10ml Type II clear & colourless glass vial with a bromobutyl stopper and aluminium and polypropylene cap.

The vials are packed in boxes of 1 or 5 vials. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling

Intravenous injection

Ceftriaxone 1 g powder for solution for injection or infusion should be dissolved in 10 ml of water for injections (resulting volume 10.8 ml, concentration 93 mg/ml). The injection should be administered over at least 2 – 4 minutes directly into the vein or via the tubing of an intravenous infusion (see section 4.2).

Intravenous infusion

Ceftriaxone 1 g powder for solution for injection or infusion should be dissolved in one of the following calcium-free infusion solutions: Sodium chloride 0.9%, sodium chloride 0.45% and glucose 2.5%, glucose 5 % or 10% infusions. See also the information included in section 6.2.

The reconstitution of the ready to use solution for infusion has to take place in two steps in order to allow the reconstitution of the necessary volume of solution for infusion:

1. Ceftriaxone 1 g powder for solution for injection or infusion is reconstituted with 10 ml of one of the compatible intravenous fluids in its vial. This solution has to be transferred into a suitable infusion bag. Controlled and validated aseptic conditions have to be observed.
2. This solution should then be diluted with 9 ml more of diluent giving a final volume of 20.5 ml and a concentration of 49 mg/ml.

This volume of 20.5 ml reconstituted solution for infusion should be administered immediately as a short time infusion over 30 minutes.

Smaller amounts for lower doses calculated on an mg/kg bodyweight basis have to be calculated proportionately.

Intramuscular injection

Ceftriaxone 1 g powder for solution for injection or infusion should be dissolved in 3.5 ml of 1 % w/v lidocaine hydrochloride injection solution.

The solution (resulting volume 4.2 ml, concentration 238 mg/ml) should be administered by deep intramuscular injection. Dosages greater than 1 g should be divided and injected on more than one site. Not more than 1 g of ceftriaxone should be injected on either side of the body (see section 4.2).

Solutions in lidocaine should not be administered intravenously.

Ceftriaxone should not be mixed in the same syringe with any medicinal product other than 1% w/v lidocaine hydrochloride solution (for intramuscular injection only).

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

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

Reconstituted solutions should be inspected visually. Only clear solutions free of visible particles should be used. The reconstituted product is for single use only and any unused solution must be discarded.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
20 Balderton Street
London W1K 6TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 14894/0342

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/03/2009

10 DATE OF REVISION OF THE TEXT

26/03/2009

CEFTRIAXONE SODIUM 2G POWDER FOR SOLUTION FOR INJECTION

PL 14894/0343

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ceftriaxone 2 g Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 g vial contains 2 g ceftriaxone (as hydrated disodium).

Also contains 7.2 mmol sodium (see section 4.4)

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

Almost white to yellowish crystalline powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ceftriaxone is indicated for the treatment of the following infections when caused by micro-organisms that are susceptible to ceftriaxone and if parenteral treatment is necessary (see section 5.1):

- Bacterial meningitis
- Infections of bones or joints
- Infections of skin or soft tissues
- Pneumonia

Ceftriaxone is indicated for perioperative prophylaxis in patients with a certain risk of severe postoperative infections (see section 4.4). Depending on the mode of surgery and the expected spectrum of pathogens ceftriaxone should be combined with an appropriate antimicrobial agent with additional anaerobic coverage.

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Route and method of administration

Ceftriaxone may be administered by intravenous infusion after reconstitution of the solution according to the directions given below (see section 6.6).

Dosage should be determined by the severity and site of infection, susceptibility of the causative micro-organism and the patient's age and condition.

For other routes of administration other strengths of ceftriaxone are available.

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 4 g, 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:

20-80 mg per kg bodyweight intravenously once daily (24-hour intervals).

In severe infections the daily dose of 80 mg per kg bodyweight must not be exceeded, except in meningitis (see section 4.2).

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.

Age group	Normal dosage	Frequency
Newborn infants (age 0-14 days)	20-50 mg/kg Maximum: 50 mg/kg	Once daily
Children 15 days-12 years of age < 50 kg	20-80 mg/kg Maximum: 80 mg/kg	Once daily
Adolescents over 12-17 years \geq 50 kg	1-2 g Maximum: 4 g	Once daily
Adults \geq 17 years	1-2 g Maximum: 4 g	Once daily
Elderly	1-2 g Maximum: 4 g	Once daily

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 helatic function is normal. In renal insufficiency with a reduced creatinine clearance <

10ml/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 section 4.4 and 5.2).

Haemodialysis or peritoneal dialysis

As ceftriaxone is dialyzable 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 the active substance, to other cephalosporins or to any of the excipients.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products (see section 4.4).

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

In infections caused by other bacteria in patients with neutropenic fever interventional treatment with ceftriaxone should be combined with an aminoglycoside.

Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-lactam-medicinal products because patients hypersensitive to these medicines may be hypersensitive to ceftriaxone as well (cross-allergy).

Hypersensitivity reactions against ceftriaxone are more likely in patients with any other type of hypersensitivity reaction or asthma bronchiale.

