ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, APPLICANTS, MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Applicant	Name	Strength	Pharmaceutical Form	Route of administration
Germany	Sandoz GmbH Biochemiestrasse 10 6250 Kundl, Austria	-	Ceftriaxon Tyrol Pharma 1g Pulver zur Herstellung einer Injektions- oder Infusionslösung	1 g	Powder for solution for injection or infusion	Intramuscular and intravenous use
Germany	Sandoz GmbH Biochemiestrasse 10 6250 Kundl, Austria	-	Ceftriaxon Tyrol Pharma 2g Pulver zur Herstellung einer Infusionslösung	2 g	Powder for solution for infusion	Intravenous use
Finland	-	Sandoz A/S C.F. Tietgens Boulevard 40 5220 Odense SØ, Denmark	Lendacin 1 g injektio-/infuusiokuiva-aine, liuosta varten	1 g	Powder for solution for injection or infusion	Intramuscular and intravenous use
Finland	-	Sandoz A/S C.F. Tietgens Boulevard 40 5220 Odense SØ, Denmark	Lendacin 2 g infuusiokuiva-aine, liuosta varten	2 g	Powder for solution for infusion	Intravenous use
United Kingdom	-	Sandoz Limited Woolmer way Bordon, Hants, GU35 9QE United Kingdom	Ceftriaxone 1g powder for solution for injection/infusion	1 g	Powder for solution for injection or infusion	Intramuscular and intravenous use
United Kingdom	-	Sandoz Limited Woolmer way Bordon, Hants, GU35 9QE United Kingdom	Ceftriaxone 2 g powder for solution for infusion	2 g	Powder for solution for infusion	Intravenous use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CEFTRIAXONE TYROL PHARMA AND ASSOCIATED NAMES (see Annex I)

Ceftriaxone is an antibiotic, a semisynthetic cephalosporin of the third generation. It is bactericidal against a wide range of Gram-positive and Gram-negative bacteria by inhibiting the mucopeptide synthesis in the bacterial cell wall. Its effectiveness in a number of clinically relevant infections has been established during more than ten years of therapeutical use.
Following parenteral administration the substance penetrates into almost all body-tissues, including the cerebro spinal fluid.
Ceftriaxone distributes primarily into extracellular water, shows concentration dependant binding to albumin and in normal adults, has a relatively long biologic half-life (t 1/2) is eliminated equally by glomerular filtration and biliary secretion

The Applicant/MAH was asked to discuss the benefit/risk of the different dosage recommendations for newborns, especially regarding the differentiation of newborns up to 14 days of age and from 15 up to 28 days of age and regarding the use of dose in excess of 50 mg/kg/day. The applicant has presented a number of publications from the literature in order to discuss the rational for deviation from the ICH Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99) and the basis of differentiation of 0-14 and 15-28 days instead of the more general definition of neonates as ‘up to 28 days after birth’, as well as the different dosing regimens used.

Benefit/risk considerations

The majority of the studies used 50 mg/kg/day in neonates in the treatment of infections. Limited data has been presented that shows use of doses in excess of 50mg /kg/din neonates in situation other than meningitis. During the first few weeks of life the ability to clear ceftriaxone changes although the exact time point at which this occurs has not been truly determined.
Despite the limited and somehow old scientific data, intensive search by the applicant did not reveal scientific evidence which makes it necessary to change these dosage recommendations which are authorised since years without safety concerns in several Member States. The WHO recommends even 80 mg/kg/day respectively 2 x 50mg/kg/every 12 hours (max single dose 4g) in meningitis for young infants aged between 7 days and 2 months.
The proposed dosage range from 20-50-80 mg/kg/day allows the continuation of long lasting therapeutic experience supported by the recommendations of learned societies.

Nonetheless it was agreed that ceftriaxone is contraindicated in hyperbilirubinaemic newborn and preterm newborn because in vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients. In addition further to some reports of fatal evolution, it was agreed to contraindicate ceftriaxone in newborn requiring concomitant calcium treatment because of rarely severe adverse reactions reported in preterm and full-term newborns, some of them being fatal. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone – calcium salt have been observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation is due to the low blood volume of the newborns. Moreover half life is longer than in adults.
Therefore taking into the consideration the long clinical experience in terms of efficacy and safety with the proposed posology further clinical trials was considered unnecessary.

The CHMP therefore agreed to recommend the following dosage recommendation:

Normal dosage
The usual dose is 1-2 g of ceftriaxone, administered once a day (every 24 hours). In cases of serious infections or infections caused by moderately sensitive micro-organisms the dose can be raised up to 4 g, administered once a day intravenously.

Newborn infants (age 0 – 14 days):
20 – 50 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 50 mg per kg bodyweight must not be exceeded.

Children 15 days-12 years of age with a body weight of < 50 kg:
20-80 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 80 mg per kg bodyweight must not be exceeded**, except in meningitis (refer to: Special dosage recommendations)**.

Children with a bodyweight of 50 kg or more receive the usual adult dosage once daily (s. above).

Special dosage recommendations
Meningitis:
Treatment is initiated with 100 mg per kg bodyweight once daily – not exceeding 4 g daily. After determining the sensitivity of the pathogen the dose may be reduced accordingly.
In new-born infants 0 – 14 days of age the dose should not exceed 50 mg/kg/24 h.

The CHMP agreed also on the following changes to the SPC:

4.3 Contraindications

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.
Calcium treatment because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

4.4 Special warnings and special precautions for use

Ceftriaxone may precipitate in the gallbladder and **kidneys** then be detectable as shadows on ultrasound (see section 4.8). This can happen in patients of any age, but is more likely in infants and small children who are usually given a larger dose of Ceftriaxone on a body weight basis. In children, doses greater than 80mg/kg body weight should be avoided – **except for meningitis** - because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of Ceftriaxone precipitate in the gallbladder is recommended.
Section 4.8

Rarely severe adverse reactions have been reported in preterm and full-term newborns. These reactions have caused death in some cases. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone – calcium salt have been observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation is due to the low blood volume of the newborns. Moreover half life is longer than in adults.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- The scope of the referral was to discuss the benefit/risk of the different dosage recommendations for newborns, especially regarding the differentiation of newborns up to 14 days of age and from 15 up to 27 days of age and regarding the use of dose in excess of 50 mg/kg/day
- The Summary of Products Characteristic, labelling and package leaflet proposed by the applicant has been assessed based on the documentation submitted and the scientific discussion within the Committee.

the CHMP has recommended by majority the granting of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Ceftriaxone Tyrol Pharma and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and package leaflet is the version that was annexed to the Commission Decision on this Article 29 referral for ceftriaxone containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone Tyrol Pharma and associated names (See Annex I) 1 g powder for solution for injection or infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 g vial contains 1 g ceftriaxone (as hydrated disodium).

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion

Almost white or yellowish, crystalline dry powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftriaxone is indicated for the treatment of the following infections when caused by micro-organisms that are susceptible to ceftriaxone and if parenteral treatment is necessary (see section 5.1):

- sepsis
- bacterial meningitis
- infections of bones or joints
- infections of skin or soft tissues
- pneumonia

Ceftriaxone is indicated for perioperative prophylaxis in patients with a certain risk of severe postoperative infections (see section 4.4). Depending on the mode of surgery and the expected spectrum of pathogens ceftriaxone should be combined with an appropriate antimicrobial agent with additional anaerobic coverage.

Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Route and method of administration

Ceftriaxone Tyrol Pharma and associated names (See Annex I) 1 g powder for solution for injection or infusion may be administered by intravenous bolus injection, by intravenous infusion or by intramuscular injection after reconstitution of the solution according to the directions given below (see section 6.6).

Dosage and mode of administration should be determined by the severity and site of infection, susceptibility of the causative micro-organism and the patient's age and condition.
An intravenous injection should be administered over at least 2 – 4 minutes directly into the vein or via the tubing of an intravenous infusion.

The intramuscular method of administration should only be used in exceptional clinical situations (see section 4.3) and should undergo a risk-benefit assessment.

For intramuscular injection the special advice below and also in section 6.6 must be followed.

For intramuscular administration Ceftriaxone Tyrol Pharma and associated names (See Annex I) 1 g powder for solution for injection dissolved in lidocaine hydrochloride solution is injected deep into the gluteus maximus muscle. Not more than 1 g of ceftriaxone should be injected on either side of the body. The maximum daily dose by intramuscular administration should not exceed 2 g. The summary of product characteristics of lidocaine hydrochloride solution 1% has to be taken into account.

Normal dosage

Adults and adolescents aged over 12 years with a body weight ≥50 kg:

The usual dose is 1 to 2 g of ceftriaxone, administered once a day (every 24 hours). In cases of serious infections or infections caused by moderately sensitive micro-organisms the dose can be raised up to 4 g, administered once a day intravenously.

Newborn infants (age 0 – 14 days):

20 – 50 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 50 mg per kg bodyweight must not be exceeded.

Children 15 days-12 years of age with a body weight of < 50 kg:

20-80 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 80 mg per kg bodyweight must not be exceeded, except in meningitis (see section 4.2.: Special dosage recommendations).

Children with a bodyweight of 50 kg or more receive the usual adult dosage once daily (see above).

Elderly:

For elderly patients the dosage recommendations are the same as for adults - without modification.

Age group	Normal dosage	Frequency
Newborn infants (age 0 – 14 days)	20 – 50 mg/kg maximum: 50 mg/kg	once daily
Children 15 days - 12 years of age < 50 kg	20 - 80 mg/kg maximum: 80 mg/kg	once daily
Adolescents over 12 - 17 years ≥ 50 kg	1 - 2 g maximum: 4 g	once daily
Adults ≥ 17 years	1 - 2 g maximum: 4 g	once daily
Elderly	1 - 2 g maximum: 4 g	once daily

Special dosage recommendations

Meningitis:

Treatment is initiated with 100 mg per kg bodyweight once daily – not exceeding 4 g daily. After determining the sensitivity of the pathogen the dose may be reduced accordingly.
In newborns 0 – 14 days of age the dose should not exceed 50 mg/kg/24 h.

Perioperative prophylaxis:

The normal daily dose of ceftriaxone should be administered 30-90 minutes prior to surgery. One single administration is usually sufficient.

