SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

FRAXONE 250 (Injection)

FRAXONE 1 g (Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Fraxone 250: Each vial contains Ceftriaxone sodium (Sterile) equivalent to Ceftriaxone 250 mg.

Fraxone 1 g: Each vial contains Ceftriaxone sodium (Sterile) equivalent to Ceftriaxone 1 g.

Sugar free

For full list of excipients, **see section 6.1**

3. PHARMACEUTICAL FORM:

FRAXONE 250: White to yellowish orange, crystalline powder in 15 ml clear glass USP type I, vials with orange coloured flip-off seals.

FRAXONE 1 g: White to yellowish orange, crystalline powder in 15 ml clear glass USP type I, vials blue flip-off seals

On constitution a pale yellow to reddish orange clear solution is obtained

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

FRAXONE is indicated for the treatment of the following infections when caused by susceptible organisms:

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- **Bacterial septicaemia** caused by *methicillin sensitive Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae 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, Pseudomonas aeruginosa, 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 penicillinase- and non-penicillinase-producing strains, and pharyngeal gonorrhoea caused by non-penicillinase-producing strains of *Neisseria gonorrhoeae*.
- **Surgical prophylaxis:** The pre-operative administration of a single 1 g dose of **FRAXONE** may reduce the incidence of post-operative infections.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:

The usual dosage is 1-2 g of **FRAXONE** once daily (every 24 hours). In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

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 **FRAXONE** should be continued for a minimum of 48 - 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Combination therapy

Synergy between **FRAXONE** 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 **FRAXONE** and aminoglycosides, the two medicines must be administered separately at the

recommended dosages.

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

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. **FRAXONE** is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age) (see section 4.3 contraindications).

FRAXONE 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.

Elderly: The dosages recommended for adults require no modification in geriatric patients provided there is no severe renal and hepatic impairment.

Patients with hepatic impairment: In patients with *liver damage* there is no need for the dosage to be reduced *provided renal function is not impaired*.

Patients with renal impairment: In patients with *impaired renal function* there is no need to reduce the dosage of **FRAXONE**, *provided hepatic function is not impaired*. In cases of severe renal failure (creatinine clearance < 10 mL/min) the **FRAXONE** 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: **FRAXONE** 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.

Meningitis

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

Gonorrhoea

For the treatment of gonorrhoea (penicillinase-producing and non-penicillinase-producing strains), a single IM dose of 250 mg ceftriaxone is recommended.

Perioperative prophylaxis

A single dose of 1-2 g ceftriaxone administered 30-90 minutes prior to surgery. In colorectal surgery, concurrent (but separate) administration of ceftriaxone with a 5-nitroimidazole, e.g., ornidazole, has proven effective.

Method of administration:

FRAXONE must be reconstituted prior use.

Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2 - 8 °C). 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 medicine.

Intramuscular Injection

For IM injection, Fraxone 250 should be dissolved in 2 ml and Fraxone 1 g in 3.5 ml of water for injection. In adults, intramuscular administrations of some cephalosporins, including **FRAXONE**, cause pain at the injection site. This can be reduced greatly by administering in combination with a local anaesthetic.

FRAXONE dissolved in a 1% lignocaine (lidocaine) solution can reduce pain at the site of injection. **FRAXONE** must be injected well within the body of a relatively large muscle. It is recommended that not more than 1 g be injected on one side. Reconstitution with 1% lidocaine (without adrenaline) has no effect on the absorption or the elimination of Ceftriaxone. The lidocaine solution must never be administered intravenously.

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

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Intravenous Injection

For IV injection, **FRAXONE** 250 is dissolved in 5 ml water for injection and **FRAXONE** 1 g dissolved in 10 ml water for injection. The intravenous administration should be given over two (2) to four (4) minutes.

Intravenous infusion

The infusion should be given over a period of at least 30 minutes. For IV infusion, 2 g of **FRAXONE** is dissolved in approximately 40 ml of sterile water for injection. Ceftriaxone solutions should not be mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, owing to possible incompatibility.

Incompatibilities

See section 6.2

4.3 Contraindications

Hypersensitivity

FRAXONE 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).

Lidocaine/Lignocaine

Contraindications to lidocaine/lignocaine must be excluded before intramuscular injection of

FRAXONE when lidocaine solution is used as a solvent (see section 4.2). See the contraindications section in the professional information of lidocaine. **FRAXONE** solutions containing lidocaine should never be administered intravenously.

