SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mesporin 250 mg Powder and solvent for solution for IV injection
250 mg/5 ml powder and solvent for solution for injection

Mesporin 500 mg Powder and solvent for solution for IV injection
500 mg/5 ml powder and solvent for solution for injection

Mesporin 1000 mg Powder and solvent for solution for IV injection
1000 mg/10 ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is ceftriaxone as the sodium salt.

Mesporin 250 mg Powder and solvent for solution for IV injection
Each vial contains 250 mg of ceftriaxone.

Mesporin 500 mg Powder and solvent for solution for IV injection
Each vial contains 500 mg of ceftriaxone.

Mesporin 1000 mg Powder and solvent for solution for IV injection
Each vial contains 1000 mg of ceftriaxone.

Excipient with known effect:

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

250 mg, 500 mg, 1 g powder and solvent for solution for injection.
Powder and solvent for solution for injection.
White or off-white crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Bacterial meningitis
Community-acquired pneumonia
Hospital-acquired pneumonia

Acute otitis media
Intra-abdominal infections
Complicated urinary tract infections (including pyelonephritis)
Bone and joint infections
Complicated skin and soft tissue infections
Gonorrhoea
Syphilis
Bacterial endocarditis

Mesporin may be used:
For treatment of acute exacerbation of chronic obstructive pulmonary disease in adults
For treatment of disseminated Lyme disease (early [stage II] and late [stage III]) in adults and children, including neonates from 15 days of age
For preoperative prophylaxis of surgical site infections
In the management of neutropenic patients with fever that is suspected to be due to a bacterial infection
In the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

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

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

4.2 Posology and method of administration

Posology

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

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

Adults and children aged over 12 years of age (≥ 50 kg)

Ceftriaxone dosage*	**Treatment frequency****	**Indications**
1-2 g	Once daily	Community-acquired pneumonia
		Acute exacerbation of chronic obstructive pulmonary disease
		Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
2 g	Once daily	Nosocomial (hospital-acquired) pneumonia
		Complicated skin and soft tissue infections
		Bone and joint infections

2-4 g	Once daily	Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
		Bacterial endocarditis
		Bacterial meningitis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.
** Twice daily administration (12 hourly) may be considered when doses greater than 2 g daily are administered.

Indications for adults and children over 12 years of age *(≥ 50 kg)* requiring specific dosage schedules:

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

Preoperative prophylaxis of surgical site infections
2 g as a single preoperative dose.

Gonorrhoea
500 mg as a single intramuscular dose.

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

Disseminated Lyme disease (early [stage II] and late [stage III])
2 g once daily for 14 – 21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Paediatric population
Neonates, infants and children from 15 days to 12 years of age (< 50 kg)
For children with a body weight of 50 kg or more, the usual adult dosage should be given.

Ceftriaxone dosage*	**Treatment frequency****	**Indications**
50-80 mg/kg	Once daily	Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
50-80 mg/kg	Once daily	Community-acquired pneumonia
		Hospital-acquired pneumonia
50-100 mg/kg (max. 4 g)	Once daily	Complicated skin and soft tissue infections
		Bone and joint infections
		Management of neutropenic patients with fever that is suspected to be due to a bacterial infection

80-100 mg/kg (max. 4 g)	Once daily	Bacterial meningitis
100 mg/kg (max. 4 g)	Once daily	Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.
** Twice daily administration (12 hourly) may be considered when doses greater than 2 g daily are administered.

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

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

Preoperative prophylaxis of surgical site infections
50-80 mg/kg as a single preoperative dose.

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

Disseminated Lyme disease (early [stage II] and late [stage III])
50-80 mg/kg once daily for 14 – 21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Neonates from 0 to 14 days of age
Mesporin is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

Ceftriaxone dosage*	**Frequency of treatment**	**Indications**
20-50 mg/kg	Once daily	Intra-abdominal infections
		Complicated skin and soft tissue infections
		Complicated urinary tract infections (including pyelonephritis)
		Community-acquired pneumonia
		Hospital-acquired pneumonia
		Bone and joint infections
		Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
50 mg/kg	Once daily	Bacterial meningitis
		Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.
A maximum daily dose of 50 mg/kg should not be exceeded.

Indications for neonates from 0 to 14 days of age requiring specific dosage schedules:

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

Preoperative prophylaxis of surgical site infections
20-50 mg/kg as a single preoperative dose.

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

Duration of therapy

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

Elderly subjects

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

Patients with liver disease

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

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

Patients with renal impairment

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided hepatic function is not impaired. Only in cases of preterminal renal impairment (creatinine clearance < 10 ml/min) should the ceftriaxone dosage not exceed 2 g daily.
In patients undergoing dialysis, no additional dose is required following dialysis. Ceftriaxone is not removed by peritoneal dialysis or haemodialysis. Close clinical monitoring of safety and efficacy is advised.