Renal insufficiency:

In patients with impaired renal function, adjustment of the ceftriaxone dose is not necessary if the hepatic function is normal. In renal insufficiency with a reduced creatinine clearance of < 10 ml/min the daily dose of ceftriaxone should not exceed 2 g in adult patients.

Hepatic insufficiency:

The dose does not need to be altered in patients with a liver disease provided that the renal function is normal (see section 4.8).

In simultaneous severe renal and hepatic insufficiency the serum ceftriaxone concentrations should be monitored regularly and the dosage adjusted appropriately for children and adults (see sections 4.4 and 5.2).

Haemodialysis or peritoneal dialysis

As ceftriaxone is dialysable only to a very minor extent there is no need for an additional dose of ceftriaxone after 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.
In patients on continuous ambulatory peritoneal dialysis (CAPD), ceftriaxone may be administered either intravenously or in case of CAPD associated infections may be added directly to the dialysis solution (e.g. 1-2 g ceftriaxone in the first dialysis fluid of the respective day of treatment) (see section 6.6).

Duration of therapy

The normal duration of therapy depends on the characteristics of the infection. Generally the administration of ceftriaxone should be continued for at least 48 to 72 hours beyond the normalisation of body temperature and evidence of bacterial eradication has been obtained. Dosage recommendations for special indications should be taken into account.

4.3 Contraindications

Hypersensitivity to the active substance, to other cephalosporins or to any of the excipients.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products (see section 4.4).

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

Calcium treatment because of the risk of precipitation of ceftriaxone-calcium salt in term newborns.

Intramuscular injection of the medicinal product is contraindicated:
- in infants < 2 years of age
- during pregnancy and lactation.

4.4 Special warnings and precautions for use

In suspected or proven infections with Pseudomonas aeruginosa, high resistance rates (> 60 %) for ceftriaxone in at least some European countries should be taken into consideration (see section 5.1).
In infections caused by Pseudomonas aeruginosa with proven sensitivity to ceftriaxone a combination with amino-glycosides is warranted to avoid secondary resistance.
In infections caused by other bacteria in patients with neutropenic fever interventional treatment with ceftriaxone should be combined with an aminoglycoside.

Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-lactam-medicinal products because patients hypersensitive to these medicines may be hypersensitive to ceftriaxone as well (cross-allergy).

Hypersensitivity reactions against ceftriaxone are more likely in patients with any other type of hypersensitivity reaction or asthma bronchiale.

Injections with ceftriaxone should be used with special caution in patients with allergic diathesis, because hypersensitivity reactions emerge faster and proceed more severely after intravenous injection (see section 4.8).

Hypersensitivity reactions may occur in all degrees of severity up to anaphylactic shock (see section 4.8).

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined in section 4.2.
In case of simultaneous impairment of renal and liver function, serum-level of ceftriaxone should be monitored in regular intervals.

Each administration of antibiotics can lead to multiplication of pathogens resistant to the active substance used. Signs of consecutive secondary infections with such pathogens (including candida and fungi) are to be heeded. Secondary infections are to be treated accordingly (see section 5.1).

Pseudomembranous colitis has been reported with almost all antibiotics, including ceftriaxone. This diagnosis should be considered in patients who develop diarrhoea during or following treatment with ceftriaxone (see. section 4.8).

Monitoring of renal and hepatic function and haematological parameters at regular intervals are indicated during long-term treatment (see section 4.8).

Ceftriaxone may precipitate in the gallbladder and kidneys and then be detectable as shadows on ultrasound (see section 4.8). This can happen in patients of any age, but is more likely in infants and small children who are usually given a larger dose of ceftriaxone on a body weight basis. In children, doses greater than 80mg/kg body weight should be avoided – except for meningitis – because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of Ceftriaxone precipitate in the gallbladder is recommended.

Patients with risk factors for biliary stasis/sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition, have increased risk of pancreatitis (see section 4.8). Trigger role of ceftriaxone-related biliary precipitation cannot be ruled-out.

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the medicinal product to produce a positive Coombs' test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins.

This medicinal product contains 3.6 mmol (or 83 mg) sodium per dose which should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglycosides:

In case of concomitant administration of cephalosporins and aminoglycosides there has been reported an increased risk of oto- and nephrotoxicity. Dose adjustment may be necessary. Furthermore, these medicinal products must be administered separately to avoid physicochemical incompatibility between ceftriaxone and the aminoglycoside.

Bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may antagonise the activity of ceftriaxone, especially in acute infections accompanied by rapid proliferation of micro-organisms. Simultaneous use of ceftriaxone and bacteriostatic antibiotics is, therefore, not recommended.

Ceftriaxone / probenecid:

Contrary to other cephalosporins, probenecid does not impede tubular secretion of ceftriaxone.

Oral contraceptives:

Ceftriaxon may adversely affect the efficacy of hormonal contraceptives Consequently, it is advisable to use supplementary non-hormonal contraceptive measures.

Other:

Laboratory-diagnostic tests
The Coombs test may be false-positive in rare cases during treatment with ceftriaxone (see section 4.4).

Non-enzymatic methods for glucose determinations in urine may yield false-positive results. For this reason, urine glucose determination during therapy with ceftriaxone should be carried out enzymatically.

Ceftriaxone may lead to false-positive results of galactose determination in blood.

4.6 Pregnancy and lactation

There are no data on the use of ceftriaxone in pregnant women. Ceftriaxone crosses the placenta. Animal studies indicate no reproductive toxicity (see section 5.3). As a precautionary measure, ceftriaxone should only be used during pregnancy after benefit/risk assessment by the physician in charge, especially during the first trimester.

Ceftriaxone is excreted in low concentrations in breast milk. Caution should be exercised when prescribing to breast-feeding women. Diarrhoea and fungal infection of the mucous membrane could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

Powder for solution for injection – intramuscular administration:
The use of ceftriaxone and lidocaine is contraindicated during pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Ceftriaxone has no or negligible influence on the ability to drive and use machines. However, undesirable effects such as hypotension or vertigo (see section 4.8) should be taken into account.

4.8 Undesirable effects

Rarely severe adverse reactions have been reported in preterm and full-term newborns. These reactions have caused death in some cases. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone – calcium salt have been observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation is due to the low blood volume of the newborns. Moreover half life is longer than in adults.

The following adverse reactions, that reverse spontaneously or after treatment discontinuation, have been observed in association with ceftriaxone use.

In this section undesirable effects are defined as follows:

very common	*(>1/10)*
common	*(>1/100, <1/10)*
uncommon	*(>1/1000, <1/100)*
rare	*(>1/10 000, <1/1000)*
very rare, including isolated reports	*(<1/10 000)*

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and Infestations
Uncommon:
Mycosis of the genital tract.

Superinfections with non- susceptible micro-organisms.

Blood and lymphatic system disorders
Rare:
Eosinophilia, leucopenia, granulocytopenia.

Very rare including isolated reports:
Agranulocytosis (<500/mm^3), mostly after 10-day treatment and a total dose of 20 g ceftriaxone and more; Coagulation disorders, Thrombocytopenia. Minor prolongation in the prothrombin time has been described.
Anaemia (including haemolytic anaemia)

Immune system disorders
Common:
Allergic skin reactions (e.g. dermatitis, urticaria, exanthema), pruritus, oedematous swelling of skin and joints

Rare:
Severe acute hypersensitivity reactions up to anaphylactic shock.

Lyell syndrome/toxic epidermolysis, Stevens-Johnson syndrome or Erythema multiforme.

Severe acute hypersensitivity reactions and anaphylactic shock require immediate discontinuation of the administration of ceftriaxon and the initiation of appropriate emergency measures.

Nervous system disorders
Uncommon:
Headache, dizziness, vertigo.

Gastrointestinal disorders
Uncommon:
Stomatitis, glossitis, anorexia, nausea, emesis, abdominal pain, loose stool or diarrhoea. These undesirable effects are mostly mild and frequently subside during, otherwise after discontinuation of therapy.

Very rare:
Pseudomembranous enterocolitis (see section 4.4).
If severe, persistent diarrhoea occurs during or after treatment, pseudomembranous colitis which is a serious, even life-threatening complication mostly caused by *clostridium difficile,* should be considered,. Discontinuation of therapy with ceftriaxone depending on the indication should be considered and appropriate treatment measures should be initiated: e.g. intake of specific antibiotics/chemotherapeutics with clinically proven efficacy. Antiperistaltics are contraindicated.

Hepato-bilary disorders
Very common:
Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of children/reversible cholelithiasis in children. This disorder is rare in adults (see below).

Common:
Elevated liver enzymes in serum (AST, ALT, alkaline phosphatase).

Rare:
Pancreatitis (see section 4.4). Increase in liver enzymes.
Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of adults, which disappeared after discontinuation or cessation of therapy with ceftriaxone. These opacities usually occurred only after administration of higher doses than the recommended standard doses. In the rare cases in which the precipitates are accompanied by clinical symptoms such as pain, symptomatic measures are recommended. Discontinuation of treatment should be considered too (see section 4.4).

Renal and urinary disorders
Uncommon:
Oliguria, increase in serum creatinine.

Rare:
Precipitates of ceftriaxone in the kidneys in paediatric patients, mostly in children older than 3 years treated either with high daily doses (e.g. 80 mg/kg BW per day and more) or with total doses above 10 g ceftriaxone and who presented several risk factors (e.g. restricted fluid supply). However, this symptomatology is reversible after discontinuation of ceftriaxone.

General disorders and administration site conditions
Common:
Phlebitis following intravenous administration. This can be minimised by slow injection (over 2-4 minutes).

Pain at the site of injection.

In rapid intravenous injection intolerability reactions in the form of sensation of heat or nausea may occur. This can be avoided by slow injection (2-4 minutes).

Pain and induration of tissue at the site of injection occur after intramuscular injection.

4.9 Overdose

No case of overdose has been reported.

Symptoms of intoxication

Typical signs of overdose can be expected to correspond to the adverse reaction profile.
Colics occurred very rarely in the presence of nephropathy or cholelithiasis when using high doses administered more frequently and more rapidly than recommended.

