

DATA SHEET

FLOXAPEN™

Flucloxacillin

Presentation

FLOXAPEN Capsules:

250mg: Caramel coloured, hard gelatine, size '2' capsule bodies fitted with black caps. Body and cap printed 'floxapen 250' in white.

500mg: Caramel coloured, hard gelatine, size 'OE' capsule bodies fitted with black caps. Body and cap printed 'floxapen 500' in white.

FLOXAPEN Syrups: Presented as white/pink powder in bottles for preparing 100mL cream coloured syrup. When reconstituted each 5mLs contains flucloxacillin magnesium equivalent to 125mg or 250mg flucloxacillin.

Clinical Particulars

Flucloxacillin is an isoxazolyl penicillin of the beta-lactam group of antibiotics, which exerts a bactericidal effect upon many Gram positive organisms including streptococci and beta-lactamase producing staphylococci.

Therapeutic Indications

FLOXAPEN is indicated for the treatment of infections due to Gram-positive organisms, including infections caused by β -lactamase producing staphylococci.

Typical indications include:

Skin and Soft Tissue Infections:

Boils, abscesses, carbuncles, furunculosis, cellulitis, infected wounds, infected burns, protection of skin grafts, and impetigo.

Infected Skin Conditions:

e.g. ulcer, eczema and acne.

Respiratory Tract Infections:

Pneumonia, lung abscess, empyema, sinusitis, pharyngitis, tonsillitis, quinsy, otitis media and externa.

Other infections caused by FLOXAPEN-sensitive organisms such as osteomyelitis, enteritis, endocarditis, urinary tract infection, meningitis, septicaemia.

Oral preparations of the β -lactamase-resistant penicillins (or flucloxacillin) should not be used as initial therapy in serious, life threatening infections. Oral therapy with flucloxacillin may be used to follow up the previous use of parenteral FLOXAPEN as soon as the clinical condition warrants.

Posology and Method of Administration

Oral Dosage

Adults (including elderly patients): 500mg initially and then either 500mg or 250mg 8-hourly depending on severity of infection.

Children 2-10 years: 250mg initially, then 125mg 8-hourly.

Children Under 2 Years: Half this dose.

Oral Administration

Oral doses should be administered 1 hour before meals.

Renal Impairment

The excretion of flucloxacillin is slowed in cases of renal failure. If creatinine clearance drops below 10mL/min, then the recommended dosage is 1g every 8 to 12 hours. (In anuric patients, the maximum dosage is 1g every 12 hours).

Neither haemodialysis nor peritoneal dialysis lower the serum levels of flucloxacillin. Therefore, dialysis need not be accompanied by an additional dose.

Contraindications

Flucloxacillin is a penicillin and should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (eg. penicillins, cephalosporins) or excipients.

Flucloxacillin is contraindicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.

Ocular administration.

Special Warnings and Special Precautions for Use

Before initiating therapy with flucloxacillin, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactams. Cross-sensitivity between penicillins and cephalosporins is well documented.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving beta-lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity. If an allergic reaction occurs, flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions may require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation, may also be required.

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, those with serious underlying disease, and the elderly. In these patients, hepatic events may be severe, and in extremely rare circumstances, deaths have been reported (see Adverse Effects).

Special caution is essential in the newborn because of the risk of hyperbilirubinemia. Studies have shown that, at high dose following parenteral administration, flucloxacillin can displace bilirubin from plasma protein binding sites, and may therefore predispose to kernicterus in a jaundiced baby. In addition, special

caution is essential in the newborn because of the potential for high serum levels of flucloxacillin due to a reduced rate of renal excretion.

During prolonged treatments (eg osteomyelitis, endocarditis), regular monitoring of hepatic and renal functions is recommended.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Sodium content:

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

Magnesium content:

Each 1g of flucloxacillin magnesium contains approximately 1mmol of magnesium. This should be considered for patients with impaired renal function (creatinine clearance of less than 30mL/min).

Precautions:

Dosage should be adjusted in renal impairment. (See Posology and method of administration)

Floxapen Syrup contains sodium benzoate.

Interaction with Other Medicinal Products and Other Forms of Interaction

Bacteriostatic agents may interfere with the bactericidal action of flucloxacillin.

Probenicid decreases the renal tubular secretion of flucloxacillin. Concurrent administration of probenicid delays the renal excretion of flucloxacillin.

Pregnancy and Lactation

Pregnancy:

Penicillins are generally considered safe for use in pregnancy. Animal studies with flucloxacillin have shown no teratogenic effects. Limited information is available concerning the results of the use of flucloxacillin in human pregnancy. Flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Lactation:

Trace quantities of flucloxacillin are excreted in breast milk.

Flucloxacillin may be administered during the period of lactation. With the exception of the risk of sensitization, there are no detrimental effects for the breastfed infant.

Effects on Ability to Drive and Use Machines

Adverse effects on the ability to drive or operate machinery have not been observed.

Adverse Effects

The following convention has been utilised for the classification of undesirable effects:- Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

Unless otherwise stated, the frequency of the adverse events has been derived from more than 30 years of post-marketing reports.

Blood and lymphatic system disorders

Very rare: Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued. Eosinophilia. Haemolytic anaemia.

Immune system disorders

Very rare: Anaphylactic shock (exceptional with oral administration) (see Warnings), angioneurotic oedema.

