

## SECTION 2: SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

### Ceftriaxone

#### 1 g powder for solution for injection and infusion

Ceftriaxone (as Ceftriaxone Sodium)

#### 1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone 1 g powder for solution for injection and infusion

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 g ceftriaxone as ceftriaxone sodium

*Excipient with known effect:*

Ceftriaxone contains approximately 83 mg (3.6 mmol) of sodium per gram of ceftriaxone.

#### 3. PHARMACEUTICAL FORM

Ceftriaxone is a white to yellow crystalline powder.

#### 4. CLINICAL PARTICULARS

##### 4.1. Therapeutic indications

Ceftriaxone is indicated for the treatment of the following infections in adults and children including term neonates (from birth):

- Bacterial Meningitis
- Community acquired pneumonia
- Hospital acquired pneumonia
- Acute otitis media
- Intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)
- Infections of bones and joints
- Complicated skin and soft tissue infections
- Gonorrhoea
- Syphilis
- Bacterial endocarditis

Ceftriaxone may be used:

- For treatment of acute exacerbations of chronic obstructive pulmonary disease in adults

- For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age
- For pre-operative prophylaxis of surgical site infections
- In the management of neutropenic patients with fever that is suspected to be due to a bacterial infection
- In the treatment of patients with bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Ceftriaxone should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum (see section 4.4).

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

#### 4.2. Posology and method of administration

##### Posology

The dose depends on the severity, susceptibility, site and type of infection and on the age and hepato-renal function of the patient.

The doses recommended in the tables below are the generally recommended doses in these indications. In particularly severe cases, doses at the higher end of the recommended range should be considered.

##### *Dosage in adults and children over 12 years of age ( $\geq 50$ kg)*

| <b>Ceftriaxone Dosage*</b> | <b>Treatment frequency**</b> | <b>Indications</b>   |
|----------------------------|------------------------------|--|
| 1-2 g                      | Once daily                   | Community acquired pneumonia   |
|                            |                              | Acute exacerbations of chronic obstructive pulmonary disease                                       |
|                            |                              | Intra-abdominal infections   |
|                            |                              | Complicated urinary tract infections (including pyelonephritis)                                    |
| 2 g                        | Once daily                   | Hospital acquired pneumonia  |
|                            |                              | Complicated skin and soft tissue infections  |
|                            |                              | Infections of bones and joints   |
| 2-4 g                      | Once daily                   | Management of neutropenic patients with fever that is suspected to be due to a bacterial infection |
|                            |                              | Bacterial endocarditis   |
|                            |                              | Bacterial meningitis   |

\* In documented bacteremia, the higher end of the recommended dose range should be

considered.

\*\* Twice daily (12 hourly) administration may be considered where doses greater than 2000 mg daily are administered.

Indications for adults and children over 12 years of age ( $\geq 50$  kg) that require specific dosage schedules:

*Acute otitis media*

A single intramuscular dose of Ceftriaxone 1-2 g can be given. Limited data suggest that in cases where the patient is severely ill or previous therapy has failed, Ceftriaxone may be effective when given as an intramuscular dose of 1-2 g daily for 3 days.

*Pre-operative prophylaxis of surgical site infections*

1-2 g as a single pre-operative dose.

*Gonorrhoea*

500 mg as a single intramuscular dose.

*Syphilis*

The generally recommended doses are 500 mg-1 g once daily increased to 2 g once daily for neurosyphilis for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on limited data. National or local guidance should be taken into consideration.

*Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])*

2 g once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Dosage in Pediatric Patients

*Dosage in Neonates, infants and children 15 days to 12 years of age (< 50 kg)*

| <b>Ceftriaxone Dosage*</b> | <b>Treatment frequency**</b> | <b>Indications</b>   |
|----------------------------|------------------------------|--|
| 50-80 mg/kg                | Once daily                   | Intra-abdominal infections   |
|                            |                              | Complicated urinary tract infections (including pyelonephritis)                                    |
|                            |                              | Community acquired pneumonia   |
|                            |                              | Hospital acquired pneumonia  |
| 50-100 mg/kg (max 4 g)     | Once daily                   | Complicated skin and soft tissue infections  |
|                            |                              | Infections of bones and joints   |
|                            |                              | Management of neutropenic patients with fever that is suspected to be due to a bacterial infection |
| 80-100 mg/kg (max 4 g)     | Once daily                   | Bacterial meningitis   |

|                        |            |                        |
|------------------------|------------|------------------------|
| 100 mg/kg<br>(max 4 g) | Once daily | Bacterial endocarditis |
|------------------------|------------|------------------------|

\* In documented bacteremia, the higher end of the recommended dose range should be considered.