Therapy of intoxication

Excessive serum concentration of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Symptomatic therapeutic measures are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cephalosporins and related substances, ATC code: J01DD04

Mechanism of action
Ceftriaxone has bactericidal activity that results from the inhibition of bacterial cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of β-lactamases produced by Gram-negative and Gram-positive bacteria.
Synergistic effects of ceftriaxone and aminoglycosides on certain Gram-negative bacteria have been noted in vitro.

Mechanism of resistance
Ceftriaxone is active against organisms producing some types of beta-lactamase, for example TEM-1. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes. Ceftriaxone cannot be expected to be active against the majority of bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam medicinal products. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

Breakpoints
The minimum inhibitory concentration (MIC, according to the German Institute for Standardization DIN 58940) are 4 mg/l, – (sensitive) and 32 mg/l (resistant).

The MIC breakpoints according to the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards are 8 µg/ml (sensitive), 16-32 µg/ml (intermediate) and 64 µg/ml (resistant) for Enterobacteriaceae and Staphylococcus spp..
The respective values for Streptococcus pneumoniae are 0.5 µg/ml (sensitive), 1 µg/ml (intermediate) and 2 µg/ml (resistant).
The breakpoints for sensitivity are 2 µg/ml for Haemophilus spp. and 0.25 µg/ml for Neisseria gonorrhoea.
The respective values for anaerobes are 16 µg/ml (sensitive), 32 µg/ml (intermediate) and 64 µg/ml (resistant).

Microbiology
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 the agent in at least some types of infections is questionable.

Commonly susceptible species

Gram positive aerobes

*Staphylococcus aureus**(MSSA)
Streptococcus agalactiae
Streptococcus bovis
Streptococcus pyogenes[*]
Streptococcus pneumoniae[*]

Gram-positive anaerobes

Peptococcus niger
Peptostreptococcus spp.

Gram-negative aerobes

Citrobacter koseri[1]
Escherichia coli[*1]
Haemophilus influenzae[*]
Haemophilus parainfluenzae[*]
*Klebsiella pneumoniae** [1]
*Klebsiella oxytoca** [1]
*Moraxella catarrhalis**
Morganella morganii[1]
Neisseria meningitidis[*]
Proteus mirabilis[*1]
Proteus vulgaris[1]
Providencia spp.[1]
Salmonella spp.[1]
Serratia spp.[1]
Shigella spp.

Species for which acquired resistance may be a problem

Gram-positive aerobes

*Staphylococcus epidermidis**[$] (MSSE)

Gram-negative aerobes

Citrobacter freundii [1]
Enterobacter spp. [1,3]
Pseudomonas aeruginosa [$ 2]

Inherently resistant species

Gram-positive aerobes

Enterococcus faecalis
Enterococcus faecium
Listeria monocytogenes
Staphylococcus aureus MRSA
Staphylococcus epidermidis MRSE

Gram-positive anaerobes

Clostridium difficile

Gram-negative aerobes

Acinetobacter spp.
Achromobacter spp.
Aeromonas spp.
Alcaligenes spp.
Flavobacterium spp.
Legionella gormanii

Gram-negative anaerobes

Bacteroides spp.

Others

Chlamydia spp.
Chlamydophila spp.
Mycobacterium spp.
Mycoplasma spp.
Rickettsia spp.
Ureaplasma urealyticum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
$ Species with natural intermediate susceptibility

1 Some strains produce inducible or stably derepressed chromosomally-encoded cephalosporinases and ESBLs (extended spectrum beta-lactamases) and thus are clinically resistant to cephalosporins.
2 In suspected or proven *Pseudomonas* infection combination with an aminoglycoside is necessary.
3 Clinical efficacy has been demonstrated for susceptible isolates of *Enterobacter cloacae* and *Enterobacter aerogene*s in approved clinical indications.

5.2 Pharmacokinetic properties

Ceftriaxone is a cephalosporin for parenteral administration. Ceftriaxone is not absorbed after oral application.

After a dose of 1–2 g, concentrations have been shown to remain above the MIC values for most infection-causing pathogens for over 24 hours in over 60 different tissues (including lungs, heart, bile ducts, liver, tonsils, middle ear, nasal mucosa, bones) and in many tissue fluids (including cerebrospinal fluid, pleural fluid as well as prostatic and synovial fluid).

Absorption
Ceftriaxone is completely absorbed following intramuscular administration with peak plasma concentrations (about 80 mg/l) occurring between 2 and 3 hours after dosing.

Distribution
Ceftriaxone distributes well in various compartments and also passes the placental barrier. The mean volume of distribution in healthy adults is 0.13 l/kg.

Ceftriaxone is reversibly bound to albumin. The binding is 95 % at plasma concentrations less than 100 mg/l with the binding percentage decreasing as the concentration increases (to 85 % at ceftriaxone plasma concentrations of 300 µg/ml).

Serum levels
Following an the intravenous infusion of 1 g of ceftriaxone for 30 minutes, serum levels immediately after cessation of the infusion process were at 123.2 µg/ml, and at 94.81, 57.8, 20.2 and 4.6 µg/ml, respectively, 1.5, 4, 12 and 24 hours after the onset of infusion.
Subsequent to an intramuscular injection of 1 g of ceftriaxone the serum concentration amounted to 79.2 µg/ml after 1.5 hours, and afterwards 58.2, 35.5 and 7.8 µg/ml at the respective time-points 4, 12 and 24 hours after injection.

Ceftriaxone penetrates the inflamed meninges of newborn, infants and children. In CSF the peak concentrations of 18 mg/l are achieved, after a 50–100 mg/kg intravenous dose, in about four hours. In adult patients with meningitis, therapeutic concentrations are achieved within 2–24 hours with the dose of 50 mg/kg.

Ceftriaxone crosses the placenta and is excreted in human milk at low concentrations.

Biotransformation
Ceftriaxone does not undergo systemic metabolism but it is broken down in the small intestine by bacterial action.

Elimination
Over a 0.15 to 3 g dose range, the values of elimination half-life range from 6 to 9 hours, total plasma clearance from 0.6–1.4 l/h and renal clearance from 0.3–0.7 l/h.
50–60 % of ceftriaxone is eliminated as an unchanged active substance in the urine whilst the remainder is excreted via the bile into the faeces as microbiologically inactive metabolites.
Ceftriaxone concentrates in the urine. The urine concentrations are 5–10 times higher than those found in the plasma.
Ceftriaxone cannot be removed by dialysis. This applies to both haemodialysis and peritoneal dialysis.

Urinary excretion is via glomerular filtration. No tubular secretion takes place. For this reason, no increase in the serum levels is to be expected in coincident administration of probenecid and is actually - even at higher dosage e.g. with 1-2 g probenecid - not found.

Non-Linearity
The pharmacokinetics of ceftriaxone are non-linear with respect to the dose. This non-linearity is explained by a concentration dependent decrease of binding to plasma proteins which leads to a respective increase in distribution and elimination.
With the exception of elimination half-life, all pharmacokinetic parameters are dose-dependent. Repeat dosing of 0.5 to 2 g results in 15 % –36 % accumulation above single dose values

Special patient groups

Elderly above 75 years:
The plasma elimination half-life of ceftriaxone is about 2 - 3 fold increased compared to young adults.

In newborn infants of 3 days of age, the half-life of ceftriaxone in the serum amounts to approximately 16 hours, and approximately 9 hours in newborn infants aged from 9 to 30 days.

Patients with impaired renal and/or liver function:
Patients with an impaired renal function have an increased excretion of ceftriaxone into the bile. Patients with an impaired liver function have an increased renal excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is almost not increased in these patient groups. Patients with an impaired renal function, as well as an impaired liver function, may have an increased ceftriaxone plasma elimination half-life.
In case of terminal renal insufficiency, the half-life is distinctively higher and reaches approximately 14 hours.

5.3 Preclinical safety data

The adverse reactions (e.g. gastrointestinal disturbances and nephrotoxicity) associated with high parenteral doses of cephalosporins have been shown to be reversible in animals during repeat dosing.
After high doses of ceftriaxone diarrhoea, formation of biliary caliculi in the gallbladder and nephropathy were observed in monkeys and dogs.
Ceftriaxone has no effect on fertility or reproduction. It has not been shown to possess any mutagenic activity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. In particular, ceftriaxone is not compatible with calcium-containing solutions such as Hartmann's solution and Ringer's solution.
Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

6.3 Shelf life

Unopened:
2 years.

Opened & after reconstitution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2^{o}C to 8^{o}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 24 hours at 2 to 8^{o}C, otherwise any unused portion must be discarded.

6.4 Special precautions for storage

Unopened:
Keep the container in the outer carton in order to protect from light.

For storage details of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear type III glass vials (15 ml) closed with halogenated isobutene-isoprene-rubber stoppers and aluminium caps with plastic flip-off lids.

Pack sizes: 1, 5, 10 vials.
Hospital packs: 10, 25, 50 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Instructions for use and handling

Intravenous injection
Ceftriaxone Tyrol Pharma and associated names (See Annex I) 1 g powder for solution for injection or infusion should be dissolved in 10 ml of water for injections (resulting volume 10.8 ml, concentration 93 mg/ml). The injection should be administered over at least 2 – 4 minutes directly into the vein or via the tubing of an intravenous infusion (see section 4.2).

Intravenous infusion
Ceftriaxone Tyrol Pharma and associated names (See Annex I) 1 g powder for solution for injection or infusion should be dissolved in one of the following calcium-free infusion solutions: Sodium chloride 0.9%, sodium chloride 0.45% and glucose 2.5%, glucose 5 % or 10%, dextran 6% in glucose 5%, hydroxyethyl starch 6-10% infusions. See also the information included in section 6.2.
The reconstitution of the ready to use solution for infusion has to take place in two steps in order to allow the reconstitution of the necessary volume of solution for infusion:

1. Ceftriaxone Tyrol Pharma and associated names (See Annex I) 1 g powder for solution for injection or infusion is reconstituted with 10 ml of one of the compatible intravenous fluids in its vial. This solution has to be transferred into a suitable infusion bag. Controlled and validated aseptic conditions have to be observed.
2. This solution should then be diluted with 9 ml more of diluent giving a final volume of 20.5 ml and a concentration of 49 mg/ml.

