Professional Prescribing Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

KLAFOTAXIM 500 INJECTION

KLAFOTAXIM 1000 INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KLAFOTAXIM 500 INJECTION

Each vial contains cefotaxime sodium equivalent to cefotaxime 500 mg.

KLAFOTAXIME 1000 INJECTION

Each vial contains cefotaxime sodium equivalent to cefotaxime 1000 mg.

Sugar free.

Contains sodium:

KLAFOTAXIM 500: Each gram of cefotaxime contains approximately 24,12 mg of sodium.

KLAFOTAXIM 1000: Each gram of cefotaxime contains approximately 48,25 mg of sodium.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

KLAFOTAXIM 500 INJECTION: Off white to pale yellow powder contained in 10 ml, flint USP type III, glass vials with grey butyl rubber stoppers and flip off opaque green tamper proof seals.

It gives pale yellow solution when reconstituted with water for injection (BP) within 2 minutes shaking as directed on the label.

KLAFOTAXIM 1000 INJECTION: Off white to pale yellow powder contained in 10 ml, flint USP type III, glass vials with 20 mm grey butyl rubber stoppers and 20 mm tear off plain aluminium seals.

It gives pale yellow solution when reconstituted with water for injection (BP) within 2 minutes shaking as directed on the label.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KLAFOTAXIM INJECTION is primarily indicated for genito-urinary tract infections, infections of the skin and soft tissues, respiratory tract infections, infections of the gastro-intestinal tract and meningitis in children due to the following susceptible strains of organisms:

Infections due to *Streptococcus* (Group D *Streptococci and B-haemolytic Streptococci):*

Otitis media, sinusitis, pneumonia, pharyngitis, follicular tonsillitis,

scarlet fever, urinary tract infections, (enterococci), meningitis in children, septic sore throat and cellulitis.

Infections due to *Staphylococcus* (Infections of non-penicillinase-

and penicillinase producing strains included):

Bronchitis, impetigo, furunculosis and abscess.

Infections due to *Escherichia coli:*

Infections of the urinary tract, meningitis in paediatrics and lobar pneumonia.

Infections due to *Haemophilius* influenzae:

Meningitis in paediatrics, otitis media and bronchitis of the larynx and trachea.

***Gonococcal* infections:**

Gonorrhoea.

Infections due to *Neisseria meningitides:*

Paediatric meningitis.

Infections due to *Salmonella:*

Enteritis.

Infections due to *Shigella:*

Dysentery (Bacillus).

***Pseudomonoas aeruginosa* (Sensitive strains):**

Sepsis

Infections due to *Pneumococcus:*

Cellulitis, lobar pneumonia, otitis and bronchitis.

The causative organisms and its sensitivity to cefotaxime sodium must be determined by means of bacteriological studies.

Prophylatically:

If administered peri-operatively in patients undergoing surgery, **KLAFOTAXIM INJECTION** may reduce the incidences of potentially contaminating post-operative infections. 1 g of **KLAFOTAXIM INJECTION** administered half-an-hour

(30 mins) to one-and-a-half hours (90 mins) before surgery has been found to be the **minimum effective dose.**

4.2 Posology and method of administration

Posology

Prophylactically: The minimum effective dose has been found to be 1 g

KLAFOTAXIM INJECTION 30 – 90 minutes prior to surgery.

Adults:

A 2 g dose per day is usually administered by means of two (2) by 1000 mg (1 g) injections in divided doses.

Daily doses of 3 to 4 g in two (2) to four (4) administrations may be given in severe cases.

Paediatrics:

Infants and Children:

A daily dose of 50 - 100 mg/kg body mass in two (2) to four (4) injections is usually recommended.

Up to 200 mg/kg body mass daily may be administered in exceptional cases.

Neonates:

The recommended dosage regimen for neonates is as follows:

0 - 7 days (1 week) of age: 50 mg/kg IV at 12 hour intervals.

7 -2 8 days (1 - 4 weeks) of age: 50 mg/kg IV at 8 hour intervals

The dosages above are applicable to both premature and full term infants.

Renal Failure:

Half the recommended dosage of **KLAFOTAXIM INJECTION** should be administered to patients with creatinine clearances of 20 ml/minute.

The dosage interval must not be changed.

Method of administration

For intravenous use.

4.3 Contraindications

- Hypersensitivity to cefotaxime sodium, or to any of the excipients of **KLAFOTAXIM INJECTION** listed in Section 6.1.
- **KLAFOTAXIM INJECTION** is contra-indicated in subjects allergic to cephalosporins.

4.4 Special warnings and precautions for use

KLAFOTAXIM INJECTION must be used with caution in patients allergic or sensitive to penicillin. Medical supervision (strict) should be exercised throughout therapy.