Premature Neonates

FRAXONE 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 **FRAXONE**. In vitro studies have shown that **FRAXONE** 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

FRAXONE 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-**FRAXONE** precipitates in the lungs and kidneys have been reported at autopsy in both term and preterm neonates receiving **FRAXONE** and calcium- containing fluids. In some of these cases, the same intravenous infusion line was used for

both **FRAXONE** 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 **FRAXONE** 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

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

FRAXONE 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 **FRAXONE** and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both **FRAXONE** 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 **FRAXONE** 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 **FRAXONE**. Precipitate formation can result.

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, **FRAXONE** and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-

administered to any patients irrespective of age even via different infusion lines at different sites. As a further theoretical consideration and based on 5 half-lives of ceftriaxone, **FRAXONE** 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 **FRAXONE** and oral calcium-containing products or interaction between intramuscular **FRAXONE** and calcium-containing products (IV or

oral).

Hypersensitivity

Serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). In case of severe hypersensitivity reactions, treatment with **FRAXONE** 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 **FRAXONE** 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 antibacterial including **FRAXONE**. Severe cases of haemolytic anaemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anaemia while on **FRAXONE**, the diagnosis of cephalosporin associated anaemia should be considered and **FRAXONE** discontinued until the aetiology is determined.

Clostridium difficile associated diarrhoea

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of **FRAXONE** and may range in severity from mild diarrhoea to fatal colitis. Treatment with **FRAXONE** 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 **FRAXONE** use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents, such as **FRAXONE**.

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 **FRAXONE**, 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 **FRAXONE** therapy and are rarely symptomatic. In symptomatic cases, conservative nonsurgical management is recommended, and discontinuation of **FRAXONE** 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 **FRAXONE**. 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 **FRAXONE**-related biliary precipitation cannot be ruled out.

Paediatrics

Safety and efficacy of **FRAXONE** in neonates, infants and children have been established for the dosages described under section 4.2. Studies have shown that **FRAXONE** can displace bilirubin from serum albumin. **FRAXONE** 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.

4.5 Interaction with other medicines and other forms of interaction

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

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

FRAXONE 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 **FRAXONE**.

Influence on diagnostic tests

In patients treated with **FRAXONE** the Coombs test may become false-positive. Treatment with **FRAXONE** 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 **FRAXONE** should be done enzymatically.

The presence of **FRAXONE** 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: **FRAXONE** 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 **FRAXONE** vials, or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when **FRAXONE** is mixed

with calcium-containing solutions in the same IV administration line. **FRAXONE** 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 **FRAXONE** 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 **FRAXONE** (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in human pregnancy has not been established.

Lactation:

FRAXONE crosses the placental barrier. **FRAXONE** is excreted in the breast milk. Safety in lactation has not been established.

Fertility:

Safety in human lactation has not been established.

4.7 Effects on ability to drive and use machines

During treatment with **FRAXONE**, 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

Infections and Infestations:

Less Frequent: Genital fungal infection, pseudo-membranous colitis.

Blood and lymphatic system disorders:

Frequent: Eosinophilia, leucopenia, thrombocyte penia.

Less frequent: Granulocytopenia, anemia, coagulopathy.

Nervous system disorders:

Less frequent: Headache, vomiting.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Bronchospasm

Gastrointestinal disorders:

Frequent: Diarrhoea

Less frequent: Nausea, vomiting

Hepatobiliary disorders:

Frequent: Hepatic enzyme increased.

***Unknown frequency: Hepatotoxicity*.**

Skin and subcutaneous tissue disorders:

Frequent: Rash

Less frequent: Pruritus, urticaria.

Renal and urinary disorders:

Less frequent: Haematuria, glycosuria.

General disorders and administration site conditions:

Less frequent: Phlebitis, injection site pain, pyrexia, oedema, chills.

Investigations:

Less frequent: Blood creatinine increased.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of 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: hppts://www.sahpra.or.za/Publications/Index/8

4.9 Overdose

In the case of overdosage, plasma concentration would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. Third generation cephalosporins. ATC code: J01DD04.

Mechanism of action

The following organisms have been found to be resistant to ceftriaxone:

The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis.