Patients with severe hepatic impairment and renal disease
In patients with severe hepatic impairment and renal disease, close clinical monitoring of safety and efficacy is advised.

Method of administration

Mesporin can be administered by intravenous infusion over at least 30 minutes (preferred route of administration) or by slow intravenous injection over 5 minutes, or by deep intramuscular injection. The intermittent intravenous injection should be given over 5 minutes, preferably in larger-calibre veins. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses should be given over a period of more than 60 minutes to reduce the potential risk of bilirubin encephalopathy (see section 4.3 and 4.4). Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 1 g should be injected at one site. Intramuscular injection should be considered when the intravenous route is not possible or is less appropriate for the patient. For doses greater than 2 g intravenous administration should be used.

If lidocaine is used as a solvent, the final reconstituted solution should never be administered intravenously (see section 4.3). The information in the Summary of Product Characteristics of lidocaine should be considered.

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

Calcium-containing solvents (e.g. Ringer's solution or Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone-calcium precipitation can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Therefore, ceftriaxone and calcium-containing solutions may not be mixed or administered simultaneously (see sections 4.3, 4.4 and 6.2).

For preoperative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes before surgery.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to ceftriaxone, to any other cephalosporin or to any of the excipients listed in section 6.1.
Known history of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibiotics (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 hyperbilirubinaemia, jaundice, hypoalbuminaemia or acidosis 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 plasma protein 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 warnings and precautions for use

Hypersensitivity reactions

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

Serious 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).

Interactions 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 precipitation in patients, other than neonates, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. *In vitro* studies have shown that neonates have an increased risk of precipitation of ceftriaxone-calcium compared with other age groups.

In patients of any age, ceftriaxone may 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, ceftriaxone and calcium-containing solutions may be administered sequentially, one after another, if infusion lines are used at different sites or if the infusion lines are replaced or carefully flushed with normal saline solution between infusions to prevent precipitation. In patients requiring continuous infusion of calcium-containing total parenteral nutrition (TPN) solutions, healthcare professionals may consider the use of alternative antibacterial treatments that do not have a similar risk of precipitation. If the use of ceftriaxone is considered necessary in patients requiring continuous nutrition, the TPN and ceftriaxone solutions may be administered simultaneously, although via different infusion lines and at different sites. Alternatively, infusion of the TPN solution can be stopped for the period of

ceftriaxone infusion and the infusion lines flushed carefully between solutions (see sections 4.3, 4.8, 5.2 and 6.2).

Paediatric population

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

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

Immune-mediated haemolytic anaemia

Immune-mediated haemolytic anaemia has been observed in patients treated with cephalosporin-class antibiotics, including Mesporin (see section 4.8). Serious cases of haemolytic anaemia, including fatalities, have been reported during treatment with Mesporin in adults and children.

If a patient develops anaemia during treatment with ceftriaxone, the diagnosis of cephalosporin-induced anaemia should be considered and ceftriaxone should be discontinued until the aetiology is determined.

Long-term treatment

During prolonged treatment, full blood counts should be carried out at regular intervals.

Colitis/Overgrowth of non-susceptible micro-organisms

Antibiotic-associated colitis and pseudomembranous 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 have diarrhoea during or subsequent to 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 impairment

In severe renal and hepatic impairment, close clinical monitoring of safety and efficacy is advised (see section 4.2).

Interference with serological testing

Interference with the Coombs test may occur as Mesporin mad lead to false-positive test results. Mesporin can lead to false-positive results in the galactosaemia test (see section 4.8).

Non-enzymatic methods for urinary glucose determination may give false-positive results. During treatment with Mesporin, glucose determination should be performed enzymatically (see section 4.8).

Sodium

Each gram of Mesporin contains 3.6 mmol of sodium. To be taken into consideration by 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

If a lidocaine solution is used as the solvent, ceftriaxone solutions should be used for intramuscular injection only. Contraindications to lidocaine, precautions 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

If abdominal ultrasound scans reveal signs of biliary lithiasis, the possibility of calcium-ceftriaxone precipitates should be considered. Shadows that have been mistaken for gallstones have been detected on ultrasound scans of the gallbladder, most frequently at daily ceftriaxone doses of 1 g or above. Special care should be taken in the paediatric population. Such precipitates disappear after discontinuation of ceftriaxone treatment. Rarely, calcium-ceftriaxone precipitates have been associated with symptoms. In symptomatic cases, conservative non-surgical management is recommended and discontinuation of treatment with ceftriaxone should be considered by the physician based on a specific risk-benefit assessment (see section 4.8).

