PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CEFTRIAXONE 250 PHARMA-Q sterile powder for injection

CEFTRIAXONE 500 PHARMA-Q sterile powder for injection

CEFTRIAXONE 1000 PHARMA-Q sterile powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftriaxone 250 mg, 500 mg or 1 000 mg (in the form of the disodium salt).

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sterile powder for injection.

Sterile, white to off-white crystalline, hygroscopic powder. The reconstituted solution is a pale-yellow solution free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CEFTRIAXONE PHARMA-Q is indicated for the treatment of the following infections:

Bacterial septicemia caused by:

Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, or *Klebsiella pneumoniae*.

Meningitis caused by:

Haemophilus influenzae, *Neisseria meningitides*, or *Streptococcus pneumoniae*.

Intra-abdominal infections caused by:

Escherichia coli, *Klebsiella pneumoniae*, or *Peptostreptococcus* species.

Skin and skin structure infections caused by:

Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pyogenes*, *Streptococcus viridans* group, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Morganella morganii*, *Serratia marcescens*, or *Peptostreptococcus* species.

Bone and joint infections caused by:

Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Enterobacter* species.

Renal and urinary tract infections (complicated and uncomplicated) caused by:

Escherichia coli, *Proteus mirabilis*, *Proteus Vulgaris*, *Morganella morganii*, or *Klebsiella pneumoniae*.

Respiratory tract infections caused by:

Streptococcus pneumoniae, Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus mirabilis*, or *Serratia marcescens*.

Ear, nose and throat Infections (acute bacterial otitis media) caused by: *Streptococcus pneumoniae*, *Haemophilus influenzae*, (including beta-lactamase- producing strains), or *Moraxella catarrhalis* (Including beta-lactamase-producing strains).

Uncomplicated gonorrhoea (cervical/urethral and rectal) caused by:

Neisseria gonorrhea, including both beta-lactamase-, and non-beta-lactamase- producing

strains, and pharyngeal gonorrhea caused by non-beta-lactamase- producing strains of *Neisseria gonorrhea*.

Peri-operative infection prophylaxis

4.2 Posology and method of administration

Posology

Standard dosage

Adults and children over 12 years:

The usual dosage is 1 - 2 g CEFTRIAXONE PHARMA-Q once daily. In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

Neonates, infants and children up to 12 years:

The following dosage schedules are recommended for once daily administration:

Neonates (up to 14 days):

20 - 50 mg/kg body weight once daily. The daily dose should not exceed

50 mg/kg. It is not necessary to differentiate between premature and term infants.

Infants and children (15 days to 12 years):

20 - 80 mg/kg once daily. For children with bodyweights of 50 kg or more, the usual adult dose should be used. Intravenous doses of 50 mg/kg bodyweight should be given by infusion over at least 30 minutes.

Elderly patients:

No dose modification is needed in the elderly.

Duration of therapy

The duration of therapy varies according to the course of the disease. Administration of CEFTRIAXONE PHARMA-Q should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Special dosage instructions

Meningitis:

In bacterial meningitis in neonates, infants and children, treatment begins with doses of 100 mg/kg (not to exceed 4 000 mg) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dose can be adapted accordingly.

For bacterial meningitis in adults, the recommended dose is 4 000 mg g once daily.

Gonorrhoea:

For the treatment of uncomplicated gonorrhoea (both beta-lactamase-producing and non-beta-lactamase-producing strains), a single intramuscular (IM) dose of 125 mg CEFTRIAXONE is recommended.

Peri-operative infection prophylaxis:

A single dose of 1 - 2 g CEFTRIAXONE PHARMA-Q administered 30 - 90 minutes prior to surgery. In colorectal surgery, administration of CEFTRIAXONE PHARMA-Q with or without a 5-nitroimidazole, e.g. metronidazole, has been proven effective, (separate administration: see Method of administration).

Impaired renal and hepatic function:

In patients with impaired renal function, there is no need to reduce the dosage of CEFTRIAXONE PHARMA-Q provided that hepatic function is intact.

