PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S4**

1. NAME OF THE MEDICINE

CLOXACILLIN FRESENIUS 250 mg powder for solution for injection

CLOXACILLIN FRESENIUS 500 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CLOXACILLIN FRESENIUS 250 mg

Each vial contains cloxacillin sodium equivalent to cloxacillin 250 mg.

CLOXACILLIN FRESENIUS 500 mg

Each vial contains cloxacillin sodium equivalent to cloxacillin 500 mg.

Sugar free

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

CLOXACILLIN FRESENIUS 250 mg: A white crystalline hygroscopic powder in a clear glass vial.

CLOXACILLIN FRESENIUS 500 mg: A white crystalline hygroscopic powder in a clear glass vial.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CLOXACILLIN FRESENIUS is indicated for the treatment of infections caused by penicillinase-producing staphylococci that are resistant to benzyl-penicillin, such as in:

- abscesses (skin and soft tissue);
- cellulitis;
- bacteraemia (septicaemia);
- endocarditis;

- pneumonia (respiratory tract);
- osteomyelitis (bone and joints).

4.2. Posology and method of administration

Please note: The reconstituted solution must be shaken well before use.

It is recommended that a needle not larger than 21 gauge is used to reduce fragmentation of the rubber stopper.

Route	Dosage (for Adults)	Method of Administration
IM Injection	250 mg 4 - 6 hourly	The contents of each vial should be dissolved in 1,5 mL of water for injection
Slow IV Injection	500 mg every 4 - 6 hours	500 mg of CLOXACILLIN FRESENIUS to be given over 3 to 4 minutes dissolved in 10 - 20 mL water for injection
IV Infusion	500 mg every 4 - 6 hours	CLOXACILLIN FRESENIUS is compatible with (the commonly used IV fluids) sodium chloride 0,9 % and dextrose 5 % in water and may be added to the drip container, or preferably, injected directly into the drip tube over a period of 2 - 3 minutes.

All systemic dosages may be doubled in severe infections.

Route	Dosage (for Adults)	Method of Administration
Intrapleural Injection	500 mg daily	250 mg to 500 mg CLOXACILLIN FRESENIUS to be dissolved in 2 – 5 mL of water for injections.
Intra-articular injection	500 mg daily	250 mg to 500 mg CLOXACILLIN FRESENIUS to be dissolved in 2 - 5 mL of water for injection. 0,5 % Lignocaine hydrochloride may be used as a local anaesthetic, if desired.

Paediatric population

Dosage for children: 12,5 to 25 mg/kg every 6 hours.

Under 2 years: ¼ of adult dose

2 to 10 years: ½ of adult dose

4.3. Contraindications

- Patients with hypersensitivity to cloxacillin.
- Patients with a history of penicillin allergy.
- Neonates born of mothers sensitive to penicillins.
- Patients allergic to cephalosporins may also be allergic to penicillins.
- CLOXACILLIN FRESENIUS should not be administered by sub-conjunctival injection or used as an eye drop.
- Intrathecal administration of CLOXACILLIN FRESENIUS should be avoided, since CLOXACILLIN FRESENIUS is a potent convulsant when given via this route.

4.4. Special warnings and precautions for use

Use with care in jaundiced neonates.

Incompatible with aminoglycosides, tetracyclines, erythromycin and polymyxin B (see section 4.5).

CLOXACILLIN FRESENIUS crosses the placenta and is distributed into breast milk (see section 4.6).

CLOXACILLIN FRESENIUS has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Renal, hepatic and haematological systems should be monitored during prolonged and high dose therapy.

Care should be taken when administering high doses of CLOXACILLIN FRESENIUS especially to patients with impaired renal function as there is a risk of neurotoxicity.

Plasma concentrations are enhanced if probenecid is given concomitantly (see section 4.5).

CLOXACILLIN FRESENIUS may also interact with bacteriostatic antibacterials such as

chloramphenicol and tetracyclines that interfere with active bacterial growth necessary for cloxacillin to achieve its effect.

Reduced concentrations in patients with cystic fibrosis have been attributed to enhanced non-renal clearance of CLOXACILLIN FRESENIUS.

