SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

SEPTAPEN 250 (Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITON:

SEPTAPEN 250

Each hard gelatine capsules containing flucloxacillin sodium equivalent to 250 mg flucloxacillin.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SEPTAPEN 250 capsules are black/red size “2” hard gelatine capsules.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

Infections caused by susceptible gram-positive organisms, including beta-lactamase producing staphylococci and streptococci:

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

- Septicaemia
- Meningitis
- Endocarditis
- Enterocolitis

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Adults

The usual adult dose is to take 1 capsule 4 times a day preferably 1 hour before meals.

Severe infections

Up to 8 g daily in divided doses, six to eight hourly, one hour before meals for endocarditis, osteomyelitis, skin, and soft tissue infections.

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

SEPTAPEN 250 is indicated for adults and must not be prescribed to children. Safety and efficacy has not been established in children.

Method of administration

Should be taken one hour before meals.

4.3 CONTRAINDICATIONS:

- Hypersensitivity to flucloxacillin sodium or other beta-lactam antibiotics (e.g. penicillins, cephalosporins) or to any of the excipients listed in section 6.1.Flucloxacillin is contraindicated in patients with a previous history of flucloxacillin associated jaundice / hepatic dysfunction.
- Not to be used topically in the eye.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

- **Feverish Generalised Erythema**

  The occurrence at the treatment initiation of a feverish generalised erythema associated with pustules 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.

- **Previous hypersensitivity reactions to β-lactams**

  Before initiating therapy with flucloxacillin, attention should be paid to possible cross-sensitivity with other p-lactam antibiotics e.g. Cephalosporins. 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.

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.

- **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).

- **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.

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

- **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 with evidence of hepatic dysfunction, 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).

  As for other penicillins contact with the skin should be avoided as sensitisation may occur. Patients with a known history of allergy are more likely to develop a hypersensitivity reaction.

  Prolonged use of an anti-infective agent may occasionally result in overgrowth of non-susceptible organisms. Gastro-intestinal upsets (e.g. nausea, colic, diarrhoea) have been reported. As with other penicillins, pseudomembranous colitis has been reported.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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

- Other drugs, such as piperacillin, which are excreted via renal tubular secretion, may interfere with flucloxacillin elimination.
- Oral typhoid vaccine may be inactivated by flucloxacillin.
- Flucloxacillin reduces the excretion of methotrexate which can cause methotrexate toxicity.
- Flucloxacillin may reduce the response to sugammadex.
- 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 drugs may interfere with the bactericidal action of flucloxacillin.
- 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.)
- Flucloxacillin causes subtherapeutic levels of Voriconazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Safety and efficacy has not been established in pregnant women taking **SEPTAPEN 250**.

SEPTAPEN 250 should not be used by pregnant women.

Breastfeeding

Safety and efficacy has not been established in women who are breastfeeding and taking **SEPTAPEN 250**. **SEPTAPEN 250** should not be used by women who are breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. Patients should be instructed that if they experience sedation or dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

System organ class	Frequent	Less frequent	Frequency Unknown
Blood and 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) (see Section 4.4), angioneurotic oedema. If any hypersensitivity reaction occurs, the treatment should be discontinued. (See also	

		Skin and subcutaneous tissue disorders).	
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.)	
Gastrointestinal disorders	Minor gastrointestinal disturbances.		
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. (See also Immune system disorders).	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 administration 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 professionals 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: https://www.sahpra.org.za/Publications/Index/8

4.9 OVERDOSE

If encountered, gastro-intestinal 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

Pharmacological Classification/ Category and Class: A 20.1.2 Penicillin

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

Bacteriology

Flucloxacillin exhibits bacterial activity against all Gram-positive organisms (with the exception of Strep. faecalis) e.g. haemolytic streptococci, staphylococci, Streptococcus pneumoniae and N. gonorrhoeae.

Flucloxacillin anti-staphylococcal activity is not affected by penicillinase and as 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

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.

Flucloxacillin should be taken 1 hour before meals to ensure that maximum absorption is achieved.

Excretion

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

Probenecid

Even higher 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.

5.3 PRECLINICAL SAFETY DATA

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Magnesium stearate.

Size 2 black/red hard gelatine capsule components:

Black oxide, erythrosine, gelatine, red oxide, titanium dioxide

6.2 INCOMPATIBILITIES

N/A

6.3 SHELF LIFE

HDPE containers: 24 months

PRP pouches: 15 months from packing

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25 ºC.

Store in the original container. Keep tightly closed.

Keep out of the sight and reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Amber glass bottles containing 20 or 100 capsules.

20's, 40's and 100's printed Alu/LDPE patient ready packs.

PP or HDPE Securitainers containing 20 or 100 capsules.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals (Pty) Ltd

Crownwood Office Park,

Block D, Ground floor

100 Northern Parkway

Ormonde

Johannesburg

2091

8. REGISTRATION NUMBER

A 29/20.1.2/0550

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 February 1999

10. DATE OF REVISION OF THE TEXT

09/05/2024