Ceftriaxone exerts in-vitro activity against a wide range Gram-negative and Gram-positive micro-organisms. Ceftriaxone is stable to most β-lactamases, both penicillinases and cephalosporinases, of Gram-positive and Gram-negative bacteria.

Gram positive aerobes:

Methicillin-resistant *Staphylococcus* spp. is resistant to ceftriaxone. *Enterococcus faecalis*, *Enterococcus faecium* and *Listeria monocytogenes* are resistant.

Gram negative aerobes:

Some isolates of *Acinetobacter anitratus* (mostly A. baumanii), *Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Enterobacter spp* (other), *Proteus penneri, Proteus vulgaris. Pseudomonas fluorescens, Pseudomonas* spp. (other), Providentia rettgeri, Serratia marcescens, *Serratia* spp. (other) are resistant to ceftriaxone, mainly due to the production of the chromosomally encoded ß-lactamase.

Some isolates of *Klebsiella pneumoniae* are resistant due to production of extended spectrum, plasmid-mediated ß-lactamase.

Clinical *P. aeruginosa* isolates are resistant to ceftriaxone. *Ureaplasma urealyticum*, *Mycoplasma* sp., *Mycobacterium* sp. and fungi are resistant to ceftriaxone

Anaerobic organisms:

Some isolates of *Bacteroides* spp. (bile-sensitive) are resistant to ceftriaxone due to ß-lactamase-production.

Many strains of ß-lactamase-producing *Bacteroides* spp. (notably *B. fragilis*) are resistant.

Clostridium difficile is resistant.

The WHO Antimicrobial Resistance, Global Report on Surveillance, 2014, lists the following bacteria-antibacterial medicine resistant combinations ranging between 56 % - 90 % for 3rd generation cephalosporins including ceftriaxone as:

E. coli and *K. pneumoniae* mainly conferred by extended spectrum beta-lactamases (ESBLs), and *N. gonorrhoeae*.

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 %

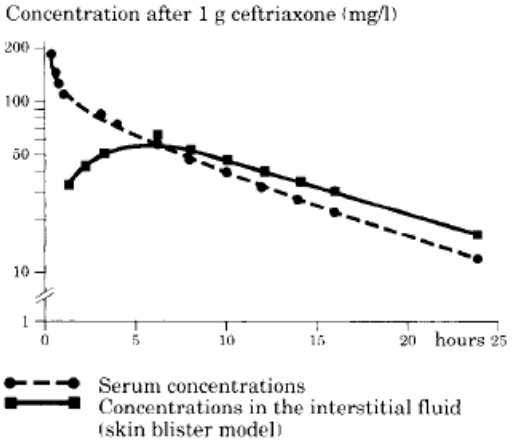
bio-availability of intramuscularly administered ceftriaxone.

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

FRAXONE 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 Rocephin vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone- calcium can also occur when **FRAXONE** is mixed with calcium-containing solutions in the same IV administration line. **FRAXONE** must not be administered simultaneously with calcium-containing IV solution including continuous

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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 **FRAXONE** and oral calcium-containing products or interaction between intramuscular **FRAXONE** and calcium-containing products (IV or oral).

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Store at or below 25 °C, protected from light and moisture. Do not freeze. Reconstituted solution to be stored in original vials and used within 6 hours, if stored at 25 °C or within 24 hours if stored at 2 – 8 °C in a refrigerator.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Fraxone 250:

White to yellowish orange, crystalline powder in 15 ml clear glass USP type I, vials with orange coloured

flip-off seals.

Cartons containing 1 clear glass USP Type I vial.

Fraxone 1g:

White to yellowish orange, crystalline powder in 15 ml clear glass USP type I, vials with blue flip-off seals.

Cartons containing 1 clear glass USP Type I vial.

On constitution a pale yellow to reddish orange clear solution is obtained.

6.6. Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals Pty (Ltd)
Crownwood Office Park
Block D, Ground Floor
100 Northern Parkway
Ormonde
Johannesburg
2091
South Africa

8. REGISTRATION NUMBER(S)

Fraxone 250: A 34/20.1.1/0320
Fraxone 1 g: A 34/20.1.1/0321

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

February 2002

10. DATE OF REVISION OF THE TEXT

01 October 2024

HOTLINE: 086 999 0912