Cefotaxime sodium should not be given to patients who are hypersensitive to it or to other cephalosporins. About 10 % of penicillin-sensitive patients may also be allergic to cephalosporins although the true incidence is uncertain: great are should be taken if cefotaxime is to be given to such patients. Care is also necessary in patients with known histories of allergy. Cefotaxime sodium should be given with caution to patients with renal impairment: a dosage reduction may be necessary. Renal and haematological status should be monitored especially during prolonged and high-dose therapy.

KLAFOTAXIM INJECTION contains sodium.

KLAFOTAXIM INJECTION 500: This medicinal product contains 24,12 mg sodium per 500 mg vial, equivalent to 1,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

KLAFOTAXIM INJECTION 1000: This medicinal product contains 48,25 mg sodium per 500 mg vial, equivalent to 2,4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Cefotaxime may interfere with the Jaffé method of measuring creatinine concentrations and may produce falsely high values; this should be borne in mind when measuring renal function.

Positive results to the direct Coombs' test have been found during treatment with cefotaxime and these can interfere with blood crossmatching. The urine of patients being treated with cefotaxime may give false-positive reactions for glucose using copper-reduction reactions. The concomitant use of a nephrotoxic drug such as the aminoglycoside antibiotic gentamicin may increase the risk

of kidney damage with cefotaxime. There is also some evidence for enhanced nephrotoxicity with a loop diuretic like frusemide. The renal excretion of cefotaxime is inhibited by pnobenecid. There may be antagonism between cefotaxime and bacteriostatic antibacterial agents.

General reactions: Skin eruptions, fever, eosinophilia and cases of diarrhoea, transient leucopaenia and temporary elevation of transaminases and alkaline phosphatases have been recorded.

INTERACTION WITH LABORATORY TESTS:

A false positive reaction can occur on testing for glucose in the urine with reducing substances, but this can be avoided with the use of methods that are specific to gluco-oxidase (enzymatic methods).

4.6 Fertility, pregnancy and lactation

It has not yet been established whether the product is safe in pregnancy, although animal studies have not shown any teratogenic effects.

4.7 Effects on ability to drive and use machines

KLAFOTAXIM INJECTION has been associated with dizziness, which may affect the ability to drive or operate machinery.

High doses of **KLAFOTAXIM INJECTION,** particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions). Patients should be advised not to drive or operate machinery if any such symptoms occur.

4.8 Undesirable effects

System Organ Class	Frequent	Less frequent	Frequency unknown
Blood and lymphatic system disorders		Eosinophilia, leucopenia, thrombocytopenia (reversible), bleeding complications related to hypoprothrombinaemia and/or platelet dysfunction	Granulocytopenia, agranulocytosis, neutropenia, haemolytic anaemia
Immune system disorders		Jarisch-Herxheimer reaction	Anaphylactic reactions, angioedema, bronchospasm, anaphylactic shock
Cardiac disorders			Arrhythmia following rapid bolus infusion through a central venous catheter

Nervous system disorders		Convulsions	Headache, dizziness, encephalopathy (e.g. impairment of consciousness abnormal movements)
Gastrointestinal disorders		Diarrhoea,	Nausea, vomiting, abdominal pain, pseudomembranous colitis
Hepatobiliary disorders		Increase in liver enzymes and/or bilirubin	Hepatitis, cholestatic jaundice
Renal and urinary disorders		Decrease in renal function/increase of creatinine (particularly when co-prescribed with aminoglycosides)	Interstitial nephritis, candidiasis
Skin and subcutaneous tissue disorders	Hypersensitivity reactions including skin rashes and pruritus.	Rash, pruritus, urticaria	Erythema multiforme, Steven-Johnson syndrome, toxic epidermal necrolysis
General disorders and administration site condition	Tenderness and pain at the injection site	Fever, inflammatory reactions at the injection site, including phlebitis/thrombophlebitis	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing 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 Reaction Reporting Form”, found online under SAHPRA’s publications.

http://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See “Section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects”.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1. Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins. ATC code: J01D A10

Mechanism of Action:

Cefotaxime is a semi-synthetic cephalosporin antibiotic. It has a broad spectrum of activity against both Gram-negative and Gram-positive bacteria.

Cefotaxime has a bactericidal mode of action and has a high degree of stability in the presence of R-lactamases.

Mechanisms of resistance

Resistance to Cefotaxime may be due to production of extended-spectrum beta-lactamases that can efficiently hydrolyse the drug, to the induction and/or constitutive expression of AmpC enzymes, to impermeability or to efflux pump mechanisms. More than one of these possible mechanisms may co-exist in a single bacterium.

