PROPOSED PROFESSIONAL INFORMATION -CLEAN

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

SEFTRY 0,5 Powder for solution for injection

SEFTRY 1,0 Powder for solution for injection

SEFTRY 2,0 Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

SEFTRY 0,5: Each vial contains: dry, sterile ceftriaxone sodium equivalent to 0,5 g Ceftriaxone.

SEFTRY 1,0: Each vial contains: dry, sterile ceftriaxone sodium equivalent to 1,0 g Ceftriaxone.

SEFTRY 2,0: Each vial contains: dry, sterile ceftriaxone sodium equivalent to 2,0 g Ceftriaxone.

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

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

SEFTRY 0,5:

White to yellowish powder.

SEFTRY 1,0:

White to yellowish powder.

SEFTRY 2,0

White to yellowish powder.

On constitution, a yellowish to brown-yellow clear solution is obtained.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

SEFTRY is indicated for the treatment of the following infections:

Bacterial septicaemia caused by:

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

Meningitis caused by:

Haemophilus influenzae, *Neisseria meningitides*, or *Streptococcus pneumoniae*.

Intra-abdominal infections caused by:

Escherichia coli, *Klebsiella pneumoniae*, 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 *Enterobacter* 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 strains, and pharyngeal gonorrhoea caused by non-beta-lactamase-producing strains of *Neisseria gonorrhoeae*.

Peri-operative infection prophylaxis.

4.2 Posology and method of administration

Posology

Standard dosage

Adults and children over 12 years:

The usual dosage is 1 to 2 g SEFTRY once daily. 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 to 50 mg/kg body weight 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 to 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 body weight should be given by infusion over at least 30 minutes.

Duration of therapy:

The duration of therapy varies according to the course of the disease. Administration of SEFTRY 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.

Special dosage instructions:

Meningitis:

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

Gonorrhoea:

For the treatment of uncomplicated gonorrhoea (both beta-lactamase-producing and non-beta-lactamase-producing strains), a single intramuscular (IM) dose of 250 mg SEFTRY is recommended.

Peri-operative infection prophylaxis:

A single dose of 1 to 2 g SEFTRY administered 30 to 90 minutes prior to surgery.

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

Special populations

Elderly patients:

No dose modification is needed in the elderly.

Impaired renal and hepatic function:

In patients with impaired renal function, there is no need to reduce the dosage of SEFTRY provided that hepatic function is intact.

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

In patients with liver damage, there is no need for the dosage to be reduced, provided that renal function is intact.

Method of administration

SEFTRY must be reconstituted prior to use. For instructions on reconstitution of SEFTRY before administration, see section 6.6. Calcium containing solutions are not among appropriate solutions described for reconstitution, due to incompatibility (see section 6.2).

Intramuscular injection:

SEFTRY can be administered by deep intramuscular injection. SEFTRY must be injected well within the bulk of a relatively large muscle. It is recommended that not more than 1 g be injected at one site. In case lignocaine is used as a solvent SEFTRY solutions should only be used for intramuscular injection.

The lignocaine solution must never be administered intravenously. (see section 4.3).

***Intravenous injection*:** SEFTRY can be administered by slow intravenous injection. The intravenous administration should be given over 2 to 4 minutes.

***Intravenous infusion*:**

SEFTRY can be administered by intravenous infusion. The infusion should be given over a period of at least 30 minutes.

4.3 Contraindications

- Hypersensitivity to ceftriaxone, to any other cephalosporin or to any of the excipients of SEFTRY listed in section 6.1.
- SEFTRY is contraindicated in patients with known hypersensitivity to beta-lactam antibiotics (penicillins, monobactams and carbapenems). In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind.
- Hyperbilirubinemic neonates, especially prematures, should not be treated with SEFTRY. *In-vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in the patients.

  SEFTRY is contraindicated in:
- Premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),

- Full-term newborns (up to 28 days of age) with jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired.
- Full-term newborns (up to 28 days of age) if they require (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium.

Contraindications to lidocaine (lignocaine) must be excluded before intramuscular injection of SEFTRY when lignocaine is used as a solvent (see section 4.4).
Ceftriaxone solutions containing lidocaine (lignocaine) should never be administered intravenously.

