SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

INOXIPHIN 250 mg (Powder for Solution for Injection)

INOXIPHIN 500 mg (Powder for Solution for Injection)

INOXIPHIN 1 g (Powder for Solution for Injection)

INOXIPHIN 2 g (Powder for Solution for Injection or Infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

INOXIPHIN

Each vial contains ceftriaxone sodium equivalent to**:**

250 mg ceftriaxone (IM or IV)

500 mg ceftriaxone (IM or IV)

1 g ceftriaxone (IM or IV)

2 g ceftriaxone for IV infusion

Sugar free

INOXIPHIN contains approximately 83 mg (3,6 mEq) of sodium per gram of ceftriaxone sodium

3. PHARMACEUTICAL FORM

Powder for Solution for Injection or Infusion

INOXIPHIN 250 mg, INOXIPHIN 500 mg and INOXIPHIN 1g:

Almost white or yellowish crystalline powder

INOXIPHIN 2 g

Almost white or yellowish crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- **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 **INOXIPHIN** may reduce the incidence of post-operative infections.
- In the treatment of infections caused by Pseudomonas aeruginosa, an aminoglycoside should be concomitantly.

4.2 Posology and method of administration

Adults and children over twelve years: The usual dosage is 1 - 2 g **INOXIPHIN** 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.

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: The dosages recommended for adults require no modification in the case of elderly patients.

Duration of therapy

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

Meningitis: In bacterial meningitis in neonates, infants 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.

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

Gonorrhoea: For the treatment of uncomplicated gonorrhoea (penicillinase-producing and non- penicillinase-producing strains), a single IM dose of

125 mg **INOXIPHIN** is recommended.

Peri-operative prophylaxis: A single dose of 1 to 2 g **INOXIPHIN** administered 30 - 90 minutes prior to surgery. In colorectal surgery, administration of **INOXIPHIN** with or without a 5- nitroimidazole, e.g. ornidazole, (separate administration: see Method of administration below) has been proven effective.

Impaired renal and hepatic function

In patients with impaired renal function, there is no need to reduce the dosage of **INOXIPHIN**, provided that the hepatic function is intact. In cases of severe renal failure (creatinine clearance < 10 L /min) the **INOXIPHIN** dosage should not exceed 2 g daily. In patients with liver damage, there is no need for the dosage to be reduced, provided renal function is intact.

Method of administration:

INOXIPHIN must be reconstituted prior to use. As a general rule, however, the solutions should be used immediately after preparation.

Intramuscular injection

INOXIPHIN must be injected well within the body of a relatively large muscle. It is recommended that not more than 1 g be injected at one site (see section 6.6).

Intravenous injection

The intravenous administration should be given over 2 - 4 minutes (see section 6.6).

Intravenous infusion:

The infusion should be given over a period of at least 30 minutes (see section 6.6).

4.3 Contraindications

Hypersensitivity to ceftriaxone or any other cephalosporin or any of the ingredient excipients of **INOXIPHIN** listed in section 6.1.

History of hypersensitivity to any other type of beta-lactam antibacterial medicine (penicillins, monobactams and carbapenems), the possibility of allergic cross-reactions should be borne in mind.

INOXIPHIN is contraindicated in:

Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age) *

Full-term neonates (up to 28 days of age):

- with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired*
- if they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt (see sections 4.4, 4.8 and 6.2*).*

* *In vitro* studies have shown that **INOXIPHIN** can displace bilirubin from its serum albumin binding sites leading to a possible risk of bilirubin encephalopathy in these patients.

Contraindications to lidocaine (lignocaine) must be excluded before intramuscular injection of. Ceftriaxone when lidocaine solution is used as a solvent (see section 4.4). See information in the professional information of lidocaine (lignocaine), especially contraindications.

INOXIPHIN solutions containing lidocaine (lignocaine) should never be administered intravenously.

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

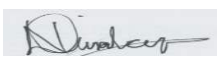
Hypersensitivity reactions

As with all beta-lactam antibacterial medicines, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). In case of severe hypersensitivity reactions, treatment with **INOXIPHIN** 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 severe hypersensitivity reactions to ceftriaxone as in **INOXIPHIN**, to other cephalosporins or to any other type of beta-lactam medicine. Caution should be used if **INOXIPHIN** 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 or Lyell's syndrome/toxic epidermal necrolysis and 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 **INOXIPHIN** treatment; however, the frequency of these events is not known (see section 4.8). When SCAR is suspected **INOXIPHIN** should be discontinued.

