PROFESSIONAL INFORMATION FOR SANDOZ FLUCLOXACILLIN 250

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

SANDOZ FLUCLOXACILLIN 250 (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SANDOZ FLUCLOXACILLIN 250 Capsule contains: Flucloxacillin sodium equivalent to 250 mg flucloxacillin.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Black and yellow opaque, size 2, hard gelatin 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

Usual adult dose: 250 mg every six hours, one hour before meals.

Doses may be doubled in severe infections; up to 8 g daily in three or four divided doses may be given for endocarditis and osteomyelitis.

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

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

4.3 Contraindications

SANDOZ FLUCLOXACILLIN should not be given to patients with a history of hypersensitivity to β-lactam antibiotics (e.g., penicillins, cephalosporins) or any of the excipients.

SANDOZ FLUCLOXACILLIN is contraindicated in patients with a previous history of flucloxacillin associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

The use of this antibiotic may lead to the appearance of resistant strains of organisms, and sensitivity testing should therefore be carried out whenever possible to ensure the appropriateness of the therapy.

Oral administration can cause gastrointestinal symptoms such as diarrhoea, nausea, heartburn and colic, pruritus ani, and disturbances of electrolyte balance, which are dose related and a result of local irritation.

It should be given with caution to patients with known histories of allergy.

Cholestatic hepatitis has been reported rarely.

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, SANDOZ FLUCLOXACILLIN should be discontinued and any subsequent administration of flucloxacillin contraindicated.

The use of SANDOZ 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.

SANDOZ 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.

Hepatitis and cholestatic jaundice have been reported. These reactions are related neither to the dose nor to the route of administration. SANDOZ FLUCLOXACILLIN should be used with caution in patients who are older than 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.

Before initiating therapy with SANDOZ 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.

If anaphylaxis occurs, SANDOZ 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.
Special caution is essential in the newborn because of the risk of hyperbilirubinaemia. Studies have shown that, at high dose following parenteral administration, SANDOZ 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 SANDOZ 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.

Caution is advised when SANDOZ 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 SANDOZ 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 SANDOZ 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 SANDOZ FLUCLOXACILLIN maintaining the clinical picture of HAGMA (see section 4.5).

Hypokalaemia (potentially life threatening) can occur with the use of SANDOZ FLUCLOXACILLIN, especially in high doses. Hypokalaemia caused by SANDOZ FLUCLOXACILLIN can be resistant to potassium supplementation. Regular measurements of potassium levels are recommended during the therapy with higher doses of SANDOZ FLUCLOXACILLIN. Attention for this risk is warranted also when combining SANDOZ FLUCLOXACILLIN with hypokalemia-inducing diuretics or when other risk factors for the development of hypokalemia are present (e.g. malnutrition, renal tubule disfunction).

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 medicines, 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 INR should be carefully monitored during addition or withdrawal of flucloxacillin.
- Bacteriostatic medicines 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 (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

Pregnancy

Safety and efficacy has not been established in pregnant women taking SANDOZ FLUCLOXACILLIN. SANDOZ FLUCLOXACILLIN should not be used by pregnant women.

Lactation

Trace quantities of SANDOZ FLUCLOXACILLIN can be detected in breast milk. The possibility of hypersensitivity reactions must be considered in breastfeeding infants. Safety and efficacy has not been established in women who are breastfeeding and taking SANDOZ FLUCLOXACILLIN. SANDOZ FLUCLOXACILLIN should not be used by women who are breastfeeding.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

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

Allergic reactions may occur, presenting as a pruritic skin rash, an erythematous skin reaction or urticaria, fever, eosinophilia, joint pains, angioneurotic oedema, or exfoliative dermatitis. Should a serious anaphylactic reaction occur, SANDOZ FLUCLOXACILLIN should be discontinued, and the patient treated with the usual agents: adrenalin, corticosteroids and antihistamines.

Blood and lymphatic system disorders:

Less frequent: Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued. haemolytic anaemia.

Immune system disorders:

Less frequent: 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).

Gastrointestinal disorders:

Frequent: Minor gastrointestinal disturbances

Less Frequent: Pseudomembranous colitis

If pseudomembranous colitis develops, SANDOZ FLUCLOXACILLIN treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.