Injections with ceftriaxone should be used with special caution in patients with allergic diathesis, because hypersensitivity reactions emerge faster and proceed more severely after intravenous infusion (see section 4.8).

Hypersensitivity reactions may occur in all degrees of severity up to anaphylactic shock (see section 4.8).

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

In case of simultaneous impairment of renal and liver function, serum-level of ceftriaxone should be monitored in regular intervals.

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

Pseudomembranous colitis has been reported with almost all antibiotics, including ceftriaxone. This diagnosis should be considered in patients who develop diarrhoea during or following treatment with ceftriaxone (see section 4.8).

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

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 for meningitis – because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of ceftriaxone precipitate in the gallbladder is recommended.

Patients with risk factors for biliary stasis/sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition, have increased risk of pancreatitis (see section 4.8). Trigger role of ceftriaxone-related biliary precipitation cannot be ruled-out.

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the 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.

This medicinal product contains approximately 7.2 mmol (or 166 mg) sodium per dose which should be taken into consideration by patients on a controlled sodium diet.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Aminoglycosides:

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

Bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may antagonise the activity of ceftriaxone, especially in acute infections accompanied by rapid proliferation of micro-organisms. Simultaneous use of ceftriaxone and bacteriostatic antibiotics is, therefore not recommended.

Ceftriaxone / probenacid:

Contrary to other cephalosporins, probenacid does not impede tubular secretion of ceftriaxone.

Oral contraceptives:

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.

Other:

Laboratory-diagnostic tests

The Coombs test may be false-positive in rare cases during treatment with ceftriaxone (see section 4.4).

Non-enzymatic methods for glucose determinations in urine may yield false-positive results. For this reason, urine glucose determination during therapy with ceftriaxone should be carried out enzymatically.

Ceftriaxone may lead to false-positive results of galactose determination in blood.

4.6 PREGNANCY AND LACTATION

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

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

Powder for solution for injection – intramuscular administration:

The use of ceftriaxone and lidocaine is contraindicated during pregnancy and 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

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

The following adverse reactions, that reverse spontaneously or after treatment discontinuation, have been observed in association with ceftriaxone use.

In this section, undesirable effects are defined as follows:

Very common	>1/10
Common	>1/100, </10
Uncommon	>1/1000, </100
Rare	>1/10000, </1000
Very rare, including isolated reports	</10000

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and Infestations

Uncommon:

Mycosis of the genital tract.

Superinfections with non-susceptible micro-organisms.

Blood and lymphatic system disorders

Rare:

Eosinophilia, leucopenia, granulocytopenia.

Very rare including isolated reports:

Agranulocytosis (<500/mm³), mostly after 10-day treatment and a total dose of 20 g ceftriaxone and more; Coagulation disorders, Thrombocytopenia. Minor prolongation in the prothrombin time has been described.

Anaemia (including haemolytic anaemia)

Immune system disorders

Common:

Allergic skin reactions (e.g. dermatitis, urticaria, exanthema), pruritus, oedematous swelling of skin and joints

Rare:

Severe acute hypersensitivity reactions up to anaphylactic shock.

Lyell syndrome/toxic epidermolysis, Stevens-Johnson syndrome or Erythema multiforme.

Severe acute hypersensitivity reactions and anaphylactic shock require immediate discontinuation of the administration of ceftriaxone and the initiation of appropriate emergency measures.

Nervous system disorders*Uncommon:*

Headache, dizziness, vertigo.

Gastrointestinal disorders*Uncommon:*

Stomatitis, glossitis, anorexia, nausea, emesis, abdominal pain, loose stool or diarrhoea. These undesirable effects are mostly mild and frequently subside during, otherwise after discontinuation of therapy.

Very rare:

Pseudomembranous enterocolitis (see section 4.4).

If severe, persistent diarrhoea occurs during or after treatment, pseudomembranous colitis which is a serious, even life-threatening complication mostly caused by *clostridium difficile*, should be considered. Discontinuation of therapy with ceftriaxone depending on the indication should be considered and appropriate treatment measures should be initiated: e.g. intake of specific antibiotics/chemotherapeutics with clinically proven efficacy. Antiperistaltics are contraindicated.

Hepato-biliary disorders*Very common:*

Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of children/reversible cholelithiasis in children. This disorder is rare in adults (see below).

Common:

Elevated liver enzymes in serum (AST, ALT, alkaline phosphatase).

Rare:

Pancreatitis (see section 4.4). Increase in liver enzymes.

Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of adults, which disappeared after discontinuation or cessation of therapy with ceftriaxone. These opacities usually occurred only after administration of higher doses than the recommended standard doses. In the rare cases in which the precipitates are accompanied by clinical symptoms such as pain, symptomatic measures are recommended. Discontinuation of treatment should be considered too (see section 4.4).

Renal and urinary disorders*Uncommon:*

Oliguria, increase in serum creatinine.

Rare:

Precipitates of ceftriaxone in the kidneys in paediatric patients, mostly in children older than 3 years treated either with high daily doses (e.g. 80 mg/kg BW per day and more) or with total doses above 10g ceftriaxone and who presented several risk factors (e.g. restricted fluid supply). However, this symptomatology is reversible after discontinuation of ceftriaxone.

