Staphylex

Flucloxacillin (as sodium)

Mylan

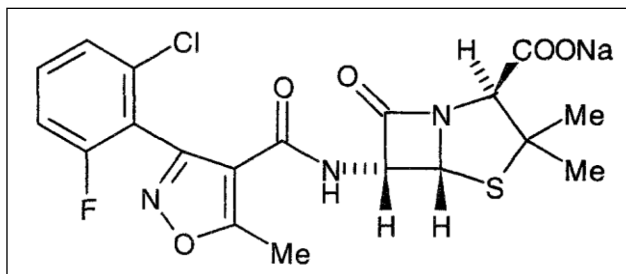
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient : Flucloxacillin sodium

Chemical name : 3-(2'-chloro-6'-fluorophenyl)-5-methyl-4-isoxazolylpenicillin monohydrate

Structural formula :



Molecular formula : $C_{19}H_{16}ClFN_3NaO_5S,H_2O$

Molecular weight : 493.9

CAS Registry no. : 1847-24-1

DESCRIPTION

Flucloxacillin is a narrow spectrum antibiotic belonging to the isoxazolyl group of semi-synthetic penicillins. It is acid stable and penicillinase resistant and is closely related to cloxacillin. It is a white or almost white powder and is hygroscopic. It is soluble in 1 part of water, in 2 parts of methanol, in 8 parts of ethanol (96%) and in 8 parts of acetone.

Staphylex 250 mg and 500 mg capsules contain Flucloxacillin (as sodium monohydrate) as the active ingredient. The capsule contains the following excipients: Povidone, purified talc, sodium starch glycolate, microcrystalline cellulose and magnesium stearate. The empty hard gelatin capsule shell cap - black transparent, body - yellow Opaque size 0 (PI 12223), and empty hard gelatin capsule shell cap - black transparent, body - yellow Opaque size 2 (PI 12364), and colloidal anhydrous silica and sodium lauryl sulphate.

PHARMACOLOGY

Microbiology

Staphylex is a narrow spectrum antibiotic with considerable activity against the following common Gram-positive organisms:

- penicillinase producing *Staphylococcus aureus*,
- penicillin sensitive *Staphylococcus aureus*,
- β-haemolytic streptococci (*Streptococcus pyogenes*),
- *Diplococcus pneumoniae*.

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

Pharmacokinetics

Staphylex is well absorbed following oral administration, with active levels being reached within half an hour, and peak levels within one hour. In the presence of food in the gastrointestinal tract, the absorption of Staphylex is delayed resulting in lower peak serum levels.

The major route of excretion is renal (by both glomerular filtration and tubular secretion) and high levels of active antibiotic are produced in the urine. In the first six hours following oral administration, approximately 50% of the dose can be recovered unchanged in the urine. When probenecid is given together with flucloxacillin, the excretion of flucloxacillin is delayed, resulting in higher and more prolonged blood levels of the antibiotic.

Staphylex, like other isoxazolyl penicillins, is highly bound to serum proteins (>92%). The low MICs of flucloxacillin against Gram-positive cocci and the free antibiotic levels achieved, however, ensure that Staphylex is fully active against susceptible pathogens.

INDICATIONS

Treatment of confirmed or suspected staphylococcal and other Gram-positive coccal infections including pneumonia, osteomyelitis, skin and soft tissue and wound infections, infected burns, cellulitis.

CONTRAINDICATIONS

Staphylex is contraindicated for:

- Patients who are hypersensitive to beta-lactam antibiotics (e.g. penicillins, cephalosporins)
- Patients with a previous history of flucloxacillin associated jaundice/hepatic dysfunction.
- Use in the eye.

PRECAUTIONS

Hepatic toxicity

WARNING: Hepatitis, predominantly of cholestatic jaundice, which may be protracted, has been reported with flucloxacillin therapy (see **ADVERSE EFFECTS**). Reports have been more frequent with increasing age (particularly over 55 years of age) or following prolonged treatment (beyond 14 days). Jaundice may appear several weeks after therapy; in several 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.

Serious, and occasionally fatal, hypersensitivity (anaphylaxis) reactions have been reported in patients receiving beta-lactam antibiotics e.g. penicillins. 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 a hypersensitivity reaction occurs, appropriate therapy should be instituted and Staphylex therapy discontinued.

Serious anaphylactoid reactions require emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation should also be administered as indicated.

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.

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

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, even though this is not a recognised predisposing factor to hepatic reactions to the drug.

Hepatitis, predominantly of a cholestatic type, has been reported (see **ADVERSE EFFECTS**). 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.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis(AGEP). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contra-indicated.

