SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DESEFIN 1 g Powder for Solution for IV Injection/Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Ceftriaxone disodium 3.5 H_2O equivalent to 1 g Ceftriaxone.

Excipients: Contains no excipients.
For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for Solution for Injection
White or yellowish, almost odorless powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections caused by pathogens sensitive to DESEFIN:

- Sepsis,
- Meningitis,
- Disseminated Lyme borreliosis (early and late stages),
- Abdominal infections (peritonitis, infections of the biliary and gastrointestinal system),
- Bone, joint, soft tissue, skin and wound infections,
- Infections in patients with impaired defense mechanisms,
- Renal and urinary tract infections,
- Respiratory tract infections, particularly pneumonia, ear-nose-throat infections, uncomplicated acute bacterial otitis media,
- Genital infections including gonorrhea,
- Preoperative prophylaxis of infection.

4.2 Posology and method of administration

Posology/frequency and duration of administration
Unless otherwise recommended by the doctor,

Standard dosage:
For adults and children over 12 years:
The usual dosage is 1-2 g of DESEFIN administered once daily (every 24 hours). In severe cases or infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, administered once daily.

Duration of therapy:
The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of DESEFIN 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.

Combination therapy:
Synergy between DESEFIN 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 microorganisms such as *Pseudomonas aeruginosa*. Because of physical incompatibility the two medicines must be administered separately at the recommended dosages.

Meningitis: In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg (not to exceed 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly. Effective results have been found with the following duration of therapy:
Neisseria meningitidis 4 days
Haemophilus influenzae 6 days
Streptococcus pneumoniae 7 days

Lyme borreliosis: 50 mg/kg to a maximum 2 g in children and adults, once daily dose 14 days.

Gonorrhea: For the treatment of gonorrhea (penicillinase-producing and non-producing strains), a single IM dose of 250 mg DESEFIN is recommended.

Preoperative prophylaxis: The recommended approach–depending on the risk of infection–is a single dose of 1–2 g DESEFIN administered 30-90 minutes prior to surgery.
In colorectal surgery, concurrent (but separate) administration of DESEFIN with or without a 5-nitroimidazole, e.g. ornidazole, has proven effective.

Method of administration
DESEFIN solution should be used immediately after preparation.

IV injection: For IV injection, 0.5 g DESEFIN should be dissolved in 5 ml and 1 g DESEFIN should be dissolved in 10 ml of water for injection. The injection should be administered over 2-4 minutes, directly into the vein or via the tubing of an intravenous infusion.

IV infusion: The infusion should be administered over at least 30 minutes. For intravenous infusion, 2 g of DESEFIN is dissolved in 40 ml of one of the following calcium-free infusion fluids: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxyethyl-starch 6 – 10%, water for injections. DESEFIN solutions should not be mixed with other solutions containing antimicrobial agents or other solutions different than listed above due to potential incompatibility.

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute DESEFIN vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when DESEFIN is mixed with calcium-containing solutions in the same intravenous administration line. DESEFIN 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 neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.

Additional information on special populations:

Renal/Hepatic impairment:
In patients with impaired renal function only, there is no need to reduce the dosage of DESEFIN provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance <10 ml/min) should the DESEFIN dosage not exceed to 2 g daily.
In patients with liver damage only there is no need for the dosage of DESEFIN to be reduced provided renal function is intact.

In cases of concomitant severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals and if necessary the dose adjusted.
In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

Pediatric population:
Neonates, infants and children up to 12 years:
The following dosage schedule is administered for once daily.

Neonates (up to 14 days): A daily dose of 20–50 mg/kg body weight, not to exceed 50 mg/kg.
It is not necessary to differentiate between premature and infants born at term.

In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy (see section 4.3 and 4.4).

Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in neonates (≤28 days). DESEFIN should not be used in neonates if they are receiving (or expected to receive) calcium-containing intravenous products (See section 4.3).

Infants and children (15 days to 12 years): A daily dose of 20-80 mg/kg.
For children with bodyweights of 50 kg or more, the usual adult dosage should be used.
For the treatment of uncomplicated acute bacterial otitis media, a single dose of 50 mg/kg (not to exceed 1 g) is recommended (single-shot therapy).

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

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 hypoalbuminemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired*
- if they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt (see sections 4.4, 4.8 and 6.2).

*Full term and premature neonates with hyperbilirubinemia should not be treated with ceftriaxone. *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 information in the Summary of Product Characteristics of lidocaine, especially contraindications.

Ceftriaxone solutions containing lidocaine should never be administered intravenously.

4.4 Special warning 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) have been reported; 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 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).

Pediatric population
Safety and effectiveness of DESEFIN 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. DESEFIN is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy (see section 4.3).

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

If a patient develops anemia while on ceftriaxone, the diagnosis of a cephalosporin-associated anemia should be considered and ceftriaxone discontinued until the etiology is determined.

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

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

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

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

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

Non-enzymatic methods for the glucose determination in urine may give false-positive results. Urine glucose determination during therapy with DESEFIN 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.

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 1 g per day and above. Caution should be particularly considered in the pediatric population. Such precipitates disappear after discontinuation of ceftriaxone therapy. Rarely precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of ceftriaxone treatment should be considered by the physician based on specific benefit risk assessment (see section 4.8).

Biliary stasis
Cases of pancreatitis, possibly of biliary obstruction etiology, have been reported in patients treated with DESEFIN (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 DESEFIN -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.

Each vial of this medicinal product contains 82.95 mg sodium. This should be considered by patients on a controlled sodium diet.

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 DESEFIN 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 Normalized Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment

with ceftriaxone (see section 4.8).

