1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

XIXIA-FLUCLOXACILLIN 250 250 mg capsules

XIXIA-FLUCLOXACILLIN S 125 mg/ 5 ml powder for suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

XIXIA-FLUCLOXACILLIN 250

Each hard gelatin capsule of XIXIA-FLUCLOXACILLIN 250 contains flucloxacillin sodium equivalent to 250 mg flucloxacillin per capsule.

Sugar free

XIXIA-FLUCLOXACILLIN S

Each 5 ml of reconstituted suspension contains flucloxacillin sodium equivalent to 125 mg flucloxacillin.

Preservative: sodium benzoate 0,13 % m/m

Contains sugar: Sucrose 3,332 mg per 5 ml

Contains sweetener: Saccharin sodium15,8 mg per 5 ml

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

XIXIA-FLUCLOXACILLIN 250 is a black/red capsule.

Suspension

XIXIA-FLUCLOXACILLIN S is a clear glass bottle containing a pinkish-white powder for reconstitution of an orange suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

XIXIA-FLUCLOXACILLIN is indicated in the treatment of infections caused by susceptible Gram-positive organisms, including beta-lactamase producing staphylococci and streptococci:

- Skin and soft tissue infections
- Orthopaedic infections
- Infected wounds and burns
- Septicaemia
- Otitis media
- Meningitis
- Urinary tract infections
- Endocarditis
- Respiratory tract infections caused by penicillinase-producing organisms
- Enterocolitis

4.2. Posology and method of administration

Posology

Adults

Each dose should be taken one hour before meals.

250 mg (one capsule or 10 ml suspension) 4 times a day preferably one hour before meals.

Skin and soft tissue infections

Up to 8 g daily in divided doses, six to eight hourly, one hour before meals.

Special populations

Renal impairment

For patients with a creatinine clearance value < 10 mL / min, consider a dose reduction or extension of dose interval. For patients with a creatinine clearance value > 10 mL / min, no dose adjustment is necessary.

Paediatric population

Children 2 – 10 years: 125 mg (5 ml suspension) 4 times a day preferably one hour before meals.

Children 2 months – 2 years: 62,5 mg (2,5 ml suspension) 4 times a day preferably one hour before meals.

Method of administration

For oral administration.

4.3. Contraindications

XIXIA-FLUCLOXACILLIN is contraindicated in:

- Patients with hypersensitivity to flucloxacillin sodium or other beta-lactam antibiotics (e.g. penicillins, cephalosporins) or to any excipients in XIXIA-FLUCLOXACILLIN (see section 6.1).
- patients with a previous history of flucloxacillin associated jaundice / hepatic dysfunction.

4.4. Special warnings and precautions for use

Hypersensitivity

Patients with a known history of allergy are more likely to develop a hypersensitivity reaction.

Previous hypersensitivity reactions to β-lactams

Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics, e.g. cephalosporins. Before initiating therapy with flucloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to β-lactams. Cross-sensitivity between penicillins and cephalosporins is well documented. Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving β-lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. These reactions are more likely to occur in individuals with a history of β-lactam hypersensitivity.

Allergic reactions may occur. These may present as a pruritic skin rash, an erythematous skin reaction or urticaria. If a skin rash occurs, treatment should be discontinued and administration of an antihistamine considered. If anaphylaxis occurs flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine). Ensure adequate airway and ventilation and give 100 % oxygen. IV crystalloids, hydrocortisone, antihistamine and nebulised bronchodilators may also be required.

Feverish Generalised Erythema

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP)

(see section 4.8). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contraindicated.

Impaired Renal Function

The use of flucloxacillin (like other penicillins) in patients with renal impairment does not usually require dosage reduction. In the presence of severe renal failure (creatinine clearance less than 10 mL/min), however, a reduction in dose or an extension of dose interval should be considered because of the risk of neurotoxicity.

Patients on Dialysis

Flucloxacillin is not significantly removed by dialysis and so no supplementary dosages need to be administered either during or at the end of the dialysis period.

Impaired Hepatic Function

Hepatitis and cholestatic jaundice have been reported. These reactions are related neither to the dose nor to the route of administration. Flucloxacillin should be used with caution in patients > 50 years or patients with underlying disease, all of whom are at increased risk of hepatic reactions. The onset of these hepatic effects may be delayed for up to two months post-treatment. In several cases, the course of the reactions has been protracted and lasted for some months. In very rare cases, a fatal outcome has been reported (see section 4.8).

General

As for other penicillins contact with the skin should be avoided as sensitisation may occur.

Prolonged use of an anti-infective agent may occasionally result in the overgrowth of non-susceptible organisms.