General disorders and administration site conditions*Common:*

Phlebitis following intravenous administration. This can be minimised by slow injection (over 2-4 minutes).

Pain at the site of injection.

In rapid intravenous injection intolerance reactions in the form of sensation of heat or nausea may occur. This can be avoided by slow injection (2-4 minutes).

4.9 OVERDOSE

No case of overdose has been reported.

Symptoms of intoxication

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

Therapy of intoxication

Excessive serum concentration of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. There is specific antidote. Symptomatic therapeutic measures are indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Cephalosporins and related substances, ATC code: J01DD04

Mechanism of action

Ceftriaxone has bactericidal activity that results from the inhibition of bacterial cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of β -lactamases produced by Gram-negative and Gram-positive bacteria.

Synergistic effects of ceftriaxone and aminoglycosides on certain Gram-negative bacteria have been noted in vitro.

Mechanism of resistance

Ceftriaxone is active against organisms producing some types of beta-lactamase, for example TEM-1. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporins, 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 drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

Breakpoints

The minimum inhibitory concentration (MIC, according to the German Institute for Standardization DIN 58940) are 4 mg/l, – (sensitive) and 32 mg/l (resistant).

The MIC breakpoints according to the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards) are 8 μ g/ml (sensitive), 16-32 μ g/ml (intermediate) and 64 μ g/ml (resistant) for Enterobacteriaceae and Staphylococcus spp..

The respective values for Streptococcus pneumoniae are 0.5 μ g/ml (sensitive), 1 μ g/ml (intermediate) and 2 μ g/ml (resistant).

The breakpoints for sensitivity are 2 μ g/ml for Haemophilus spp. and 0.25 μ g/ml for Neisseria gonorrhoea.

The respective values for anaerobes are 16 μ g/ml (sensitive), 32 μ g/ml (intermediate) and 64 μ g/ml (resistant).

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*¹
Escherichia coli *¹
Haemophilus influenzae *
Haemophilus parainfluenzae *
Klebsiella pneumoniae *¹
Klebsiella oxytoca *¹
Moraxella catarrhalis *
*Morganella morganii*¹
Neisseria meningitidis *
Proteus mirabilis *¹
*Proteus vulgaris*¹
*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 *^S (MSSE)

Gram-negative aerobes

*Citrobacter freundii*¹
Enterobacter spp.^{1,3}
Pseudomonas aeruginosa^{S 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.
Chlamydopjila spp.
Mycobacterium spp.
Mycoplasma spp.
Rickettsia spp.
Ureaplasma urealyticum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

^s Species with natural intermediate susceptibility

¹ Some strains produce inducible or stably depressed 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

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

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

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).

Serum levels

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

Subsequent to an intramuscular injection of 1 g of ceftriaxone the serum concentration amounted to 79.2 µg/ml after 1.5 hours, and afterwards 58.2, 35.5 and 7.8 µg/ml at the respective time-points 4, 12 and 24 hours after injection.

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

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

Biotransformation

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

Elimination

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

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

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

Ceftriaxone cannot be removed by dialysis. This applies to both haemodialysis and peritoneal dialysis.

Urinary excretion is via glomerular filtration. No tubular secretion takes place. For this reason, no increase in the serum levels is to be expected in coincident administration of probenecid and is actually - even at higher dosage e.g. with 1-2 g probenecid - not found.

Non-Linearity

The pharmacokinetics of ceftriaxone 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 % accumulations above single dose values

Special patient groups

Elderly above 75 years:

The plasma elimination half-life of ceftriaxone is about 2 - 3 fold increased compared to young adults.

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

Patients with impaired renal and/or liver function:

Patients with an impaired renal function have an increased excretion of ceftriaxone into the bile.

Patients with an impaired liver function have an increased renal excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is almost not increased in these patient groups.

Patients with an impaired renal function, as well as an impaired liver function, may have an increased ceftriaxone plasma elimination half-life.

In case of terminal renal insufficiency, the half-life is distinctively higher and reaches approximately 14 hours.

5.3 PRECLINICAL SAFETY DATA

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

After high doses of ceftriaxone diarrhoea, formation of biliary calculi in the 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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. In particular, ceftriaxone is not compatible with calcium-containing solutions such as Hartmann's solution and Ringer's solution. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

6.3 SHELF LIFE

Unopened:

Powder: 3 years.

Opened and after reconstitution:

For reconstituted solution, chemical and physical in-use stability has been demonstrated for 6 hours at 25°C and for 24 hours 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 or 6 hours at 25°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. Keep the container in the outer carton in order to protect from light.

For storage details of the reconstituted medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Ceftriaxone sodium is supplied in a 50ml Type II clear & colourless glass vial with a bromobutyl stopper and aluminium and polypropylene cap.

The vials are packed in boxes of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling*Intravenous infusion*

Ceftriaxone 2 g powder for solution for infusion should be dissolved in 40 ml of one of the following calcium-free infusion solutions: Sodium chloride 0.9%, sodium chloride 0.45% and glucose 2.5%, glucose 5 % or 10% infusions. See also the information included in section 6.2. The infusion should be administered over at least 30 minutes.