In cases of severe renal failure (creatinine clearance < 10 ml/min) the CEFTRIAXONE PHARMA-Q dosage should not exceed 2 000 mg daily.

In patients with liver damage, there is no need for the dosage to be reduced, provided that renal function is intact

Method of administration

CEFTRIAXONE PHARMA-Q must be reconstituted prior to use. Reconstituted solutions retain

their physical and chemical stability for 6 hours at room temperature or 24 hours in the refrigerator at + 5 °C. As a general rule, however, the solutions should be used immediately after preparation. The solutions range in colour from pale yellow to amber, depending on the concentration and length of storage. The colouration of the solutions is of no significance for the efficacy or tolerance of the medicine.

Intramuscular injection:

For IM injection, CEFTRIAXONE PHARMA-Q 250 mg or 500 mg is dissolved in 2 ml and CEFTRIAXONE PHARMA-Q 1 000 mg in 3,5 ml of water for injection. CEFTRIAXONE PHARMA-Q dissolved in a 1 % lignocaine solution instead of water for injection can reduce pain at the site of injection. It is recommended that not more than 1 000 mg is injected at one site. Reconstitution with 1 % lignocaine (without adrenaline) has no effect on the absorption or elimination of CEFTRIAXONE PHARMA-Q.

Intravenous injection:

The lignocaine solution must never be administered intravenously.

For IV injection CEFTRIAXONE PHARMA-Q 250 mg or 500 mg is dissolved in 5 ml, and CEFTRIAXONE PHARMA-Q 1 000 mg in 10 ml sterile water for injection. The intravenous administration should be given over 2 to 4 minutes.

Incompatibilities: See section 6.2

4.3 Contraindications

- Hypersensitivity to ceftriaxone, to any other cephalosporin or to any of the excipients of CEFTRIAXONE PHARMA-Q (see section 6.1).
- History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial medicines (penicillins, monobactams and carbapenems).

- Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age)*
- Full-term neonates (up to 28 days of age):

  - with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubinbinding 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 (see sections 4.4, 4.8 and 6.2).

  * *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 section 4.4). See the contraindications section in the professional information of lidocaine.

  Ceftriaxone solutions containing lidocaine should never be administered intravenously.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8).

In case of severe hypersensitivity reactions, treatment with CEFTRIAXONE PHARMA-Q 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 medicine. Caution should be used if CEFTRIAXONE PHARMA-Q is given to patients with a history of non-severe hypersensitivity to other beta-lactam medicines.

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 life-threatening or fatal have been reported in association of ceftriaxone treatment; however, the frequency of these events is not known (see section 4.8).

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 PHARMA-Q 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 PHARMA-Q 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 total parenteral nutrition (TPN) 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 PHARMA-Q is considered necessary in patients requiring continuous nutrition, TPN solutions and CEFTRIAXONE PHARMA-Q can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of CEFTRIAXONE PHARMA-Q infusion and the infusion lines flushed between solutions (see sections 4.3, 4.8, 5.2 and 6.2).

Paediatric population

Safety and effectiveness of CEFTRIAXONE PHARMA-Q in neonates, infants and children have been established for the dosages described under Posology (see section 4.2). Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. CEFTRIAXONE PHARMA-Q is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy (see section 4.3).

Immune mediated haemolytic anaemia

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including CEFTRIAXONE PHARMA-Q (see section 4.8). Severe cases of haemolytic anaemia, including fatalities, have been reported during CEFTRIAXONE PHARMA-Q treatment in both adults and children.

If a patient develops anaemia while on CEFTRIAXONE PHARMA-Q, the diagnosis of a cephalosporin-associated anaemia should be considered and CEFTRIAXONE PHARMA-Q discontinued until the aetiology is determined.

Long term treatment

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

Colitis/Overgrowth of non-susceptible microorganisms

Antibacterial medicine-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial medicines, including CEFTRIAXONE PHARMA-Q, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of CEFTRIAXONE PHARMA-Q (see section 4.8). Discontinuation of therapy with CEFTRIAXONE PHARMA-Q and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

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

medicines.