4.4 Special warnings and precautions for use

In patients of any age SEFTRY must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age SEFTRY and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used, or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of SEFTRY is considered necessary in patients requiring continuous nutrition, TPN solutions and SEFTRY can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of SEFTRY infusion, considering the advice to flush infusion lines between solutions. Cases of fatal reactions with calcium-

ceftriaxone precipitates in lungs and kidneys in both premature and full-term newborns aged less than 1 month have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than newborns, treated with SEFTRY and calcium-containing solutions or any other calcium-containing products. *In vitro* studies demonstrated that newborns have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups. (see section 4.3 and 4.8)
Do not use diluents containing calcium, such as Ringer's solutions or Hartman's solution to reconstitute SEFTRY or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously.

Prescribers should adhere to the principles of antibiotic stewardship.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported with beta-lactam antibiotics (see section 4.8). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). In case of severe hypersensitivity reactions, treatment with SEFTRY must be discontinued immediately and adequate emergency measures should be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone as in SEFTRY, to other cephalosporins or to any other type of beta-lactam medicine. Caution should be used if SEFTRY is given to patients with a history of non-severe hypersensitivity to other beta-lactam medicines.

Severe cutaneous adverse reactions (SCAR) such as Stevens Johnson syndrome (SJS), or Lyell's syndrome/toxic epidermal necrolysis (TEN), “drug reaction with eosinophilia and systemic symptoms” (DRESS) and generalised exanthematous pustulosis (AGEP) which can be life-threatening or fatal have been reported in association with beta-lactam antibiotics such as SEFTRY treatment. The frequency of these events is not known (see section 4.8). When SCAR is suspected SEFTRY should be discontinued.

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, SEFTRY 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, SEFTRY and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient (see sections 4.3, 4.8, 5.2 and 6.2).

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).

Paediatric population

Safety and effectiveness of ceftriaxone as in SEFTRY in neonates, infants and children have been established for the dosages described under Posology and Method of Administration (see

section 4.2). Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

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

Immune mediated haemolytic anaemia

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone as in SEFTRY (see section 4.8). Severe cases of haemolytic anaemia, including fatalities, have been reported during treatment in both adults and children.

If a patient develops anaemia while on SEFTRY, the diagnosis of a cephalosporin-associated anaemia should be considered and SEFTRY discontinued until the aetiology is determined.

Long term treatment

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

Colitis/Overgrowth of non-susceptible microorganisms

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

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

Severe renal and hepatic insufficiency

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

Interference with serological testing

Interference with Coombs tests may occur, as ceftriaxone as in SEFTRY may lead to false-positive test results. SEFTRY can also lead to false-positive test results for galactosaemia (see section 4.8).

Non-enzymatic methods for the glucose determination in urine may give false-positive results. Urine glucose determination during therapy with SEFTRY should be done enzymatically (see section 4.8).

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

Antibacterial spectrum

Ceftriaxone as in SEFTRY has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed (see section 4.2). In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone as in SEFTRY, administration of an additional antibiotic should be considered.

Use of lidocaine (lignocaine)

In case a lidocaine (lignocaine) solution is used as a solvent, ceftriaxone as in SEFTRY solutions must only be used for intramuscular injection. Contraindications to lidocaine (lignocaine), warnings and other relevant information as detailed in the professional information of lidocaine (lignocaine) must be considered before use (see section 4.3). The lidocaine (lignocaine) solution should never be administered intravenously.

Biliary lithiasis

When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium-ceftriaxone. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at ceftriaxone as in SEFTRY doses of 1 g per day and above. Caution should be particularly considered in the paediatric population. Such precipitates disappear after discontinuation of ceftriaxone therapy. Precipitates of calcium-ceftriaxone have been associated with symptoms in a few cases. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of SEFTRY treatment should be considered by the medical practitioner based on specific benefit risk assessment (see section 4.8).

Biliary stasis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with ceftriaxone as in SEFTRY (see section 4.8). Most patients presented with risk factors for biliary stasis and biliary sludge e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor of ceftriaxone-related biliary precipitation cannot be ruled out.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone as in SEFTRY (see section 4.8). In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the medical practitioner based on specific benefit risk assessment.