Interaction with calcium containing products

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term neonates aged less than 1 month have been described. At

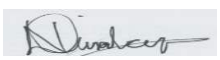


least one of them had received ceftriaxone as in **INOXIPHIN** and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with ceftriaxone as in **INOXIPHIN** and calcium-containing solutions or any other calcium-containing products. *In vitro* studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age **INOXIPHIN** must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age **INOXIPHIN** 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 total parenteral nutrition (TPN) solutions, healthcare provider may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If the use of **INOXIPHIN** is considered necessary in patients requiring continuous nutrition, TPN solutions and **INOXIPHIN** can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion and the infusion lines flushed between solutions (see sections 4.3, 4.8, 5.2 and 6.2).

Paediatric population

Safety and effectiveness of ceftriaxone as in **INOXIPHIN** 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 as in **INOXIPHIN**, like some other cephalosporins, can displace bilirubin from serum albumin.

INOXIPHIN 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 **INOXIPHIN** (see section 4.8). Severe cases of haemolytic anaemia, including fatalities, have been reported during **INOXIPHIN** treatment in both adults and children.

If a patient develops anaemia while on **INOXIPHIN**, the diagnosis of a cephalosporin-associated anaemia should be considered and **INOXIPHIN** 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 medicines, including ceftriaxone as in **INOXIPHIN**, 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 **INOXIPHIN** (see section 4.8). Discontinuation of therapy with **INOXIPHIN** and the administration of specific treatment for *Clostridium*

difficile should be considered. Appropriate fluid and electrolyte management should be instituted. 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

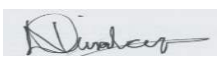
Interference with Coombs tests may occur, as ceftriaxone as in **INOXIPHIN** may lead to false-positive test results. Ceftriaxone as in **INOXIPHIN** can also lead to false-positive test results for galactosaemia (see section 4.8).

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

The presence of ceftriaxone as in **INOXIPHIN** 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 **INOXIPHIN** has a limited spectrum of antibacterial activity and may not be suitable for use as a single medicine 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 **INOXIPHIN**, 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 **INOXIPHIN** 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 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 **INOXIPHIN** doses of 1 g per day and above. Caution should be particularly considered in the paediatric population. Such precipitates disappear after discontinuation of **INOXIPHIN** 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 **INOXIPHIN** 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 **INOXIPHIN** (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 **INOXIPHIN** (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 **INOXIPHIN** treatment is started. JHR is usually a self - limiting condition or can be managed by symptomatic treatment. **INOXIPHIN** treatment should not be discontinued if such reaction occurs.

Sodium

Each gram of **INOXIPHIN** contains 3.6 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

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute **INOXIPHIN** vials or to further dilute a reconstituted vial for

intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when **INOXIPHIN** is mixed with calcium-containing solutions in the same intravenous administration line. **INOXIPHIN** 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, **INOXIPHIN** 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).

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 **INOXIPHIN** (see section 4.8).

No impairment of renal function has been observed after concurrent administration of large doses of **INOXIPHIN** and potent diuretics (e.g. furosemide). There is no evidence that **INOXIPHIN** increases renal toxicity of aminoglycosides

It was reported that in an *in-vitro* study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone as in **INOXIPHIN**.

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

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

Ceftriaxone as in **INOXIPHIN** like other antibiotics, may result in false-positive tests for galactosaemia.

Likewise, non-enzymatic methods for glucose determination in urine may yield false-positive results. For this reason, glucose level determination in urine during therapy with ceftriaxone as in **INOXIPHIN** should be carried out enzymatically.

Simultaneous administration of probenecid does not reduce the elimination of **INOXIPHIN** ceftriaxone.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in human pregnancy has not been established. Ceftriaxone crosses the placental barrier.

Breast feeding

Ceftriaxone as in **INOXIPHIN** is excreted into human milk in low concentrations, caution is advised in breastfeeding mothers. However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from **INOXIPHIN** therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

INOXIPHIN may cause dizziness, which may influence the ability to rive and use machines. Patients should not drive or operate machines until they know how **INOXIPHIN** affects them.

