SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Medaxone 1g powder for solution for injection/infusion
Medaxone 2g powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Medaxone 1g vial contains 1g ceftriaxone as ceftriaxone sodium.
Medaxone 2g vial contains 2g ceftriaxone as ceftriaxone sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.
Almost white or yellowish crystalline powder, slightly hygroscopic.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Medaxone 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

Medaxone 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.
- *Infections in patients with impaired defense mechanisms*

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

General

Standard dosage

Adults and children over 12 years

The usual dosage is 1-2 g of Ceftriaxone once daily (every 24 hours). In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

Duration of Treatment

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

Combination treatment

Synergy between Ceftriaxone and aminoglycosides has been demonstrated with many gram-negative bacteria under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life threatening infections due to micro-organisms such as Pseudomonas aeruginosa. Due to chemical incompatibility between Ceftriaxone and aminoglycosides, the two drugs must be administered separately at the recommended dosages.

Chemical incompatibility with Ceftriaxone has also been observed with IV administration of amsacrine, vancomycin and fluconazole.

Method of administration

As a general rule the solutions should be used immediately after preparation.

Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2 – 8 °C). The solutions range in colour from pale yellow to amber,

depending on the concentration and length of storage. The coloration of the solutions is of no significance for the efficacy or tolerance of the drug.

Intramuscular injection

For i.m. injection, Ceftriaxone 1 g is dissolved in 3.5 ml, of 1% lidocaine hydrochloride solution and injected well within the body of a relatively large muscle. It is recommended that not more than 1 g be injected at one site. The lidocaine solution should never be administered intravenously *(see section 4.3)*.

Intravenous injection

For i.v. injection, Ceftriaxone 1 g is dissolved in 10 ml sterile water for injections. The intravenous administration should be given over 2-4 minutes.

Intravenous infusion

The infusion should be given over at least 30 minutes. For i.v. infusion, 2 g Ceftriaxone is dissolved in 40 ml of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, water for injections. Ceftriaxone solutions should not be mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, owing to possible incompatibility.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone must not be administered simultaneously with calcium-containing IV 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 (see sections 4.3, 4.4 and 4.5).

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

Special Dosage Instructions

Pediatric use

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 bodyweight once daily. The daily dose should not exceed 50 mg/kg.

Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41weeks (gestational age + chronological age) (see section 4.3).

Ceftriaxone is contraindicated in neonates (≤28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see 4.3).

For neonates, 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 dosage should be used. Intravenous doses of ≥ 50 mg/kg bodyweight, in infants and children up to 12 years of age, should be given by infusion over at least 30 minutes. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.

Meningitis

In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg(up to a maximum of 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly. The following duration of therapy has shown to be effective:

Neisseria meningitidis 4 days

Haemophilus influenza 6 days

Streptococcus pneumoniae 7 days

Geriatric use

No dose adjustment of Ceftriaxone is required in patients ≥ 65 years of age provided there is no severe renal and hepatic impairment**.**

Renal impairment

No dose adjustment is required, 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.

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

Hepatic impairment

No dose adjustment of Ceftriaxone is required, provided renal function is not impaired.

Severe renal and hepatic impairment

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

Lyme borreliosis

50 mg/kg to a maximum of 2 g in children and adults, once daily for 14 days.

Gonorrhea (penicillinase-producing and nonpenicillinase-producing strains)

A single i.m. dose of 250 mg.

Perioperative prophylaxis

A single dose of 1-2 g depending on the risk of infection of 30-90 minutes prior to surgery. In colorectal surgery, administration of Ceftriaxone with or without a 5-nitroimidazole, e.g. ornidazole (separate administration) has been proven effective.

4.3 Contraindications

Hypersensitivity to ceftriaxone, to any other cephalosporin or to any of the excipients listed in section 6.1.
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 hypoalbuminaemic 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 (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).

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 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).

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 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 is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion 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 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 haemolytic anaemia

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

If a patient develops anaemia while on ceftriaxone, the diagnosis of cephalosporin associated anaemia should be considered and ceftriaxone 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 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 diarrhoea 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 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 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 Medaxone contains 3.6 mmol (83 mg) sodium. This should be taken into consideration in patients on a controlled sodium diet.

Antibacterial spectrum

Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed (see section 4.2). 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 1g per day and above. Caution should be particularly considered in the paediatric 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 aetiology, 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.

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, 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 (sees 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, the Coombs' test may lead to false-positive test results.

Ceftriaxone, 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 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/foetal, perinatal and postnatal development (see section 5.3). 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 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 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

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

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

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

- Very common (≥1/10);
- Common (≥1/100 to <1/10);
- Uncommon (≥1/1,000 to <1/100);
- Rare (≥1/10,000 to <1/1,000);
- Very rare (<1/10,000);
- Not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare	Not known[a]
Infections and infestations		Genital fungal infection	Pseudomembranous colitis[b]	Superinfection[b]
Blood and lymphatic system disorders	Eosinophilia Leukopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia[b] Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity[b] Jarisch-Herxheimer reaction (see section 4.4)
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo

System Organ Class	Common	Uncommon	Rare	Not known[a]
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b] Loose stools	Nausea Vomiting		Pancreatitis[b] Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation[b] Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome[b] Toxic epidermal necrolysis[b] Erythema multiforme Acute generalised exanthematous pustulosis Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	

System Organ Class	Common	Uncommon	Rare	Not known[a]
Investigations		Blood creatinine increased		Coombs test false positive[b] Galactosaemia test false positive[b] Non enzymatic methods for glucose determination false positive[b]

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

[b]See section 4.4

Description of selected adverse reactions

Infections and infestations

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

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in preterm 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). The risk of precipitate formation is increased in immobilized or dehydrated patients. This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and post renal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Other beta-lactam antibacterials, Third-generation cephalosporins, ATC code: J01DD04.