This volume of 20.5 ml reconstituted solution for infusion should be administered immediately as a short time infusion over 30 minutes.
Smaller amounts for lower doses calculated on an mg/kg bodyweight basis have to be calculated proportionately.

Intramuscular injection
Ceftriaxone Tyrol Pharma and associated names (See Annex I) 1 g powder for solution for injection or infusion should be dissolved in 3.5 ml of 1 % w/v lidocaine hydrochloride injection solution.
The solution (resulting volume 4.2 ml, concentration 238 mg/ml) should be administered by deep intramuscular injection. Dosages greater than 1 g should be divided and injected on more than one site Not more than 1 g of ceftriaxone should be injected on either side of the body (see section 4.2).

Solutions in lidocaine should not be administered intravenously (see section 4.4).

Ceftriaxone should not be mixed in the same syringe with any medicinal product other than 1% w/v lidocaine hydrochloride solution (for intramuscular injection only).

The reconstituted solution should be shaken up to 60 seconds to ensure complete dissolution of ceftriaxone**.**

When reconstituted for intramuscular or intravenous injection, the white to yellowish crystalline powder gives a pale yellow to amber solution.

Reconstituted solutions should be inspected visually. Only clear solutions free of visible particles should be used. The reconstituted product is for single use only and any unused solution must be discarded.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone Tyrol Pharma and associated names (See Annex I) 2 g powder for solution for infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 g infusion bottle contains 2 g ceftriaxone (as hydrated disodium).

3. PHARMACEUTICAL FORM

Powder for solution for infusion

Almost white or yellowish, crystalline dry powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftriaxone is indicated for the treatment of the following infections when caused by micro-organisms that are susceptible to ceftriaxone and if parenteral treatment is necessary (see section 5.1):

- sepsis
- bacterial meningitis
- infections of bones or joints
- infections of skin or soft tissues
- pneumonia

Ceftriaxone is indicated for perioperative prophylaxis in patients with a certain risk of severe postoperative infections (see section 4.4). Depending on the mode of surgery and the expected spectrum of pathogens ceftriaxone should be combined with an appropriate antimicrobial agent with additional anaerobic coverage.

Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Route and method of administration

Ceftriaxone Tyrol Pharma and associated names (See Annex I) 2 g powder for solution for infusion should be administered by intravenous infusion after reconstitution of the solution according to the directions given below (see section 6.6).

Dosage should be determined by the severity and site of infection, susceptibility of the causative micro-organism and the patient’s age and condition.

For other routes of administration other strengths of ceftriaxone are available.

Normal dosage

Adults and adolescents aged over 12 years with a body weight ≥50 kg:

The usual dose is 1 to 2 g of ceftriaxone, administered once a day (every 24 hours). In cases of serious infections or infections caused by moderately sensitive micro-organisms the dose can be raised up to 4 g, administered once a day intravenously.

Newborn infants (age 0 – 14 days):

20 – 50 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 50 mg per kg bodyweight must not be exceeded.

Children 15 days-12 years of age with a body weight of < 50 kg:

20-80 mg per kg bodyweight intravenously once daily (24-hour intervals).
In severe infections the daily dose of 80 mg per kg bodyweight must not be exceeded, except in meningitis (see section 4.2.: Special dosage recommendations).

Children with a bodyweight of 50 kg or more receive the usual adult dosage once daily (see above).

Elderly:

For elderly patients the dosage recommendations are the same as for adults - without modification.

Age group	Normal dosage	Frequency
Newborn infants (age 0 – 14 days)	20 – 50 mg/kg maximum: 50 mg/kg	once daily
Children 15 days - 12 years of age < 50 kg	20 - 80 mg/kg maximum: 80 mg/kg	once daily
Adolescents over 12 - 17 years ≥ 50 kg	1 - 2 g maximum: 4 g	once daily
Adults ≥ 17 years	1 - 2 g maximum: 4 g	once daily
Elderly	1 - 2 g maximum: 4 g	once daily

Special dosage recommendations

Meningitis:

Treatment is initiated with 100 mg per kg bodyweight once daily – not exceeding 4 g daily. After determining the sensitivity of the pathogen the dose may be reduced accordingly.
In newborns 0 – 14 days of age the dose should not exceed 50 mg/kg/24 h.

Perioperative prophylaxis:

The normal daily dose of ceftriaxone should be administered 30-90 minutes prior to surgery. One single administration is usually sufficient.

Renal insufficiency:

In patients with impaired renal function, adjustment of the ceftriaxone dose is not necessary if the hepatic function is normal. In renal insufficiency with a reduced creatinine clearance of < 10 ml/min the daily dose of ceftriaxone should not exceed 2 g in adult patients.

Hepatic insufficiency:

The dose does not need to be altered in patients with a liver disease provided that the renal function is normal (see section 4.8).

In simultaneous severe renal and hepatic insufficiency the serum ceftriaxone concentrations should be monitored regularly and the dosage adjusted appropriately for children and adults (see sections 4.4 and 5.2).

Haemodialysis or peritoneal dialysis

As ceftriaxone is dialysable only to a very minor extent there is no need for an additional dose of ceftriaxone after 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.
In patients on continuous ambulatory peritoneal dialysis (CAPD), ceftriaxone may be administered either intravenously or in case of CAPD associated infections may be added directly to the dialysis solution (e.g. 1-2 g ceftriaxone in the first dialysis fluid of the respective day of treatment) (see section 6.6).

Duration of therapy

The normal duration of therapy depends on the characteristics of the infection. Generally the administration of ceftriaxone should be continued for at least 48 to 72 hours beyond the normalisation of body temperature and evidence of bacterial eradication has been obtained. Dosage recommendations for special indications should be taken into account.

4.3 Contraindications

Hypersensitivity to the active substance, to other cephalosporins or to any of the excipients.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products (see section 4.4).

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

Calcium treatment because of the risk of precipitation of ceftriaxone-calcium salt in term newborns.

4.4 Special warnings and precautions for use

In suspected or proven infections with Pseudomonas aeruginosa, high resistance rates (> 60 %) for ceftriaxone in at least some European countries should be taken into consideration (see section 5.1).
In infections caused by Pseudomonas aeruginosa with proven sensitivity to ceftriaxone a combination with amino-glycosides is warranted to avoid secondary resistance.
In infections caused by other bacteria in patients with neutropenic fever interventional treatment with ceftriaxone should be combined with an aminoglycoside.

Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-lactam-medicinal products because patients hypersensitive to these medicines may be hypersensitive to ceftriaxone as well (cross-allergy).

Hypersensitivity reactions against ceftriaxone are more likely in patients with any other type of hypersensitivity reaction or asthma bronchiale.

Infusions with ceftriaxone should be used with special caution in patients with allergic diathesis, because hypersensitivity reactions emerge faster and proceed more severely after intravenous infusion (see section 4.8).

Hypersensitivity reactions may occur in all degrees of severity up to anaphylactic shock (see section 4.8).

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined in section 4.2.
In case of simultaneous impairment of renal and liver function, serum-level of ceftriaxone should be monitored in regular intervals.

Each administration of antibiotics can lead to multiplication of pathogens resistant to the active substance used. Signs of consecutive secondary infections with such pathogens (including candida and fungi) are to be heeded. Secondary infections are to be treated accordingly (see section 5.1).

Pseudomembranous colitis has been reported with almost all antibiotics, including ceftriaxone. This diagnosis should be considered in patients who develop diarrhoea during or following treatment with ceftriaxone (see. section 4.8).

Monitoring of renal and hepatic function and haematological parameters at regular intervals are indicated during long-term treatment (see section 4.8).

Ceftriaxone may precipitate in the gallbladder and kidneys and then be detectable as shadows on ultrasound (see section 4.8). This can happen in patients of any age, but is more likely in infants and small children who are usually given a larger dose of ceftriaxone on a body weight basis. In children, doses greater than 80mg/kg body weight should be avoided – except for meningitis – because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of Ceftriaxone precipitate in the gallbladder is recommended.

Patients with risk factors for biliary stasis/sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition, have increased risk of pancreatitis (see section 4.8). Trigger role of ceftriaxone-related biliary precipitation cannot be ruled-out.

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the medicinal product to produce a positive Coombs' test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins.

This medicinal product contains 7.2 mmol (or 166 mg) sodium per dose which should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglycosides:

In case of concomitant administration of cephalosporins and aminoglycosides there has been reported an increased risk of oto- and nephrotoxicity. Dose adjustment may be necessary. Furthermore, these medicinal products must be administered separately to avoid physicochemical incompatibility between ceftriaxone and the aminoglycoside.

Bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may antagonise the activity of ceftriaxone, especially in acute infections accompanied by rapid proliferation of micro-organisms. Simultaneous use of ceftriaxone and bacteriostatic antibiotics is, therefore, not recommended.

Ceftriaxone / probenecid:

Contrary to other cephalosporins, probenecid does not impede tubular secretion of ceftriaxone.

Oral contraceptives:

Ceftriaxon may adversely affect the efficacy of hormonal contraceptives Consequently, it is advisable to use supplementary non-hormonal contraceptive measures.

Other:

Laboratory-diagnostic tests
The Coombs test may be false-positive in rare cases during treatment with ceftriaxone (see section 4.4).

Non-enzymatic methods for glucose determinations in urine may yield false-positive results. For this reason, urine glucose determination during therapy with ceftriaxone should be carried out enzymatically.

Ceftriaxone may lead to false-positive results of galactose determination in blood.

4.6 Pregnancy and lactation

There are no data on the use of ceftriaxone in pregnant women. Ceftriaxone crosses the placenta. Animal studies indicate no reproductive toxicity (see section 5.3). As a precautionary measure, ceftriaxone should only be used during pregnancy after benefit/risk assessment by the physician in charge, especially during the first trimester.

Ceftriaxone is excreted in low concentrations in breast milk. Caution should be exercised when prescribing to breast-feeding women. Diarrhoea and fungal infection of the mucous membrane could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

Powder for solution for injection – intramuscular administration:
The use of ceftriaxone and lidocaine is contraindicated during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Ceftriaxone has no or negligible influence on the ability to drive and use machines. However, undesirable effects such as hypotension or vertigo (see section 4.8) should be taken into account.

