

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 sodium salt).

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.

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

Flucloxacillin should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin.

Before initiating therapy with flucloxacillin, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactams. Cross-sensitivity between penicillins and cephalosporins is well documented. 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. These reactions are more likely to occur in individuals with a history of beta-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. Intravenous crystalloids, hydrocortisone, antihistamine and nebulised bronchodilators, may also be required.

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 contra-indicated.

Hepatitis and cholestatic jaundice have been reported. These reactions are related neither to the dose nor to the route of administration. 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 (see section 4.2). Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, patients > 50 years and those with underlying disease all of whom are at risk of hepatic reactions. In these

patients, hepatic events may be severe, and in very rare circumstances, deaths have been reported (see section 4.8).

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.

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

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

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

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 (see section 4.5).

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

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It is important to consider this diagnosis in patients who develop severe and persistent diarrhoea during or after receiving flucloxacillin. In this situation, even if *Clostridium difficile* is only suspected, administration of flucloxacillin should be discontinued and appropriate treatment given.

Sodium content:

Each 1 gram of flucloxacillin sodium contains 2.2 mmol of sodium. This should be included in the daily allowance of patients on sodium restricted diets.

Interference with laboratory tests

Penicillins may interfere with:

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

4.5 Interaction with other medicines and other forms of interaction

Probenecid and sulfapyrazone 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 may reduce the response to sugammadex.

There are rare 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.

The efficacy of oral contraceptives may be impaired under concomitant administration of flucloxacillin, which may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception. Bacteriostatic drugs may interfere with the bactericidal action of flucloxacillin.

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

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

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 decision to administer any drug during pregnancy should be taken with the utmost care. Therefore flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Lactation

Trace quantities of flucloxacillin 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 breast-feeding 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 convention has been utilised for the classification of undesirable effects: Very common ($\geq 1/10$), common ($\geq 1/100$, $<1/10$), uncommon ($\geq 1/1000$, $<1/100$), rare ($\geq 1/10,000$, $<1/1000$), very rare ($<1/10,000$), not known (cannot be estimated from the available data).

Unless otherwise stated, the frequency of the adverse events has been derived from more than 30 years of post-marketing reports.

Blood and lymphatic system disorders

Very rare: Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued. Eosinophilia and haemolytic anaemia.

Metabolism and nutrition disorders

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

Immune system disorders

Very rare: Anaphylactic shock (exceptional with oral administration) (see section 4.4), angioneurotic oedema.

If any hypersensitivity reaction occurs, flucloxacillin should be discontinued (see also Skin and subcutaneous tissue disorders).

Gastrointestinal disorders

*Common: Minor gastrointestinal disturbances.

Very rare: Pseudomembranous colitis.

If Pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice (see section 4.4). Changes in liver function laboratory test results (reversible when treatment is discontinued). These reactions are related to neither 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 death 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

*Uncommon: 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 generalised exanthematous pustulosis (see section 4.4)

Cutaneous vasculitis has also been reported.

Musculoskeletal and connective tissue disorders

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

Renal and urinary disorders

Very rare: Interstitial nephritis.

This is reversible when treatment is discontinued.

General disorders and administration site conditions

Very rare: Fever sometimes develops more than 48 hours after the start of the treatment.

*The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adults 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. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

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.

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.

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.

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. 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%.

6. Pharmaceutical Particulars

6.1 *List of excipients*

Capsule contents:

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

Capsule shells also contain:

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

STAPHLEX capsules do not contain gluten or lactose.

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

STAPHLEX 250 mg capsules

Bottles pack size of 100 and 500 capsules: 2 years

Bottle pack size of 250 capsules: 1.5 years

STAPHLEX 500 mg capsules

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

Bottle pack size of 500 capsules: 1.5 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

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

20 February 1986

10. Date of Revision of the Text

1 July 2020

4.4	Additional information relating to dialysis, skin sensitisation
4.5	Additional information relating to interactions with sugammadex, piperacillin, oral typhoid vaccine, warfarin and bacteriostatic drugs
4.8	AEGP added
4.9	Neurotoxicity added