\*\* Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

For children with bodyweight of 50 kg or more, the usual adult dosage should be given.

Indications for neonates, infants and children 15 days to 12 years (< 50 kg) that require specific dosage schedules:

*Acute otitis media*

For initial treatment of acute otitis media, a single intramuscular dose of Ceftriaxone 50 mg/kg can be given. Limited data suggest that in cases where the child is severely ill or initial therapy has failed, Ceftriaxone may be effective when given as an intramuscular dose of 50 mg/kg daily for 3 days.

*Pre-operative prophylaxis of surgical site infections*

50-80 mg/kg as a single pre-operative dose.

*Syphilis*

The generally recommended doses are 75-100 mg/kg (max 4 g) once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

*Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])*

50–80 mg/kg once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Neonates 0-14 days

Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

| <b>Ceftriaxone dosage*</b> | <b>Treatment frequency</b> | <b>Indications</b>  |
|----------------------------|----------------------------|---|
| 20-50 mg/kg                | Once daily                 | Intra-abdominal infections                                      |
|                            |                            | Complicated skin and soft tissue infections                     |
|                            |                            | Complicated urinary tract infections (including pyelonephritis) |
|                            |                            | Community acquired pneumonia                                    |
|                            |                            | Hospital acquired pneumonia                                     |
|                            |                            | Infections of bones and joints                                  |

|          |            |  |
|----------|------------|--|
|          |            | Management of neutropenic patients with fever that is suspected to be due to a bacterial infection |
| 50 mg/kg | Once daily | Bacterial meningitis   |
|          |            | Bacterial endocarditis   |

\* In documented bacteremia, the higher end of the recommended dose range should be considered.

A maximum daily dose of 50 mg/kg should not be exceeded.

***Indications for neonates 0-14 days that require specific dosage schedules:***

*Acute otitis media*

For initial treatment of acute otitis media, a single intramuscular dose of Ceftriaxone 50 mg/kg can be given.

*Pre-operative prophylaxis of surgical site infections*

20-50 mg/kg as a single pre-operative dose.

*Syphilis*

The generally recommended dose is 50 mg/kg once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

*Duration of therapy*

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for 48 - 72 hours after the patient has become afebrile or evidence of bacterial eradication has been achieved.

*Older people*

The dosages recommended for adults require no modification in older people provided that renal and hepatic function is satisfactory.

*Patients with hepatic impairment*

Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment provided renal function is not impaired.

There are no study data in patients with severe hepatic impairment (see section 5.2).

*Patients with renal impairment*

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided hepatic function is not impaired. Only in cases of preterminal renal failure (creatinine clearance < 10 ml/min) should the ceftriaxone dosage not exceed 2 g daily.

In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Ceftriaxone is not removed by peritoneal- or hemodialysis. Close clinical monitoring

for safety and efficacy is advised.

*Patients with severe hepatic and renal impairment*

In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

*Method of administration*

*Intramuscular administration*

Ceftriaxone can be administered by deep intramuscular injection. Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 1 g should be injected at one site.

As the solvent used is lidocaine, the resulting solution should never be administered intravenously. The information in the Summary of Product Characteristics of lidocaine should be considered.

*Intravenous administration*

Ceftriaxone can be administered by intravenous infusion over at least 30 minutes or by slow intravenous injection over 5 minutes. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy. Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient. For doses greater than 2000 mg intravenous administration should be used.

*Ceftriaxone is contraindicated in neonates ( $\leq 28$  days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.*

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

For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery.

For instructions on reconstitution of the medicinal product before administration, see

section 6.6.

### 4.3. Contraindications

Hypersensitivity to ceftriaxone or to any other cephalosporin.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

Ceftriaxone is contraindicated in:

- Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age)\*
- Full-term neonates (up to 28 days of age):
  - with hyperbilirubinemia, jaundice, or who are hypoalbuminemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired\*
  - if they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt.

\* In vitro studies have shown that ceftriaxone can displace bilirubin from its serum albumin binding sites leading to a possible risk of bilirubin encephalopathy in these patients.

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent. See information in the Summary of Product Characteristics (SPC) of lidocaine, especially contraindications.