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 PHARMA-Q may lead to false-positive test results. CEFTRIAXONE PHARMA-Q can also lead to false-positive test results for galactosaemia (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 PHARMA-Q should be done enzymatically (see section 4.8).

The presence of CEFTRIAXONE PHARMA-Q 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.

Antibacterial spectrum

CEFTRIAXONE PHARMA-Q has a limited spectrum of antibacterial activity and may not be suitable for use as a single medicine for the treatment of some types of infections unless the pathogen has already been confirmed. In polymicrobial infections, where suspected pathogens include organisms resistant to CEFTRIAXONE PHARMA-Q, the administration of an additional antibiotic should be considered.

Use of lidocaine

In case a lidocaine solution is used as a solvent, CEFTRIAXONE PHARMA-Q solutions must only be used for intramuscular injection. Contraindications to lidocaine, warnings and other relevant information as detailed in the Professional information 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 paediatric population. Such precipitates disappear after discontinuation of ceftriaxone therapy. Less frequently precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of CEFTRIAXONE PHARMA-Q treatment should be considered by the medical practitioner based on specific benefit risk assessment (see section 4.8).

Biliary stasis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with CEFTRIAXONE PHARMA-Q (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 PHARMA-Q -related biliary precipitation cannot be ruled out.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of CEFTRIAXONE PHARMA-Q (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 medical practitioner 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 PHARMA-Q 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.

Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone (see section 4.8), particularly in elderly patients with severe renal impairment (see section 4.2) or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of CEFTRIAXONE PHARMA-Q should be considered.

Sodium

CEFTRIAXONE 250 PHARMA-Q sterile powder for injection contains 48,42 mg sodium per vial.

CEFTRIAXONE 500 PHARMA-Q sterile powder for injection contains 96,85 mg sodium per vial.

CEFTRIAXONE 1000 PHARMA-Q sterile powder for injection contains 193,70 mg sodium per vial.

4.5 Interaction with other medicines and other forms of interaction

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute CEFTRIAXONE PHARMA-Q 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 PHARMA-Q is mixed with calcium-containing solutions in the same intravenous administration line. CEFTRIAXONE PHARMA-Q 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 PHARMA-Q 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, 4.3, 4.4, 4.8 and 6.2).

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 PHARMA-Q (see section 4.8).

There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. The recommended monitoring of aminoglycoside levels (and renal function) in clinical practice should be closely adhered to in such cases.

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 PHARMA-Q, the Coombs' test may lead to false-positive test results.

CEFTRIAXONE PHARMA-Q, like other antibiotics, may result in false-positive tests for galactosaemia.

Likewise, 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 PHARMA-Q should be carried out enzymatically.

No impairment of renal function has been observed after concurrent administration of large doses of CEFTRIAXONE PHARMA-Q and potent diuretics (e.g. furosemide).

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

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

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/foetal, perinatal and postnatal development.

Breastfeeding

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 diarrhoea 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 breastfeeding or to discontinue/abstain from CEFTRIAXONE PHARMA-Q therapy.

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 PHARMA-Q, 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

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

b. Tabulated summary of adverse reactions

The adverse reactions have been grouped according to system organ class and with the following frequency classifications: frequent, less frequent and frequency unknown.

System organ class	Frequency	Adverse reactions
Infections and infestations	Less frequent	Genital fungal infection, pseudo-membranous colitis (see section 4.4)
	Frequency unknown	Superinfection (see section 4.4)
Blood and lymphatic system disorders	Frequent	Eosinophilia, leukopenia, thrombocytopenia
	Less frequent	Granulocytopenia, anaemia, coagulopathy
	Frequency unknown	Haemolytic anaemia, agranulocytosis (see section 4.4)
Immune system disorders	Frequency unknown	Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, Jarisch-Herxheimer reaction (see section 4.4)
Nervous system disorders	Less frequent	Headache, dizziness, encephalopathy
	Frequency unknown	Convulsion
Ear and labyrinth disorders	Frequency unknown	Vertigo