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.

Reconstituted solutions should be inspected visually. Only clear solutions free of visible particles should be used. The reconstituted product is for single use only and any unused solution must be discarded.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
20 Balderton Street
London W1K 6TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL: 14894/0343

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY

26/03/2009

10 DATE OF REVISION OF THE TEXT

26/03/2009

CEFTRIAXONE SODIUM 1G & 2G POWDER FOR SOLUTION FOR INJECTION

PL 14894/0342-3

PATIENT INFORMATION LEAFLET



PACKAGE LEAFLET: INFORMATION FOR THE USER

Ceftriaxone 1g Powder for Solution for Injection or Infusion
Ceftriaxone 2g Powder for Solution for Infusion
 (Ceftriaxone Sodium)

Read all of this leaflet carefully before you start using this medicine.

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

In this leaflet:

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

1. WHAT CEFTRIAXONE IS AND WHAT IT IS USED FOR

Ceftriaxone is an antibiotic. It belongs to a group of antibiotics that are called cephalosporins. These types of antibiotic are similar to penicillin. Ceftriaxone kills bacteria and it can be used against various sorts of infections. Like all antibiotics, ceftriaxone is only effective against some types of bacteria. Thus it is only suitable for treating some types of infection.

Ceftriaxone can be used to treat:

- infection of the meninges (meningitis)
- bone or joint infections
- infections of the respiratory tract
- infections in the skin and soft tissues

Ceftriaxone can also be used to help prevent infections before, during and after surgery in patients with a certain risk of severe infections associated with surgical measures. Depending on the mode of surgery and the expected pathogens ceftriaxone should be combined with an appropriate antimicrobial agent with additional coverage of complicating pathogens.

2. BEFORE YOU USE CEFTRIAXONE

Do not use Ceftriaxone if:

- You are allergic (hypersensitive) to ceftriaxone or any other ingredients of this medicine
- You are allergic (hypersensitive) to any other cephalosporin type antibiotic.
- You have ever had a severe allergic reaction to any penicillin – or to another beta-lactam-antibiotic because you might also be allergic to this medicine.
- Ceftriaxone should not be used in newborn with jaundice (hyperbilirubinaemia) or preterm newborn because the use of ceftriaxone, the active substance of ceftriaxone can lead to complications with possible brain damage in these patients.
- Ceftriaxone sodium 1g powder for solution for injection or infusion should not be used by intramuscular injection
 - in infants under 2 years of age and
 - during pregnancy and lactation
- Ceftriaxone should not be used together with calcium treatment, because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

If you feel uncertain, ask your doctor or pharmacist.

Take special care with Ceftriaxone if:

- You have ever had an allergic reaction to any antibiotic, tell your doctor or pharmacist before you take this medicine
- You have ever had other types of allergic reactions or asthma. Hypersensitivity reactions against ceftriaxone tend to occur more frequently in persons with a tendency for any allergic reactions and may occur in all degrees of severity up to anaphylactic shock.
- You have ever been told that your kidneys and/or liver do not work very well
- You have ever had gall bladder or kidney stones, or you are nourished intravenously
- You have ever had inflammation of your bowel, called colitis, or any other severe disease affecting your gut

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

This medicine can also alter the results of non-enzymatic urine tests for sugar. If you have diabetes and routinely test your urine, tell your doctor. This is because other tests may have to be used to monitor your diabetes while you are having this medicine.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicine, including medicines you have obtained without a prescription. This medicine can be affected by other medicines that are removed by the kidneys. This is especially if these other medicines also affect how well kidneys work. There are many medicines that can do this, so you should check with your doctor or pharmacist before taking this medicine.

In particular, tell your doctor or pharmacist if you are using:

- Other antibiotics for treating infections like aminoglycosides
- Oral contraceptive pills. It is advisable to use supplementary non-hormonal contraceptive measures.
- Other active substances like Probenacid.

Pregnancy and breast-feeding

- If you are pregnant, or think you may be pregnant you must tell your doctor. Although this medicine is not known to harm the unborn child, it will only be given to a pregnant woman if it is really necessary.
- This medicine should not be given to women who are breast feeding. This is because small amounts of it enter the milk and thus the breast-fed infant.
- In pregnancy the intramuscular administration is contraindicated when used together with lidocaine.

Ask your doctor or pharmacist for advice before you use ceftriaxone.

Driving and using machines

You may get dizzy when taking this medicine. This may affect your ability to drive or operate machinery. If this happens, do not drive or use machines.

Important information about some of the ingredients of Ceftriaxone

The 1g product contains 3.6 mmol (or 83 mg) sodium per dose and the 2g product contains 7.2 mmol (or 166 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE CEFTRIAXONE

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

Ceftriaxone is normally given by a doctor or nurse

Ceftriaxone 1g:

- Is given as an injection
- The injection is given as a slow injection into a vein or a deep injection into a large muscle.