4.8 Undesirable effects

Rarely severe adverse reactions have been reported in preterm and full-term newborns. These reactions have caused death in some cases. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone – calcium salt have been observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation is due to the low blood volume of the newborns. Moreover half life is longer than in adults.

The following adverse reactions, that reverse spontaneously or after treatment discontinuation, have been observed in association with ceftriaxone use.

In this section undesirable effects are defined as follows:

very common	*(>1/10)*
common	*(>1/100, <1/10)*
uncommon	*(>1/1000, <1/100)*
rare	*(>1/10 000, <1/1000)*
very rare, including isolated reports	*(<1/10 000)*

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and Infestations
Uncommon:
Mycosis of the genital tract.

Superinfections with non- susceptible micro-organisms.

Blood and lymphatic system disorders
Rare:
Eosinophilia, leucopenia, granulocytopenia.

Very rare including isolated reports:
Agranulocytosis (<500/mm^3), mostly after 10-day treatment and a total dose of 20 g ceftriaxone and more; Coagulation disorders, Thrombocytopenia. Minor prolongation in the prothrombin time has been described.
Anaemia (including haemolytic anaemia)

Immune system disorders
Common:
Allergic skin reactions (e.g. dermatitis, urticaria, exanthema), pruritus, oedematous swelling of skin and joints

Rare:
Severe acute hypersensitivity reactions up to anaphylactic shock.

Lyell syndrome/toxic epidermolysis, Stevens-Johnson syndrome or Erythema multiforme.

Severe acute hypersensitivity reactions and anaphylactic shock require immediate discontinuation of the administration of ceftriaxon and the initiation of appropriate emergency measures.

Nervous system disorders
Uncommon:
Headache, dizziness, vertigo.

Gastrointestinal disorders
Uncommon:
Stomatitis, glossitis, anorexia, nausea, emesis, abdominal pain, loose stool or diarrhoea. These undesirable effects are mostly mild and frequently subside during, otherwise after discontinuation of therapy.

Very rare:
Pseudomembranous enterocolitis (see section 4.4).
If severe, persistent diarrhoea occurs during or after treatment, pseudomembranous colitis which is a serious, even life-threatening complication mostly caused by *clostridium difficile*, should be considered,. Discontinuation of therapy with ceftriaxone depending on the indication should be considered and appropriate treatment measures should be initiated: e.g. intake of specific antibiotics/chemotherapeutics with clinically proven efficacy. Antiperistaltics are contraindicated.

Hepato-bilary disorders
Very common:
Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of children/reversible cholelithiasis in children. This disorder is rare in adults (see below).

Common:
Elevated liver enzymes in serum (AST, ALT, alkaline phosphatase).

Rare:
Pancreatitis (see section 4.4). Increase in liver enzymes.
Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of adults, which disappeared after discontinuation or cessation of therapy with ceftriaxone. These opacities usually occurred only after administration of higher doses than the recommended standard doses. In the rare cases in which the precipitates are accompanied by clinical symptoms such as pain, symptomatic measures are recommended. Discontinuation of treatment should be considered too (see section 4.4).

Renal and urinary disorders
Uncommon:
Oliguria, increase in serum creatinine.

Rare:
Precipitates of ceftriaxone in the kidneys in paediatric patients, mostly in children older than 3 years treated either with high daily doses (e.g. 80 mg/kg BW per day and more) or with total doses above 10 g ceftriaxone and who presented several risk factors (e.g. restricted fluid supply). However, this symptomatology is reversible after discontinuation of ceftriaxone.

General disorders and administration site conditions
Common:
Phlebitis following intravenous administration. This can be minimised by slow injection (over 2-4 minutes).

Pain at the site of infusion.

In rapid intravenous injection intolerability reactions in the form of sensation of heat or nausea may occur. This can be avoided by slow injection (2-4 minutes).

Pain and induration of tissue at the site of injection occur after intramuscular injection.

4.9 Overdose

No case of overdose has been reported.

Symptoms of intoxication

Typical signs of overdose can be expected to correspond to the adverse reaction profile.
Colics occurred very rarely in the presence of nephropathy or cholelithiasis when using high doses administered more frequently and more rapidly than recommended.

Therapy of intoxication

Excessive serum concentration of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Symptomatic therapeutic measures are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cephalosporins and related substances, ATC code: J01DD04

Mechanism of action
Ceftriaxone has bactericidal activity that results from the inhibition of bacterial cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of β-lactamases produced by Gram-negative and Gram-positive bacteria.
Synergistic effects of ceftriaxone and aminoglycosides on certain Gram-negative bacteria have been noted in vitro.

Mechanism of resistance
Ceftriaxone is active against organisms producing some types of beta-lactamase, for example TEM-1. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes. Ceftriaxone cannot be expected to be active against the majority of bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam medicinal products. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

Breakpoints
The minimum inhibitory concentration (MIC, according to the German Institute for Standardization DIN 58940) are 4 mg/l, – (sensitive) and 32 mg/l (resistant).

The MIC breakpoints according to the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards are 8 µg/ml (sensitive), 16-32 µg/ml (intermediate) and 64 µg/ml (resistant) for Enterobacteriaceae and Staphylococcus spp..
The respective values for Streptococcus pneumoniae are 0.5 µg/ml (sensitive), 1 µg/ml (intermediate) and 2 µg/ml (resistant).
The breakpoints for sensitivity are 2 µg/ml for Haemophilus spp. and 0.25 µg/ml for Neisseria gonorrhoea.
The respective values for anaerobes are 16 µg/ml (sensitive), 32 µg/ml (intermediate) and 64 µg/ml (resistant).

Microbiology
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 the agent in at least some types of infections is questionable.

Commonly susceptible species
Gram positive aerobes
*Staphylococcus aureus**(MSSA)
Streptococcus agalactiae
Streptococcus bovis
Streptococcus pyogenes[*]

Streptococcus pneumoniae[*]

Gram-positive anaerobes

Peptococcus niger
Peptostreptococcus spp.

Gram-negative aerobes

Citrobacter koseri[2]
Escherichia coli[*1]
Haemophilus influenzae[*]
Haemophilus parainfluenzae[*]
*Klebsiella pneumoniae** [1]
*Klebsiella oxytoca** [1]
*Moraxella catarrhalis**
Morganella morganii[1]
Neisseria meningitidis[*]
Proteus mirabilis[*1]
Proteus vulgaris[1]
Providencia spp.[1]
Salmonella spp.[1]
Serratia spp.[1]
Shigella spp.

<u>Species for which acquired resistance may be a problem</u>

Gram-positive aerobes

*Staphylococcus epidermidis**[$] (MSSE)

Gram-negative aerobes

Citrobacter freundii [1]
Enterobacter spp. [1,3]
Pseudomonas aeruginosa [$ 2]

<u>Inherently resistant species</u>

Gram-positive aerobes

Enterococcus faecalis
Enterococcus faecium
Listeria monocytogenes
Staphylococcus aureus MRSA
Staphylococcus epidermidis MRSE

Gram-positive anaerobes

Clostridium difficile

Gram-negative aerobes

Acinetobacter spp.
Achromobacter spp.
Aeromonas spp.
Alcaligenes spp.
Flavobacterium spp.
Legionella gormanii

Gram-negative anaerobes

Bacteroides spp.

Others

Chlamydia spp.
Chlamydophila spp.
Mycobacterium spp.
Mycoplasma spp.
Rickettsia spp.
Ureaplasma urealyticum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
$ Species with natural intermediate susceptibility

1 Some strains produce inducible or stably derepressed chromosomally-encoded cephalosporinases and ESBLs (extended spectrum beta-lactamases) and thus are clinically resistant to cephalosporins.
2 In suspected or proven *Pseudomonas* infection combination with an aminoglycoside is necessary.
3 Clinical efficacy has been demonstrated for susceptible isolates of *Enterobacter cloacae* and *Enterobacter aerogene*s in approved clinical indications.

5.2 Pharmacokinetic properties

Ceftriaxone is a cephalosporin for parenteral administration. Ceftriaxone is not absorbed after oral application.

After a dose of 1–2 g, concentrations have been shown to remain above the MIC values for most infection-causing pathogens for over 24 hours in over 60 different tissues (including lungs, heart, bile ducts, liver, tonsils, middle ear, nasal mucosa, bones) and in many tissue fluids (including cerebrospinal fluid, pleural fluid as well as prostatic and synovial fluid).

Absorption
Ceftriaxone is completely absorbed following intramuscular administration with peak plasma concentrations (about 80 mg/l) occurring between 2 and 3 hours after dosing.

Distribution
Ceftriaxone distributes well in various compartments and also passes the placental barrier. The mean volume of distribution in healthy adults is 0.13 l/kg.

Ceftriaxone is reversibly bound to albumin. The binding is 95 % at plasma concentrations less than 100 mg/l with the binding percentage decreasing as the concentration increases (to 85 % at ceftriaxone plasma concentrations of 300 µg/ml).

Serum levels
Following an the intravenous infusion of 1 g of ceftriaxone for 30 minutes, serum levels immediately after cessation of the infusion process were at 123.2 µg/ml, and at 94.81, 57.8, 20.2 and 4.6 µg/ml, respectively, 1.5, 4, 12 and 24 hours after the onset of infusion.
Subsequent to an intramuscular injection of 1 g of ceftriaxone the serum concentration amounted to 79.2 µg/ml after 1.5 hours, and afterwards 58.2, 35.5 and 7.8 µg/ml at the respective time-points 4, 12 and 24 hours after injection.

Ceftriaxone penetrates the inflamed meninges of newborn, infants and children. In CSF the peak concentrations of 18 mg/l are achieved, after a 50–100 mg/kg intravenous dose, in about four hours. In adult patients with meningitis, therapeutic concentrations are achieved within 2–24 hours with the dose of 50 mg/kg.

Ceftriaxone crosses the placenta and is excreted in human milk at low concentrations.

Biotransformation
Ceftriaxone does not undergo systemic metabolism but it is broken down in the small intestine by bacterial action.