System organ class	Frequency	Adverse reactions
Cardiac disorders	Frequency unknown	Kounis syndrome
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchospasm
Gastrointestinal disorders	Frequent	Diarrhoea, loose stools (see section 4.4)
	Less frequent	Nausea, vomiting
	Frequency unknown	Pancreatitis (see section 4.4), stomatitis, glossitis
Hepato-biliary disorders	Frequent	Hepatic enzyme increased
	Frequency unknown	Gall bladder precipitation, kernicterus, hepatitis, hepatitis cholestatic (see section 4.4)
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Pruritus, urticaria
	Frequency unknown	Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4), linear IgA disease
Renal and urinary disorders	Less frequent	Haematuria, glycosuria
	Frequency unknown	Oliguria, renal precipitation (reversible)

System organ class	Frequency	Adverse reactions
General disorders and administration site conditions	Less frequent	Phlebitis, injection site reactions, pyrexia, oedema, chills
Investigations	Less frequent	Blood creatinine increased
	Frequency unknown	Coombs test false positive, galactosaemia test false positive, non enzymatic methods for glucose determination false positive (see section 4.4)

c. Description of selected adverse reactions

Infections and infestations

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

Ceftriaxone-calcium salt precipitation

Less frequently, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4, and 5.2).

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have 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 PHARMA-Q (see section 4.4).

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than there commended 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 PHARMA-Q (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In the case of over dosage, plasma concentration would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Antibacterials for systemic use. Third generation cephalosporins.

ATC code: J01DD04.

Mechanism of action

Ceftriaxone is a third-generation cephalosporin. The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis.

Ceftriaxone exerts *in vitro* activity against a wide range Gram-negative and Gram-positive microorganisms. Ceftriaxone is stable to most β-lactamases, both penicillinases and cephalosporinases, of Gram-positive and Gram-negative bacteria.

Resistance

The following organisms have been found to be resistant to ceftriaxone:

Gram positive aerobes:

Methicillin-resistant *Staphylococcus* spp. is resistant to ceftriaxone. *Enterococcus faecalis*, *Enterococcus faecium* and *Listeria monocytogenes* are resistant.

Gram negative aerobes:

Some isolates of *Acinetobacter anitratus* (mostly *A. baumanii*), *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter* spp (other), *Proteus penneri*, *Proteus vulgaris*, *Pseudomonas fluorescens*, *Pseudomonas* spp. (other), *Providentia rettgeri*, *Serratia marcescens*, *Serratia* spp. (other) are resistant to ceftriaxone, mainly due to the production of the chromosomally encoded ß-lactamase.

Some isolates of *Klebsiella pneumoniae* are resistant due to production of extended spectrum, plasmid-mediated ß-lactamase. Clinical *P. aeruginosa* isolates are resistant to ceftriaxone. *Ureaplasma urealyticum*, *Mycoplasma* sp., *Mycobacterium* sp. and fungi are resistant to ceftriaxone.

Anaerobic organisms:

Some isolates of *Bacteroides* spp. (bile-sensitive) are resistant to ceftriaxone due to ß-lactamase production. Many strains of ß-lactamase-producing *Bacteroides* spp. (notably *B. fragilis*) are resistant. *Clostridium difficile* is resistant.

The WHO Antimicrobial Resistance, Global Report on Surveillance, lists the following bacteria-antibacterial medicine resistant combinations ranging between 56 % - 90 % for 3rd generation

cephalosporins including ceftriaxone as: *E. coli* and *K. pneumoniae* mainly conferred by extended spectrum beta-lactamases (ESBLs), and *N. gonorrhoeae*.

5.2 Pharmacokinetic properties

Absorption

The maximum concentration after a single intramuscular (IM) dose of 1 000 mg is about 81 mg/litre and is reached within 2-3 hours after administration. The area under the plasma concentration versus time curve (AUC) after intramuscular administration is equivalent to that after intravenous (IV) administration of equivalent dose, indicating 100 % bioavailability of intramuscularly (IM) administered ceftriaxone.