There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. 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 galactosemia.

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.

Ceftriaxone may adversely affect the efficacy of hormonal contraceptives. Consequently, it is advisable to use supplementary and non-hormonal contraceptive measures during treatment and in the month following treatment.

4.6 Fertility, pregnancy and lactation

General advice: Pregnancy category is B.

Women with child-bearing potential/Contraception
Clinical data as to use of DESEFIN in women of child-bearing potential is not available.
However; ceftriaxone may adversely affect the efficacy of hormonal contraceptives. Consequently, it is advisable to use supplementary and non-hormonal contraceptive measures during treatment and in the month following treatment.

Pregnancy
Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/fetal, perinatal and postnatal development (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 diarrhea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitization

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, leucopenia, thrombocytopenia, diarrhea, rash, and increased hepatic enzymes.
Data to determine the frequency of ceftriaxone adverse reactions was derived from clinical trials.

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[a] (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare	Not Known [a]
Infections and infestations		Genital fungal infection	Pseudo-membranous colitis[b]	Superinfection[b]
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anemia Coagulopathy		Hemolytic anemia[b] Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity[b]
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhea[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 generalized exanthematous pustulosis
Renal and urinary disorders			Hematuria Glycosuria	Oliguria Renal precipitation (reversible)

General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Edema Chills	
Investigations		Blood creatinine increased		Coombs test false positive[b] Galactosemia 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 categorized as not known.
[b] See section 4.4

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

Ceftriaxone-calcium salt precipitation
Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged <28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (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 g) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. 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 diarrhea can occur. Ceftriaxone concentrations cannot be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdose should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other beta-lactam antibiotics (Third-generation cephalosporins)
ATC code: J01DD04

Mode of action

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

Resistance

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

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

Susceptibility testing breakpoints

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

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

a) Susceptibility inferred from cefoxitin susceptibility.
b) Susceptibility inferred from penicillin susceptibility.
c) Isolates with a ceftriaxone MIC above the susceptible breakpoint are rare and, if found, should be re-tested and, if confirmed, should be sent to a reference laboratory.
d) Breakpoints apply to a daily intravenous dose of 1×1 g and a high dose of at least 1×2 g.

Clinical efficacy against specific pathogens

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of ceftriaxone in at least some types of infections is questionable.

Commonly susceptible species

Gram-positive aerobes *Staphylococcus aureus* (methicillin-susceptible)[£] Staphylococci coagulase-negative (methicillin-susceptible)[£] *Streptococcus pyogenes* (Group A) *Streptococcus agalactiae* (Group B) *Streptococcus pneumoniae* Viridans Group *Streptococci* Gram-negative aerobes *Borrelia burgdorferi* *Haemophilus influenzae* *Haemophilus parainfluenzae* *Moraxella catarrhalis* *Neisseria gonorrhoea* *Neisseria meningitidis* *Proteus mirabilis* *Providencia* spp *Treponema pallidum*
Species for which acquired resistance may be a problem
Gram-positive aerobes *Staphylococcus epidermidis*[+] *Staphylococcus haemolyticus*[+] *Staphylococcus hominis*[+] Gram-negative aerobes *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli*[%] *Klebsiella pneumoniae*[%] *Klebsiella oxytoca*[%] *Morganella morganii* *Proteus vulgaris* *Serratia marcescens* Anaerobes *Bacteroides* spp. *Fusobacterium* spp. *Peptostreptococcus* spp. *Clostridium perfringens*
Inherently resistant organisms
Gram-positive aerobes *Enterococcus* spp. *Listeria monocytogenes* Gram-negative aerobes *Acinetobacter baumannii* *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia* Anaerobes *Clostridium difficile* Others: *Chlamydia* spp. *Chlamydophila* spp. *Mycoplasma* spp. *Legionella* spp. *Ureaplasma urealyticum*

£ All methicillin-resistant staphylococci are resistant to ceftriaxone.

[+] Resistance rates >50% in at least one region
[%] ESBL producing strains are always resistant

5.2 Pharmacokinetic properties

General specifications

Absorption

Intramuscular administration

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

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

Intravenous administration

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

Distribution

The volume of distribution of ceftriaxone is 7-12 l. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An 8 - 15 % increase in mean peak plasma concentration (C_{max}) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in 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 metabolized 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.

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.

Characteristics in patients

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

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

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

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.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None.

6.2 Incompatibilities
Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole and aminoglycosides 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 bottles or to further dilute a reconstituted vial or bottle for intravenous administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition (see section 4.2, 4.3, 4.4 and 4.8).

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store at room temperature below 25°C protected from light.
It should be used immediately after dilution.

6.5 Nature and contents of container
15 ml colorless glass (Type III) vial with rubber stopper and aluminum safety ring and a colorless glass (Type I) ampoule with ring containing 10 ml of water for injection.
Each carton box contains 1 vial and 1 ampoule of solvent.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

Preparation of solutions for injection and infusion
As a general rule, the solutions should be used immediately after preparation.

IV Administration
IV injection: For IV injection, 0.5 g DESEFIN should be dissolved in 5 ml and 1 g DESEFIN should be dissolved in 10 ml of water for injection. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.

IV infusion: For intravenous infusion, 2 g of DESEFIN is dissolved in 40 ml of one of the following calcium-free infusion fluids: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxyethyl-starch 6 – 10%, water for injections. The infusion should be administered over at least 30 minutes. (See section 6.2.)

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

Concentration for intravenous injection: 100 mg/ml
Concentration for intravenous infusion: 50 mg/ml
(See section 4.2 for further information)

7. MARKETING AUTHORIZATION HOLDER

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