Jarisch-Herxheimer reaction (JHR)

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after ceftriaxone as in SEFTRY treatment is started. JHR is usually a self - limiting condition or can be managed by symptomatic treatment. SEFTRY treatment should not be discontinued if such reaction occurs.

Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone (see section 4.8), particularly in elderly patients with severe renal impairment (see section 4.2) or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g., decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of SEFTRY should be considered.

Sodium

SEFTRY contains sodium:

SEFTRY 0,5 contains about 42 mg (1,8 mmol) sodium.

SEFTRY 1,0 contains about 83 mg (3,6 mmol) sodium.

SEFTRY 2,0 contains about 166 mg (7,2 mmol) sodium.

This should be taken into consideration in patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Interactions of SEFTRY with calcium containing products:

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute SEFTRY vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when SEFTRY is mixed with calcium-containing solutions in the same intravenous administration line.

SEFTRY must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, SEFTRY and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. It has been reported that *in vitro* studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (see sections 4.2, 4.3, 4.4, 4.8 and 6.2).

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

Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K medicine adjusted accordingly, both during and after treatment with SEFTRY (see section 4.8).

Renal function impairment has not been observed after concurrent administration of large doses of SEFTRY and potent diuretics (e.g. furosemide).

There is no evidence that SEFTRY increases renal toxicity of aminoglycosides.

No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of SEFTRY.
Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.

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

The elimination of SEFTRY is not altered by probenecid.

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

Interaction with laboratory tests:

In patients treated with SEFTRY the Coombs' test and tests for galactosaemia may in rare cases be false-positive.
Non-enzymatic methods for glucose determination in urine may give false-positive results.
For this reason, glucose level determination in urine during therapy with ceftriaxone as in SEFTRY should be carried out enzymatically.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in human pregnancy has not been established. Ceftriaxone crosses the placental barrier. Adequate data on the use of SEFTRY in pregnant women are not available. SEFTRY should therefore not be used pregnancy.

Breastfeeding

As ceftriaxone as in SEFTRY is excreted in the breast milk at low concentrations, caution is advised in breastfeeding mothers.

Fertility

Reproductive studies have shown no evidence of adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

Since SEFTRY sometimes induces dizziness the ability to drive and use machines can be impaired.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse events

System Organ Class	**Frequent**	**Less frequent**	**Not known[a]**
Infections and Infestations		Genital fungal infection, Pseudo-membranous	Superinfection[b]

		colitis[b]	
Blood and lymphatic system disorders:	Eosinophilia, leucopenia, thrombocytopenia	Granulocytopenia, anaemia, coagulopathy,	Haemolytic anaemia[b], agranulocytosis, neutropenia, haematoma or bleeding, lymphopenia, prolongation of prothrombin time
Immune system disorders:			Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity[b], Jarisch-Herxheimer reaction[b]
Nervous system disorders		Headache, dizziness, encephalopathy	Convulsion
Ear and labyrinth disorders			Vertigo
Cardiac disorders			Kounis syndrome
Respiratory,		Bronchospasm	

thoracic and mediastinal disorders			
Gastrointestinal disorders	Diarrhoea[b], loose stools	Nausea, vomiting	Pancreatitis[b], stomatitis, glossitis
Hepato-biliary disorders:	Hepatic enzyme increased		Gall bladder precipitation[b], kernicterus hepatitis[c], cholestatic hepatitis[b,c]
Skin and subcutaneous tissue disorder	Rash	Urticaria, exanthema, allergic dermatitis, pruritus	Stevens Johnson syndrome[b], toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)[b], exfoliative dermatitis, petechiae, purpura, diaphoresis, flushing,

			Linear IgA disease
Renal and urinary disorders		Haematuria, glycosuria	Oliguria, renal precipitation (reversible)
General disorders and administrative site conditions		Phlebitis, injection site pain, pyrexia, oedema, chills	
Investigations		Blood creatinine increased	False-positive Coombs test[b], false-positive galactosaemia test[b], false-positive non-enzymatic methods for glucose determination[b]

[a] Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

[b] See section 4.4

[c] Usually reversible upon discontinuation of ceftriaxone

Description of selected adverse reactions

Infections and infestations

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

Ceftriaxone-calcium salt precipitation

Severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4, and 5.2).