Newborns

Special caution is essential in the newborn because of the risk of hyperbilirubinaemia. Studies have shown that, at high dose following parenteral administration, flucloxacillin can displace bilirubin from plasma protein binding sites, and may therefore predispose to kernicterus in a jaundiced baby. In addition, special caution is essential in the newborn because of the potential for high serum levels of flucloxacillin due to a reduced rate of renal excretion.

Monitoring

During prolonged treatments (e.g. osteomyelitis, endocarditis), regular monitoring of hepatic and renal functions is recommended.

Patients taking Paracetamol

Caution is advised when flucloxacillin is administered concomitantly with paracetamol due to the increased risk of high anion gap metabolic acidosis (HAGMA). Patients at high risk of HAGMA are in particular those with severe renal impairment, sepsis or malnutrition especially if the maximum daily doses of paracetamol are used.

After co-administration of flucloxacillin and paracetamol, a close monitoring is recommended in order to detect the appearance of acid-base disorders, namely HAGMA, including the search of urinary 5-oxoproline.

If flucloxacillin is continued after cessation of paracetamol, it is advisable to ensure that there are no signals of HAGMA, as there is a possibility of flucloxacillin maintaining the clinical picture of HAGMA (see section 4.5).

Hypokalaemia

Hypokalaemia (potentially life threatening) can occur with the use of flucloxacillin, especially in high doses. Hypokalaemia caused by flucloxacillin can be resistant to

potassium supplementation. Regular measurements of potassium levels are recommended during the therapy with higher doses of flucloxacillin. Attention for this risk is warranted also when combining flucloxacillin with hypokalaemia-inducing diuretics or when other risk factors for the development of hypokalaemia are present (e.g. malnutrition, renal tubule disfunction).

Excipients

XIXIA-FLUCLOXACILLIN contains sodium benzoate

Sodium benzoate may increase jaundice in newborn babies (up to 4 weeks old). Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (nonconjugated bilirubin deposits in the brain tissue).

XIXIA-FLUCLOXACILLIN contains sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5. Interaction with other medicines and other forms of interaction

Probenecid and sulfinpyrazone

Probenecid and sulfinpyrazone slow down the excretion of flucloxacillin by decreasing tubular secretion.

Piperacillin

Other medicines, such as piperacillin, which are excreted via renal tubular secretion, may interfere with flucloxacillin elimination.

Oral typhoid vaccine

Oral typhoid vaccine may be inactivated by flucloxacillin.

Methotrexate

Flucloxacillin reduces the excretion of methotrexate which can cause methotrexate toxicity.

Sugammadex

Flucloxacillin may reduce the response to sugammadex.

Warfarin

There are cases of altered international normalised ratio (INR) in patients taking warfarin and prescribed a course of flucloxacillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored during addition or withdrawal of flucloxacillin.

Bacteriostatic medicines

Bacteriostatic medicines may interfere with the bactericidal action of flucloxacillin.

Paracetamol

Caution should be taken when flucloxacillin is used concomitantly with paracetamol as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors. (See section 4.4.)

Voriconazole

Flucloxacillin (CYP450 inducer) has been reported to significantly decrease plasma voriconazole concentrations. If concomitant administration of flucloxacillin with voriconazole cannot be avoided, monitor for potential loss of voriconazole effectiveness

(e.g. by therapeutic drug monitoring); increasing the dose of voriconazole may be needed.

4.6. Fertility, pregnancy and lactation

The safety of XIXIA-FLUCLOXACILLIN in pregnancy and lactation has not been established.

Pregnancy

Animal studies with flucloxacillin have shown no teratogenic effects. Flucloxacillin has been in clinical use since 1970 and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effects.

Safety in pregnancy has not yet been established and XIXIA-FLUCLOXACILLIN should not be used by pregnant women.

Breastfeeding

XIXIA-FLUCLOXACILLIN is excreted in the breast milk and should not be used by women who are breastfeeding.

The possibility of hypersensitivity reactions must be considered in breastfeeding infants.

Fertility

No data available

4.7. Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed in patients taking XIXIA-FLUCLOXACILLIN

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that XIXIA-FLUCLOXACILLIN do not adversely affect their ability to do so safely.

4.8. Undesirable effects

a) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued. Eosinophilia, haemolytic anaemia.	
Immune system disorders		Angioedema, Anaphylactic shock (exceptional with oral administration) If any hypersensitivity reaction occurs, the treatment should be discontinued.	
Metabolism and nutrition disorders		Very rare case of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)	Hypokalaemia
Gastrointestinal disorders	Minor gastrointestinal disturbances (nausea, colic, diarrhoea)	Pseudomembranous colitis. If pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.	
Hepatobiliary disorders		Hepatitis and cholestatic jaundice (see section 4.4). Changes in liver function laboratory test results (reversible when treatment is discontinued). These reactions are related neither to the dose nor to the route of administration. Hepatitis and cholestatic jaundice may be delayed for	

