NEW ZEALAND DATA SHEET

STAPHLEX

1. Product Name

Staphlex, 250 mg and 500 mg capsules.

2. Qualitative and Quantitative Composition

Each capsule contains 250 mg or 500 mg flucloxacillin (as the monohydrate sodium salt).

Excipient with known effect: gelatin capsules and microcrystalline cellulose contain sulfites.

Allergen Declaration:
250 mg capsule: contains sulfites and 14 mg of elemental sodium per capsule.
500 mg capsule: contains sulfites and 26 mg of elemental sodium per capsule.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Staphlex 250 mg capsule: Yellow body, Black Cap, Size 2, contains a white powder.

Staphlex 500 mg capsule: Yellow body, Black Cap, Size 0, contains a white powder.

4. Clinical Particulars

4.1 Therapeutic indications

Flucloxacillin is indicated for the treatment of infections due to sensitive Gram-positive organisms, including β-lactamase producing staphylococci and streptococci.

Typical indications include:

Skin and soft tissue infections

Boils, abscesses, carbuncles, furunculosis, cellulitis, infected wounds, infected burns, protection of skin grafts, and impetigo.

Infected skin conditions

Ulcer, eczema and acne.

Respiratory tract infections

Pneumonia, lung abscess, empyema, sinusitis, pharyngitis, tonsillitis, quinsy, otitis media and externa.

Other infections caused by flucloxacillin-sensitive organisms such as osteomyelitis, enteritis, endocarditis, urinary tract infection, meningitis, septicaemia.

Oral preparations of the β-lactamase-resistant penicillins (or flucloxacillin) should not be used as initial therapy in serious, life threatening infections. Oral therapy with flucloxacillin may be used to follow-up the previous use of parenteral flucloxacillin as soon as the clinical condition warrants.

4.2 Dose and method of administration

Adults (including elderly patients):

Oral – 250 mg four times a day.

Oral doses should be administered 1 hour before meals.

Osteomyelitis, endocarditis – Up to 8 g daily, in divided doses six to eight hourly.

Special populations

Abnormal renal function

In common with other penicillins, flucloxacillin usage in patients with renal impairment does not usually require dosage reduction. However, in the presence of severe renal failure (creatinine clearance < 10 mL/min) a reduction in dose or extension of dose interval should be considered. Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need to be administered either during, or at the end of the dialysis period. The maximum recommended dose in adults is 1 g every 8 to 12 hours.

Hepatic Impairment

Adjustment of dosage may not be necessary as flucloxacillin sodium monohydrate is not metabolised in the liver to any appreciable extent. However, during prolonged treatment it is advisable to check periodically for hepatic dysfunction.

4.3 Contraindications

Flucloxacillin is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to beta-lactam antibiotics (e.g. cephalosporins or penicillins).

Hypersensitivity 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.

4.4 Special warnings and precautions for use

Warning

Liver toxicity

Flucloxacillin can cause severe hepatitis and cholestatic jaundice, which may be protracted. This reaction is more frequent in older patients and those who take the drug for prolonged periods (see section 4.8).

Anaphylaxis

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY REACTIONS (ANAPHYLAXIS) HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAM ANTIBIOTICS. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL THERAPY. BEFORE COMMENCING THERAPY WITH ANY

BETA-LACTAM ANTIBIOTIC, CAREFUL ENQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, APPROPRIATE THERAPY SHOULD BE INSTITUTED AND FLUCLOXACILLIN THERAPY DISCONTINUED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous Colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including flucloxacillin. A toxin produced with *Clostridium difficile,* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Hepatitis, predominantly of a cholestatic type, has been reported (see section 4.8). Reports have been more frequent with increasing age (particularly over 55 years of age) or following prolonged treatment (more than 14 days). Jaundice may appear several weeks after therapy; in some cases the course of the reactions has been protracted and lasted for several months. Resolution has occurred with time in most cases. In rare cases, deaths have been reported, nearly always in patients with serious underlying disease or receiving concomitant medication.

During long-term treatment, regular monitoring of renal function is recommended.

Caution should be exercised in the treatment of patients with an allergic diathesis.