Mechanism of action

The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis. Ceftriaxone exerts in vitro activity against a wide range of gram-negative and gram-positive micro-organisms. Ceftriaxone is highly stable to most ß-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria. Ceftriaxone is usually active against the following micro-organisms in vitro and in clinical infections (see section 4).

Gram-positive aerobes

Staphylococcus aureus (methicillin-sensitive), Staphylococci coagulase-negative, *Streptococcus pyogenes* (ß-hemolytic, group A), *Streptococcus agalactiae* (ß-hemolytic, group B), ß-hemolytic Streptococci (non-group A or B), *Streptococcus viridans, Streptococcus pneumoniae.*
Note: Methicillin-resistant *Staphylococcus* spp. is resistant to cephalosporins, including ceftriaxone. In general, *Enterococcus faecalis, Enterococcus faecium* and *Listeria monocytogenes* are resistant.

Gram-negative aerobes

Acinetobacter lwoffi, Acinetobacter anitratus (mostly A. baumanii)*, *Aeromonas hydrophila, Alcaligenes faecalis, Alcaligenes odorans, Alcaligenes-like bacteria, Borrelia burgdorferi, Capnocytophaga spp., Citrobacter diversus (including C. amalonaticus), Citrobacter freundii*, Escherichia coli, Enterobacter aerogenes*, Enterobacter cloacae*, Enterobacter spp. (other)*, Haemophilus ducreyi, Haemophilus influenzae, Haemophilus parainfluenzae, Hafnia alvei, Klebsiella oxytoca, Klebsiella pneumoniae**, Moraxella catarrhalis (former Branhamella catarrhalis), Moraxella osloensis, Moraxella spp. (other), Morganella morganii, Neisseria gonorrhoea, Neisseria meningitidis, Pasteurella multocida, Plesiomonas shigelloides, Proteus mirabilis, Proteus penneri*, Proteus vulgaris*, Pseudomonas fluorescens*, Pseudomonas spp. (other)*, Providentia rettgeri*, Providentia spp. (other), Salmonella typhi, Salmonella spp. (non-typhoid), Serratia marcescens*, Serratia spp. (Other)*, Shigella spp., Vibrio spp., Yersinia enterocolitica, Yersinia spp. (other).*

** Some isolates of these species are resistant to ceftriaxone, mainly due to the production of the chromosomally encoded ß-lactamase.*

*** Some isolates of these species are resistant due to production of extended spectrum, plasmid-mediated ß-lactamase.*

Note: Many strains of the above micro-organisms that are multiple resistant to other antibiotics, e.g. amino-penicillins and ureido-penicillins, older cephalosporins and aminoglycosides, are susceptible to ceftriaxone. Treponema pallidum is sensitive in vitro and in animal experiments. Clinical investigations indicate that primary and secondary syphilis respond well to ceftriaxone therapy. With a few exceptions clinical P. aeruginosa isolates are resistant to ceftriaxone.

Anaerobic organisms

Bacteroides spp. (bile-sensitive), Clostridium spp. (excluding C. difficile), Fusobacterium nucleatum, Fusobacterium spp. (other), Gaffkia anaerobica (formerly Peptococcus), Peptostreptococcus spp.*

** Some isolates of these species are resistant to ceftriaxone due to ß-lactamase-production.*

Note: Many strains of ß-lactamase-producing Bacteroides spp. (notably B. fragilis) are resistant. Clostridium difficile is resistant.

Susceptibility to ceftriaxone can be determined by the disk diffusion test or by the agar or broth dilution test using standardized techniques for susceptibility testing such as those recommended by the National

Committee for Clinical Laboratory Standards (NCCLS). The NCCLS issued the following interpretative breakpoints for ceftriaxone:

	Susceptible	Moderately susceptible	Resistant
Dilution test Inhibitory concentrations in mg/l	≤ 8	16 – 32	≥ 64
Diffusion test (disk with 30 µg ceftriaxone), inhibition zone diameter in mm	≥ 21	20 – 14	≤ 13

Micro-organisms should be tested with the ceftriaxone disk since it has been shown by *in vitro* tests to be active against certain strains resistant to cephalosporin class disks.

Where NCCLS recommendations are not in daily use, alternative, well standardized, susceptibility-interpretative guidelines such as those issued by DIN, ICS and others may be substituted.

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

Distribution

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

administration; steady state is reached in most cases within 48-72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25% of plasma levels compared to 2% of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (see section 4.6).

Protein binding

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

Biotransformation

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

Elimination

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

Patients with renal or hepatic impairment

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

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

In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of

ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

Older people

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

Paediatric population

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

The plasma clearance and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults.

Linearity/non-linearity

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

Pharmacokinetic/pharmacodynamic relationship(s)

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

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

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

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

6.3 Shelf life

3 years.

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

6.4 Special precautions for storage

Store below 30°C in the original packaging, in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Medaxone 1g is supplied in clear type I glass vials, nominal capacity 10 ml, sealed with grey bromobutyl rubber stopper and aluminium cap, in a carton with a leaflet.
Medaxone 2g are clear type I glass vials having a nominal capacity of 20 ml sealed with grey bromobutyl rubber stopper and an aluminium cap, in a carton with a leaflet.
Cartons containing 1, 10, 25, 50, or 100 vials are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling Please refer to section 4.2 for instructions for reconstitution.

Any antibiotic residual solution as well as all materials that have been used for administration should be disposed of in accordance with local requirements.

7. MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

06/2021