Distribution

The apparent volume of distribution of ceftriaxone is 0,13 - 0,19 litres/kg. Ceftriaxone shows good tissue penetration and body-fluid distribution after a dose of 1 000 – 2 000 mg; concentrations well above the minimum inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in body-fluids or tissues including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids.

Protein binding

Ceftriaxone is reversibly bound to albumin. There is proportionally decreased albumin binding with an increase in plasma concentration of ceftriaxone.

Penetration into particular tissues

Paediatrics:

Ceftriaxone penetrates the inflamed meningitis of neonates, infants and children. Ceftriaxone concentrations exceed 1,4 mg/litre in the cerebrospinal fluid (CSF) 24 hours after IV injection

in doses of 50 mg/kg in neonates to 100 mg/kg in infants. Peak concentration in CSF with a mean of 18 mg/litre is reached about 4 hours after intravenous injection. Mean CSF concentrations are 17 % of plasma concentrations in patients with bacterial meningitis and 4 % in patients with aseptic meningitis. The mean values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after a 50 mg/kg IV dose and after a 75 mg/kg IV dose in paediatric patients suffering from bacterial meningitis are shown in the table below.

Mean pharmacokinetic parameters of ceftriaxone in paediatric patients with meningitis:

	50 mg/kg IV	75 mg/kg IV
Maximum plasma concentrations(mcg/ml)	216	275
Elimination half-life (hr)	4,6	4,3
Plasma clearance (ml/hr/kg)	49	60
Volume of distribution (ml/kg)	338	373
CSF concentration - inflamed meninges (mcg/ml)	5,6	6,4
Range (mcg/ml)	1,3 - 185	1,3 - 44
Time after dose (hr)	3,7 (± 1,6)	3,3 (± 1,4)

Adults:

In meningitis in adults, administration of 50 mg/kg leads within 2 - 24 hours to CSF concentrations several times higher than the minimum In vitro inhibitory concentrations required for the most common meningitis pathogens.

Ceftriaxone crosses the placental barrier and is excreted in the breast milk in low concentrations.

In healthy, young adult volunteers the total plasma clearance is 10 - 22 ml/min.

The renal clearance is 5 - 12 ml/min. Fifty to sixty percent of ceftriaxone is excreted unchanged in the urine, while 40 - 50 % is excreted unchanged in the bile. The elimination half-life in adults is about 8 hours.

Pharmacokinetics in special clinical situations:

Neonates - urinary recovery accounts for about 70 % of the dose.

Infants less than eight days old and elderly persons aged over 75 years - elimination half-life is usually 2 - 3 times that in young adults.

Patients with renal or hepatic dysfunction - the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased.

Impaired kidney function alone - biliary elimination of ceftriaxone is increased.

Impaired liver function alone - renal elimination of ceftriaxone is increased.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

CEFTRIAXONE PHARMA-Q should not be added to solutions containing calcium, such as Hartmann's solution and Ringer's solution. Ceftriaxone is incompatible with vancomycin, fluconazole and aminoglycosides.

6.3 Shelf life

24 months

6.4 Special precautions for storage

The product is for single use only; any unused portion must be discarded.

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

CEFTRIAXONE 250 PHARMA-Q: 10 ml clear, colourless glass vials. One vial per outer carton.

CEFTRIAXONE 500 PHARMA-Q: 10 ml clear, colourless glass vials. One vial per outer carton.

CEFTRIAXONE 1 000 PHARMA-Q: 10 ml clear, colourless glass vials. One vial per outer carton.

6.6 Special precautions for disposal and other handling

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q (Pty) Ltd

50 Commando Road

Industria West 2003

Johannesburg

South Africa

info@pharmaq.co.za

Tel: 011 247 1600

8 REGISTRATION NUMBERS

CEFTRIAXONE 250 PHARMA-Q: 37/20.1.1/0046

CEFTRIAXONE 500 PHARMA-Q: 37/20.1.1/0048

CEFTRIAXONE 1 000 PHARMA-Q: 37/20.1.1/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 July 2004

10 DATE OF REVISION OF THE TEXT

08 August 2025