Ceftriaxone 2g:

- Is given as an infusion.
- The infusion is given as a slow infusion into a vein

The dose your doctor gives depends on the type of infection and how bad the infection is. It also depends on your weight and how your kidneys are working. Your doctor will explain this to you. The usual doses are:

Adults, older people and children 12 years and over whom weigh more than 50kg

- 1 to 2g once a day
- In serious infections, this can be increased to 4g a day, injected into a vein.

Newborn babies (up to 14 days old)

- 20-50mg for each kg of body weight once a day, injected into a vein
- More than 50mg per kg must not be given, even in severe infections.

Children between 15 days and 12 years old

- 20-80mg for each kg of body weight once a day, injected into a vein
- More than 80mg per kg must not be given, even in severe infections - except in meningitis.

Special dose information:

- For infection of the meninges (meningitis) at first 100mg per kg is given once a day (but no more than 4g a day). In newborn babies, no more than 50mg/kg must be given.
- When given before an operation, the normal daily dose is given 30-90 minutes before the operation. Usually only one dose is given
- For people with kidney problems, the dose does not need to be reduced, if hepatic function is normal. If the condition of the kidney is very poor (creatinine clearance of < 10 ml/min), the daily dose of ceftriaxone should not exceed 2 g in adult patients.
- People with liver problems do not need the dose reducing unless they have kidney problems as well.
- In simultaneous severe renal and hepatic insufficiency the blood ceftriaxone concentrations should be monitored regularly and the dosage adjusted appropriately for children and adults.
- If you are on dialysis, the doctor will do tests to make sure you are on the right dose.

Ceftriaxone is usually given once a day.

- The length of treatment is usually at least 2 days beyond the normalisation of body temperature
- It may continue for a total of 7 to 14 days.

If the patient is a child under 2 years old or a pregnant or breast feeding woman, ceftriaxone should only be given by slow injection into a vein.

If you use more Ceftriaxone than you should:

This medicine is usually given to you by a doctor or nurse. If you think you may have received too much medicine please tell your doctor or nurse at once.

If you forget to use Ceftriaxone:

This medicine is usually given to you by a doctor or nurse. If you think you have missed a dose please tell your doctor or nurse.

If you stop using Ceftriaxone

It is important to finish the course of treatment your doctor has prescribed, even if you start to feel better. If you do not finish the course of treatment, your infection may get worse again.

If you do not feel well at the end of the prescribed treatment course or feel worse during treatment, you should talk to your doctor.

Please ask your nurse, doctor or pharmacist if you require any advice about taking your medicine.

4. POSSIBLE SIDE EFFECTS

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

If any of the following **serious side effects** happen, stop taking this medicine and tell your doctor **immediately** or go to your nearest hospital accident and emergency department.

The following side effects are **rare** (affect less than 1 in 1000 people).

- Allergic reactions such as sudden wheeziness and tightness of the chest, swelling of the eyelids, face or lips, severe skin rashes that can blister and may involve the eyes, mouth and throat and genitals, loss of consciousness (fainting).

The following side effects are **very rare** (affect less than 1 out of 10,000 people)

- Diarrhoea that is serious, lasts a long time or has blood in it, with stomach pain or fever. This can be a sign of a serious bowel inflammation (called "pseudomembranous colitis") that can happen after taking antibiotics.

Very common side effects

- (affects more than 1 out of 10 people):
- Gall stones in children

Common side effects

(affects less than 1 out of 10 people):

- allergic reactions (skin rash, itching, nettle rash, swellings of the skin and joints)
- changes in blood tests that check how your liver is working
- pain and hardness when injected into a muscle
- pain and redness when injected into a vein

Uncommon side effects

(affects less than 1 out of 100 people)

- nausea, vomiting, stomach pain, diarrhoea
- sores, inflammation of the tongue, loss of appetite
- headache, dizziness
- infections: Having a course of ceftriaxone can temporarily increase the chance that you can get infections caused by other pathogens. For example, thrush may occur
- kidney problems: changed in kidney function and reduced urine production

Rare side effects

(affects less than 1 out of 1,000 people)

- severe cramps in the belly (caused by inflammation of the pancreas)
- gall stones in adults
- drops in the numbers of white blood cells (sometimes severe with increased risk of severe infection)
- kidney stones in children

Very rare side effects

(affects less than 1 out of 10,000 people)

- reduced or damaged blood cells (increased chance of bleeding, bruising or infection)
- a type of anaemia that can be severe and is caused by red blood cells breaking up. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are taking this medicine as it may affect your result.

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

5. HOW TO STORE CEFTRIAZONE

Keep this medicine out of the reach and sight of children.

Always keep this medicine in the closed original pack, in order to protect from moisture.

Do not store above 25°C. Keep vial in the outer carton. Once reconstituted, this medicine should be used within 24 hours if stored at a temperature of 2-8°C or within 6 hours if stored at 25°C.

This medicine should be used before the expiry date (EXP) printed on the pack.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Ceftriaxone contains:

Ceftriaxone Injection contains the active ingredient ceftriaxone sodium, which is an antibacterial agent used for treatment of infections caused by bacteria.

What Ceftriaxone looks like and contents of the pack

Ceftriaxone 1g powder for solution for injection or infusion is an almost white to yellowish crystalline powder. The ready-to-use solutions are pale yellow to amber.

