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1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone Advagen Powder for Solution for Injection 1g

Ceftriaxone Advagen Powder for Solution for Injection 2g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ceftriaxone Advagen Powder for Solution for Injection 1g

Each vial contains Ceftriaxone Sodium equivalent to Ceftriaxone (Anhydrous) 1g.

Ceftriaxone Advagen Powder for Solution for Injection 2g

Each vial contains Ceftriaxone Sodium equivalent to Ceftriaxone (Anhydrous) 2g.

3. PHARMACEUTICAL FORM

White to yellowish orange crystalline powder

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION(S)

Ceftriaxone is indicated for the treatment of the following infections:

- Sepsis
- Meningitis
- Disseminated Lyme Borreliosis (early and late stages of the disease
- Abdominal Infections (peritonitis, infections of the biliary and gastrointestinal tracts)
- Infections of the bones, joints, soft tissue, skin and of wounds
- Infections in patients with impaired defense mechanisms
- Renal and urinary tract infections
- Respiratory tract infections, particularly pneumonia, and ear, nose and throat infections
- Genital infections, including gonorrhea
- Perioperative prophylaxis of infections

4.2 DOSAGE AND 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

Generally, the solutions should be used immediately after preparation.

Intramuscular injection

For intramuscular injection, 1 g of ceftriaxone 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 Contraindications).

Intravenous injection

For intravenous injection, 1 g of ceftriaxone 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 intravenous infusion, 2 g of 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 Contraindications, 4.4 Warnings and Precautions and 4.8 Interactions with other Medicinal Products and other Forms of Interaction).

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).

4.2.1 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 41 weeks (gestational age + chronological age) (see section 4.3 contraindications). 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 Contraindications).

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 intramuscular 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, see 4.2 Dosage and Administration) has been proven effective.

4.3 CONTRAINDICATIONS

Hypersensitivity

Ceftriaxone is contraindicated in patients with known hypersensitivity to ceftriaxone, any of its excipients or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta lactam agents may be at a greater risk of hypersensitivity to ceftriaxone (see section 4.4.1 Warnings and Precautions: General – Hypersensitivity).

Lidocaine

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent (see section 4.2 Dosage and Administration). See contraindications section in the prescribing information of lidocaine. Ceftriaxone solutions containing lidocaine should never be administered intravenously.

Premature Neonates

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

Hyperbilirubinemic newborns

Hyperbilirubinaemic newborns should not be treated with ceftriaxone. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin leading to a possible risk of bilirubin encephalopathy can possibly develop in these patients.

Neonates and Calcium Containing IV Solutions

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 4.2 Dosage and Administration and 4.8 Interactions with other Medicinal Products and other Forms of Interaction).

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftriaxone and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone and calcium- containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates (see section 4.6.2 Post-marketing experience).

4.4 WARNINGS AND PRECAUTIONS

4.4.1. GENERAL

Hypersensitivity

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.6.2 Post-marketing experience). 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 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 hypersensitivity to other beta- lactam agents.

Hemolytic Anemia
An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone. Severe cases of hemolytic anemia, including fatalities, have been reported during 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.

Clostridium difficile associated diarrhea (CDAD)
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.
C. difficile produces toxins A and B which contribute to the development of CDAD. Toxin hyperproducing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

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

Calcium-ceftriaxone precipitates
Calcium-ceftriaxone precipitates in the gallbladder have been observed on ultrasound scan in patients receiving ceftriaxone, particularly at doses of 1 g per day and above. The probability of such precipitates appears to be greatest in pediatric patients. Precipitates disappear after discontinuation of ceftriaxone therapy and are rarely symptomatic. In symptomatic cases, conservative nonsurgical management is recommended, and discontinuation of ceftriaxone treatment should be considered by the physician based on an individual benefit-risk assessment.
In the available scientific data, there are no reports of intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. However, ceftriaxone should not be mixed or administered to any patient simultaneously with calcium-containing solutions, even via different infusion lines (see 4.3 Contraindications for information regarding newborns, 4.8 Interactions with other Medicinal Products and other Forms of Interaction, and 4.6.2 Post-marketing experience). As a theoretical consideration and based on 5 half-lives of ceftriaxone (at which point negligible amounts of the original ceftriaxone dose would be present), ceftriaxone and IV calcium-containing solutions should not be administered within 5 days of each other in neonates and in infants up to 10 weeks of age (by ten weeks of age the ceftriaxone half-life is generally less than 10 hours).

Pancreatitis
Cases of pancreatitis, possibly of biliary obstruction aetiology, have been rarely reported in patients treated with ceftriaxone. 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 role of ceftriaxone-related biliary precipitation cannot be ruled out.

Pediatrics
Safety and effectiveness of ceftriaxone in neonates, infants and children have been established for the dosages described under Dosage and Administration. Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Ceftriaxone should not be used in neonates (especially prematures) at risk of developing bilirubin encephalopathy (see 4.3 Contraindications).

Blood Monitoring
During prolonged treatment the complete blood count should be done at regular intervals.

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

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.

4.4.2. DRUG ABUSE AND DEPENDENCE
Not applicable

4.4.3. 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 4.6 Undesirable Effects). Patients should be cautious when driving or operating machinery.

4.5 USE IN SPECIAL POPULATIONS
4.5.1 FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Fertility
Reproductive studies have shown no evidence of adverse effects on male or female fertility.

4.5.2 PREGNANCY

Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed.

4.5.3. LACTATION

Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when ceftriaxone is administered to a nursing woman.

4.5.4 PEDIATRIC USE

See section 4.2.1 Special Dosage Instructions.

4.5.5 GERIATRIC USE

See section 4.2.1 Special Dosage Instructions.