Elimination
Over a 0.15 to 3 g dose range, the values of elimination half-life range from 6 to 9 hours, total plasma clearance from 0.6–1.4 l/h and renal clearance from 0.3–0.7 l/h.
50–60 % of ceftriaxone is eliminated as an unchanged active substance in the urine whilst the remainder is excreted via the bile into the faeces as microbiologically inactive metabolites.
Ceftriaxone concentrates in the urine. The urine concentrations are 5–10 times higher than those found in the plasma.
Ceftriaxone cannot be removed by dialysis. This applies to both haemodialysis and peritoneal dialysis.

Urinary excretion is via glomerular filtration. No tubular secretion takes place. For this reason, no increase in the serum levels is to be expected in coincident administration of probenecid and is actually - even at higher dosage e.g. with 1-2 g probenecid - not found.

Non-Linearity
The pharmacokinetics of ceftriaxone are non-linear with respect to the dose. This non-linearity is explained by a concentration dependent decrease of binding to plasma proteins which leads to a respective increase in distribution and elimination.
With the exception of elimination half-life, all pharmacokinetic parameters are dose-dependent. Repeat dosing of 0.5 to 2 g results in 15 % –36 % accumulation above single dose values

Special patient groups

Elderly above 75 years:
The plasma elimination half-life of ceftriaxone is about 2 - 3 fold increased compared to young adults.

In newborn infants of 3 days of age, the half-life of ceftriaxone in the serum amounts to approximately 16 hours, and approximately 9 hours in newborn infants aged from 9 to 30 days.

Patients with impaired renal and/or liver function:
Patients with an impaired renal function have an increased excretion of ceftriaxone into the bile. Patients with an impaired liver function have an increased renal excretion of ceftriaxone. The plasma elimination half-life of ceftriaxone is almost not increased in these patient groups. Patients with an impaired renal function, as well as an impaired liver function, may have an increased ceftriaxone plasma elimination half-life.
In case of terminal renal insufficiency, the half-life is distinctively higher and reaches approximately 14 hours.

5.3 Preclinical safety data

The adverse reactions (e.g. gastrointestinal disturbances and nephrotoxicity) associated with high parenteral doses of cephalosporins have been shown to be reversible in animals during repeat dosing.
After high doses of ceftriaxone diarrhoea, formation of biliary caliculi in the gallbladder and nephropathy were observed in monkeys and dogs.
Ceftriaxone has no effect on fertility or reproduction. It has not been shown to possess any mutagenic activity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. In particular, ceftriaxone is not compatible with calcium-containing solutions such as Hartmann's solution and Ringer's solution.
Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

6.3 Shelf life

Unopened:
2 years.

Opened & after reconstitution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, otherwise any unused portion must be discarded.

6.4 Special precautions for storage

Unopened:
Keep the container in the outer carton in order to protect from light.

For storage details of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear type II infusion bottles (50 ml) closed with halogenated isobutene-isoprene-rubber stoppers and aluminium caps with plastic flip-off lids.

Pack sizes: 1, 5, 10 vials.
Hospital packs: 10, 25, 50 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Instructions for use and handling

Intravenous infusion
Ceftriaxone Tyrol Pharma and associated names (See Annex I) 2 g powder for solution for infusion should be dissolved in 40 ml of one of the following calcium-free infusion solutions: Sodium chloride 0.9%, sodium chloride 0.45% and glucose 2.5%, glucose 5 % or 10%, dextran 6% in glucose 5%, hydroxyethyl starch 6-10% infusions (resulting volume 41.0 ml, concentration 49 mg/ml). See also the information included in section 6.2. The infusion should be administered over at least 30 minutes.

The reconstituted solution should be shaken up to 60 seconds to ensure complete dissolution of ceftriaxone.

When reconstituted for intravenous infusion, the white to yellowish crystalline powder gives a pale yellow to amber solution.

Reconstituted solutions should be inspected visually. Only clear solutions free of visible particles should be used. The reconstituted product is for single use only and any unused solution must be discarded.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard carton

1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone Tyrol Pharma and associated names (See Annex I) 1 g powder for solution for injection or infusion
[See Annex I - To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 g vial contains 1g ceftriaxone (as hydrated disodium). (sodium content of the powder: 83 mg, equivalent to 3.6 mmol).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

The reconstituted solutions should be used immediately. Only clear solutions should be used.

Read the package leaflet before use.

For intramuscular and intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the container in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial

1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone Tyrol Pharma and associated names (See Annex I) 1 g powder for solution for injection or infusion
[See Annex I - To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 g vial contains 1g ceftriaxone (as hydrated disodium). (sodium content of the powder: 83 mg, equivalent to 3.6 mmol).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

The reconstituted solutions should be used immediately. Only clear solutions should be used.

Read the package leaflet before use.

For intramuscular and intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the container in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard carton

1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone Tyrol Pharma and associated names (See Annex I) 2 g powder for solution for infusion
[See Annex I - To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 2 g infusion bottle contains 2 g ceftriaxone (as hydrated disodium). (sodium content of the powder: 166 mg, equivalent to 7.2 mmol).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

The reconstituted solutions should be used immediately. Only clear solutions should be used.

Read the package leaflet before use.

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the container in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle

1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone Tyrol Pharma and associated names (See Annex I) 2 g powder for solution for infusion
[See Annex I - To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 2 g infusion bottle contains 2 g ceftriaxone (as hydrated disodium). (sodium content of the powder: 166 mg, equivalent to 7.2 mmol).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

The reconstituted solutions should be used immediately. Only clear solutions should be used.

Read the package leaflet before use.

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the container in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMTION FOR THE USER

Ceftriaxone Tyrol Pharma 1g powder for solution for infusion or injection
(ceftriaxone sodium)

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Ceftriaxone Tyrol Pharma 1g is and what it is used for

Ceftriaxone is an antibiotic. It belongs to a group of antibiotics that are called cephalosporins. These types of antibiotic are similar to penicillin.

Ceftriaxone kills bacteria and it can be used against various sorts of infections.

Like all antibiotics, ceftriaxone is only effective against some types of bacteria. Thus it is only suitable for treating some types of infection.

Ceftriaxone can be used to treat:

- blood poisoning (sepsis)
- infection of the meninges (meningitis)
- bone or joint infections
- infections of the respiratory tract
- infections in the skin and soft tissues

Ceftriaxone can also be used to help prevent infections before, during and after surgery in patients with a certain risk of severe infections associated with surgical measures. Depending on the mode of surgery and the expected pathogens ceftriaxone should be combined with an appropriate antimicrobial agent with additional coverage of complicating pathogens.

2. Before you use Ceftriaxone Tyrol Pharma 1g

Do not use Ceftriaxone Tyrol Pharma 1g if:
- You are allergic (hypersensitive) to ceftriaxone or to any of the other ingredients of this medicine
- You are allergic (hypersensitive) to any other cephalosporin type of antibiotic.
- You have ever had a severe allergic reaction to any penicillin - or to an other beta-laktam-antibiotic because you might also be allergic to this medicine.

- Ceftriaxone Tyrol Pharma 1g should not be used in newborn with jaundice (hyperbilirubinaemia) or preterm newborn because the use of ceftriaxone, the active substance of Ceftriaxone Tyrol Pharma 1g can leed to complications with possible brain damage in these patients.
- Ceftriaxone Tyrol Pharma 1g should not be used by intramuscular injection
    - in infants under 2 years of age and
    - during pregnancy and lactation
- Ceftriaxone Tyrol Pharma 1g should not be used together with calcium treatment, because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

If you feel uncertain, ask your doctor or pharmacist.

Take special care with Ceftriaxone Tyrol Pharma 1g if:
- You have ever had an allergic reaction to any antibiotic, tell your doctor or pharmacist before you take this medicine
- You have ever had other type of allergic reaction or asthma. Hypersensitivity reactions against ceftriaxone tend to occur more frequently in persons with a tendency for any allergic reactions and may occur in all degrees of severity up to anaphylactic shock.
- You have ever been told that your kidneys and/or liver do not work very well
- You have ever had gall bladder or kidney stones, or you are nourished intravenously
- If you have ever had inflammation of your bowel, called colitis, or any other severe disease affecting your gut
- This medicine can alter the results of some blood tests (such as the Coombs' test). It is important to tell the doctor that you are taking this medicine if you have to have any of these tests.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines you have obtained without a prescription.

This medicine can be affected by other medicines that are removed by the kidneys. This is especially if these other medicines also affect how well kidneys work. There are many medicines that can do this, so you should check with your doctor or pharmacist before taking this medicine.

In particular, tell your doctor or pharmacist if you are using:
- other antibiotics for treating infections like aminoglycosides
- oral contraceptive pills. It is advisable to use supplementary non-hormonal contraceptive measures
- other active substances like Probenecid.

This medicine can alter the results of some blood tests (such as the Coombs' test, or measuring galactose in your blood). It is important to tell the doctor that you are taking this medicine if you have to have any of these tests.

This medicine can also alter the results of non-enzymatic urine tests for sugar. If you have diabetes and routinely test your urine, tell your doctor. This is because other tests may have to be used to monitor your diabetes while you are having this medicine.

Pregnancy and breast feeding
- Are you pregnant, or do you think you might be pregnant? Although this medicine is not known to harm the unborn child, it will only be given to a pregnant woman if it is really necessary.
- Are you breast-feeding? This medicine should not be given to women who are breastfeeding. This is because small amounts of it enter the milk and thus the breast-fed infant.
- In pregnancy the intramuscular administration is contraindicated when used together with lidocain.

Ask your doctor or pharmacist for advice before you use Ceftriaxone Tyrol Pharma 1g.

Driving and using machines
You may get dizzy when taking this medicine. This may affect your ability to drive or operate machinery. If this happens, do not drive or use machines.

Important information about some of the ingredients of Ceftriaxone Tyrol Pharma 1g
Ceftriaxone Tyrol Pharma 1g contains 83mg (equivalent to approx. 3.6mmol) sodium per dose. Talk to your doctor if you have been told to limit the amount of sodium in your diet.

3. How to use Ceftriaxone Tyrol Pharma 1g

Always use Ceftriaxone exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Ceftriaxone is normally given by a doctor or nurse
- It is given as an injection.
- The injection is given as a slow injection into a vein or a deep injection into a large muscle.