Ceftriaxone 2g powder for solution for infusion is an almost white to yellowish crystalline powder. The ready-to-use solutions are pale yellow to amber.

Each vial contains either 1g or 2g of ceftriaxone as the sodium salt. There are no other ingredients.

Ceftriaxone 1g and 2g are available in packs of 1 vial.

Ceftriaxone 1g is also available in packs of 5 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:
Panbavy (UK) Limited, 20 Balderton Street, London W1K 6TL, United Kingdom

Manufacturer:
Laboratory Reig Jofra,
Gran Capria, 16-08970 Sant Joan Despí, Barcelona, Spain

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

This leaflet was last approved in February 2009

Ceftriaxone 2g Powder for Solution for Injection
UKPAR Ceftriaxone 2g Powder for Solution for Injection

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
 Each 2 g sachet contains 2 ceftriaxone sodium (anhydrous) (ceftriaxone). Also contains 7 mmol sodium chloride in 4.4 g sachet.

3. PHARMACEUTICAL FORM
 Powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftriaxone is indicated for the treatment of the following infections when caused by micro-organisms that are susceptible to ceftriaxone and/or parenteral treatment is necessary (see section 5.1):

- Bacterial meningitis
- Infections of the ear, nose and throat
- Infections of the skin and soft tissue
- Infections of the urinary tract

Ceftriaxone is indicated for parenteral prophylaxis in patients with a confirmed or suspected invasive pneumococcal infection (see section 4.4). Depending on the mode of surgery and the spectrum of pathogens, ceftriaxone should be combined with an appropriate antimicrobial agent which should be taken into consideration by additional prescriber guidance. Consultation should be given to general practice or the appropriate use of antimicrobial agents.

4.2 Dosage and method of administration

Route and method of administration

Ceftriaxone may be administered by intravenous infusion after reconstitution by the method according to the instructions given below (see section 6.2).

Infusion should be administered by the doctor and the effect of infusion, susceptibility of the causative micro-organism and the patient's age and condition.

After the first administration, the strength of ceftriaxone is available.

Adult dosage

Adults (18 years of age and over): 1 g or 2 g once daily with a body weight > 50 kg. The usual dose is 1 g or 2 g of ceftriaxone administered once daily (see section 4.4). In cases of severe infections or infections caused by micro-organisms the dose can be raised to 4 g, administered once daily intravenously.

Adults < 18 years: 1 g or 2 g once daily with a body weight > 50 kg. The usual dose is 1 g or 2 g of ceftriaxone administered once daily (see section 4.4). In severe infections the daily dose of 5 g once daily by weight must not be exceeded.

Children 15 days to 12 years of age with a body weight < 50 kg: 20 to 50 mg/kg of ceftriaxone administered once daily (see section 4.4). In severe infections the daily dose of 50 mg/kg by weight must not be exceeded, except in meningitis (see section 4.4).

Children with a body weight < 15 kg: 20 mg/kg once daily with a body weight < 15 kg or more receive the adult dose once daily (see section 4.4).

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

Age group	Normal dosage	Frequency
Newborn infants (up to 14 days)	20-50 mg/kg	Once daily
Children 15 days to 12 years of age < 50 kg	20-50 mg/kg	Once daily
Adults over 18 years > 50 kg	1-2 g	Once daily
Adults < 18 years > 50 kg	1-2 g	Once daily
Elderly	1-2 g	Once daily

Special dosage recommendations for the same as for adults, without modification.

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Special dosage recommendations for the same as for adults, without modification.

5.1 Pharmacokinetic properties

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

Ceftriaxone has a half-life of 8-12 hours. Concentrations have been shown to remain above the MIC values for most infection-causing pathogens for over 24 hours in over 60 different patients including young, healthy, elderly, liver, kidney, middle ear, nasal, sinus, bronchi and respiratory tract (including otitis media), pleural fluid, peritoneal fluid and cerebrospinal fluid.

Ceftriaxone is completely absorbed following intramuscular administration with peak plasma concentrations about 50 mg/ml occurring between 1 and 2 hours after dosing.

Ceftriaxone distributes well in various compartments and also penetrates the brain. The mean volume of distribution in healthy adults is 1.7 l/kg.

Ceftriaxone is reversibly bound to albumin. The binding is 85% at plasma concentrations less than 100 mg/ml with the binding percentage decreasing as the concentration increases (to 85% at a ceftriaxone plasma concentration of 200 mg/ml).

Elimination of the intravenous infusion of 1 g of ceftriaxone by 30 minutes, serum levels immediately after cessation of the infusion process were 1.02 µg/ml and 0.43, 0.18, 0.07 and 0.03 µg/ml, respectively, 1, 4, 12 and 24 hours after the onset of infusion. Subsequent to intramuscular injection of 1 g of ceftriaxone the serum concentration amounted to 78 µg/ml after 1.5 hours, and afterwards 59, 25, 5 and 1.2 µg/ml at the respective time-points 4, 12 and 24 hours after dosing.