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g., ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g., dehydration, confinement to bed). This event may be asymptomatic or symptomatic and may lead to ureteric obstruction and postrenal acute renal failure but is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

Precipitation of ceftriaxone-calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. It has been reported in children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes) (see section 4.2). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

Reporting of suspected adverse reactions

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

4.9 Overdose:

In the case of overdosage nausea, vomiting, diarrhoea, can occur. SEFTRY concentration cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics.

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

ATC code: J01DD04

Ceftriaxone is a third generation cephalosporin. The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis. Ceftriaxone exerts *in-vitro* activity against a wide range of gram-negative and gram-positive microorganisms. SEFTRY is stable to most β-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria. See section 4.1.

Resistance

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

Species for which acquired resistance may be a problem:

Gram-positive aerobes

Staphylococcus epidermidis+

Staphylococcus haemolyticus+

Staphylococcus hominis+

Gram-negative aerobes

Citrobacter freundii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli %

Klebsiella pneumoniae %

Klebsiella oxytoca %

Morganella morganii

Proteus vulgaris

Serratia marcescens

Anaerobes

Bacteroides spp.

Fusobacterium spp.

Peptostreptococcus spp.

Clostridium perfringens

Inherently resistant organisms

Gram-positive aerobes

Enterococcus spp.

Listeria monocytogenes

Gram-negative aerobes

Acinetobacter baumannii

Pseudomonas aeruginosa

Stenotrophomonas maltophilia

Anaerobes

Clostridium difficile

Others:

Chlamydia spp.

Chlamydophila spp.

Mycoplasma spp.

Legionella spp.

Ureaplasma urealyticum

£ All methicillin-resistant staphylococci are resistant to SEFTRY.

+ Resistance rates > 50 % in at least one region

% ESBL producing strains are always resistant

5.2 Pharmacokinetic properties

The pharmacokinetics of ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations.

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 % bioavailability of intramuscularly administered ceftriaxone.

Distribution:

The apparent volume of distribution of ceftriaxone is 0,13 to 0,19 l/kg. Ceftriaxone shows good tissue penetration and body-fluid distribution after a dose of 1 to 2 g; concentrations well above the minimum inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in body-fluids or tissues including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids.

Protein binding:

Ceftriaxone is reversibly bound to albumin. There is proportionally decreased albumin binding with an increase in plasma concentration of ceftriaxone.

Penetration into particular tissues:

Paediatrics:

Ceftriaxone penetrates the inflamed meninges of neonates, infants and children. Ceftriaxone concentrations exceed 1,4 mg/l in the cerebrospinal fluid (CSF) 24 hours after IV injection in doses of 50 mg/kg in neonates to 100 mg/kg in infants. Peak concentration in CSF with a mean of 18 mg/l is reached about 4 hours after intravenous injection.

Mean CSF concentrations are 17 % of plasma concentrations in patients with bacterial meningitis and 4 % in patients with aseptic meningitis.

The mean values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after a 50 mg/kg IV dose and after a 75 mg/kg IV dose in paediatric patients suffering from bacterial meningitis are shown in the table below.

Mean pharmacokinetic parameters of ceftriaxone in paediatric patients with meningitis

	50 mg/kg IV	**75 mg/kg IV**
Maximum Plasma Concentrations (µg/ml)	216	275
Elimination half-life (hr)	4,6	4,3
Plasma Clearance (ml/hr/kg)	49	60
Volume of distribution (ml/kg)	338	373
CSF Concentration – inflamed meninges (µg/ml)	5,6	6,4
Range (µg/ml)	1,3 – 18,5	1,3 – 44

Time after dose (hr)	3,7 (± 1,6)	3,3 (± 1,4)

Adults:

In meningitis in adults, administration of 50 mg/kg leads within 2 to 24 hours to CSF concentrations several times higher than the minimum *in-vitro* inhibitory concentrations required for the most common meningitis pathogens.

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

Biotransformation

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

Elimination

In healthy, young adult volunteers the total plasma clearance is 10 to 22 ml/min.

The renal clearance is 5 to 12 ml/min. 50 to 60 % of ceftriaxone is excreted unchanged in the urine, while 40 to 50 % is excreted unchanged in the bile. The elimination half-life in adults is about 8 hours.

