PRODUCT INFORMATION

FLOPEN®
(flucloxacillin)

NAME OF THE MEDICINE

FLOPEN® (as flucloxacillin sodium or magnesium) is a member of the beta-lactamase-stable group of penicillins derived from the penicillin nucleus, 6-amino-penicillanic acid. Flucloxacillin sodium is the sodium salt of \((2S,5R,6R)\)-6-[3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid whereas flucloxacillin magnesium is magnesium \((6R)\)-6-[3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxamido]penicillanate octahydrate. Flucloxacillin sodium and flucloxacillin magnesium have the following structure:

Flucloxacillin sodium has a molecular weight of 493.9 and a CAS number, 1847-24-1. Flucloxacillin magnesium has a molecular weight of 1074.2 and a CAS number, 58486-36-5.

DESCRIPTION

FLOPEN® 250 mg capsules contain flucloxacillin 250 mg as the sodium salt, magnesium stearate, titanium dioxide, erythrosine CI45430, sunset yellow FCF CI15985, brilliant blue FCF CI42090 and Opacode White S-1-7085 in a hard gelatin capsule.

FLOPEN® 500 mg capsules contain flucloxacillin 500 mg as the sodium salt, magnesium stearate, titanium dioxide, erythrosine CI45430, brilliant blue FCF CI42090, iron oxide yellow CI77492, iron oxide red CI77491 and Opacode White S-1-7085 in a hard gelatin capsule.

* FLOPEN® 125 mg/5 mL and 250 mg/5 mL powders for oral liquid contain flucloxacillin as the magnesium salt, saccharin sodium, citric acid anhydrous (FLOPEN® 125 mg/5 mL only), citric acid monohydrate (FLOPEN® 250 mg/5 mL only), sodium benzoate, sucrose, sodium citrate and xanthan gum with flavourings tutti frutti 51880 AP0551, blood orange flav-o-lok 600001e and menthol dry flavour 600061e.

(* not currently marketed in Australia)
PHARMACOLOGY

Microbiology
FLOPEN® is a narrow spectrum antibiotic with considerable activity against the following Gram-positive organisms:

- Beta-lactamase-producing *Staphylococcus aureus*
- Penicillin sensitive *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Streptococcus pneumoniae*

It is less active than benzylpenicillin against organisms which are sensitive to benzylpenicillin.

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

Pharmacokinetics
Blood level studies in fasting subjects show that flucloxacillin is well absorbed following oral administration with peak levels being achieved within one hour. The presence of food in the gastrointestinal tract delays the absorption of flucloxacillin 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. Following oral administration approximately 50% of the oral dose can be recovered unchanged in the urine in the first six hours. At least 10% of the dose is excreted as an active metabolite which can rise to as high as 50% in renal failure.

The concurrent administration of probenecid delays the excretion of flucloxacillin resulting in higher and more prolonged blood levels of the antibiotic.

Flucloxacillin, in common with other isoxazolylpenicillins, is highly bound to serum proteins. However, the low minimum inhibitory concentrations of flucloxacillin against Gram-positive cocci and the free antibiotic levels achieved ensure that the preparation is fully active against susceptible pathogens.

INDICATIONS

For the treatment of confirmed or suspected Staphylococcal and other Gram-positive coccal infections.

Indications include pneumonia, osteomyelitis, skin and skin structure and wound infections, infected burns and cellulitis.

CONTRA-INDICATIONS

History of flucloxacillin associated jaundice or hepatic dysfunction.

History of a hypersensitivity reaction to beta-lactam antibiotics eg. penicillins.

Use in the eye.
PRECAUTIONS

Hepatic 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 ADVERSE EFFECTS). |

Serious, and occasionally fatal, hypersensitivity reactions (anaphylaxis) 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 FLOPEN® 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 by *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, eg. 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.

FLOPEN® should be used with caution in patients with evidence of hepatic dysfunction even though the latter 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.

Each gram of flucloxacillin sodium contains 2.2 mmol of sodium.

Each gram of flucloxacillin magnesium contains approximately 1 mmol of magnesium. In children with severely impaired renal function, repeated administration may lead to magnesium retention and adverse effects.
Use in 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 effect. The use of flucloxacillin in pregnancy should be reserved for cases considered essential by the clinician.

Use in lactation
Flucloxacillin is excreted in breast milk in trace amounts. An alternative feeding method is recommended to avoid any possible sensitisation of the newborn.

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 FLOPEN® may result in increased and prolonged blood levels of flucloxacillin.

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

ADVERSE 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 PRECAUTIONS).

The following adverse effects have been reported as associated with the use of flucloxacillin:

HEPATIC: Hepatitis and cholestatic jaundice (occasionally severe) have been reported with a frequency of about 1 in 15,000 exposures (see PRECAUTIONS).

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

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

RENAL: Isolated cases of nephritis and haematuria have been reported.

HAEMATOLOGICAL: Reactions such as anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia 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.

CNS: 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.

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 ½ to 1 hour before meals.

**Usual adult dose:**
250 mg 6-hourly

**Usual children's dose:**
2 to 10 years Half of the adult dose
under 2 years Quarter of the 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 patients with renal failure is increased. However dosage recommendations for various plasma creatinine levels for patients with impaired renal function are not available. Flucloxacillin is not significantly removed by haemodialysis.

**Directions for mixing syrup:**
Reconstitute with 60 mL of water at time of dispensing as follows: tap bottle until all powder flows freely; add approximately half the total volume of water for reconstitution and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

**OVERDOSAGE**

No information is available, but it could be anticipated that overdosage with oral FLOPEN® 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.

Contact the Poisons Information Centre on 131126 for management of overdose.

**PRESENTATION AND STORAGE CONDITIONS**

**Capsules 250 mg**  
Powder blue cap/caramel body both overprinted with "F250" in white ink. Each capsule contains flucloxacillin sodium equivalent to 250 mg of flucloxacillin in a blister pack of 24.

**Capsules 500 mg**  
Deep blue cap/brown body, both overprinted with "F500" in white ink. Each capsule contains flucloxacillin sodium equivalent to 500 mg of flucloxacillin in a blister pack of 24.

* 125 mg/mL Powder for oral liquid  
Bottles containing powder for the preparation of 100 mL fruit-flavoured mixture. When dispensed, each 5 mL contains flucloxacillin magnesium equivalent to 125 mg of flucloxacillin.

* 250 mg/mL Powder for oral liquid  
Bottles containing powder for the preparation of 100 mL fruit-flavoured mixture. When dispensed, each 5 mL contains flucloxacillin magnesium equivalent to 250 mg of flucloxacillin.

(* not currently marketed in Australia)

**Storage**  
All presentations should be stored in dry place, protected from light, at less than 25°C.

FLOPEN® powder for oral liquid, when reconstituted as syrup, should be stored at 2 to 8°C (Refrigerate. Do not freeze) and discarded after 14 days.

**NAME AND ADDRESS OF THE SPONSOR**

Aspen Pharmacare Australia Pty Ltd  
34-36 Chandos St  
St Leonards NSW 2065

**POISON SCHEDULE OF THE MEDICINE**

S4

**DATE OF APPROVAL**

Date of TGA Approval: October 1999