Ceftriaxone penetrates the inflammation of meningitis, pleuritis, otitis media and others. In CSF the peak concentration of 10 mg/l are achieved after a 50-100 mg/kg intravenous dose, in about two hours. In adult patients with meningitis, peak concentrations of 10 mg/l were achieved 2-24 hours with the dose of 50 mg/kg.

Ceftriaxone penetrates the pleural and is excreted in human milk at low concentrations.

Excretion of ceftriaxone is primarily renal. In patients with renal impairment, ceftriaxone is excreted in the urine. Urinary excretion is significantly reduced in tubular secretion phase. For the reason, increase in plasma levels is to be expected in case of renal impairment. In case of renal impairment, a higher dose or a higher dosage interval is to be considered.

The pharmacokinetics of ceftriaxone are non-linear with respect to the dose. The 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. Peak dosing of 0.5 to 2 g results in 15% to 25% accumulation above single-dose values.

Special populations

Elderly over 75 years: Ceftriaxone is not excreted in the half-life of ceftriaxone is about 7-8 hours increased compared to young adults.

Patients with impaired renal function: The half-life of ceftriaxone in the serum amounts to approximately 16 hours, and approximately 16 hours in patients with impaired renal function (see section 4.2).

Patients with impaired renal function have an increased excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is not increased in these patient groups. Patients with an impaired renal function, as well as an impaired liver function, may have an increased excretion of ceftriaxone.

In case of urinary acid insufficiency, the half-life is distinctly higher than in patients with normal renal function.

5.2 Preclinical safety data

The acute toxicity (LD₅₀) of ceftriaxone in mice is about 2-3 g/kg increased compared to young adults.

Patients with impaired renal function: The half-life of ceftriaxone in the serum amounts to approximately 16 hours, and approximately 16 hours in patients with impaired renal function (see section 4.2).

Patients with impaired renal function have an increased excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is not increased in these patient groups. Patients with an impaired renal function, as well as an impaired liver function, may have an increased excretion of ceftriaxone.

In case of urinary acid insufficiency, the half-life is distinctly higher than in patients with normal renal function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.5. In particular, ceftriaxone is not compatible with calcium containing solutions such as 0.9% sodium chloride and 0.9% sodium lactate. Caution should be taken with ceftriaxone in not compatible with anesthetic, vasopressor, antihypertensive, and hypotensive agents.

6.3 Shelf life

Unopened vials: 3 years.

Special use after reconstitution: The shelf life of ceftriaxone after reconstitution is 24 hours at 2-8°C and 48 hours at 20-25°C. From a microbiological point of view, once opened, the product should be used immediately. It is not used immediately in case of long storage times and conditions prior to use are not recommended for the use and should normally not be longer than 24 hours at 2-8°C or 48 hours at 20-25°C, unless notification has been given in a controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vials: 3 years.

Special use after reconstitution: The shelf life of ceftriaxone after reconstitution is 24 hours at 2-8°C and 48 hours at 20-25°C. From a microbiological point of view, once opened, the product should be used immediately. It is not used immediately in case of long storage times and conditions prior to use are not recommended for the use and should normally not be longer than 24 hours at 2-8°C or 48 hours at 20-25°C, unless notification has been given in a controlled and validated aseptic conditions.

6.5 Route and contents of container

This medicinal product is supplied in a 300 mg Type I dose. A cuboid container with a brominated stopper and a aluminium and polypropylene cap. The vial is packed in a box of 10.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling

Intravenous infusion

Ceftriaxone 2g powder for solution for injection should be dissolved in 10 ml of 0.9% sodium chloride. The infusion should be administered over 10-15 minutes. The infusion should be administered over at least 30 minutes.

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

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

Reconstituted solution should be inspected visually. Only clear solutions free of visible particles should be used. The reconstituted product is for single use only and any unused solution must be discarded.

6.7 BACTERIAL ANTIMETABOLITES

None.

6.8 BACTERIAL ANTIMETABOLITES

None.

6.9 BACTERIAL ANTIMETABOLITES

None.

6.10 BACTERIAL ANTIMETABOLITES

None.

6.11 BACTERIAL ANTIMETABOLITES

None.

6.12 BACTERIAL ANTIMETABOLITES

None.

6.13 BACTERIAL ANTIMETABOLITES

None.

6.14 BACTERIAL ANTIMETABOLITES

None.

6.15 BACTERIAL ANTIMETABOLITES

None.

6.16 BACTERIAL ANTIMETABOLITES

None.

6.17 BACTERIAL ANTIMETABOLITES

None.

6.18 BACTERIAL ANTIMETABOLITES

None.

6.19 BACTERIAL ANTIMETABOLITES

None.

6.20 BACTERIAL ANTIMETABOLITES

None.

6.21 BACTERIAL ANTIMETABOLITES

None.

6.22 BACTERIAL ANTIMETABOLITES

None.

6.23 BACTERIAL ANTIMETABOLITES

None.

6.24 BACTERIAL ANTIMETABOLITES

None.

6.25 BACTERIAL ANTIMETABOLITES

None.

6.26 BACTERIAL ANTIMETABOLITES

None.

6.27 BACTERIAL ANTIMETABOLITES

None.