It should be recognised that each 1 g of flucloxacillin sodium contains sodium 2.2 mmol. This should be included in the daily allowance of patients on sodium restricted diets.

During long-term treatments regular monitoring of hepatic and renal function is recommended.

Use in Pregnancy (Category: B1)

The safety of Staphylex in the first trimester of pregnancy has not yet been established. 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 effect. Flucloxacillin should not be used in pregnancy unless considered essential by the physician.

Use in Lactation

Flucloxacillin is excreted in breast milk in trace amounts. In nursing mothers, an alternative feeding method is recommended because of the risk of allergic sensitisation in the infant.

Use in Neonates

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.

INTERACTIONS WITH OTHER DRUGS

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

In common with other antibiotics, patients should be warned that Staphylex may reduce the effectiveness of oral contraceptives.

ADVERSE REACTIONS

As with all penicillins, the possibility of hypersensitivity reactions should always be considered. Reactions are more likely to occur in those with an allergic diathesis. Anaphylactic shock is most likely to occur with injected penicillins (See **PRECAUTIONS**).

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

Gastrointestinal

Nausea, vomiting, diarrhoea, dyspepsia. As with other antibiotics, pseudomembranous colitis has rarely been reported (see **PRECAUTIONS**).

Hypersensitivity reactions

Erythematous maculopapular rashes, urticaria, purpura, eosinophilia, angioneurotic oedema. Anaphylaxis and erythema multiforme have been reported rarely. Certain reactions (fever, arthralgia, myalgia) sometimes develop more than 48 hours after the start of treatment. Whenever such reactions occur, Staphylex should be discontinued. (Note: Urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids).

Renal

Cases of nephritis, interstitial nephritis and haematuria have been reported.

Hepatic

Cases of hepatitis and cholestatic jaundice (occasionally severe) have been reported (see **PRECAUTIONS**). These may be delayed for up to two months post treatment. A frequency of about 1 in 15,000 exposures have been reported for cholestatic jaundice. Changes in liver function tests may occur, but are reversible when treatment is discontinued.

Haematological

Haemolytic anaemia has been reported during therapy with flucloxacillin. Reactions such as anaemia, thrombocytopenia, thrombocytopenic purpura, eosiophilia, leucopenia, neutropenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System

Adverse effects have been reported rarely. They include dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses. As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of flucloxacillin in patients with meningitis.

Skin and Other Subcutaneous Tissue Disorders

A red, scaly rash with bumps under the skin and blisters-AGEP -acute generalized exanthematous pustulosis.

Other

Vaginal or oral moniliasis may occur following the use of antibiotics.

Amongst the adverse events reported spontaneously to ADRAC, 61% were dermatological effects, 17% were jaundice, 16% were gastrointestinal reactions and 2.5% were CNS related.

DOSAGE AND ADMINISTRATION

The oral dose should be administered half to one hour before meals.

Usual Adult Dose:

250 mg, 6 hourly.

Children:

2 to 10 years: half adult dose.

NOTE: In severe infections the dosage may be increased.

Dosage in patients with impaired liver function

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

Dosage in patients with impaired renal function

As flucloxacillin is excreted to a large extent by the kidney, the dose or dose interval may need modification in patients with renal failure, as the half-life in these patients is increased. Dosage recommendations for various plasma creatinine levels for patients with impaired renal function are not available. Flucloxacillin is not significantly removed by haemodialysis.

OVERDOSAGE

No information is available, but it could be anticipated that overdosage with oral flucloxacillin would cause gastro-intestinal and CNS symptoms (see **ADVERSE EFFECTS**). As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of flucloxacillin in patients with meningitis.

Flucloxacillin is not significantly removed from the circulation by haemodialysis. General supportive measures should be instituted and consideration given to the use of activated charcoal to minimise gastro-intestinal absorption.

For information on the management of overdosage, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Staphylex 250 mg capsule:	Each 250 mg capsule contain Flucloxacillin (as sodium monohydrate) as the active ingredient, presented as a yellow body with black cap. Available in PVC/PE/PVDC/Al blister packs of 24's
Staphylex 500 mg capsule:	Each 500 mg capsule contains Flucloxacillin (as sodium monohydrate) as the active ingredient, presented as a yellow body with black cap. Available in PVC/PE/PVDC/A blister packs of 24's
	Staphylex capsules should be kept in a well closed container and stored in a dry place

Storage
Store below 25°C.

POISON SCHEDULE

S4 (Prescription Only Medicine)

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited

Level 1, 30 The Bond

30 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

www.mylan.com.au

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

20/09/1991

DATE OF MOST RECENT AMENDMENT:

8/08/2017

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