The dose your doctor gives depends on the type of infection and how bad the infection is. It also depends on your weight and how your kidneys are working. Your doctor will explain this to you. The usual doses are:

Adults, older people and children 12 years and over who weigh more than 50kg
- 1 to 2g once a day
- In serious infections, this can be increased to 4g a day, injected into a vein.

Newborn babies (up to 14 days old)
- 20-50mg for each kg of body weight once a day, injected into a vein
- More than 50mg per kg must not be given, even in severe infections.

Children between 15 days and 12 years old
- 20-80mg for each kg of body weight once a day, injected into a vein
- More than 80mg per kg must not be given, even in severe infections -except in meningitis.

Special dose information:

- For infection of the meninges (meningitis) at first 100mg per kg is given once a day (but no more than 4g a day). In newborn babies, no more than 50mg/kg must be given.
- When given before an operation, the normal daily dose is given 30-90 minutes before the operation. Usually only one dose is given
- For people with kidney problems, the dose does not need to be reduced, if hepatic function is normal. If the condition of the kidney is very poor (creatinine clearance of < 10 ml/min), the daily dose of ceftriaxone should not exceed 2 g in adult patients..
- People with liver problems do not need the dose reducing unless they have kidney problems as well.
- In simultaneous severe renal and hepatic insufficiency the blood ceftriaxone concentrations should be monitored regularly and the dosage adjusted appropriately for children and adults.
- If you are on dialysis, the doctor will do tests to make sure you are on the right dose.

Ceftriaxone is usually given once a day.
- The length of treatment is usually at least 2 days beyond the normalisation of body temperature
- It may continue for a total of 7 to 14 days.

If the patient is a child under 2 years old or a pregnant or breastfeeding woman, Ceftriaxone should only be given by slow injection into a vein.

If you use more Ceftriaxone than you should
If too much Ceftriaxone was used than it should be, talk to your doctor straight away or go to the nearest hospital accident and emergency department. Take the medicine with you in the carton, so that the staff will know exactly what has been used.

If you stop taking Ceftriaxone
It is important that this medicine is used in the prescribed course which should not be interrupted only because you feel well again. If the treatment course is stopped too early the infection may start up again.
If you do not feel well at the end of the prescribed treatment course or even feel worse during treatment you should talk to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist as well.

4. Possible side effects

Like all medicines Ceftriaxone can cause side effects, although not everybody gets them.

If any of the following **serious side effects** happen, stop taking this medicine and tell your doctor immediately or go to your nearest hospital accident and emergency department.

Following side effects are **rare** (affect less than 1 in 1000 people).
- Allergic reactions such as sudden wheeziness and tightness of the chest, swelling of the eyelids, face or lips, severe skin rashes that can blister and may involve the eyes, mouth and throat and genitals, loss of consciousness (fainting).

Following side effects are very rare (**affect less than 1 out of 10,000 people**)
- Diarrhoea that is serious, lasts a long time or has blood in it, with stomach pain or fever. This can be a sign of a serious bowel inflammation (called “pseudomembranous colitis”) that can happen after taking antibiotics.

Very common side effects (affects more than 1 out of 10 people):
- Gall stones in children

Common side effects (affects less than 1 out of 10 people):
- allergic reactions (skin rash, itching, nettle rash, swellings of the skin and joints)
- changes in blood tests that check how your liver is working
- pain and hardness when injected into a muscle
- pain and redness when injected into a vein

Uncommon side effects (affects less than 1 out of 100 people)
- nausea, vomiting, stomach pain, diarrhoea
- sores, inflammation of the tongue, loss of appetite
- headache, dizziness
- Infections: Having a course of ceftriaxone can temporarily increase the chance that you can get infections caused by other pathogens. For example, thrush may occur
- Kidney problems: changed in kidney function and reduced urine production

Rare side effects (affects less than 1 out of 1,000 people)
- severe cramps in the belly (caused by inflammation of the pancreas)
- Gall stones in adults
- drops in the numbers of white blood cells (sometimes severe with increased risk of severe infection)
- Kidney stones in children

Very rare side effects (affects less than 1 out of 10,000 people)

- reduced or damaged blood cells (increased chance of bleeding, bruising or infection)
- a type of anaemia that can be severe and is caused by red blood cells breaking up. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are taking this medicine as it may affect your result.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. How to store Ceftriaxone Tyrol Pharma 1g

Keep out of the reach and sight of children.

Do not use Ceftriaxone after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

Keep the container in the outer carton in order to protect from light.

The solutions should be used immediately after their reconstitution. Only clear solutions should be used.

The contents of the vials, once opened, should be used immediately.

Any unused injection or infusion solutions should be disposed of.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Further information

What Ceftriaxone Tyrol Pharma 1g contains:

Ceftriaxone Tyrol Pharma 1g
The active substance is ceftriaxone disodium 3.5 H_2O.
Each 1 g vial contains 1g ceftriaxone (as hydrated disodium).

There are no other ingredients.

What Ceftriaxone Tyrol Pharma 1g looks like and contents of the pack

Ceftriaxone Tyrol Pharma 1g: powder for solution for infusion or injection

Ceftriaxone Tyrol Pharma 1 g is a white to yellowish crystalline powder. The ready-to-use solutions are pale yellow to amber.

Do not use Ceftriaxone Tyrol Pharma 1 g if you notice the following: The solution is not clear.

Ceftriaxone Tyrol Pharma 1g, powder for solution for injection or infusion is supplied in packs of 1, 5 and 10 vials as well as in hospital packs.

Marketing Authorisation holder and manufacturer

Sandoz GmbH
Biochemiestraße 10
A-6250 Kundl

Austria

This leaflet was last approved in {MM/YYYY}

The following information is intended for medical or healthcare professionals only:

Method and route of administration of Ceftriaxone Tyrol Pharma 1g powder for solution for injection/infusion

Ceftriaxone Tyrol Pharma 1g is injected into a vein (intravenous administration); however, it can also be injected into a muscle (intramuscular administration).

Intravenous injection (injection into a vein)

Ceftriaxone Tyrol Pharma 1g for IV injection is dissolved in water for injections (concentration 0.1 g/ml).

The content of a 1 g vial is dissolved in 10 ml of water for injections by swirling.

The duration of injection is between 2 and 4 minutes.

Intravenous infusion (infusion into a vein)
Ceftriaxone Tyrol Pharma 1g for infusion is administered as a short intravenous infusion.

The content of the vial is dissolved in 10 ml in one of the following calcium-free infusion solutions by swirling, resulting in a concentration of
0.1 g/ml: sodium chloride solution 0.9 %, sodium chloride (0.45 %) and glucose (2.5 %) solution, glucose solution 5 % or 10 %, dextran 6 % in glucose solution 5 %, hydroxyethylen starch solution 6 – 10 %. and is then further diluted under controlled and validated aseptic conditions down to the a final volume of 20,5 ml and a concentration of 49 mg/ml.
See also section "Principal chemical intolerances“.
The time of infusion is at least 30 minutes.

Intramuscular injection (injection into a muscle)

Ceftriaxone Tyrol Pharma 1g can be administered by the intramuscular route.

The content of the 1g injection vial is dissolved completely in 3.5 ml of 1% lidocaine hydrochloride solution for injection by swirling (concentration 0.3 g/ml).
The solution is injected deeply into the buttocks muscle (intragluteally). No more than 1 g ceftriaxone should be injected on one side.
An injection into the blood vessels must be strictly avoided.

(Please note the manufacturer's information on the risks of lidocaine hydrochloride in the relevant information documents on the respective lidocaine preparations used).

Treatment with injection into a muscle is only justified in exceptional cases and after a careful risk/benefit evaluation. See also section 2 “Take special care with Ceftriaxone Tyrol Pharma 1g”.

For other routes of administration other strengths of Ceftriaxone Tyrol Pharma are available.

Miscibility
As a matter of principle, ceftriaxone solutions must always be administered separately from other solutions for infusion.

Under no circumstances must ceftriaxone solutions be mixed with solutions containing calcium.

Principal chemical intolerances

Ceftriaxone Tyrol Pharma 1g must never be mixed with any of the following solutions:

- solutions containing calcium such as Hartmann's and Ringer's solutions.

- aminoglycosides (when given concurrently, these preparations must be administered separately)

- Ceftriaxone Tyrol Pharma 1g must not be administered in the same syringe as other antibiotics or other bactericidal agents.

- A chemical intolerance of ceftriaxone has also been reported with amsacrine (antitumour agent), vancomycin (antibiotic) and fluconazole (fungicide).

PACKAGE LEAFLET: INFORMTION FOR THE USER

Ceftriaxone Tyrol Pharma 2g, powder for solution for infusion
(ceftriaxone sodium)

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Ceftriaxone Tyrol Pharma 2g is and what it is used for

Ceftriaxone is an antibiotic. It belongs to a group of antibiotics that are called cephalosporins. These types of antibiotic are similar to penicillin.

Ceftriaxone kills bacteria and it can be used against various sorts of infections.

Like all antibiotics, ceftriaxone is only effective against some types of bacteria. Thus it is only suitable for treating some types of infection.

Ceftriaxone can be used to treat:

- blood poisoning (sepsis)
- infection of the meninges (meningitis)
- bone or joint infections
- infections of the respiratory tract
- infections in the skin soft tissues

Ceftriaxone can also be used to help prevent infections before, during and after surgery in patients with a certain risk of severe infections associated with surgical measures. Depending on the mode of surgery and the expected pathogens ceftriaxone should be combined with an appropriate antimicrobial agent with additional coverage of complicating pathogens.

2. Before you use Ceftriaxone Tyrol Pharma 2g

Do not use Ceftriaxone Tyrol Pharma 2g if:
- You are allergic (hypersensitive) to ceftriaxone or to any of the other ingredients of this medicine
- You are allergic (hypersensitive) to any other cephalosporin type of antibiotic.
- You have ever had a severe allergic reaction to any sort of penicillin - or to an other beta-laktam-antibiotic because you might also be allergic to this medicine.

- Ceftriaxone Tyrol Pharma 2g should not be used in newborn with jaundice (hyperbilirubinaemia) or preterm newborn because the use of ceftriaxone, the active substance of Ceftriaxone Tyrol Pharma 2g can leed to complications with possible brain damage in these patients.
- Ceftriaxone Tyrol Pharma 2g should not be used together with calcium treatment, because of the risk of precipitation of ceftriaxone-calcium salt in term newborn.