4.8 Undesirable effects

Infections and infestation:

Less frequent: Genital fungal infection, pseudomembranous colitis.

Frequency not known: Superinfection

Blood and lymphatic system disorders:

***Frequent**:* Eosinophilia, leucopenia, thrombocytopenia, hematoma

***Less frequent**:* Granulocytopenia, anaemia, coagulopathy

***Frequency not known*:** Haemolytic anaemia, agranulocytosis

Immune system disorders:

Frequency not known: Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, Jarisch-Herxheimer reaction

Nervous system disorders:

***Less frequent**:* Headache, dizziness.

Frequency not known: Convulsion

Ear and labyrinth disorders:

***Frequency not known**:* Vertigo

Respiratory a, thoracic and mediastinal disorders

***Less frequent**:* Bronchospasm

Gastrointestinal disorders:

***Frequen**t:* Diarrhoea, loose stools

***Less frequent**:* Nausea.

Frequency not known: Pancreatitis, stomatitis, and glossitis

Hepatobiliary disorders:

Frequent: Hepatic enzyme increased

***Frequency not known**:* Gall bladder precipitation of ceftriaxone, kernicterus,

***Hepatotoxicity*.**

Skin and subcutaneous tissue disorders:

***Frequent**:* Rash, pruritis, petechiae, purpura, diaphoresis, flushing, urticaria, allergic dermatitis, exanthema.

***Frequency not known**: Stevens* Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis (AGEP), oedema, drug reaction with eosinophilia and systemic symptoms (DRESS) and exfoliative dermatitis.

Renal and urinary disorders:

***Less frequent**:* Haematuria, glycosuria.

***Frequency not known**:* Oliguria, renal precipitation (reversible)

General disorders and administration site conditions:

***Less frequent**:* Phlebitis, injection site pain, pyrexia, oedema, chills (shivering)

Investigations:

***Less frequent**:* Blood creatinine increased.

***Frequency not known**:* Coomb's test false positive, galactosaemia test false positive, non-enzymatic methods for glucose determination false positive

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 overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Plasma concentrations of ceftriaxone as in **INOXIPHIN** cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdose should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A20.1.1 Broad and medium spectrum antibiotics.

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 micro- organisms.

Ceftriaxone is stable to most β-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria. Ceftriaxone is usually active against the micro-organisms *in vitr*o and in clinical infections. See section 4.1,

Inherent 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

5.2 Pharmacokinetic properties

Except the elimination half-life of ceftriaxone, it has non-linear, dose dependent pharmacokinetic parameters.

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 volume of distribution of ceftriaxone is 7 - 12 litres. Ceftriaxone is widely distributed in tissue and body fluids. Concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in 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.

Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in concentration. Owing to the lower albumin content the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

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 of **INOXIPHIN** in doses of 50 – 100 mg/kg (neonates and infants respectively). Peak concentration in CSF is reached about 4 hours after IV injection and gives an average value of 18 mg/ℓ. Mean CSF levels are 17 % of plasma concentrations in patients with bacterial meningitis and 4 % in patients with aseptic meningitis.

The average 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

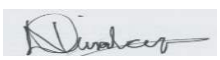


table below.

Average pharmacokinetic parameters of ceftriaxone in paediatric patients with meningitis

	50 mg/kg IV	75 mg/kg IV
Maximum Plasma Concentrations (ug/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	5.6	6.4

(ug/mL)		
Range (ug/mL)	1.3-18.5	1.3-44
Time after dose (hr)	3.7(±1.6)	3.3(±1.4)

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

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

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

Elimination: In young adults, the total plasma clearance is 10 - 22 mℓ/min. The renal clearance is 5 - 12 mℓ/min. 50 - 60 % 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.

Special populations

Paediatric and elderly patients

In neonates, urinary recovery accounts for about 70 % of the dose. In infants aged

less than 8 days and in elderly persons aged over 75 years, the average elimination half-life is usually 2 - 3 times that in young adults.

Patients with renal or hepatic dysfunction:

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone is only minimally altered, and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased. If liver function alone is impaired, renal elimination is increased.