5.2 Pharmacokinetic properties

Cefotaxime is given by injection as the sodium salt. It is rapidly absorbed after intramuscular injection and mean peak plasma concentrations of about 12 and 20 micrograms/rnL have occurred 30 minutes after doses of 500 mg and 1 g of cefotaxirne, respectively. Immediately after intravenous injection of 0,5, 1, or 2 g of cefotaxime, mean peak plasma concentrations of 38, 102, and 215 micrograms/rnl, respectively, have occurred with concentrations ranging from about 1 to 3 micrograms/rnl after 4 hours. The plasma half-life of cefotaxime is about 1 hour and that of the active metabolite desacetylcefotaxime about 1.5 hours; half-lives are increased in neonates and

in patients with severe renal impairment, especially those of the metabolite, and a reduction in dosage may be necessary. The effects of liver disease on clearance of cefotaxime and its metabolite have been variable, but in general dosage adjustment has not been considered necessary. About 40 % of cefotaxime is reported to be bound to plasma proteins.

Cefotaxime and desacetylcefotaxime are widely distributed in body tissues and fluids; therapeutic concentrations occur in the CSF particularly when the meninges are inflamed. Cefotaxime crosses the placenta and low concentrations have been detected in breast milk.

After partial metabolism in the liver to desacetylcefotaxime and inactive metabolites, elimination is mainly by the kidneys and about 40 to 60 % of a dose has been recovered unchanged in the urine within 24 hours; a further 20 % is excreted as the desacetyl metabolite. Relatively high concentrations of cefotaxime and desacetylcefotaxime occur in bile and about 20 % of a dose has been recovered in the faeces.

Probenecid competes for renal tubular secretion with cefotaxime resulting in higher and prolonged plasma concentrations of cefotaxime and its desacetyl metabolite. Cefotaxime and its metabolites are removed by haemodialysis.

When microbiological assays have been used, reported pharmacokinetic values may relate to cefotaxime plus its active metabolite, desacetylcefotaxime.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

Cefotaxime sodium has been reported to be incompatible with alkaline solutions such as sodium bicarbonate.

Cefotaxime should be given separately from aminogylcosides. If they are used concurrently they should be administered in separate sites.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place, at or below 25 °C. Protect from light.

Do not freeze.

Discard any unused portion.

Do not remove vials from unit carton until required for use.

Reconstituted solution to be stored in original vial.

6.5 Nature and contents of container

KLAFOTAXIM INJECTION 500: 10 ml flint vial, containing 500 mg powder for reconstitution.

KLAFOTAXIM INJECTION 1000 INJECTION: 10 ml flint vial, containing 1000 mg powder for reconstitution.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.

Therapeutically: KLAFOTAXIM INJECTION must be dissolved in Water for Injection (BP) as indicated below. The reconstituted injection must be shaken well until it is dissolved. The entire (reconstituted) contents must be withdrawn from the vial into an unused syringe and must be used immediately.

VIAL SIZE	ROUTE OF ADMINISTRATION	VOLUME OF WFI REQUIRED

500 mg	IM / IV	2 ml
1000 mg	IM / IV	4 ml

Intravenous infusion: **KLAFOTAXIM INJECTION** may also be given via intravenous infusion:

The **KLAFOTAXIM INJECTION 1000 INJECTION** (1 g vials) may be administered by intravenous infusion by dissolving 1 to 2 vials (1 to 2 g) in 40 to 100 ml of Water for Injection (BP) or in the fluids listed under heading *"Infusion fluids-Stability".*

Administer the prepared infusion solution over a period of 20 to 60 minutes.

Infusion Fluids - Stability

Reconstituted solutions of **KLAFOTAXIM INJECTION** sterile may be diluted in any one of the following solutions:

0,9 % Sodium chloride injection, 5 % or 10 % dextrose injection, 5 % dextrose and 0.45 % sodium chloride injection, 5 % dextrose or 0.2 % sodium chloride injection, Lactated Ringer's solution, sodium lactate injection, 10 % invert sugar injection. Solution of **KLAFOTAXIM INJECTION** sterile reconstituted in 0,9 % sodium chloride injection or 5 % dextrose injection in Viaflex^{R} plastic containers maintain satisfactory potency for 24 hours (at or below 22 °C), 5 days under refrigeration (at or below 5 °C). DO NOT FREEZE.

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose must be administered for at least 10 days. The freshly prepared solution must be used.

KLAFOTAXIM INJECTION injection should not be mixed with another antibiotic in the same infusion or syringe.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd.

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8 REGISTRATION NUMBER(S)

KLAFOTAXIM 500 INJECTION	31/20.1.1/0328 (S.A)
KLAFOTAXIM 500 INJECTION	NS2 10/20.1.1/0155 (Namibia)
KLAFOTAXIM 1000 INJECTION	31/20.1.1/0329 (S.A)
KLAFOTAXIM 1000 INJECTION	NS2 10/20.1.1/0156 (Namibia)
KLAFOTAXIM 1000 INJECTION	S2 BOT 0500805

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 October 1998

10 DATE OF REVISON OF THE TEXT

11 November 2022