AUSTRALIAN PRODUCT INFORMATION – APO- FLUCLOXACILLIN (FLUCLOXACILLIN SODIUM MONOHYDRATE)

1 NAME OF THE MEDICINE
Flucloxacillin sodium monohydrate.

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM
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.

Each capsule contains 250 mg or 500 mg flucloxacillin (as sodium monohydrate) as the active ingredient. In addition, each capsule contains the following inactive ingredients: magnesium stearate, titanium dioxide, indigo carmine, methyl hydroxybenzoate, propyl hydroxybenzoate, gelatin, shellac, isopropyl alcohol and ethanol.

500 mg capsule:
Size 0 capsule with blue cap and blue body printed with “F500”.

250 mg capsule:
Size 2 capsule with blue cap and blue body printed with “F250”.

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

Usual Adult Dose: 250 mg, 6 hourly.

Children: 2–10 years: half adult dose.

NOTE: In severe infections the dosage may be increased.

Impaired Hepatic 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.

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.

4.3 CONTRAINDICATIONS

Flucloxacillin 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in Hepatic Impairment

WARNING: Hepatitis, predominantly of cholestatic jaundice, which may be protracted, has been reported with flucloxacillin therapy (see Section 4.8 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 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.

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.

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.

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

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.

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

Animal studies have demonstrated that high doses of flucloxacillin reduce albumin-bound bilirubin to 50–70% of the baseline concentration. Flucloxacillin should therefore be used with extreme caution in jaundiced neonates or premature infants.

**Use in the elderly**
No data available.

**Paediatric use**
Animal studies show that high doses of flucloxacillin reduce albumin-bound bilirubin to 50–70% of the baseline 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**

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

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

**4.6 FERTILITY, PREGNANCY AND LACTATION**

**Effects on fertility**
No data available.

**Use in pregnancy (category B1)**
The safety of flucloxacillin 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.
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).

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.

**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, flucloxacillin 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 Section 4.4 Special warnings and 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, eosinophilia, 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 generalised 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.

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No information is available, but it could be anticipated that overdosage with oral flucloxacillin would cause gastrointestinal and CNS symptoms (see Section 4.8 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. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Flucloxacillin is a narrow spectrum antibiotic with considerable activity against the following common Gram-positive organisms: penicillinase producing Staphylococcus aureus, penicillin sensitive Staphylococcus aureus, ß-haemolytic streptococci (Streptococcus pyogenes), Diplococcus pneumoniae. It is not active against Gram-negative bacilli, methicillin resistant Staphylococcus aureus, nor Streptococcus faecalis.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Flucloxacillin 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 flucloxacillin is delayed resulting in lower peak serum levels.

**Distribution**
Flucloxacillin, 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 flucloxacillin is fully active against susceptible pathogens.

**Metabolism**
No data available.

**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, the excretion of flucloxacillin 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**
See Section 2 and 3 – Qualitative and quantitative composition and pharmaceutical form.

6.2 **INCOMPATIBILITIES**
See Section 4.5-Interactions with other medicines and other forms of interactions

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°C.

6.5 **NATURE AND CONTENTS OF CONTAINER**
Blister pack (PVC/PVDC/Al) of 24 or 48 capsules (AUST R 226382).
Blister pack (PVC/PVDC/Al) of 24 or 48 capsules (AUST R 226374).
*Not all strengths or pack sizes may be available.
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
Chemical Name: sodium salt of 3-(2'-chloro-6'-fluorophenyl)-5-methyl-4-isoxazolylpenicillin monohydrate.
Structural Formula:

![Structural Formula](image)

Molecular Formula: C19H16ClFN3NaO5S•H2O
Molecular Weight: 493.9

CAS number
34214-51-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Australia

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9 DATE OF FIRST APPROVAL

10th June 2015

10 DATE OF REVISION

29 May 2018
## Summary table of changes

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of new information</th>
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<tr>
<td>All</td>
<td>Reformatted product information, no other changes to the PI have been made, other than the safety-related request changes applied for in section 4.4.</td>
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| 4.4             | Safety-related request (SRR)  
Renal - Cases are no longer isolated and addition of interstitial nephritis |