If any hypersensitivity reaction occurs, the treatment should be discontinued. (See also *Skin and subcutaneous tissue disorders*).

Nervous system disorders

Very rare: In patients suffering from renal failure, neurological disorders with convulsions are possible with the I.V. injection of high doses.

Gastrointestinal disorders

Clinical Trial Data

***Common:** Minor gastrointestinal disturbances.

Post Marketing Data

Very rare: Pseudomembranous colitis.

If pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice. (See Special Warnings and Special Precautions for Use). Changes in liver function laboratory test results (reversible when treatment is discontinued).

Hepatitis and cholestatic jaundice may be delayed for up to two months post-treatment. In some cases the course has been protracted and lasted for several months. Very rarely, deaths have been reported, almost always in patients with serious underlying disease.

Skin and subcutaneous tissue disorders

Clinical Trial Data

***Uncommon:** Rash, urticaria and purpura.

Post Marketing Data

Very rare: Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. (See also Immune system disorders).

Musculoskeletal and connective tissue disorders

Very rare: Arthralgia and myalgia sometimes develop more than 48 hours after the start of the treatment.

Renal and urinary disorders

Very rare: Interstitial nephritis.

This is reversible when treatment is discontinued.

General disorders and administration site conditions

Very rare: Fever sometimes develops more than 48 hours after the start of the treatment.

*The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.

Overdose

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically.

Flucloxacillin is not removed from the circulation by haemodialysis.

Pharmacological Properties

Pharmacodynamic Properties

Properties:

Flucloxacillin is a narrow spectrum antibiotic of the group of isoxazolympenicillins; it is not inactivated by staphylococcal beta-lactamases.

Activity:

Flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on streptococci, staphylococci, including the beta-lactamase-producing strains, *clostridia* and *neisseria*. It is not active against methicillin-resistant staphylococci.

Strains of the following organisms are generally sensitive to the bactericidal action of flucloxacillin *in vitro*.

(The minimal inhibitory concentrations (MIC) of flucloxacillin are quoted below.)

Micro-organisms	MIC (mg/L)
<i>Staphylococcus aureus</i>	0.1 - 0.25
<i>Staphylococcus aureus</i> (beta- lactamase +)	0.25 - 0.5
<i>Streptococcus pneumoniae</i>	0.25
<i>Streptococcus pyogenes</i> (Group A beta-haemolytic)*	0.1
<i>Streptococcus viridans</i> group	0.5

<i>Clostridium tetani</i>	0.25
<i>Clostridium welchii</i>	0.25
<i>Neisseria meningitidis</i>	0.1
<i>Neisseria gonorrhoeae</i>	0.1
<i>Neisseria gonorrhoeae</i> (beta-lactamase +)	2.5

* The Group A beta-haemolytic streptococci are less sensitive to the isoxazolyl penicillins than to penicillin G or penicillin V.

Pharmacokinetic properties

1. **Absorption:** Flucloxacillin is stable in acid media and can therefore be administered by the oral route. The peak serum levels of flucloxacillin reached after 1 hour are as follows.
 - After 250mg by the oral route (in fasting subjects): approximately 8.8 mg/L.
 - After 500mg by the oral route (in fasting subjects): approximately 14.5 mg/L.

The total quantity absorbed by the oral route represents approximately 79% of the quantity administered.
2. **Distribution:** Flucloxacillin diffuses well into most tissues. Specifically, active concentrations of flucloxacillin have been recovered in bones: 11.6 mg/L (compact bone) and 15.6 mg/L (spongy bone), with a mean serum level of 8.9 mg/L.
Crossing the meningeal barrier: flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.
Crossing into mother's milk: flucloxacillin is excreted in small quantities in mother's milk.
3. **Metabolism:** In normal subjects approximately 10% of the flucloxacillin administered is metabolized to penicilloic acid. The elimination half-life of flucloxacillin is of the order of 53 minutes .
4. **Excretion:** Excretion occurs mainly through the kidney. Between 65.5% (oral route) and 76.1% (parenteral route) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.
5. **Protein Binding:** The serum protein binding rate is 95%.

Preclinical Safety Data

No further information of relevance to add.

Pharmaceutical Particulars

Incompatibilities

Flucloxacillin must not be dissolved in solutions of proteins or protein hydrolysates, nor in lipid solutions, nor in blood or plasma.

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

Shelf-life

Capsules: 36 months

Syrups (dry powder): 24 months

Special precautions for storage

Flucloxacillin suspension/vials should be stored below 25°C.

All medicines should be kept out of reach of children.

Once reconstituted, FLOXAPEN Syrups remain stable for 14 days if kept in a cool place.

Unbuffered solutions of FLOXAPEN for intramuscular injection should be freshly prepared.

Instructions for Use and Handling

ADMINISTRATION ORAL ROUTE:

Preparation of the syrup: Before dispensing this medicine, add 60mL of distilled water to the powder, and shake well. This will yield 100mL of syrup. Before each use, invert the bottle containing the reconstituted mixture and shake thoroughly until well dissolved.

Medicines Classification

Prescription Only Medicine

Package Quantities

Capsules: 250mg 24s and 500mg 24s.

Syrup: 125mg 100mL bottles, 250mg 100mL bottles.

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