6.28 BACTERIAL ANTIMETABOLITES

None.

6.29 BACTERIAL ANTIMETABOLITES

None.

6.30 BACTERIAL ANTIMETABOLITES

None.

6.3 Pharmacokinetic properties

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

Ceftriaxone has a half-life of 8-12 hours. Concentrations have been shown to remain above the MIC values for most infection-causing pathogens for over 24 hours in over 60 different patients including young, healthy, elderly, liver, kidney, middle ear, nasal, sinus, bronchi and respiratory tract (including otitis media), pleural fluid, peritoneal fluid and cerebrospinal fluid.

Ceftriaxone is completely absorbed following intramuscular administration with peak plasma concentrations about 50 mg/ml occurring between 1 and 2 hours after dosing.

Ceftriaxone distributes well in various compartments and also penetrates the brain. The mean volume of distribution in healthy adults is 1.7 l/kg.

Ceftriaxone is reversibly bound to albumin. The binding is 85% at plasma concentrations less than 100 mg/ml with the binding percentage decreasing as the concentration increases (to 85% at a ceftriaxone plasma concentration of 200 mg/ml).

Elimination of the intravenous infusion of 1 g of ceftriaxone by 30 minutes, serum levels immediately after cessation of the infusion process were 1.02 µg/ml and 0.43, 0.18, 0.07 and 0.03 µg/ml, respectively, 1, 4, 12 and 24 hours after the onset of infusion. Subsequent to intramuscular injection of 1 g of ceftriaxone the serum concentration amounted to 78 µg/ml after 1.5 hours, and afterwards 59, 25, 5 and 1.2 µg/ml at the respective time-points 4, 12 and 24 hours after dosing.

Ceftriaxone penetrates the inflammation of meningitis, pleuritis, otitis media and others. In CSF the peak concentration of 10 mg/l are achieved after a 50-100 mg/kg intravenous dose, in about two hours. In adult patients with meningitis, peak concentrations of 10 mg/l were achieved 2-24 hours with the dose of 50 mg/kg.

Ceftriaxone penetrates the pleural and is excreted in human milk at low concentrations.

Excretion of ceftriaxone is primarily renal. In patients with renal impairment, ceftriaxone is excreted in the urine. Urinary excretion is significantly reduced in tubular secretion phase. For the reason, increase in plasma levels is to be expected in case of renal impairment. In case of renal impairment, a higher dose or a higher dosage interval is to be considered.

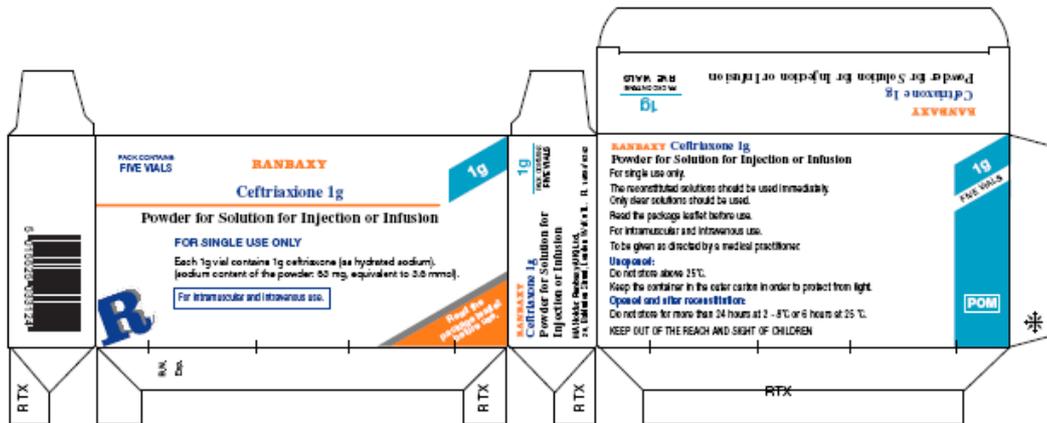
The pharmacokinetics of ceftriaxone are non-linear with respect to the dose. The non-linearity is explained by a concentration-dependent decrease of binding to plasma proteins, which leads to a respective increase in distribution and elimination.

CEFTRIAXONE SODIUM 1G POWDER FOR SOLUTION FOR INJECTION

PL 14894/0342 LABELLING

Carton

1 vial carton



5 vial carton



Bottle label

RANBAXY Ceftriaxone 1g		MA Holder: Ranbaxy (UK) Ltd. 33 Balderton Street, London W1K 6TL	1g <small>POM</small>
Powder for Solution for Injection or Infusion			PL 14894/0342
Each 1g vial contains 1g ceftriaxone (as hydrated sodium). (sodium content of the powder: 83 mg, equivalent to 3.6 mmol).			
For intramuscular and intravenous use.			
B.N.	Required for batch	For single use only. The reconstituted solutions should be used immediately.	
Exp.	and Expiry printing	Only clear solutions should be used. Read the package leaflet before use. To be given as directed by a medical practitioner	

CEFTRIAXONE SODIUM 2G POWDER FOR SOLUTION FOR INJECTION

PL 14894/0343

Carton



Bottle label

