Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRIAXIPHIN 1 g

TRIAXIPHIN 250 mg

TRIAXIPHIN 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRIAXIPHIN 250 mg

Each vial contains ceftriaxone in the form of the disodium salt (approximately 83 mg (3,6 mEq) of sodium per gram) equivalent to 250 mg ceftriaxone.

Sugar free

TRIAXIPHIN 500 g

Each vial contains ceftriaxone in the form of the disodium salt (approximately 83 mg (3,6 mEq) of sodium per gram) equivalent to 500 mg ceftriaxone.

Sugar free

TRIAXIPHIN 1 g

Each vial contains ceftriaxone in the form of the disodium salt (approximately 83 mg (3,6 mEq) of sodium per gram) equivalent to 1 g ceftriaxone.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection.

Sterile, white to yellowish-orange powder in clear glass vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRIAXIPHIN is indicated for the treatment of the following infections:

Bacterial septicemia caused by Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, or *Klebsiella pneumoniae.*

Meningitis caused by *Haemophilus influenzae*, *Neisseria meningitidis*, or *Streptococcus pneumoniae.*

Intra-abdominal infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, Clostridium species *(*Note: most strains of *Clostridium difficile are resistant)* or *Peptostreptococcus* species.

Skin and skin structure infections caused by Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pyogenes*,

Streptococcus viridans group, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Morganella morganii*, *Serratia marcescens*, or *Peptostreptococcus* species.

Bone- and joint infections caused by Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae*,

Escherichia coli, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Enterobacte*r species.

Renal and urinary tract infections (complicated and uncomplicated) caused by *Escherichia coli*, *Proteus mirabilis*, *Proteus vulgaris*, *Morganella morganii* or *Klebsiella pneumoniae*.

Respiratory tract infections caused by *Streptococcus pneumoniae*, Methicillin-sensitive *Staphylococcus aureus* (MSSA),

Haemophilus influenzae, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus mirabilis*, or *Serratia marcescens*.

Ear, nose and throat infections (Acute Bacterial Otitis Media) caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, (including beta-lactamase-producing strains), or *Moraxella catarrhalis* (including beta-lactamase-producing strains).

Uncomplicated gonorrhoea (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both ~~beta-lactamase-, and non-beta-lactamase-producing~~ penicillinase- and non-penicillinase-producing strains, and pharyngeal gonorrhoea caused by non-beta-lactamase-producing strains of *Neisseria gonorrhoeae*.

Surgical prophylaxis*:* The pre-operative administration of a single 1 g dose of TRIAXIPHIN may reduce the incidence of post-operative infections.

4.2 Posology and method of administration

Posology

Standard dosage

Adults and children over 12 years.

The usual dosage is 1 – 2 g **TRIAXIPHIN** once daily <u>(every 24 hours).</u> In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

Neonates, infants and children up to 12 years.

The following dosage schedules are recommended for once daily administration:

Neonates (up to 14 days):

20 – 50 mg/kg bodyweight once daily. The daily dose should not exceed 50 mg/kg. It is not necessary to differentiate between premature and term infants.

Infants and children (15 days to 12 years):

20 – 80 mg/kg once daily. For children with bodyweights of 50 kg or more, the usual adult dose should be used. Intravenous doses of ≥ 50 mg/kg bodyweight should be given by infusion over at least 30 minutes.

Elderly patients.

No dose modification is needed in the elderly

Refer below to Special dosage instructions for other patient populations.

Duration of therapy: The duration of therapy varies according to the course of the disease. Administration of **TRIAXIPHIN** should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Combination therapy:

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

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

Special dosage instructions

Meningitis:

In bacterial meningitis in *neonates, infants and children*, treatment begins with doses of 100 mg/kg (not to exceed 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dose can be adapted accordingly.

For bacterial meningitis in *adults*, the recommended dose is 4 g once daily.

Gonorrhoea:

In the treatment of uncomplicated gonorrhoea (penicillinase-producing and non- penicillinase-producing strains) a single *IM* dose of 250 mg is recommended.

Peri-operative Infection Prophylaxis:

A single dose of 1 – 2 g **TRIAXIPHIN** administered 30 – 90 minutes prior to surgery.