If you feel uncertain, ask your doctor or pharmacist.

Take special care with Ceftriaxone Tyrol Pharma 2g if:
- You have ever had an allergic reaction to any antibiotic, tell your doctor or pharmacist before you take this medicine
- You have ever had other type of allergic reaction or asthma. Hypersensitivity reactions against ceftriaxone tend to occur more frequently in persons with a tendency for any allergic reactions and may occur in all degrees of severity up to anaphylactic shock.
- You have ever been told that your kidneys and/or liver do not work very well
- You have ever had gall bladder or kidney stones, or you are nourished intravenously
- If you have ever had inflammation of your bowel, called colitis, or any other severe disease affecting your gut
- This medicine can alter the results of some blood tests (such as the Coombs' test). It is important to tell the doctor that you are taking this medicine if you have to have any of these tests.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines you have obtained without a prescription.

This medicine can be affected by other medicines that are removed by the kidneys. This is especially if these other medicines also affect how well kidneys work. There are many medicines that can do this, so you should check with your doctor or pharmacist before taking this medicine.

In particular, tell your doctor or pharmacist if you are using:
- other antibiotics for treating infections like aminoglycosides
- oral contraceptive pills. It is advisable to use supplementary non-hormonal contraceptive measures
- other active substances like Probenecid.

This medicine can alter the results of some blood tests (such as the Coombs' test, or measuring galactose in your blood). It is important to tell the doctor that you are taking this medicine if you have to have any of these tests.

This medicine can also alter the results of non-enzymatic urine tests for sugar. If you have diabetes and routinely test your urine, tell your doctor. This is because other tests may have to be used to monitor your diabetes while you are having this medicine.

Pregnancy and breast feeding
- Are you pregnant, or do you think you might be pregnant? Although this medicine is not known to harm the unborn child, it will only be given to a pregnant woman if it is really necessary.
- Are you breast-feeding? This medicine should not be given to women who are breastfeeding. This is because small amounts of it enter the milk and thus the breast-fed infant.
- In pregnancy the intramuscular administration is contraindicated when used together with lidocain.

Ask your doctor or pharmacist for advice before you use Ceftriaxone Tyrol Pharma 2g.

Driving and using machines
You may get dizzy when taking this medicine. This may affect your ability to drive or operate machinery. If this happens, do not drive or use machines.

Important information about some of the ingredients of Ceftriaxone Tyrol Pharma 2g
Ceftriaxone Tyrol Pharma 2g contains 166mg, (equivalent to approx. 7.2mmol) sodium per dose. Talk to your doctor if you have been told to limit the amount of sodium in your diet.

3. How to use Ceftriaxone Tyrol Pharma 2g

Always use Ceftriaxone exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Ceftriaxone is normally given by a doctor or nurse
- It is given as an infusion.
- The infusion is given as a slow infusion into a vein.

The dose your doctor gives depends on the type of infection and how bad the infection is. It also depends on your weight and how your kidneys are working. Your doctor will explain this to you. The usual doses are:

Adults, older people and children 12 years and over who weigh more than 50Kg
- 1 to 2g once a day
- In serious infections, this can be increased to 4g a day, injected into a vein.

Newborn babies (up to 14 days old)
- 20-50mg for each kg of body weight once a day, injected into a vein
- More than 50mg per kg must not be given, even in severe infections.

Children between 15 days and 12 years old
- 20-80mg for each kg of body weight once a day, injected into a vein
- More than 80mg per kg must not be given, even in severe infections-except in meningitis.

Special dose information:
- For infection of the meninges (meningitis) at first 100mg per kg is given once a day (but no more than 4g a day). In newborn babies, no more than 50mg/kg must be given.
- When given before an operation, the normal daily dose is given 30-90 minutes before the operation. Usually only one dose is given
- For people with kidney problems, the dose does not need to be reduced, if hepatic function is normal. If the condition of the kidney is very poor (creatinine clearance of < 10 ml/min), the daily dose of ceftriaxone should not exceed 2 g in adult patients.
- People with liver problems do not need the dose reducing unless they have kidney problems as well.
- In simultaneous severe renal and hepatic insufficiency the blood ceftriaxone concentrations should be monitored regularly and the dosage adjusted appropriately for children and adults.
- If you are on dialysis, the doctor will do tests to make sure you are on the right dose.

Ceftriaxone is usually given once a day.
- The length of treatment is usually at least 2 days beyond the normalisation of body temperature.
- It may continue for a total of 7 to 14 days.

If the patient is a child under 2 years old or a pregnant or breastfeeding woman, Ceftriaxone should only be given by slow injection into a vein.

If you use more Ceftriaxone than you should
If too much Ceftriaxone was used than it should be, talk to your doctor straight away or go to the nearest hospital accident and emergency department. Take the medicine with you in the carton, so that the staff will know exactly what has been used.

If you stop taking Ceftriaxone

It is important that this medicine is used in the prescribed course which should not be interrupted only because you feel well again. If the treatment course is stopped too early the infection may start up again.
If you do not feel well at the end of the prescribed treatment course or even feel worse during treatment you should talk to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist as well.

4. Possible side effects

Like all medicines Ceftriaxone can cause side effects, although not everybody gets them.

If any of the following **serious side effects** happen, stop taking this medicine and tell your doctor **immediately** or go to your nearest hospital accident and emergency department.

Following side effects are **rare** (affect less than 1 in 1000 people).
- Allergic reactions such as sudden wheeziness and tightness of the chest, swelling of the eyelids, face or lips, severe skin rashes that can blister and may involve the eyes, mouth and throat and genitals, loss of consciousness (fainting).

Following side effects are very rare **(affect less than 1 out of 10,000 people)**.
- Diarrhoea that is serious, lasts a long time or has blood in it, with stomach pain or fever. This can be a sign of a serious bowel inflammation (called “pseudomembranous colitis”) that can happen after taking antibiotics.

Very common side effects (affects more than 1 out of 10 people):
- Gall stones in children

Common side effects (affects less than 1 out of 10 people):
- allergic reactions (skin rash, itching, nettle rash, swellings of the skin and joints)
- changes in blood tests that check how your liver is working
- pain and hardness when injected into a muscle
- pain and redness when injected into a vein

Uncommon side effects (affects less than 1 out of 100 people)
- nausea, vomiting, abdominal pain, loose stool or diarrhoea
- sores, inflammation of the tongue, loss of appetite
- headache, dizziness
- Infections: Having a course of ceftriaxone can temporarily increase the chance that you can get infections caused by other pathogens. For example, thrush may occur
- Kidney problems: changed in kidney function and reduced urine production

Rare side effects (affects less than 1 out of 1,000 people)
- severe cramps in the belly (caused by inflammation of the pancreas)
- Gall stones in adults
- drops in the numbers of white blood cells (sometimes severe with increased risk of severe infection)
- Kidney stones in children

Very rare side effects (affects less than 1 out of 10,000 people)
- reduced or damaged blood cells (increased chance of bleeding, bruising or infection)
- a type of anaemia that can be severe and is caused by red blood cells breaking up. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are taking this medicine as it may affect your result.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. How to store Ceftriaxone Tyrol Pharma 2g

Keep out of the reach and sight of children.

Do not use Ceftriaxone after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

Keep the container in the outer carton in order to protect from light.

The solutions should be used immediately after their reconstitution. Only clear solutions should be used.

The contents of the infusion bottles, once opened, should be used immediately.

Any unused infusion solution should be disposed of.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Further information

What Ceftriaxone Tyrol Pharma 2g contains:

Ceftriaxone Tyrol Pharma 2g
The active substance is ceftriaxone disodium 3.5 H_2O.
Each 2 g bottle contains 2 g ceftriaxone (as hydrated disodium).

There are no other ingredients.

What Ceftriaxone Tyrol Pharma 2g looks like and contents of the pack

Ceftriaxone Tyrol Pharma 2g: powder for solution for infusion

Ceftriaxone Tyrol Pharma 2 g is a white to yellowish crystalline powder. The ready-to-use solutions are pale yellow to amber.

Do not use Ceftriaxone Tyrol Pharma 2 g if you notice the following: The solution is not clear.

Ceftriaxone Tyrol Pharma 2g, powder for solution for infusion, is supplied in packs of 1, 5 and 10 infusion bottles as well as in hospital packs.

Marketing Authorisation holder and manufacturer
Sandoz GmbH
Biochemiestraße 10
A-6250 Kundl
Austria

This leaflet was last approved in {MM/YYYY}

The following information is intended for medical or healthcare professionals only:

Method and route of administration of Ceftriaxone Tyrol Pharma 2 g powder for solution for infusion

Ceftriaxone Tyrol Pharma 2g is injected into a vein (intravenous administration).

Intravenous infusion (infusion into a vein)
Ceftriaxone Tyrol Pharma 2g is administered as a short intravenous infusion.

The content of the infusion bottle is dissolved in 40 ml of one of the following calcium-free infusion solutions by swirling, resulting in a concentration of
0.05 g/ml: sodium chloride solution 0.9 %, sodium chloride (0.45 %) and glucose (2.5 %) solution, glucose solution 5 % or 10 %, dextran 6 % in glucose solution 5 %, hydroxyethylen starch solution 6 – 10 %.
See also section "Principal chemical intolerances“.
The time of infusion is at least 30 minutes.

For other routes of administration other strengths of Ceftriaxone Tyrol Pharma 2g are available.

Miscibility
As a matter of principle, ceftriaxone solutions must always be administered separately from other solutions for infusion.

Under no circumstances must ceftriaxone solutions be mixed with solutions containing calcium.

Principal chemical intolerances

Ceftriaxone Tyrol Pharma 2g must never be mixed with any of the following solutions:

- solutions containing calcium such as Hartmann's and Ringer's solutions.
- aminoglycosides (when given concurrently, these preparations must be administered separately)
- Ceftriaxone Tyrol Pharma 2g must not be administered in the same syringe as other antibiotics or other bactericidal agents.
- A chemical intolerance of ceftriaxone has also been reported with amsacrine (antitumour agent), vancomycin (antibiotic) and fluconazole (fungicide).