Biliary stasis

Cases of pancreatitis, possibly due to biliary obstruction, have been reported in patients treated with Mesporin (see section 4.8). Most patients presented with risk factors for biliary stasis and biliary sludge, e.g. preceding major treatment, serious illness and total parenteral nutrition. A trigger or cofactor role of biliary precipitation related to Mesporin cannot be ruled out.

Renal lithiasis

There have been reports of cases of renal lithiasis, which is reversible after discontinuation of ceftriaxone (see section 4.8). In symptomatic cases, an ultrasound scan should be performed. Use

in patients with a history of renal lithiasis or with hypercalciuria should be considered by the physician based on a specific risk-benefit assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium-containing solvents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute Mesporin vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone-calcium precipitation can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone should not be administered concomitantly with calcium-containing intravenous solutions, including calcium-containing continuous infusions such as parenteral nutrition, via a Y connector. However, in non-neonatal patients, ceftriaxone and calcium-containing solutions may be administered sequentially if infusion lines are carefully flushed with a compatible liquid between infusions. *In vitro* studies using adult plasma and umbilical cord blood from neonates have shown that neonates have an increased risk of ceftriaxone-calcium precipitation (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 haemorrhage. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the dosage of the anti-vitamin K drug adjusted accordingly 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. Monitoring of aminoglycoside levels (and renal function) in clinical practice is recommended.

In an *in vitro* study, antagonistic effects were observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is not known.

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

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

Ceftriaxone, like other antibiotics, may yield false-positive results in tests for galactosaemia.

Likewise, non-enzymatic methods for urinary glucose determination may yield false-positive results. For this reason, urinary glucose levels should be determined enzymatically during treatment with ceftriaxone.

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 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 be administered during pregnancy, and in particular in the first trimester of pregnancy, only if the benefit outweighs the risk.

Breastfeeding

Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, the risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breastfeeding 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, there may be undesirable effects (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 machines.

4.8 Undesirable effects

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

The data for determining the frequency of ceftriaxone adverse drug reactions were derived from clinical trials.

The following convention has been used for the classification of frequency:
Very common (≥ 1/10)
Common (≥ 100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Rare (≥ 1/10000 to < 1/1000)
Not known (cannot be estimated from the available data)

System organ classes	Common	Uncommon	Rare	Not known[a]
Infections and infestations		Genital fungal infection	Pseudomembranous colitis[b]	Superinfection[b]
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia[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	Diarrhoea[b] Loose stools	Nausea Vomiting		Pancreatitis[b] Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzymes increased			Gallbladder calculi[b] Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson syndrome[b] Toxic epidermal necrolysis[b] Erythema multiforme Acute generalised exanthematous pustulosis
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		False-positive Coombs test[b] False-positive galactosaemia test[b] False-positive non-enzymatic glucose determination methods

[a] Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, a precise estimate of frequency is not possible and this is therefore categorised as not known.
[b] See section 4.4

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

Ceftriaxone-calcium salt precipitation
Serious and in some cases fatal adverse reactions have been reported rarely in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Ceftriaxone-calcium salt precipitates have been observed post-mortem in lungs and kidneys. The increased risk of precipitation in neonates is due to their reduced blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4 and 5.2).

Cases of renal precipitation have been reported, primarily in children older than 3 years of age who were treated with either high daily doses (e.g. ≥ 80 mg/kg/day) or total doses exceeding 10 g and who presented with other risk factors (e.g. fluid restriction or confinement to bed). The risk of precipitate formation is increased in immobilised or dehydrated patients. This event may be symptomatic or asymptomatic, may lead to renal impairment and anuria, and is reversible on discontinuation of treatment with 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. Prospective studies in children revealed a variable incidence of precipitation with intravenous injection, in some studies above 30%. The incidence appears to be lower with slower infusions (20-30 minutes). This effect is generally asymptomatic, but in rare cases precipitation was accompanied by clinical symptoms such as pain, nausea and vomiting. In these cases, symptomatic treatment is recommended. Precipitation is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

To report any side effects:

- ***Saudi Arabia:***

– The National Pharmacovigilance and Drug Safety Centre (NPC)
  - Fax: +966-11-205-7662
  - Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340.
  - Toll free phone: 8002490000
  - E-mail: npc.drug@sfda.gov.sa
  - Website: www.sfda.gov.sa/npc

- ***Other GCC States:***

– Please contact the relevant competent authority.

