PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

FLUCLOXACILLIN 250 mg OETHMAAN (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each capsule contains flucloxacillin sodium equivalent to 250 mg flucloxacillin.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

Size 2, caramel and black coloured hard gelatin capsule filled with white to almost white granular powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

FLUCLOXACILLIN 250 mg OETHMAAN is indicated for the treatment of infections caused by penicillinase producing staphylococci.

4.2 Posology and method of administration

Posology

Usual adult dose:

250 mg every six hours, taken on an empty stomach, preferably, one hour before meals.

Special Populations

Patients with renal impairment:

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe.

Paediatric population

FLUCLOXACILLIN 250 mg OETHMAAN is indicated for adults and must not be prescribed to children.

Safety and efficacy has not been established in children.

Method of administration

FLUCLOXACILLIN 250 mg OETHMAAN should be taken on an empty stomach, one hour before meals. The capsules should be swallowed with liquid and should not be chewed.

4.3 Contraindications

FLUCLOXACILLIN 250 mg Oethmaan is contraindicated in –

- Patients with hypersensitivity to penicillins, cephalosporins, any other beta-lactam antibiotics, or to any of the excipients listed in section 6.1.
- Patients with a previous history of jaundice/ hepatic dysfunction associated with penicillin use.
- **FLUCLOXACILLIN 250 mg OETHMAAN** should not be used in patients with a history of jaundice/hepatic dysfunction related to its use.

4.4 Special warnings and precautions for use

Previous hypersensitivity reactions to β-lactams

Before initiating therapy with **FLUCLOXACILLIN 250 mg OETHMAAN,** careful enquiry should be made concerning previous hypersensitivity reactions with beta-lactam antibiotics or other allergens (see section 4.3).

Impaired Hepatic Function

Changes in liver function tests have been observed in patients treated with penicillins such as **FLUCLOXACILLIN 250 mg OETHMAAN.**

Hepatitis and cholestatic jaundice have been reported with **FLUCLOXACILLIN 250 mg OETHMAAN.** It should not be used in patients with evidence of hepatic dysfunction (see section 4.3). In some patients, almost always those with serious underlying hepatic disease, fatalities have occurred. The onset of hepatic adverse effects may be delayed for up to 2 months after stopping treatment, and is not related to the dose or to the route. Older patients and those receiving treatment for more than 2 weeks are at increased risk.

Porphyria

FLUCLOXACILLIN 250 mg OETHMAAN has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/ or sensitivity to multiple allergens.

If an allergic reaction occurs, **FLUCLOXACILLIN 250 mg OETHMAAN** therapy should be discontinued and appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with epinephrine (adrenaline). Oxygen, intravenous corticosteroids and airways management, including intubation may also be required.

FLUCLOXACILLIN 250 mg OETHMAAN should be used with caution in patients with a known history of allergies.

Contact with **FLUCLOXACILLIN 250 mg OETHMAAN** should be avoided since skin sensitisation may occur.

FLUCLOXACILLIN 250 mg OETHMAAN is not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of rash.
FLUCLOXACILLIN 250 mg OETHMAAN should be avoided if infectious mononucleosis is suspected, since the occurrence of morbilliform rash has been associated with this condition following the use of penicillins.

Patients with lymphatic leukaemia and patients with hyperuricaemia being treated with allopurinol may also be at an increased risk of developing skin rashes.

Prolonged use of **FLUCLOXACILLIN 250 mg OETHMAAN** may result in overgrowth of non-susceptible organisms.

Pseudomembranous enterocolitis may occur.
The possibility of super-infections should be kept in mind during therapy. If super-infections occur, **FLUCLOXACILLIN 250 mg OETHMAAN** should be discontinued and appropriate therapy instituted.

Prothrombin time prolongation/ INR increase may occur in patients receiving **FLUCLOXACILLIN 250 mg OETHMAAN**; appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

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.

When high doses are administered adequate fluid intake and urinary output should be maintained.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

Periodic assessment of organ system function, including renal, hepatic and haematopoietic function is advisable during prolonged therapy with **FLUCLOXACILLIN 250 mg OETHMAAN**

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.

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).

Kounis Syndrome:

Cases of Kounis syndrome, also known as allergic angina or allergic myocardial infarction, have been reported in association with the use of **FLUCLOXACILLIN 250 mg OETHMAAN**. Kounis syndrome is characterized by the concurrence of acute coronary syndromes with allergic or hypersensitivity reactions, leading to coronary artery spasm, plaque rupture, or stent thrombosis.

Patients with a history of allergies, hypersensitivity reactions, or cardiovascular disease may be at increased risk. Therefore, careful consideration should be given before prescribing **FLUCLOXACILLIN 250 mg OETHMAAN** to these patients. Close monitoring for signs and symptoms of an allergic reaction or myocardial ischemia is recommended.

In the event of an allergic reaction or signs suggestive of Kounis syndrome (e.g., chest pain, shortness of breath, palpitations), the administration of **FLUCLOXACILLIN 250 mg OETHMAAN** should be discontinued immediately and appropriate medical treatment initiated. Emergency measures should include the administration of epinephrine, antihistamines, corticosteroids, and other supportive treatments as indicated.

Linear IgA Bullous Dermatosis:

Cases of Linear IgA bullous dermatosis (LABD) have been reported in association with the use of **FLUCLOXACILLIN 250 mg OETHMAAN**. LABD is an autoimmune blistering disorder characterized by the linear deposition of IgA at the basement membrane zone, presenting with blistering skin eruptions.

Healthcare professionals should be aware of this potential risk and monitor patients for signs and symptoms of LABD, such as:

- Itchy or painful blistering lesions, often arranged in a linear pattern
- Erosions and areas of denuded skin

If signs or symptoms of LABD occur, **FLUCLOXACILLIN 250 mg OETHMAAN** should be discontinued immediately, and appropriate dermatological evaluation and treatment should be initiated.