In colorectal surgery, administration of **TRIAXIPHIN** with or without a 5-nitroimidazole, e.g. metronidazole, has been proven effective, (separate administration: see '**Method of administration'**)

Method of administration

Ceftriaxone must be reconstituted prior to use. Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature or 24 hours in the refrigerator at +5 °C. As a general rule, however, the solutions should be used immediately after preparation. The solutions range in colour from pale yellow to amber, depending on the concentration and length of storage. The colouration of the solutions is of no significance for the efficacy or tolerance of the ~~drug~~ (medicine).

Intramuscular injection

For i.m. injection, **TRIAXIPHIN** 250 mg or 500 mg is dissolved in 2 ml and **TRIAXIPHIN** 1 g in 3.5 ml, of water for injection. **TRIAXIPHIN** dissolved in a 1 % lignocaine solution instead of water for injection can reduce pain at the site of injection. It is recommended that not more than 1 g be injected at one site.

Reconstitution with 1 % lignocaine (without adrenaline) has no effect on the absorption or the elimination of **TRIAXIPHIN**.

Intravenous injection

The lignocaine solution must never be administered intravenously.

For i.v. injection, **TRIAXIPHIN** 250 mg or 500 mg is dissolved in 5 ml, and **TRIAXIPHIN** 1 g in 10 ml sterile water for injection. The intravenous administration should be given over 2 to 4 minutes.

Patients with hepatic impairment*:*

In patients with liver damage, there is no need for the dosage to be reduced, provided that renal function is not impaired.

Patients with renal impairment:

In patients with impaired renal function, there is no need to reduce the dosage of **TRIAXIPHIN,** provided that hepatic function is not impaired.

In cases of severe renal failure (creatinine clearance < 10 ml/min) the **TRIAXIPHIN** dosage should not exceed 2 g daily.

In patients with *both severe renal and hepatic dysfunction*, the plasma concentrations of ceftriaxone should be determined at regular intervals and if necessary the dose should be adjusted

Dialysis: **TRIAXIPHIN** is not removed by peritoneal- or hemodialysis. In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Plasma concentrations should however be monitored, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be altered.

Patients with severe renal and hepatic impairment

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

Special dosage instructions

Children:

Neonates, infants and children up to 12 years: The following dosage schedules are recommended for *once daily* administration.

Neonates (up to 14 days): 20 - 50 mg/kg bodyweight once daily. The daily dose should not exceed 50 mg/kg. **TRIAXIPHIN** is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age) (see section 4.3 contraindications).

TRIAXIPHIN is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see sections 4.3, 4.4 and 4.8).

For neonates, infants and children (15 days to 12 years): 20 - 80 mg/kg once daily.

For children with bodyweights of 50 kg or more, the usual adult dosage should be used.

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

For children with bodyweights of 50 kg or more, the usual adult dosage should be used.

4.3 Contraindications

- *Hypersensitivity*

  TRIAXIPHIN is contraindicated in patients with known hypersensitivity to ceftriaxone, any of its excipients or to any other cephalosporin.

  Patients with previous hypersensitivity reactions to penicillin and other beta lactam medicines may be at greater risk of hypersensitivity to ceftriaxone (see section 4.4 – Hypersensitivity).

- *Lidocaine/Lignocaine*

  Contraindications to lidocaine/lignocaine must be excluded before intramuscular injection of **TRIAXIPHIN** when lidocaine solution is used as a solvent (see section 4.2). **TRIAXIPHIN** solutions containing lidocaine should never be administered intravenously.

- *Premature Neonates*

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

- *Hyperbilirubinemic newborns*

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

- *Neonates and Calcium Containing IV Solutions*

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

  A small number of cases of fatal outcomes with calcium-**TRIAXIPHIN** precipitates in the lungs and kidneys have been reported at autopsy in both term and preterm neonates receiving **TRIAXIPHIN** and calcium- containing fluids.

  In some of these cases, the same intravenous infusion line was used for both **TRIAXIPHIN** and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line.

At least one fatality has been reported in a neonate to whom **TRIAXIPHIN** and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate.

There have been no similar reports in patients other than neonates, (see sections 4.2, 4.4 and 4.8).

4.4 Special warnings and precautions for use

TRIAXIPHIN must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. **TRIAXIPHIN** and IV calcium-containing solutions or products must not be administered within 48 hours of each other. Precipitation of ceftriaxone-calcium may occur when **TRIAXIPHIN** is mixed with calcium-containing solutions in the same IV administration line.

TRIAXIPHIN must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. Fatal outcomes have been reported in neonates receiving **TRIAXIPHIN** and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both **TRIAXIPHIN** and calcium- containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom **TRIAXIPHIN** and calcium-containing fluids were administered at different time points via different intravenous lines. In some cases times of administration of ceftriaxone and calcium-containing solutions differed (see sections 4.2, 4.3, 4,5 and 4.8).