		up to two months post-treatment; in several cases the course of the reactions has been protracted and lasted for some months. Hepatic events may be severe and in very rare circumstances a fatal outcome has been reported. Most reports of deaths have been in patients ≥50 years and inpatients with serious underlying disease. There is evidence that the risk of flucloxacillin induced liver injury is increased in subjects carrying the HLA- B*5701allele. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA-B*5701 allele for liver injury is very low (0,12%) and routine screening for this allele is not recommended.	
Skin and subcutaneous tissue disorders		Rash, urticaria and purpura. erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.	AGEP – acute generalized exanthematous pustulosis (see section 4.4)
Musculoskeletal and connective tissue disorders		Arthralgia and myalgia sometimes develop more than 48 hours after the start of the treatment.	
Renal and urinary disorders		Interstitial nephritis. This is reversible when treatment is discontinued.	
General disorders and administrative site conditions		Fever sometimes develops more than 48 hours after the start of the treatment.	

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 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

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Oral administration can cause gastrointestinal symptoms such as transient diarrhoea, nausea, and colic which are dose related and as a result of local irritation and not toxicity.

Treatment

Problems with overdosage are unlikely to occur. If encountered, gastrointestinal symptoms and disturbances of the fluid and electrolyte balance may be evident. They may be treated symptomatically with attention to the water/electrolyte balance. Flucloxacillin cannot be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 20.1.2 Penicillins

Pharmacotherapeutic group: Beta-lactamase resistant penicillins

ATC code: J01CF05

Mechanism of action

XIXIA-FLUCLOXACILLIN is a semi-synthetic, penicillinase-stable penicillin derived from 6-amino-penicillanic acid.

Bacteriology

XIXIA-FLUCLOXACILLIN exhibits antibacterial activity against all Gram-positive organisms (with the exception of Strep. faecalis) e. g. haemolytic streptococci, staphylococci, Streptococcus pneumoniae and N. gonorrhoeae. *In vitro* efficacy does not imply *in vivo* efficacy.

XIXIA-FLUCLOXACILLIN's anti-staphylococcal activity is not affected by penicillinase and as XIXIA-FLUCLOXACILLIN is active against virtually all strains of Staph. aureus (methicillin-resistant strains being the only exception), it is primarily indicated in the treatment of staphylococcal infections.

The minimum inhibitory concentrations of benzylpenicillin against staphylococci are lower than those of flucloxacillin except in the case of the penicillinase-producing staphylococci.

Resistant organisms

Group D (*Enterococcus faecalis*) staphylococci

Methicillin-resistant staphylococci

5.2. Pharmacokinetic properties

Absorption

XIXIA-FLUCLOXACILLIN is very well absorbed orally. A single 250 mg oral dose achieves an average peak serum level virtually equal to that achieved by an equivalent IM injection. The peak serum level is achieved half to one hour after administration. Approximately 60 % of an oral dose is excreted unchanged in the active form into the urine within 6 hours.

XIXIA-FLUCLOXACILLIN should be taken one hour before meals to ensure that maximum absorption is achieved.

Elimination

Approximately 60 % of an oral dose and 90 % of an intramuscular and intravenous dose of XIXIA-FLUCLOXACILLIN is excreted unchanged in the active form into the urine within 6 hours.

Probenecid

Even higher XIXIA-FLUCLOXACILLIN serum levels may be achieved after oral administration in patients with normal renal function by the simultaneous administration of a renal blocking agent such as probenecid. Probenecid should not be given in the presence of abnormal renal function.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

XIXIA-FLUCLOXACILLIN 250

Magnesium Stearate

XIXIA-FLUCLOXACILLIN S

Colour sunset yellow, disodium edetate, flavour blood orange dry, flavour menthol dry, flavour tutti frutti dry, glycamil, saccharin sodium, sodium citrate anhydrous, sodium benzoate sucrose.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

XIXIA-FLUCLOXACILLIN 250: 24 months

XIXIA-FLUCLOXACILLIN S: 24 months

6.4. Special precautions for storage

Xixia-Flucloxacillin 250

Store below 25 º C.

Keep tightly closed.

Store in a dry place.

Xixia-Flucloxacillin S

Keep tightly closed.

Store the dry powder below 25 º C in a dry place.

The reconstituted suspension must be used within 7 days if stored below 25 º C or 14 days if stored in a refrigerator (5 º C).

6.5. Nature and contents of container

Xixia-Flucloxacillin 250 – Amber glass bottles containing 20 or 100 capsules.

Xixia-Flucloxacillin S – Clear glass bottles containing powder for reconstitution of 100 ml suspension.

Not all packs or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBERS

Xixia-Flucloxacillin 250 – 29/20.1.2/0550

Xixia-Flucloxacillin S – 29/20.1.2/0551

9. DATE OF FIRST AUTHORISATION

02.12.1994

10. DATE OF REVISION OF TEXT

19 April 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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