4.5 Interaction with other medicines and other forms of interaction

Concurrent use of other hepatotoxic medicines with **FLUCLOXACILLIN 250 mg OETHMAAN** may increase the potential for hepatotoxicity.

Probenecid and sulfinpyrazone decreases the renal tubular secretion of penicillins when used concurrently. This effect results in increased and prolonged serum concentrations, prolonged elimination half-life, and increased risk of toxicity.

FLUCLOXACILLIN 250 mg OETHMAAN may reduce the efficacy of oral contraceptives and patients should be warned accordingly. It should be recommended that additional contraceptive precautions should be taken during and for 7 days after stopping a short treatment course.

Bacteriostatic anti-bacterial medicines such as chloramphenicol and tetracyclines may interfere with the bactericidal effects of flucloxacillin such as contained in **FLUCLOXACILLIN 250 mg OETHMAAN**.

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.

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 international normalised ratio 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.)

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of **FLUCLOXACILLIN 250 mg OETHMAAN** for use in human pregnancy has not been established.

Breastfeeding:

FLUCLOXACILLIN 250 mg OETHMAAN is distributed into human breast milk. Although significant problems have not been documented, the use of **FLUCLOXACILLIN 250 mg OETHMAAN** by nursing mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions in patients treated with **FLUCLOXACILLIN 250 mg OETHMAAN** were headache, nausea, insomnia, oral candidiasis and vaginal candidiasis.

b. Tabulated list of adverse reactions

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Oral candidiasis, vaginal candidiasis	Frequent
Blood and lymphatic system disorders	Agranulocytosis, leukopenia or neutropenia, haemolytic anaemia, prolonged bleeding time	Frequency unknown
Immune system disorders	Anaphylaxis; allergic reactions presenting as a pruritic skin rash, an erythematous skin reaction or urticaria, fever, eosinophilia, joint pains, angio-oedema, or exfoliative dermatitis. Should an allergic or anaphylactic reaction occur, **FLUCLOXACILLIN 250 mg OETHMAAN** should be discontinued and the appropriate treatment instituted.	Less frequent

	Severe allergic reactions, including anaphylaxis, which may be associated with Kounis syndrome.	Frequency unknown
Metabolism and nutrition disorders	Disturbances of electrolyte balance. Acute attacks of porphyria (see section 4.4). 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.)	Frequency unknown
Nervous system disorders	Headache	Frequent
	Seizures	Frequency unknown
Cardiac disorders	Kounis syndrome (allergic coronary artery spasm leading to myocardial ischemia)	Frequency unknown
Gastrointestinal disorders	Diarrhoea, nausea, vomiting	Frequent
	Heartburn, colic, pruritus ani, *Clostridium difficile* colitis	Frequency unknown
Hepatobiliary disorders:	Hepatotoxicity, hepatitis, cholestatic jaundice (see section 4.4)	Frequency unknown
	Rash, urticaria and purpura.	Less frequent

Skin and subcutaneous tissue disorders	Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. AGEP – acute generalized exanthematous pustulosis (see section 4.4) Linear IgA bullous dermatosis (LABD)	Frequency unknown
Musculoskeletal and connective tissue disorders	Arthralgia and myalgia sometimes develop more than 48 hours after the start of the treatment.	Less frequent
Renal and urinary disorders	Interstitial nephritis. This is reversible when treatment is discontinued.	Less frequent
General disorders and administration site conditions	Fever sometimes develops more than 48 hours after the start of the treatment.	Less frequent

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 Medicine Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Treatment is symptomatic and supportive. **FLUCLOXACILLIN 250 mg OETHMAAN** is not removed from the circulation to a significant degree by haemodialysis.

Overdosage may be asymptomatic, however, gastro-intestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically. Adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 20.1.2 Penicillins

ATC Code: J01CF05

Flucloxacillin is a semi-synthetic isoxazolyl penicillin which is resistant to hydrolysis by staphylococcal penicillinase. Flucloxacillin exhibits bactericidal activity against Gram-positive organisms, particularly penicillinase producing strains of *Staphylococcus aureus*.

Enterococcus faecalis is inherently resistant to flucloxacillin.

5.2 Pharmacokinetic properties

Absorption

Flucloxacillin is rapidly but incompletely absorbed from the gastrointestinal tract. 30 – 50 % is absorbed and a peak serum concentration of 6-10 mcg/ml is attained 1 hour after administration of a 250 mg oral dose. Absorption is more efficient when flucloxacillin is taken on an empty stomach and should preferably be administered one hour before or two hours after meals to ensure better absorption. 94 % of flucloxacillin is plasma protein bound.

Elimination

50 – 65 % of flucloxacillin is excreted unchanged by the kidney in the first six hours after a conventional oral dose. The half-life of flucloxacillin is 0,7 – 1,3 hours when creatinine clearance is > 50 ml/min.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Magnesium stearate

Capsule components

Cap:

Iron oxide black

Titanium dioxide

Gelatine

Body:

Iron oxide red

Iron oxide yellow

Titanium dioxide

Gelatine

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

Do not remove the blister from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

20, 28 and 40 capsules packed in opaque white PVC/silver aluminium foil blister strips packed in cardboard cartons or 20, 40 and 100's capsules packed in aluminium laminated PRP pouch and 100's packed in securitainers.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

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Victory Park

Johannesburg

2195

8 REGISTRATION NUMBER(S):

44/20.1.2/0816

9 DATE OF FIRST AUTHORISATION

06 March 2014

10 DATE OF REVISION OF THE TEXT

To be advised