CLOXACILLIN FRESENIUS is not removed by haemodialysis.

Sensitivity reactions may include skin rashes, angioedema, bronchospasm, serum sickness and anaphylaxis, and sometimes death within minutes.

Treatment with epinephrine (adrenaline), corticosteroids, aminophyllin or antihistamine may be necessary. A generalised sensitivity reaction can develop within a few hours or weeks of commencing treatment, including urticaria, fever, joint pains and eosinophilia. Other allergic reactions include exfoliative dermatitis and other skin reactions, interstitial nephritis and vasculitis. Haemolytic anaemia, leucopoenia, prolonged bleeding time and defective platelet function.

Superinfection with *C. albicans*, other fungi or organisms resistant to CLOXACILLIN FRESENIUS may occur.

Patients with syphilis may exhibit the Jarish–Herxheimer reaction and should also therefore be monitored.

A skin test for sensitivity may be used to determine those patients most likely to develop allergic reactions to penicillins.

4.5. Interaction with other medicines and other forms of interaction

Aminoglycosides and CLOXACILLIN FRESENIUS are physically and/or chemically incompatible and can mutually inactivate each other *in vitro*. *In vitro* mixing of CLOXACILLIN FRESENIUS and aminoglycosides should be avoided during concomitant therapy, and the medicines should be administered separately (see section 4.4).

CLOXACILLIN FRESENIUS may also interact with bacteriostatic antibacterials such as chloramphenicol and tetracyclines that interfere with active bacterial growth necessary for cloxacillin to achieve its effect.

The possibility of a prolonged bleeding time should be borne in mind in patients receiving anticoagulants.

CLOXACILLIN FRESENIUS may decrease the efficacy of oral contraceptives.

CLOXACILLIN FRESENIUS may enhance the effects of methotrexate, by decreasing its renal excretion.

As with other penicillins, concurrent administration of probenecid enhances the serum concentration of cloxacillin.

4.6. Fertility, pregnancy and lactation

Pregnancy

The safety of this preparation in pregnancy has not been established.

Breastfeeding

Penicillins including CLOXACILLIN FRESENIUS pass into the breastmilk. Even though only small amounts may pass into breastmilk, allergic reactions associated with penicillin side effects may occur.

4.7. Effects on ability to drive and use machines

The effect on the ability to drive and operate machinery is unknown however care should be taken due to the risk of convulsions.

4.8. Undesirable effects

Tabulated list of adverse reactions

System Organ Class	***Frequency***	***Side effects***
Blood and lymphatic system disorders	Less frequent	Leucopoenia, defective platelet function, neutropenia
Immune system disorders	Less frequent	Allergic reactions such as skin rashes, angioedema, bronchospasm, serum sickness, anaphylaxis, and

		sometimes death within minutes, exfoliative dermatitis, interstitial nephritis
Nervous system disorders	Less frequent	Convulsions and signs of toxicity to the CNS may occur with intravenous administration or in patients with renal failure.
Vascular disorders	Frequency unknown	Phlebitis, thrombophlebitis
Gastrointestinal disorders	Frequent	sore mouth or tongue; transient diarrhoea; nausea, vomiting
	Frequency unknown	black hairy tongue, heartburn, pruritus ani, pseudomembranous colitis, epigastric discomfort, flatulence, loose stools
Hepato-biliary disorders	Frequency unknown	Increases in liver enzyme values, hepatitis, cholestatic jaundice
Skin and subcutaneous tissue disorders	Less frequent	Pain and sterile inflammatory reaction at the site of intra-muscular injection,

Description of selected adverse reactions

The following side effects have been reported and the ***frequencies are unknown:***

Infections and Infestations: Symptoms due to overgrowth of non-susceptible organisms (Aerobacter aerogenes, Pseudomonas, Candida, etc.) may appear and then CLOXACILLIN FRESENIUS should be discontinued and specific or supportive therapy instituted.

Blood and lymphatic system disorders: Haemolytic anaemia and prolongation of bleeding time, usually following high intravenous doses.

Eosinophilia, thrombocytopenia, thrombocytopenic, purpura, and agranulocytosis have been reported during therapy with penicillins.