Animal studies show that high doses of flucloxacillin reduce albumin bound bilirubin to 50 to 70% of the base line concentration. The drug should therefore be used with extreme caution in jaundiced neonates or premature infants.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, flucloxacillin should be discontinued immediately and an alternative treatment should be considered.

The occurrence of a febrile generalised erythema in connection with pustules at the start of treatment can be a symptom of acute generalised exanthematous pustulosis (AGEP). In the event of AGEP diagnosis, flucloxacillin must be discontinued and all subsequent administration of flucloxacillin is contraindicated.

Metabolic acidosis

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 for 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.

Use in hepatic impairment

During prolonged treatment it is advisable to check periodically for hepatic dysfunction in patients with impaired hepatic function.

Prolonged use of flucloxacillin may occasionally result in an overgrowth of non-susceptible organisms or yeast and patients should be observed carefully for superinfections.

Use in renal impairment

The dose or dose interval may need modification in patients with renal failure as the half-life in patients with renal failure is increased. As renal function is not fully developed in the neonate the risk/benefit ration should be considered before administration to such patients.

Very high doses of Flucloxacillin can cause hypokalaemia and sometimes hypernatraemia. In patients undergoing high-dose treatment for more than 5 days, electrolyte balance, blood counts, and renal function should be monitored. Additionally, use of a potassium-sparing diuretic may be helpful.

Use in the elderly

Flucloxacillin sodium monohydrate can cause severe hepatitis and cholestatic jaundice, which may be protracted. This reaction is more frequent in older patients and those who take the drug for prolonged periods (see Section 4.8).

Paediatric use

Animal studies show that high doses of flucloxacillin reduce albumin bound bilirubin to 50 to 70% of the base line concentration. The drug should therefore be used with extreme caution in jaundiced neonates or premature infants.

Effects on laboratory tests

No data available

Sodium content

Flucloxacillin capsules contains sodium. This should be taken into consideration when treating patients who have been prescribed a low-salt diet (see Section 2).

4.5 Interaction with other medicines and other forms of interaction

Flucloxacillin may require dose adjustment when used in combination with methotrexate and warfarin. Cases have been reported, in which the efficacy of warfarin decreased during concomitant oral treatment with flucloxacillin.

Probenecid decreases the renal tubular secretion of flucloxacillin. Concurrent use with flucloxacillin may result in increased and prolonged blood levels of flucloxacillin.

Penicillins may reduce the excretion of methotrexate thereby increasing the risk of methotrexate toxicity.

Penicillins may interfere with:
-Urinary glucose test
-Coomb's tests
-Tests for urinary or serum proteins
-Tests which use bacteria e.g.Guthrie test.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B1

Animal studies with flucloxacillin have shown no teratogenic effects. The product 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. The use of flucloxacillin in pregnancy should be reserved for cases considered essential by the clinician. Pregnant woman should be treated only if the expected benefit outweighs the possible risk to the pregnant woman and foetus.

Breastfeeding

Trace quantities of penicillins can be detected in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidosis) in the breast-fed infant. Consequently, breastfeeding might have to be discontinued. Therefore flucloxacillin should only be administered to a breastfeeding mother when the potential benefits outweigh the potential risks associated with treatment.

4.7 Effects on ability to drive and use machines

During treatment with flucloxacillin, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions) which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

The following adverse reactions have been reported as associated with the use of flucloxacillin.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 and < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Event
Infections and infestations	Rare	Pseudomembranous colitis
Blood and lymphatic system disorders	Uncommon	Eosinophilia
	Rare	Agranulocytosis, anaemia, thrombocytopenia, thrombocytopenic purpura, leucopoenia
	Not Known	Haemolytic anaemia
Immune system disorders	Rare	Anaphylactic reactions