Do not use diluents containing calcium, such as Ringer's lactate solution or Hartmann's solution to reconstitute **TRIAXIPHIN**. Precipitate formation can result.

Interaction with Calcium-Containing Products:

There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions.

However, the theoretical possibility exists for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, **TRIAXIPHIN** and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different sites. As a further theoretical consideration and based on 5 half-lives of ceftriaxone (**TRIAXIPHIN**) and IV calcium-containing solutions should not be administered within 48-hours of each other in any patient, (see sections 4.2, 4.3, 4.5 and 4.8)

No data are available on potential interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

Hypersensitivity

Serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8 Undesirable effects). In case of severe hypersensitivity reactions, treatment with **TRIAXIPHIN** must be

discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of hypersensitivity reactions to ceftriaxone, to other cephalosporins, or to any other type of beta-lactam medicine. Caution should be used if **TRIAXIPHIN** is given to patients with a history of hypersensitivity to other beta-lactam medicines.

Haemolytic anaemia

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin

class antibacterials including **TRIAXIPHIN**. Severe cases of haemolytic anaemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anaemia while

on **TRIAXIPHIN**, the diagnosis of cephalosporin associated anaemia should be considered and **TRIAXIPHIN** discontinued until the aetiology is determined.

Clostridium difficile associated diarrhoea

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of **TRIAXIPHIN**, and may range in severity from mild diarrhoea to fatal colitis. Treatment with **TRIAXIPHIN** alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Toxin hyper-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following **TRIAXIPHIN** use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents, such as **TRIAXIPHIN**.

If CDAD is suspected or confirmed, on-going antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. Superinfection with non-susceptible micro-organisms may occur as with other antibacterial agents.

Superinfections

Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents. Calcium-ceftriaxone precipitates in the gallbladder have been observed on ultrasound scan in patients receiving **TRIAXIPHIN**, particularly at doses of 1 g per day and above. The probability of such precipitates appears to be greatest in paediatric patients. Precipitates disappear after discontinuation of **TRIAXIPHIN** therapy and are rarely symptomatic. In symptomatic cases, conservative nonsurgical management is recommended, and discontinuation of **TRIAXIPHIN** treatment should be considered by the medical practitioner based on an individual benefit-risk assessment.

Pancreatitis

Cases of pancreatitis, possible of biliary obstruction aetiology, have been rarely reported in patients treated with **TRIAXIPHIN**. Most patients presented with risk factors for biliary stasis and biliary sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor role of **TRIAXIPHIN**-related biliary precipitation cannot be ruled out.

Paediatrics

Safety and efficacy of **TRIAXIPHIN** in neonates, infants and children have been established for the dosages described under section 4.2. Studies have shown that **TRIAXIPHIN** can displace bilirubin from serum albumin. **TRIAXIPHIN** should not be used in neonates (especially prematures) at risk of developing bilirubin encephalopathy (see section 4.3).

Blood monitoring

During prolonged treatment a complete blood count should be carried out at regular intervals.

Special groups

Patients with reduced renal and liver function: Refer to section 4.2**.**

The elderly: Refer to section 4.2.

Children: Refer to section 4.2.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per the maximum recommended dose, that is to say essentially 'sodium-free

4.5 Interaction with other medicines and other forms of interaction

Interaction with other medicines and other forms of interaction

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

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

The recommended monitoring of aminoglycoside levels and renal function in clinical practice should be closely adhered to in such cases.

No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of **TRIAXIPHIN**.

TRIAXIPHIN does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems.

In an *in vitro* study, antagonistic effects have been observed with the combination of chloramphenicol and **TRIAXIPHIN**.

Influence on diagnostic tests

In patients treated with **TRIAXIPHIN** the Coombs test may become false-positive. Treatment with **TRIAXIPHIN** may result in false-positive test for galactosemia. Likewise, non-enzymatic methods for the glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with **TRIAXIPHIN** should be done enzymatically**.**

The presence of **TRIAXIPHIN** may falsely lower estimated blood glucose values obtained with some blood glucose monitoring systems. Please refer to instructions for use for each system. Alternative testing methods should be used if necessary.

Interaction with calcium-containing products: **TRIAXIPHIN** should not be added to solutions containing calcium.