Ceftriaxone solutions containing lidocaine should never be administered intravenously.

### 4.4. Special warnings and precautions for use

Hypersensitivity reactions. As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if ceftriaxone is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS)) which can be lifethreatening or fatal, have been reported in association of ceftriaxone

treatment; however, the frequency of these events is not known (see section 4.8).

#### Jarisch-Herxheimer reaction (JHR)

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after ceftriaxone treatment is started. JHR is usually a self – limiting condition or can be managed by symptomatic treatment. The antibiotic treatment should not be discontinued if such reaction occurs.

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

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

Pediatric population. Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described under Posology and Method of Administration (see section 4.2). Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Ceftriaxone is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy (see section 4.3).

Immune mediated hemolytic anemia. An immune mediated hemolytic anemia has been



observed in patients receiving cephalosporin class antibacterials including Ceftriaxone (see section 4.8). Severe cases of hemolytic anemia, including fatalities, have been reported during Ceftriaxone treatment in both adults and children. If a patient develops anemia while on ceftriaxone, the diagnosis of a cephalosporin-associated anemia should be considered and ceftriaxone discontinued until the etiology is determined.

Long term treatment. During prolonged treatment complete blood count should be performed at regular intervals.

Colitis/Overgrowth of non-susceptible microorganisms. Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of ceftriaxone (see section 4.8). Discontinuation of therapy with ceftriaxone and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents.

Severe renal and hepatic insufficiency. In severe renal and hepatic insufficiency, close clinical monitoring for safety and efficacy is advised (see section 4.2).

Interference with serological testing. Interference with Coombs tests may occur, as Ceftriaxone may lead to false-positive test results. Ceftriaxone can also lead to false-positive test results for galactosemia (see section 4.8).

Non-enzymatic methods for the glucose determination in urine may give false-positive results. Urine glucose determination during therapy with Ceftriaxone should be done enzymatically (see section 4.8).

The presence of ceftriaxone may falsely lower estimated blood glucose values obtained with some blood glucose monitoring systems. Please refer to instructions for use for each system. Alternative testing methods should be used if necessary.

Sodium. Each gram of Ceftriaxone contains 83 mg (3.6 mmol) sodium. This should be taken into consideration in patients on a controlled sodium diet.

Antibacterial spectrum. In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone, administration of an additional antibiotic should be considered.

Use of lidocaine. In case a lidocaine solution is used as a solvent, ceftriaxone solutions must only be used for intramuscular injection. Contraindications to lidocaine, warnings and other

relevant information as detailed in the Summary of Product Characteristics of lidocaine must be considered before use (see section 4.3). The lidocaine solution should never be administered intravenously.

*Biliary lithiasis.* When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at ceftriaxone doses of 1 g per day and above. Caution should be particularly considered in the pediatric population. Such precipitates disappear after discontinuation of ceftriaxone therapy. Rarely precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of ceftriaxone treatment should be considered by the physician based on specific benefit risk assessment (see section 4.8).

*Biliary stasis.* Cases of pancreatitis, possibly of biliary obstruction etiology, have been reported in patients treated with Ceftriaxone (see section 4.8). Most patients presented with risk factors for biliary stasis and biliary sludge e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor of Ceftriaxone-related biliary precipitation cannot be ruled out.

*Renal lithiasis.* Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone (see section 4.8). In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the physician based on specific benefit risk assessment.

#### *Jarisch-Herxheimer reaction (JHR)*

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after ceftriaxone treatment is started. JHR is usually a self - limiting condition or can be managed by symptomatic treatment. The antibiotic treatment should not be discontinued if such reaction occurs.

### **4.5. Interaction with other medicinal products and other forms of interaction**

*Calcium-containing diluents*, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be administered simultaneously with *calcium-containing intravenous solutions*, including continuous calcium-containing infusions such as

parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (see sections 4.2 and 4.3).

Concomitant use with *oral anticoagulants* may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone (see section 4.8).

There is conflicting evidence regarding a potential increase in renal toxicity of *aminoglycosides* when used with cephalosporins. If patients renal function impaired, the recommended monitoring of aminoglycoside levels (and renal function) in clinical practice should be closely adhered to in cases of concomitant usage of cephalosporins and aminoglycosides.

In an in-vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (intravenous or oral).

In patients treated with ceftriaxone, the *Coombs' test* may lead to false-positive test results.

Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosemia.

Non-enzymatic methods for glucose determination in urine may yield false-positive results.

For this reason, glucose level determination in urine during therapy with ceftriaxone should be carried out enzymatically.

No impairment of renal function has been observed after concurrent administration of large doses of ceftriaxone and *potent diuretics* (e.g. furosemide).

Simultaneous administration of *probenecid* does not reduce the elimination of ceftriaxone.

#### **4.6. Fertility, pregnancy and lactation**

Pregnancy. Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/fetal, perinatal and postnatal development. Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Breast-feeding. Ceftriaxone is excreted into human milk in low concentrations but at

therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

***Fertility.*** Reproductive studies have shown no evidence of adverse effects on male or female fertility.

#### **4.7. Effects on ability to drive and use machines**

During treatment with ceftriaxone, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8). Patients should be cautious when driving or operating machinery.

#### **4.8. Undesirable effects**

##### ***a. Summary of the safety profile***

Ceftriaxone is tolerated well when it is used in recommended dosages and dosing regimens. The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhea, rash, and hepatic enzymes increased.

##### ***b. Tabulated list of adverse reactions***

For estimation of development frequency of side effects the following criteria are used: very common ( $\geq 1/10$ ), common (from  $\geq 1/100$  to  $< 1/10$ ), uncommon (from  $\geq 1/1000$  to  $< 1/100$ ), rare (from  $\geq 1/10\ 000$  to  $< 1/1000$ ), very rare (from  $< 1/10\ 000$  including individual case safety report), and “the frequency is not known” (according to the available data, it is not possible to estimate the frequency).

| <b>System Organ Class</b>            | <b>Common</b>                                  | <b>Uncommon</b>                            | <b>Rare</b>                            | <b>Not Known<sup>a</sup></b>                      |
|--------------------------------------|--|--|--|---|
| Infections and infestations          |  | Genital fungal infection                   | Pseudo-membranous colitis <sup>b</sup> | Superinfection <sup>b</sup>                       |
| Blood and lymphatic system disorders | Eosinophilia<br>Leucopenia<br>Thrombocytopenia | Granulocytopenia<br>Anemia<br>Coagulopathy |  | Haemolytic anemia <sup>b</sup><br>Agranulocytosis |
| Immune system disorders              |  |  |  | Anaphylactic shock<br>Anaphylactic reaction       |

|  |                                       |   |                         |   |
|--|---------------------------------------|---|-------------------------|---|
|  |                                       |   |                         | Anaphylactoid reaction<br>Hypersensitivity <sup>b</sup><br>Jarisch-Herxheimer reaction (see section 4.4).   |
| Nervous system disorders                             |                                       | Headache<br>Dizziness                       |                         | Convulsion  |
| Ear and labyrinth disorders                          |                                       |   |                         | Vertigo   |
| Respiratory, thoracic and mediastinal disorders      |                                       |   | Bronchospasm            |   |
| Gastrointestinal disorders                           | Diarrhea <sup>b</sup><br>Loose stools | Nausea<br>Vomiting                          |                         | Pancreatitis <sup>b</sup><br>Stomatitis<br>Glossitis  |
| Hepatobiliary disorders                              | Hepatic enzyme increased              |   |                         | Gall bladder precipitation <sup>b</sup><br>Kernicterus  |
| Skin and subcutaneous tissue disorders               | Rash                                  | Pruritus                                    | Urticaria               | Stevens Johnson Syndrome <sup>b</sup><br>Toxic epidermal necrolysis <sup>b</sup><br>Erythema multiforme<br>Acute generalised exanthematous pustulosis<br>Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4). |
| Renal and urinary disorders                          |                                       |   | Hematuria<br>Glycosuria | Oliguria<br>Renal precipitation (reversible)  |
| General disorders and administration site conditions |                                       | Phlebitis<br>Injection site pain<br>Pyrexia | Edema<br>Chills         |   |
| Investigations                                       |                                       | Blood creatinine increased                  |                         | Coombs test false positive <sup>b</sup>   |

|  |  |  |  |  |
|--|--|--|--|--|
|  |  |  |  | Galactosemia test false positive <sup>b</sup><br>Non enzymatic methods for glucose determination false positive <sup>b</sup> |
|--|--|--|--|--|