System Organ Class	Frequency	Adverse Event
Nervous system disorders	Unknown	Dizziness In patients suffering from renal failure, neurological disorders with convulsions are possible with at high doses.
Gastrointestinal disorders	Common	Nausea, diarrhoea,
	Not known	Vomiting, dyspepsia, constipation, abdominal pain, heart burn, loss of appetite
Hepatobiliary disorders	Rare	Hepatitis and cholestatic jaundice (occasionally severe). Liver disorders, most commonly mixed cholestatic-hepatocellular type.
Skin and subcutaneous tissue disorders	Common	Exanthema
	Uncommon	Urticaria,
	Rare	Anaphylaxis and erythema multiforme
	Very rare	Pruritus,
	Not known	Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermalnecrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) Erythematous maculopapular rashes, purpura, eosinophilia, angioneurotic oedema, erythema nodosum, cutaneous vasculitis
Renal and urinary disorders	Not known	Nephritis, interstitial nephritis, frequency of micturition and haematuria
Metabolism and nutrition disorders	Very rare	High anion gap metabolic acidosis (HAGMA), whenflucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors.
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm.
Other	Not known	Malaise, bad taste, sore throat, sore tongue, pruritus vulvae, arthralgia depression, headache, vaginal or oral moniliasis

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 https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

With high doses (mainly parenteral) neurotoxicity may develop.

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically.

Flucloxacillin is not removed from the circulation by haemodialysis.

Symptomatic treatment should be given considering the use of activated charcoal.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactamase resistant penicillins, ATC code: J01CF05

Flucloxacillin is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins; it is not inactivated by staphylococcal beta-lactamases.

Activity

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

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.

Mechanism of action

Flucloxacillin is an isoxazolyl penicillin of the beta-lactam group of antibiotics, which exerts a bactericidal effect upon many Gram positive organisms including beta-lactamase producing staphylococci and streptococci.

It is not active against Gram-negative bacilli, methicillin resistant *Staphylococcus aureus*, nor *Streptococcus faecalis.*

5.2 Pharmacokinetic properties

Absorption

Flucloxacillin is stable in acid media and can therefore be administered by the oral 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 tissues. 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 mother's milk: flucloxacillin is excreted in small quantities in mother's milk.
Protein binding: flucloxacillin, in common with other isoxazolylpenicillins, is highly bound to serum proteins. The low MICs of flucloxacillin against Gram-positive cocci and the free antibiotic levels achieved however ensure that the preparation is fully active against susceptible pathogens.

Metabolism

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

Excretion

Excretion occurs mainly through the kidney (by both glomerular filtration and tubular secretion) and high levels of active antibiotic are produced in the urine. 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.

5.3 Preclinical safety data

No data available.

6. Pharmaceutical Particulars

6.1 List of excipients

Capsule contents:

- talc
- povidone
- microcrystalline cellulose
- magnesium stearate
- sodium starch glycollate

Capsule shells also contain:

- gelatin
- FD&C Blue 1
- red iron oxide
- yellow iron oxide
- titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Staphlex 250 mg capsules

Bottles pack size of 100 and 500 capsules: 2 years

Staphlex 500 mg capsules

Bottle pack size of 50, 100, 250, 500 capsules: 2 years

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Staphlex 250 mg capsules: HDPE bottles, pack sizes of 100, 250, 500 capsules.

Staphlex 500 mg capsules: HDPE bottles, pack sizes of 50, 100, 250, 500 capsules.

Not all strengths or pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

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Telephone 0800 168 169

9. Date of First Approval

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12 August 2024

Summary table of changes

Section	Summary of new information
1, 2, 3, 4.6, 4.8, 6.3, 6.5	Minor Editorial Changes

Section	Summary of new information
2	Addition of monohydrate to sodium salt information Addition of allergen declarations
4.4	Addition of information on: • regular monitoring of renal function during long term treatment • acute generalised exanthematous pustulosis (AGEP). • sodium content for patients on a low-salt diet.
4.5	Addition of information on: • dose adjustment if used in combination with methotrexate and warfarin
4.8	Addition of information on: • system organ class and frequency • anaphylaxis reactions • liver disorders, most commonly mixed cholestatic-hepatocellular type • exanthema Tabulation of the adverse event frequency information Updated adverse reactions reporting URL
4.9	Addition of • Symptomatic treatment should be given considering the use of activated charcoal
5.3	Addition of section
10	Updated Date of Revision of the Text