Pharmacokinetics in special clinical situations:

Neonates:

Urinary recovery accounts for about 70 % of the dose.

Infants less than eight days old and elderly persons aged over 75 years:

Elimination half-life is usually 2 to 3 times that in young adults.

Patients with renal or hepatic dysfunction:

The pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased.

Impaired kidney function alone:

Biliary elimination of ceftriaxone is increased.

Impaired liver function alone:

Renal elimination of ceftriaxone is increased.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

There are no excipients used in this formulation.

6.2 Incompatibilities

SEFTRY should not be mixed with or piggybacked into solutions containing other antimicrobial medicines or into diluent solutions other than those listed in section 6.6, owing to possible incompatibility.

SEFTRY should not be added to solutions containing calcium, such as Hartmann's solution and Ringer's solution or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when SEFTRY is mixed with calcium-containing solutions in the same IV administration line.

SEFTRY must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, SEFTRY and calcium-containing solutions may be administered sequentially, of one another, if the infusion lines are thoroughly flushed between infusions with a compatible fluid. *In vitro* studies using adult and neonatal plasma from umbilical

cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

SEFTRY is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

6.3 Shelf life

Unopened vials: 3 years

The reconstituted solution is intended for immediate use, but the solution may be stored in the original vials in the refrigerator at 2 to 8 °C for 48 hours or below 25 °C for 24 hours. After use, discard any remaining solution.

6.4 Special precautions for storage

Store in the original packaging (in the carton) below 25 °C and protect the vials from light. For storage conditions of the reconstituted medicine, see section 6.3.

6.5 Nature and contents of container

Packs for IM, IV or for IV infusion containing:

SEFTRY 0,5, 1,0 and 2,0 Powder for solution for injection is packed in cartons containing 1 or 10 single dose colourless glass vial with a grey rubber stopper and aluminium cap with a colourless flip-off seal.

6.6 Special precautions for disposal and other handling

SEFTRY must be reconstituted prior to use.

For single use only. See sections 6.3 and 6.4.

Concentrations for the intravenous injection: 100 mg/mL

Concentrations for the intravenous infusion: 50 mg/mL

Concentrations for the intramuscular injection: 250 mg/mL

(Please refer to section 4.2 for further information).

Preparation of solutions for injection and infusion

The use of freshly prepared solutions is recommended. Solutions are light yellow to brownish yellow. For storage conditions of the reconstituted medicinal product, see section 6.3.

SEFTRY should not be mixed in the same syringe with any medicine other than 1 % lidocaine (lignocaine) hydrochloride solution (for intramuscular injection only).

The infusion line should be flushed after each administration.

Intramuscular injection:

For IM injection SEFTRY 0,5 is dissolved in 2 ml and SEFTRY 1,0 is dissolved in 3,5 ml of water for injection. Intramuscular administrations, of some cephalosporins, cause pain at the injection site. This can be reduced greatly by administering in combination with a local anesthetic.

SEFTRY dissolved in 3,5 ml of 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 % lidocaine (lignocaine) (without epinephrine (adrenaline)) has no effect on the absorption or the elimination of SEFTRY.

Intravenous injection:

For IV injection, SEFTRY 0,5 is dissolved in 5 ml, and SEFTRY 1 g in 10 ml, sterile water for injection.

Intravenous infusion:

For IV infusion, 2 g SEFTRY is dissolved in approximately 40 ml of one of the following calcium-free infusion solutions:

- Sodium chloride 0,9 %
- Sodium chloride 0,45 % + dextrose 2,5 %
- Dextrose 5 %
- Dextrose 10 %
- Dextran 6 % in dextrose 5 %
- Hydroxy ethyl starch 6 – 10 % infusions
- Sterile water for injection.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

207A Sherwood House

Greenacres Office Park

c/o Victory and Rustenburg Roads

Victory Park

Johannesburg

Telephone number: 011 433 0602

8 REGISTRATION NUMBER(S):

SEFTRY 0,5: 41/20.1.1/0869

SEFTRY 1,0: 41/20.1.1/0870

SEFTRY 2,0: 41/20.1.1/0871

9 DATE OF FIRST AUTHORISATION

Date of registration: 25 November 2011

10 DATE OF REVISION OF THE TEXT

To be advised