Not known: Abdominal pain, vomiting

Not Known: Oesophageal pain and related events *

* oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain

Hepatobiliary disorders:

Less frequent: 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 in patients with serious underlying disease.

There is evidence that the risk of flucloxacillin induced liver injury is increased in subjects carrying the HLA-B*5701 allele. 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:

**Less frequent:* Rash, urticaria and purpura.

Very rare: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. (See also Immune system disorders).

Frequency not known: AGEP – acute generalized exanthematous pustulosis (see section 4.4)

Musculoskeletal and connective tissue disorders:

Less frequent: Arthralgia and myalgia sometimes develop more than 48 hours after the start of the treatment.

Renal and urinary disorders:

Less frequent: Interstitial nephritis.

This is reversible when treatment is discontinued.

General disorders and administration site conditions:

Less frequent: Fever sometimes develops more than 48 hours after the start of the treatment.

Metabolism and nutrition disorders:

Post marketing experience: very rare case of high anion gap metabolic acidosis, when SANDOZ FLUCLOXACILLIN is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)

Not known: Hypokalaemia

*The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.

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

Suspected side effects can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

(See section 4.4 and 4.8).

Treatment is symptomatic and supportive.

With high doses (mainly parenteral) neurotoxicity may develop.

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically with attention to water/electrolyte balance.

SANDOZ FLUCLOXACILLIN is not removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 20.1.2 Penicillins

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Beta-Lactamase Resistant Penicillins

ATC code: J01CF05

Properties: SANDOZ FLUCLOXACILLIN is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins; it is not inactivated by staphylococcal β-lactamases.

Pharmacological action:

Flucloxacillin is a semi-synthetic, penicillinase-stable penicillin with bactericidal activity against Gram-positive organisms, particularly penicillinase-producing strains of *Staphylococcus aureus.*

Activity: Flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on *streptococci* except those of group D (Enterococcus faecali*s) staphylococci*. It is not active against methicillin-resistant *staphylococci.*

5.2 Pharmacokinetic properties

Absorption:

Flucloxacillin is stable in acid media and can therefore be administered either by the oral or parenteral route. The peak serum levels of flucloxacillin reached after one hour are as follows:

- After 250 mg by the oral route (in fasting subjects): Approximately 8,8 mg/l
- After 500 mg by the oral route (in fasting subjects): Approximately 14,5 mg/l
- After 500 mg by the IM route: Approximately 16,5 mg/l

The total quantity absorbed by the oral route represents approximately 79 % of the quantity administered.

Distribution:

Flucloxacillin diffuses well into most tissue. Specifically, active concentrations of flucloxacillin have been recovered in bones: 11,6 mg/l (compact bone) and 15,6 mg/l (spongy bone), with a mean serum level of 8,9 mg/l.

Crossing the meningeal barrier: Flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed. Crossing into mothers' milk: flucloxacillin is excreted in small quantities in mothers' milk.

Biotransformation:

In normal subjects approximately 10 % of the flucloxacillin administered is metabolised to penicilloic acid. The elimination half-life of flucloxacillin is in the order of 53 minutes.

Excretion:

Excretion occurs mainly through the kidney. Between 65,5 % (oral route) and 76,1 % (parenteral route) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

Protein binding: The serum protein-binding rate is 95 %.

5.3 Preclinical safety data

No further information of relevance to add.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Brilliant Blue FCF (CI 42090), gelatine BP, iron oxide red (CI 77491), iron oxide yellow (CI 77492), magnesium stearate, microcrystalline cellulose, Povidone K29/32 (polyvinylpyrrolidone), silica colloidal anhydrous, sodium lauryl sulphate, sodium starch glycolate, talc, titanium dioxide (CI 77891).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store tightly closed in a dry place at or below 25 °C.

Protect from light.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

Amber glass bottles or securitainers with 20, 40 or 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Gauteng 2090 South Africa

8. REGISTRATION NUMBER

T/20.1.2/33

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 May 1989

10. DATE OF REVISION OF THE TEXT

11 September 2023

[1]Company Reg. No.: 1990/001979/07