FLOXAPEN® PRODUCT INFORMATION
(flucloxacillin sodium/flucloxacillin magnesium)

DESCRIPTION
FLOXAPEN (flucloxacillin) is the sodium or magnesium salt of 3-(2'-chloro-6'-fluorophenyl)-5-methyl-4-isoxazolylpenicillin monohydrate. It is a member of the penicillinase-stable group of penicillins derived from the penicillin nucleus, 6-aminopenicillanic acid, isolated at Beecham Research Laboratories. Flucloxacillin is closely related to cloxacillin.

MICROBIOLOGY
FLOXAPEN 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*)
Streptococcus pneumoniae (*Diplococcus pneumoniae*)

It is not active against Gram-negative bacilli, methicillin resistant *Staphylococcus aureus*, or *Streptococcus faecalis*.

PHARMACOLOGY
Blood level studies in fasting subjects show that FLOXAPEN 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 FLOXAPEN 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.

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

FLOXAPEN, in common with other isoxazolylpenicillins, is highly bound to serum proteins. The low MICs of FLOXAPEN against Gram-positive cocci and the free antibiotic levels achieved, however, 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 soft tissue and wound infections, infected burns, cellulitis.

CONTRAINDICATIONS
FLOXAPEN should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (eg penicillins, cephalosporins). FLOXAPEN should not be used in the eye, either conjunctivally or locally.

Patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.

WARNINGS

WARNING
LIVER 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 PRECAUTIONS, ADVERSE REACTIONS).

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY REACTIONS (ANAPHYLAXIS) HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAM ANTIBIOTICS. ANAPHYLAXIS HAS OCCURRED IN PATIENTS ON ORAL THERAPY. CROSS-SENSITIVITY BETWEEN PENICILLINS AND CEPHALOSPORINS IS WELL DOCUMENTED. BEFORE COMMENCING THERAPY WITH ANY PENICILLIN, CAREFUL ENQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, APPROPRIATE THERAPY SHOULD BE INSTITUTED AND FLOXAPEN THERAPY DISCONTINUED.

SERIOUS ANAPHYLACTIC 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 antibiotic 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.

PRECAUTIONS
Hepatitis, predominantly of a cholestatic type, has been reported (see Adverse Reactions). Reports have been more frequent with increasing age or following prolonged treatment (more than 14 days). Jaundice may first appear several weeks after therapy; in several cases the course of the reaction 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 receiving concomitant medication or with serious underlying diseases.

Flucloxacillin 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.

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

Dosage should be adjusted in patients with renal impairment (see Dosage and Administration).

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

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.

FLOXAPEN Syrup and Syrup Forte contain sodium benzoate.

Use in Pregnancy: Category B1
Animal studies with FLOXAPEN have shown no teratogenic effects. The product has been in clinical use since 1970 and the limited number of reported cases in human pregnancy have shown no evidence of untoward effect. The use of FLOXAPEN 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 Infants
Animal studies show that high doses of flucloxacillin reduce albumin bound bilirubin to 50 - 70% of the base line concentration. The drug should therefore be used with extreme caution in jaundiced neonates or premature infants. Parenteral flucloxacillin can displace plasma protein binding sites, and may predispose a jaundiced neonate to kernicterus. In addition, special caution is essential in the neonate because of the potential for high serum levels of flucloxacillin due to a reduced rate of renal excretion.

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

Loss of activity or physical incompatibility in solution with numerous other drugs has been reported

ADVERSE REACTIONS
The following adverse reactions have been reported as associated with the use of FLOXAPEN.

Gastro-intestinal: Nausea, vomiting, diarrhoea, dyspepsia. As with other antibiotics, pseudomembraneous colitis has been reported rarely (see WARNINGS).

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, FLOXAPEN 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.

Liver: Hepatitis and cholestatic jaundice (occasionally severe) have been reported. These may be delayed for up to two months post treatment. A frequency of about 1 in 15,000 exposures has been reported for cholestatic jaundice. (see WARNINGS) Changes in liver function test results may occur, but are reversible when treatment is discontinued.

Haemic and lymphatic systems: 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.

DOSAGE AND ADMINISTRATION

The oral dose should be administered 1/2 to one hour before meals.

Usual Adult Dosage

Oral	250mg 6-hourly

Usual Children's Dosage

2 - 10 years	1/2 adult dose
Under 2 years	1/4 adult dose

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. If creatinine clearance drops below 10ml/min, then the recommended dosage is 1g every 8 to 12 hours. In anuric patients, the maximun dosage is 1g every 12 hours. Flucloxacillin is not significantly removed by haemodialysis or peritoneal dialysis. Dialysis need not be accompanied by an additional dose.

OVERDOSAGE

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically. FLOXAPEN is not removed from the circulation by haemodialysis.

DIRECTIONS FOR USE:

Directions for mixing syrup:

Reconstitute with 60mL 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.

STABILITY AND STORAGE:

Storage

FLOXAPEN capsules should be kept in a well closed container. All presentations should be stored in a dry place at less than 25°C.

When dispensed, the syrup should be stored at 2°C - 8°C (Refrigerate. Do not freeze), and discarded after 14 days.

AVAILABILITY:

CAPSULES

250mg (Black/Caramel) overprinted with FLOXAPEN 250. Each capsule contains flucloxacillin sodium equivalent to 250mg flucloxacillin in blister packs of 24.

500mg (Black/Caramel) overprinted with FLOXAPEN 500. Each capsule contains flucloxacillin sodium equivalent to 500mg flucloxacillin in blister packs of 24.

SYRUP

Bottles containing powder for the reconstitution of fruit-flavoured syrup:100mL. When dispensed, each 5mL contains 125mg flucloxacillin as the magnesium salt.

SYRUP FORTE

Bottles containing powder for the reconstitution of fruit flavoured syrup: 100mL. When dispensed each 5mL contains 250mg flucloxacillin as the magnesium salt.

SENSITIVITY DISCS

Sensitivity discs, containing 5mcg flucloxacillin per disc, are available on request.

SPONSOR:

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