AUSTRALIAN PRODUCT INFORMATION

STAPHYLEX

Flucloxacillin (as sodium monohydrate) capsule

1 NAME OF THE MEDICINE

Flucloxacillin sodium monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flucloxacillin sodium monohydrate 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.

Each Staphylex 250 mg and 500 mg capsule contains 250 mg or 500 mg of Flucloxacillin (as sodium monohydrate) as the active ingredient.

Excipients with known effect: sulphites

For the full list of excipients, see **Section 6.1 List of excipients.**

3 PHARMACEUTICAL FORM

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.
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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

Usual Adult Dose: 250 mg, 6 hourly.

Children: 2 to 10 years: half adult dose.

NOTE: In severe infections the dosage may be increased.

Method of administration

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

Dosage adjustment in:

renal impairment

As flucloxacillin sodium monohydrate 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 sodium monohydrate is not significantly removed by haemodialysis.

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 (***see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE***).

4.3 CONTRAINDICATIONS

Staphylex is contraindicated for:

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

High anion gap metabolic acidosis

Caution is advised when flucloxacillin sodium monohydrate 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 sodium monohydrate and paracetamol, close monitoring is recommended in order to detect the appearance of acid–base disorders, namely HAGMA, including testing for urinary 5-oxoproline.

If flucloxacillin sodium monohydrate 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 sodium monohydrate maintaining the clinical picture of HAGMA. (***See 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS) and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).***

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 sodium monohydrate should be discontinued immediately and an alternative treatment should be considered.

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 sodium monohydrate should be discontinued and any subsequent administration of flucloxacillin sodium monohydrate contra-indicated.

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

Use in Hepatic Impairment

Hepatitis
WARNING: Hepatitis, predominantly of cholestatic jaundice, which may be protracted, has been reported with flucloxacillin sodium monohydrate therapy (***see section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

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

Flucloxacillin sodium monohydrate 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.

Use in Renal Impairment

During long-term treatments, regular monitoring of renal function is recommended. See also section 4.2 Dosage and Administration – Dosage in renal impairment.

Hypersensitivity and Anaphylaxis

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

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including flucloxacillin sodium monohydrate. 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.

Use in the Elderly

No data available.

Paediatric Use

Use in Neonates

Animal studies show that high doses of flucloxacillin sodium monohydrate 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Caution should be taken when flucloxacillin sodium monohydrate 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 *SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS***)).

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Use in Pregnancy

Pregnancy Category: B1

The safety of Staphylex in the first trimester of pregnancy has not yet been established. Animal studies with flucloxacillin sodium monohydrate 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 sodium monohydrate should not be used in pregnancy unless considered essential by the physician.

Use in Lactation

Flucloxacillin sodium monohydrate 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 section* 4.4 *SPECIAL WARNINGS AND PRECAUTIONS FOR USE***)).

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

Metabolism and nutrition disorders
Post marketing experience: very rare cases of high anion gap metabolic acidosis, when flucloxacillin sodium monohydrate is used concomitantly with paracetamol, generally in the presence of risk factors (***see*** sections **4.4 *SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS*)**.

Skin and Other Subcutaneous Tissue Disorders
Severe cutaneous adverse reactions, including 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 beta-lactam antibiotics**.**

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

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 sodium monohydrate in patients with meningitis.

Gastrointestinal
Nausea, vomiting, diarrhoea, dyspepsia. As with other antibiotics, pseudomembranous colitis has rarely been reported (***see section* 4.4 *SPECIAL WARNINGS AND PRECAUTIONS FOR USE***).

Haematological
Haemolytic anaemia has been reported during therapy with flucloxacillin sodium monohydrate. 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.

Hepatic
Cases of hepatitis and cholestatic jaundice (occasionally severe) have been reported (***see section* 4.4 *SPECIAL WARNINGS AND PRECAUTIONS FOR USE***)). 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.

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.

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.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No information is available, but it could be anticipated that overdosage with oral flucloxacillin sodium monohydrate would cause gastro-intestinal and CNS symptoms (***see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS***)). As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of flucloxacillin sodium monohydrate in patients with meningitis.

Flucloxacillin sodium monohydrate 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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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*.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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.

Distribution

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

Excretion

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 sodium monohydrate, the excretion of flucloxacillin sodium monohydrate is delayed, resulting in higher and more prolonged blood levels of the antibiotic.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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.

Refer to Section 2 – Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^{o}C.

Staphylex capsules should be kept in a well closed container and stored in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PE/PVDC/Al

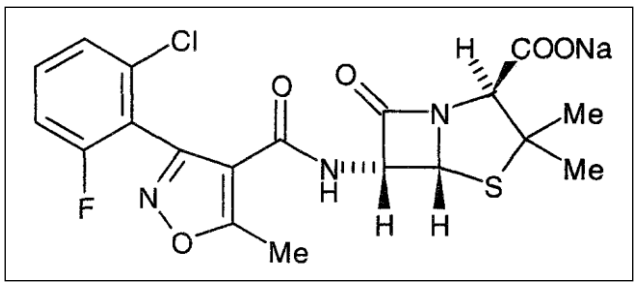
Pack sizes: 24's

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical Name

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

CAS Number

The Chemical Abstracts Service (CAS) Registry Number of the medicine: 1847-24-1

Molecular formula

$C_{19}H_{16}ClFN_3NaO_5S,H_2O$

Molecular weight

493.9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Limited

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

www.mylan.com.au

9 DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods.: 20/09/1991

10 DATE OF REVISION

Date of the most recent TGA approved changes to an approved PI: 09/04/2019

Summary Table of Changes

Section Changed	Summary of New Information
All	Reformat
Section 4.4, 4.5 and 4.8	Flucloxacillin sodium monohydrate and interactions with paracetamol causing high anion gap metabolic acidosis (HAGMA)
Section 4.4 and 4.8	Severe cutaneous adverse reactions (SCAR)

STAPHYLEX_pi\April 19/02