4.9 Overdose

In the case of overdose, 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. Third-generation cephalosporins, ATC code: J01DD04.

Mechanism of action

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

Mechanism of resistance

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

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

Susceptibility testing breakpoints

The 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 tested afresh and, if confirmed, should be sent to a reference laboratory.
d. Breakpoints apply to a daily intravenous dose of 1 g x 1 and a high dose of at least 2 g x 1.

Clinical efficacy against specific pathogens

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) £ Coagulase-negative *Staphylococci* (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* *Providentia* 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
% Beta-lactamase-producing strains are always resistant

5.2 Pharmacokinetic properties

Absorption

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 mg/l and 200 mg/l, respectively. After intravenous infusion of 500 mg, 1 g and 2 g of ceftriaxone, plasma ceftriaxone levels are approximately 80 mg/l, 150 mg/l and 250 mg/l, respectively. After 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 2-3 hours after administration.
The area under the plasma concentration-time curve after intramuscular administration is equivalent to that obtained after intravenous administration of an equivalent dose.

Distribution

The volume of distribution of ceftriaxone is 7-12 litres. Concentrations well above the minimum inhibitory concentrations of most relevant pathogens are detectable in tissues including the lungs, heart, biliary tract/liver, tonsils, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An increase of 8-15% in the 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 of specific tissues

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

Plasma protein binding

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

Biotransformation

Ceftriaxone is not metabolised systemically; however, it is converted into inactive metabolites by the intestinal 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 impairment or hepatic disease

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone is only minimally altered, with the half-life slightly increased (less than twofold), 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 the plasma free

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

Elderly subjects

In elderly persons over 75 years of age, the mean elimination half-life is normally 2 to 3 times greater than that in 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 elimination and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults.

Linearity/non-linearity

The pharmacokinetics of ceftriaxone is 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 the dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone, but not for free (unbound) ceftriaxone.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic/pharmacodynamic index demonstrating the best correlation with *in vivo* efficacy is the percentage of the dosing interval that the free 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 salts led to the formation of concrements and precipitates in the gallbladder of dogs and monkeys that proved to be reversible.
Animal studies produced no evidence of toxicity to reproduction or of genotoxicity.
Carcinogenicity studies have not been conducted on ceftriaxone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

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

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

6.3 Shelf life

Closed container: 36 months.

After reconstitution: the reconstituted solution remains stable for at least:
- 6 hours - Store at room temperature (15-25 °C) and
- 24 hours - Store in a refrigerator (2ºC – 8ºC).

6.4 Special precautions for storage

Do not store above 30 °C.
Store in the original package in order to protect from moisture and light.

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

6.5 Nature and contents of container

Glass vial containing powder for solution for injection and IV solvent ampoules containing water for injections, packaged in a carton.
Mesporin 250 mg Powder and solvent for solution for IV injection and Mesporin 500 mg Powder and solvent for solution for IV injection.
Each ampoule of IV solvent contains water for injections q.s. 5.0 ml.

Mesporin 1000 mg Powder and solvent for solution for IV injection
Each ampoule of IV solvent contains water for injections q.s. 10.0 ml.

There are packs of 1, 2 and 4 units.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ceftriaxone is usually administered by IV infusion. It can also be administered by rapid injection.

Instructions for use and handling

For intermittent IV infusion, the bottles containing 250 mg, 500 mg or 1000 mg of ceftriaxone must be reconstituted with 2.4, 4.8 and 9.6 ml, respectively, of a compatible IV solution to obtain a solution containing about 100 mg/ml.

The reconstituted solutions of the substance must first be diluted in an appropriate IV solution, generally at a concentration of 10-40 mg/ml, although lower concentrations can be used.

The injection must not be used in sequence with other plastic containers as it may result in a gas embolism of the residual air from the primary container before the administration of the liquid in the secondary container is complete.

Intermittent IV infusions of ceftriaxone must generally be infused over 15-30 minutes in newborns or children.

Although intermittent IV infusion is recommended, the substance has also been administered by direct intermittent IV injection of an appropriate dose of ceftriaxone directly into the vein over a period of 2-4 minutes.

Please refer to section 4.2 for further information.

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

7. MARKETING AUTHORISATION HOLDER

Acino AG
Am Windfeld 35, D-83714 Miesbach
Germany

8. MARKETING AUTHORISATION NUMBER(S)

MESPORIN 250 mg I.V. : 17-222-05

MESPORIN 500 mg I.V. : 15-222-05

MESPORIN 1000 mg I.V. : 14-222-05

9. DATE OF FIRST AUTHORISATION

2005

10. DATE OF REVISION OF THE TEXT

June 2018