Do not use diluents containing calcium such as Ringer's lactate solution or Hartmann's solution to reconstitute **TRIAXIPHIN** vials, or to further dilute a reconstituted vial for *IV* administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when **TRIAXIPHIN** is mixed with calcium-containing solutions in the same *IV* administration line. **TRIAXIPHIN** must not be administered simultaneously with calcium containing *IV* solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site (see sections 4.2, 4.3, 4.4 and 4.8).

Concomitant use of **TRIAXIPHIN** with Vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjusted accordingly, both during and after treatment with **TRIAXIPHIN** (see section 4.8).

4.6 Fertility, pregnancy and lactation

Safety in human pregnancy has not been established. **TRIAXIPHIN** crosses the placental barrier. **TRIAXIPHIN** is excreted in the breast-milk. Safety in lactation has not been established.

4.7 Effects on ability to drive and use machines

During treatment with **TRIAXIPHIN**, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8). Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile:

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

System Organ Class	**Frequent**	**Less frequent**	**Frequency unknown**
Infections and infestations		Genital fungal infection, pseudo-membranous colitis	Superinfections
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy	Blood and lymphatic system disorders , Coagulation disorders Haemolytic Anaemia Agranulocytosis
Immune system disorders:			Anaphylactic shock Anaphylactic reaction Anoranaphylactoid reactions Hypersensitivity Jarisch-Herxheimer reaction

Nervous system disorders		Headach, dizziness Encephelopathy	Convulsion
Ear and Labyrinth disorders			Vertigo
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Gastrointestinal disorders	Diarrhoea Loose stools	Nausea, vomiting	Pancreatitis, stomatitis, glossitis. Pseudomembranous enterocolitis
Hepatobiliary disorders	Hepatic enzyme increased Risk		Symptomatic precipitation of ceftriaxone-calcium salt in the gallbladder, kernicterus Hepatitis* Hepatitis* cholestatic

Skin and subcutaneous tissue disorders	Rash	Pruritus, urticaria	Acute generalised exanthematous pustulosis (AGEP), cutaneous adverse reactions (erythema multiforme, Stevens Johnson Syndrome or Lyell's Syndrome/toxic epidermal necrolysis). Toxic epidermalnecrolysis Drug reaction with eosinphyllia and sysytemic symptoms (Dress)
Renal and urinary disorders		Haematuria Glycosuria	Oliguria. Renal Precipition (reversible)
General disorders and administration site conditions		Phlebitis , injection site pain , pyrexia , oedema , chills	Phlebitis reactions after IV administration
Investigations		Blood creatinine increased	Coombs test false positive, galactosemia test false positive, non-enzymatic methods for glucose determination false positive (see section 4.5).

*** Usually reversible upon discontinuation of ceftriaxone**

c. Description of selected adverse reactions from clinical trials

Interaction with calcium: Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. 80 mg/kg/day) or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure but is usually reversible upon discontinuation of **TRIAXIPHIN**.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In the case of over-dosage, plasma concentration would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic properties

Category and Class: A 20.1.1: Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Antibacterials for systemic use. Third generation cephalosporins.

ATC code: J01DD04.

Mechanism of action

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

Resistance

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

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

5.2 Pharmacokinetic properties

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

Absorption:

The maximum plasma concentration after a single *IM* dose of 1,0 g is about 81 mg/L and is reached within 2 - 3 hours after administration. The area under the plasma concentration-time curve after *IM* administration is equivalent to that after *IV* administration of an equivalent dose,

indicating 100 % bio-availability of intramuscularly administered ceftriaxone. After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/L respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively. Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose.

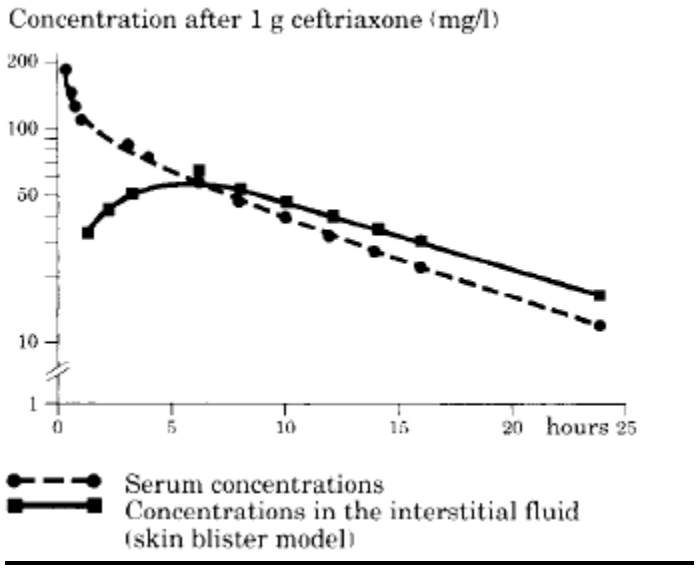
Distribution:

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

On intravenous administration, ceftriaxone diffuses into the interstitial fluid, where if it is given in the recommended dosage range, bactericidal concentrations lasting 24 hours may be maintained.

Protein binding*:*

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



Penetration into particular tissues*:*

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection.

Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

Metabolism:

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

Elimination:

Total plasma clearance is 10 - 22 mL/min. Renal clearance is 5 - 12 mL/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine, while 40 - 50 % is excreted unchanged in the bile.

The elimination half-life in adults is about 8 hours.

Pharmacokinetics in special populations

Children:

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

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

Elderly:

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

Renal or hepatic impairment:

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

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

In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

TRIAXIPHIN and calcium-containing infusions such as parenteral nutrition, should not be mixed or co administered to any patient irrespective of age even via different infusion lines at different sites as it can cause the formation of intravascular precipitates. Do not use diluents containing calcium such as Hartmann's solution or Ringer's lactate solution to reconstitute **TRIAXIPHIN** vials or to further dilute a reconstituted vial for *IV* administration because a precipitate can form. Precipitation of ceftriaxone- calcium can also occur when **TRIAXIPHIN** is mixed with calcium-containing solutions in the same *IV* administration line. **TRIAXIPHIN** must not be administered simultaneously with calcium-containing *IV* solution including continuous calcium-containing infusions such as parenteral nutrition via a Y-site (see sections 4.2, 4.3 4.4 and 4.8). There have been no reports of an interaction between **TRIAXIPHIN** and oral calcium-containing products or interaction between intramuscular **TRIAXIPHIN** and calcium-containing products (IV or oral)

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN

Storage Directions for Reconstituted Product:

Store for up to 6 hours at or below 25 °C or 24 hours at 2 – 8 °C.

Do not freeze the reconstituted product.

6.5 Nature and contents of container

TRIAXIPHIN 250 mg: 10 ml Clear glass vial with grey bromo butyl stopper and aluminium flip off seal with green plastic top, containing powder equivalent to 250 mg ceftriaxone for reconstitution. Vials are supplied in cartons containing singles.

TRIAXIPHIN 500 mg: 10 ml Clear glass vial with grey bromo butyl stopper and aluminium flip off seal with light blue plastic top, containing powder equivalent to 500 mg ceftriaxone for reconstitution. Vials are supplied in cartons containing singles.

TRIAXIPHIN 1 g: 15 ml Clear glass vial with grey bromo butyl stopper and aluminium flip off seal with grey plastic top, containing powder equivalent to 1 g ceftriaxone for reconstitution.

Vials are supplied in cartons containing singles.

6.6 Special precautions for disposal and other handling

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

Intramuscular injection

For i.m. injection, **TRIAXIPHIN** 250 mg or 500 mg is dissolved in 2 ml and **TRIAXIPHIN** 1 g in 3,5 ml, of water for injection. **TRIAXIPHIN** dissolved in a 1 % lignocaine solution instead of water for injection can reduce pain at the site of injection. It is recommended that not more than 1 g be injected at one site.

Reconstitution with 1 % lignocaine (without adrenaline) has no effect on the absorption or the elimination of **TRIAXIPHIN**.

Intravenous injection

The lignocaine solution must never be administered intravenously.

For i.v. injection, **TRIAXIPHIN** 250 mg or 500 mg is dissolved in 5 ml, and **TRIAXIPHIN** 1 g in 10 ml sterile water for injection. The intravenous administration should be given over 2 to 4 minutes.

7 HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD.

14 LAUTRE ROAD

STORMILL

EXT.1

ROODEPOORT

1724

SOUTH AFRICA

8 REGISTRATION NUMBER(S)

TRIAXIPHIN 250 mg: A38/20.1.1/0551

TRIAXIPHIN 500 mg: A38/20.1.1/0552

TRIAXIPHIN 1 g: A38/20.1.1/0550

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 June 2005

10 DATE OF REVISON OF THE TEXT

06 December 2022