Immune system disorders: Treatment with epinephrine (adrenaline), corticosteroids, aminophylline or antihistamine may be necessary.
When CLOXACILLIN FRESENIUS is administered to a hypersensitive patient, allergic reactions may occur including urticaria and skin rashes, exfoliative dermatitis, interstitial nephritis, vasculitis, eosinophilia, angioneurotic oedema, fever and swollen joints. These reactions are more common after parenteral use but may occur after oral administration of any penicillin derivative in persons who have become hypersensitised after a previous course of treatment. The onset of symptoms varies; it may occur within a few hours or days of the beginning of treatment or not until therapy with a penicillin derivative is resumed on a subsequent occasion.

Nervous system disorders: The administration of high doses to children may cause cerebral irritation and convulsions.

Skin and subcutaneous tissue disorders: Erythema multiforme type of rash for up to 15 days after stopping administration.

General disorders and administrative site conditions: Care should be taken when treating patients with syphilis, as the Jarisch-Herxheimer reaction may occur shortly after starting treatment. This reaction, manifesting as fever, chills, headache and reactions at the site of the lesion, can be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as optic atrophy.

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 providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9. Overdose

Disturbance of electrolyte balance may occur following administration of large doses. Convulsions and other signs of toxicity to the central nervous system may occur with very high doses, particularly when administered intravenously to patients with renal failure, since patients with normal kidneys excrete penicillins at a fast rate. Nephrotoxicity may occur in patients with diminished renal function. Treatment of overdosage is symptomatic and supportive. No specific treatment can be recommended.

In patients with severe allergic reactions, general supportive measures (if the patient is in shock) or symptomatic therapy similar to that applied in all cases of hypersensitivity are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class of medicine: A.20.1.2. Penicillins

Cloxacillin is an isoxazolyl penicillin and is stable to penicillinase. It is active against penicillinase-producing staphylococci and, in general, is less effective against organisms susceptible to penicillin G e.g., Streptococci and Pneumococci, and is not useful against gram negative organisms.

Cloxacillin exerts a bacterial action against susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptides.

Resistant organisms:

Cloxacillin is active against both penicillin-sensitive and penicillin-resistant staphylococci, as well as Streptococcus pyogenes and Streptococcus pneumonia. However, it is less potent than penicillin G against penicillin-sensitive bacteria, and has very little activity against Enterococcus faecalis and gram-negative organisms.

5.2. Pharmacokinetic properties

Cloxacillin is rapidly but incompletely absorbed from the gastrointestinal tract (30-80 %). As absorption is more efficient on an empty stomach, it is ideally administered 1 hour before or 2 hours after meals. Peak concentrations in plasma are attained by 1 hour. It is highly bound to plasma albumin (>90 %) and is not removed from the circulation to a significant degree by haemodialysis. Cloxacillin is excreted rapidly by the kidneys. Normally, it is excreted in the urine within 6 hours of an oral dose. It is also eliminated in the bile.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

No excipients

6.2. Incompatibilities

This medicine must not be mixed with other medicines (see section 4.5).

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at or below 25 ºC.

Solutions for injection should preferably be freshly prepared but will retain their anti-bacterial potency for 24 hours at room temperature or for 4 days at 4 ºC.

6.5. Nature and contents of container

Packs of 10 and 50 vials.

The container closure system consists of 15 mL clear glass vials type II (Ph Eur), which after filling with the powder for injection is closed with a halobutyl stopper and plastic flip-off cap.

6.6. Special precautions for disposal and other handling

No special requirements for disposal.

For instructions on dilution before administration, see section 4.2.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House, Extension 7

Midrand, 1682

Gauteng

South Africa

Telephone number: +27 (0) 11 545 0000

8. REGISTRATION NUMBER(S)

CLOXACILLIN FRESENIUS 250 mg: M/20.1.2/227

CLOXACILLIN FRESENIUS 500 mg: M/20.1.2/228

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 November 2010

10. DATE OF REVISION OF TEXT

16 September 2024

Botswana:	250 mg: BOT08001156 S2
Namibia:	250 mg: NS2 90/20.1.2/0037
	500 mg: NS2 90/20.1.2/0038