<sup>a</sup> Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

<sup>b</sup> See section 4.4

*c. Description of selected adverse reactions*

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

*Ceftriaxone-calcium salt precipitation.* Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults. Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g.  $\geq 80$  mg/kg/day or total doses exceeding 10 g) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone (see section 4.4). Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

*Reporting of suspected adverse reactions.* Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report any side effect(s):

|  |
|--|
| <ul style="list-style-type: none"><li>• _____:</li></ul> <p>- _____</p> <p>Fax: _____</p> <p>Call ____ at _____, Exts: _____.</p> <p>Toll free phone: _____</p> <p>E-mail ____ @ _____</p> <p>Website: _____</p> |
|--|

#### **4.9. Overdose**

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

### **5. PHARMACODYNAMIC PROPERTIES**

#### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: antibacterials for systemic use, third-generation cephalosporins.

ATC code: [J01DD04].

##### Mechanism of Action

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

##### Mechanism of resistance

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

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

##### Susceptibility test interpretive criteria for ceftriaxone

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

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

a. Susceptibility inferred from cefoxitin susceptibility.

b. Susceptibility inferred from penicillin susceptibility.

c. Isolates with a ceftriaxone MIC above the susceptible breakpoint are rare and, if found, should be re-tested and, if confirmed, should be sent to a reference laboratory.

d. Breakpoints apply to a daily intravenous dose of 1 g x 1 and a high dose of at least 2 g x 1.

#### Clinical efficacy against specific pathogens

| Commonly susceptible species  |
|---|
| <u>Gram-positive aerobes</u>  |
| <i>Staphylococcus aureus</i> (methicillin-susceptible) <sup>a</sup>     |
| Staphylococci coagulase-negative (methicillin-susceptible) <sup>a</sup> |
| <i>Streptococcus pyogenes</i> (Group A)                                 |
| <i>Streptococcus agalactiae</i> (Group B)                               |
| <i>Streptococcus pneumoniae</i>   |
| Viridans Group <i>Streptococci</i>                                      |
| <u>Gram-negative aerobes</u>  |
| <i>Borrelia burgdorferi</i>   |
| <i>Haemophilus influenzae</i>   |
| <i>Haemophilus parainfluenzae</i>                                       |
| <i>Moraxella catarrhalis</i>  |
| <i>Neisseria gonorrhoea</i>   |
| <i>Neisseria meningitidis</i>   |
| <i>Proteus mirabilis</i>  |
| <i>Providencia</i> spp.   |
| <i>Treponema pallidum</i>   |
| Species for which acquired resistance may be a problem                  |
| <u>Gram-positive aerobes</u>  |
| <i>Staphylococcus epidermidis</i> <sup>b</sup>                          |
| <i>Staphylococcus haemolyticus</i> <sup>b</sup>                         |



|  |
|--|
| <p><i>Staphylococcus hominis</i><sup>b</sup></p> <p><u>Gram-negative aerobes</u></p> <p><i>Citrobacter freundii</i></p> <p><i>Enterobacter aerogenes</i></p> <p><i>Enterobacter cloacae</i></p> <p><i>Escherichia coli</i></p> <p><i>Klebsiella pneumoniae</i></p> <p><i>Klebsiella oxytoca</i></p> <p><i>Morganella morganii</i></p> <p><i>Proteus vulgaris</i></p> <p><i>Serratia marcescens</i></p> <p><u>Anaerobes</u></p> <p><i>Bacteroides</i> spp.</p> <p><i>Fusobacterium</i> spp.</p> <p><i>Peptostreptococcus</i> spp.</p> <p><i>Clostridium perfringens</i></p> |
| <p><b>Inherently resistant organisms</b></p>   |
| <p><u>Gram-positive aerobes</u></p> <p><i>Enterococcus</i> spp.</p> <p><i>Listeria monocytogenes</i></p> <p><u>Gram-negative aerobes</u></p> <p><i>Acinetobacter baumannii</i></p> <p><i>Pseudomonas aeruginosa</i></p> <p><i>Stenotrophomonas maltophilia</i></p> <p><u>Anaerobes</u></p> <p><i>Clostridium difficile</i></p> <p><u>Others:</u></p> <p><i>Chlamydia</i> spp.</p> <p><i>Chlamydophila</i> spp.</p> <p><i>Mycoplasma</i> spp.</p> <p><i>Legionella</i> spp.</p> <p><i>Ureaplasma urealyticum</i></p>  |

<sup>a</sup> All methicillin-resistant staphylococci are resistant to ceftriaxone.