5.3 Pre-Clinical safety data

There is evidence from animal studies that high doses of **INOXIPHIN** calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity. Carcinogenicity studies on **INOXIPHIN** were not conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

There are no excipients in **INOXIPHIN**

6.2 Incompatibilities

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

Diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute **INOXIPHIN** vials or bottles or to further dilute a reconstituted vial or bottle for intravenous administration because a precipitate can form (see section 4.2, 4.3, 4.4 and 4.8).

If treatment with a combination of another antibiotic with **INOXIPHIN** is intended, administration should not occur in the same syringe or in the same infusion solution.

INOXIPHIN must not be mixed with other medicines except those mentioned in section 6.6 (1% Lidocaine Hydrochloride solution (for intramuscular injection only).

Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2-8 °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 solution is of no significance for the efficacy or tolerance of the medicine.

Intramuscular injection

For IM injection, **INOXIPHIN 250 mg** or **500 mg** is dissolved in 2 L mℓ and **PRODUCT NAME 1 g** in 3,5 L mℓ, of water for injection. **INOXIPHIN** dissolved in a 1 % lidocaine (lignocaine) solution instead of water for injection can reduce pain at the site of injection. Reconstitution with 1 % lidocaine (lignocaine) (without adrenaline) has no effect on the absorption or the elimination of **INOXIPHIN**. The lidocaine (lignocaine) solution must never be administered intravenously.

Intravenous injection

For IV injection, **INOXIPHIN 250 mg** or **500 mg** is dissolved in 5 mℓ, and **INOXIPHIN 1 g** in 10 mℓ sterile water for injection.

Intravenous infusion:

For IV infusion, 2 g of **INOXIPHIN** 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 %; hydroxyethyl starch 6 - 10 % infusions; sterile water for injection. **INOXIPHIN** solutions should not be mixed with or piggybacked into solutions containing other antimicrobial medicines or into diluent solutions other than those listed above, owing to possible incompatibility.

6.3 Shelf life

2 years from date of manufacturing

Reconstituted solutions: 6 hours at room temperature (at or below 25 °C) or 24 hours in the refrigerator

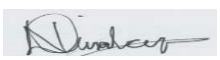
(2-8 °C).

6.4 Special Precautions for storage

Store at or below 25 °C. Keep product in outer container until required for use.

Storage Directions for Reconstituted Product:

Store for up to 6 hours at or below 25 °C or 24 hours in the refrigerator at or below 2 - 8 °C. This medicine should not be used after the expiry date (EXP) shown on the pack



6.5 Nature and contents of container

Packs for IM or IV injection containing:

INOXIPHIN 250 mg: 1vial with dry substance equivalent to 250 mg ceftriaxone packed in a unit carton

INOXIPHIN 500 mg: 1vial with dry substance equivalent to 500 mg ceftriaxone packed in a unit carton

INOXIPHIN 1 g: 1 vial with dry substance equivalent to 1 g ceftriaxone packed in a unit carton.

Pack for IV infusion containing:

INOXIPHIN 2 g: 1 vial with dry substance equivalent to 2 g ceftriaxone packed in a unit carton.

INOXIPHIN 250 mg, INOXIPHIN 500 mg and INOXIPHIN 1g:

Almost white or yellowish crystalline powder filled in 15 mL moulded Type I clear glass vials with 20 mm grey bromobutyl rubber stoppers and sealed with aluminium seal with a white coloured poly propylene disc for the 250 mg strength, cream coloured poly propylene disc for the 500 mg strength and chrome yellow for the 1 g strength.

INOXIPHIN 2 g

Almost white or yellowish crystalline powder. filled in 50 mL moulded Type I clear glass vials with 20 mm grey bromobutyl rubber stoppers and sealed with aluminium seal with a lemon-yellow coloured poly propylene disc.

6.6 Special precautions for disposal and other handling

Preparation of solutions for injection and infusion:

The use of freshly prepared solutions is recommended. For storage conditions of the reconstituted medicine , see section 6.3.

INOXIPHIN 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals (Pty) LTD

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. REGISTRATION NUMBERS

INOXIPHIN 250 mg 51/20.1.1/0770

INOXIPHIN 500 mg 51/20.1.1/0771

INOXIPHIN 1 g 51/20.1.1/0772

INOXIPHIN 2 g 51/20.1.1/0773

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

October 2020

10. DATE OF REVISION OF THE TEXT

22 August 2023