4.5.6 RENAL IMPAIRMENT

See section 4.2.1 Special Dosage Instructions.

4.5.7 HEPATIC IMPAIRMENT

See section 4.2.1 Special Dosage Instructions.

4.6 UNDESIRABLE EFFECTS

4.6.1. CLINICAL TRIALS

Summary of the safety profile

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhea, rash, and hepatic enzymes increased. Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000).

System Organ Class	Common	Uncommon	Rare
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy	
Gastrointestinal disorders	Diarrhoea Loose stools	Nausea Vomiting	
General disorders and administration site conditions		Phlebitis Injection site reactions Pyrexia	Oedema Chills
Hepatobiliary disorders	Hepatic enzyme increased		
Infections and infestations		Genital fungal infection	Pseudo- membranous colitis
Investigations		Blood creatinine increased	
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria
Renal and urinary disorders			Haematuria Glycosuria
Nervous system disorders		Headache Dizziness	
Respiratory, thoracic and mediastinal disorders		Bronchospasm	

4.6.2. POST-MARKETING EXPERIENCE

The following adverse drug reactions have been identified from postmarketing experience with ceftriaxone. These reactions are reported from a population of uncertain size, therefore, it is not always possible to reliably estimate their frequency and/or establish a causal relationship to drug exposure.

Systemic side effects

Gastrointestinal complaints: pancreatitis, stomatitis and glossitis.

Hematological changes: Isolated cases of agranulocytosis (<500/mm3) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

Skin reactions: Acute generalized exanthematous pustulosis (AGEP) and isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson syndrome or Lyell's Syndrome/toxic epidermal necrolysis) have been reported.

Nervous system disorders: convulsion, encephalopathy
Reversible encephalopathy has been reported with the use of cephalosporins, including ceftriaxone, particularly when high doses are administered in patients with renal impairment and additional predisposing factors such as older age, pre-existing central nervous system disorders.
Infections and Infestations: superinfection

Other, rare side effects
Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder, kernicterus, oliguria, and anaphylactic or anaphylactoid reactions.

Interaction with calcium
Two in vitro studies, one using adult plasma and the other neonatal plasma from umbilical cord blood have been carried out to assess interaction of ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved in vivo following administration of 2 grams ceftriaxone infused over 30 minutes) were used in combination with calcium concentrations up to 12 mM (48 mg/dL). Recovery of ceftriaxone from plasma was reduced with calcium concentrations of 6 mM (24 mg/dL) or higher in adult plasma or 4 mM (16 mg/dL) or higher in neonatal plasma. This may be reflective of ceftriaxone-calcium precipitation.

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftriaxone and calcium containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom Ceftriaxone and calcium- containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates (see 4.4 Warnings and Precautions).

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.

Local side effects
In rare cases, phlebitis reactions occurred after intravenous administration. These may be minimized by slow (2-4 minutes) injection.
Investigations: Coombs test false positive, galactosemia test false positive, non-enzymatic methods for glucose determination false positive.

4.7 OVERDOSE

In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal

dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

4.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

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

No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins. The elimination of ceftriaxone is not altered by probenecid. In an in-vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

Concomitant use of ceftriaxone with Vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjusted accordingly, both during and after treatment with ceftriaxone (see section 4.6 Undesirable Effects).

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. 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 4.2 Dosage and Administration and 4.3 Contraindications).

5. PHARMACOLOGICAL PROPERTIES AND EFFECTS

5.1 PHARMACODYNAMICS PROPERTIES

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

5.1.1. 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 4. Clinical Particulars).

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

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.

Absorption

Rocephin is administered as an intramuscular injection or as an IV injection or infusion.

Intramuscular administration

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, indicating 100% bioavailability of intramuscularly administered ceftriaxone.

Intravenous administration

After intravenous bolus administration of ceftriaxone 500 mg and 1.5 g, mean peak plasma ceftriaxone levels are approximately 151 and 286 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. Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose.

Distribution

The volume of distribution of ceftriaxone is 7-12 l. Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1-2 g; concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in over 60 tissues or body fluids including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids.

On intravenous administration, ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.

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). Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

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.

Metabolism

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

Elimination

Total plasma clearance is 10-22 ml/min. Renal clearance is 5-12 ml/min.

50-60% 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 POPULATIONS

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.

Geriatric population

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

Renal impairment

In patients with renal impairment, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased (less than two fold) even in patients with severely impaired renal function. The 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.

Hepatic impairment

In patients with hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased (less than two fold). In this patient population, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 INCOMPATIBILITIES

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

Solutions containing ceftriaxone should not be mixed with or added to other agents. 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.

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

This medicinal product must not be mixed with other medicinal products.

6.2 Storage

Do not store above 30 °C, keep vial in the outer container. Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2-8 °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 not be longer than the times stated above for the chemical and physical in-use stability.

Shelf life

36 months. This medicine should not be used after the expiry date (EXP) shown on the pack.

6.3 NATURE AND CONTENTS OF CONTAINER

Ceftriaxone Advagen Powder for Solution for Injection 1g
10 ml Plain glass vial with 20 mm Grey Bromo Butyl Rubber Stopper and Sealed with 20 mm Colored Flip off Seal

Ceftriaxone Advagen Powder for Solution for Injection 2g
20 ml Plain glass vial with 20 mm Grey Bromo Butyl Rubber Stopper and Sealed with 20 mm Colored Flip off Seal

6.4 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Instructions for reconstitution: see section 4.2 Dosage and Administration

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established ‘collection systems’ if available in your location.

Disposal of syringes/sharps
The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.

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

7. MARKETING AUTHORISATION HOLDER

ADVAGEN Pte Ltd
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Ubi Techpark

Singapore 408564

8. DATE OF REVISION OF THE TEXT

June 2023