<sup>b</sup> ESBL producing strains are always resistant

## 5.2 Pharmacokinetic properties

### Absorption

#### *Intramuscular administration*

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

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

### *Intravenous administration*

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

### *Distribution*

The volume of distribution of ceftriaxone is 7-12 l. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An 8-5 % increase in mean peak plasma concentration ( $C_{max}$ ) is seen on repeated administration; steady state is reached in most cases within 48-72 hours depending on the route of administration.

### *Penetration into particular tissues*

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in cerebrospinal fluid (CSF) in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninfamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

### *Protein binding*

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

### *Biotransformation*

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

### *Elimination*

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

### *Patients with renal or hepatic impairment*

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

severely impaired renal function.

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

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

#### Older people

Compared to that healthy subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects.

#### Pediatric population

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

#### Linearity/non-linearity

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

#### Pharmacokinetic/pharmacodynamic relationship

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

### **5.3. Preclinical safety data**

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible.

Animal studies produced no evidence of toxicity to reproduction and genotoxicity.

Carcinogenicity studies on ceftriaxone were not conducted.

## **5. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

None.

### **6.2. Incompatibilities**

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

Solutions containing ceftriaxone should not be mixed with or added to other agents except those mentioned in section 6.6. In particular diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or bottles or to further dilute a reconstituted vial or bottle for intravenous administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition (see section 4.2, 4.3, 4.4 and 4.8).

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

### **6.3. Shelf life**

Unopened vials or bottles: 3 years

Chemical and physical in-use stability of the reconstituted product has been demonstrated for at least 6 hours at or below 25°C or 24 hours at 2-8°C.

### **6.4. Special precautions for storage**

Do not store above 30°C, keep vial in the outer carton in order to protect from light.

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

### **6.5 Nature and contents of container**

Ceftriaxone 1 g powder for solution for injection or infusion

10 ml glass vial with rubber stopper and aluminium or flip-off cap containing a sterile powder, equivalent to 1 g ceftriaxone.

The following pack sizes are available:

1 vial together with leaflet is inserted into a cardboard box

50 vials together with 50 leaflets are inserted into a corrugated box

Not all pack sizes may be marketed.

## **6.6. Special precautions for disposal and other handling**

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

Ceftriaxone should not be mixed in the same syringe with any drug other than 1% Lidocaine Hydrochloride solution (for intramuscular injection only).

The infusion line should be flushed after each administration.

### *Intravenous (IV) Administration*

*For IV injection* 1 g Ceftriaxone is dissolved in 10 ml of water for injections. After reconstitution, each 1 ml of solution contains approximately 100 mg equivalent of ceftriaxone. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.

*For IV infusion* 1 g Ceftriaxone is dissolved in one of the following calcium-free infusion fluids: 0.9% sodium chloride solution, 5% dextrose solution, 10% dextrose solution, 5% dextrose + 0.45% sodium chloride solution, 2.5% dextrose + 0.45% sodium chloride solution, 5% dextrose + 0.9% sodium chloride solution, **dextran 6% in dextrose 5%, hydroxyethylstarch 6 – 10%**, water for injections. Concentrations between 10 mg/ml and 40 mg/ml are recommended; however, lower concentrations may be used if desired. The infusion should be administered over at least 30 minutes. See also the information in section 6.2.

In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.

### *Intramuscular (IM) Administration*

For IM injection 1 g Ceftriaxone is dissolved in 3.5 ml of 1% Lidocaine Hydrochloride solution. Inject diluent into vial, shake vial thoroughly to form solution. After reconstitution, each 1 ml of solution contains approximately 250 mg equivalent of ceftriaxone. Withdraw entire contents of vial into syringe to equal total labeled dose. The solution should be administered by deep intramuscular injection. Dosages greater than 1 g should be divided and injected at more than one site.

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

**7. Marketing authorisation holder**

“KRASPHARMA” OJSC

Russia, 660042, 60 let Oktyabrya st. 2, Krasnoyarsk

Tel.: +7 (391) 261-25-90. Fax: +7 (391) 261-17-44

**8. Marketing authorisation number(s)**

Ceftriaxone 1000 mg powder for solution for injection or infusion \_\_\_\_\_

**9. Date of first Authorisation/ renewal of the authorisation**

\_\_\_\_\_.

**10. Date of revision of the text**

\_\_\_\_\_.