

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 125mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted as directed each 5 ml contains flucloxacillin 125 mg as flucloxacillin sodium.

Excipients with known effect:

Contains 18 mg sodium, 3.1 g of sucrose and 5mg sodium benzoate per 5ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.

Unreconstituted powder: a pink granular powder with a characteristic odour of pineapple.

Reconstituted solution: a pink coloured solution with a characteristic flavour and odour of pineapple.

4 CLINICAL PARTICULARS

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

4.1 Therapeutic indications

Flucloxacillin is indicated for the treatment of infections due to sensitive Gram-positive organisms, including β -lactamase-producing staphylococci and streptococci. Typical indications include:

Skin and soft tissue infections:

Boils, cellulitis, infected burns, abscesses, infected skin conditions, e.g. ulcer, eczema, and acne, protection for skin grafts, carbuncles, furunculosis, infected wounds, impetigo

Respiratory tract infections:

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

Other infections caused by flucloxacillin-sensitive organisms:

Osteomyelitis, urinary tract infection, enteritis, meningitis, endocarditis, septicaemia

Flucloxacillin is also indicated for use as a prophylactic agent during major surgical procedures when appropriate; for example cardiothoracic and orthopaedic surgery.

Parenteral usage is indicated where oral dosage is inappropriate.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The dosage depends on the age, weight and renal function of the patient, as well as the severity of the infection.

Usual adult dosage (including elderly patients)

Oral - 250 mg four times a day.

In serious infections, the dosage may be doubled.

Osteomyelitis, endocarditis - Up to 8 g daily, in divided doses six to eight hourly.

Surgical prophylaxis - 1 to 2 g IV at induction of anaesthesia followed by 500 mg six hourly IV, IM or orally for up to 72 hours.

Paediatric population

10-18 years: 250mg four times daily

2-10 years: 125mg four times daily.

Under 2 years: 62.5mg four times daily.

Premature infants, neonates, sucklings and infants

Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

Abnormal renal function: In common with other penicillins, flucloxacillin usage in patients with renal impairment does not usually require dosage reduction. However, in the presence of severe renal failure (creatinine clearance < 10 ml/min) a reduction in dose or an extension of dose interval should be considered. The maximum recommended dose in adults is 1 g every 8 to 12 hours.

Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need to be administered either during, or at the end of the dialysis period.

Hepatic impairment

Dose reduction in patients with reduced hepatic function is not necessary.

Method of administration

Flucloxacillin powder for oral suspension should be taken at least 1 hour before or 2 hours after meals.

A full glass of water (250 ml) should be taken afterwards, to reduce the risk of oesophageal pain (see section 4.8). Patients should not lay down immediately after flucloxacillin intake.

4.3 Contraindications

Hypersensitivity to the active substance, β -lactam antibiotics (e.g. penicillins, cephalosporins) or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contra-indicated.

The use of flucloxacillin (like other penicillins) in patients with renal impairment does not usually require dosage reduction. In the presence of severe renal failure (creatinine clearance less than 10ml/min), however, a reduction in dose or an extension of dose interval should be considered because of the risk of neurotoxicity.

Flucloxacillin is not significantly removed by dialysis and so no supplementary dosages need to be administered either during or at the end of the dialysis period.

Hepatitis and cholestatic jaundice have been reported. These reactions are related neither to the dose nor to the route of administration.

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

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving β -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 β -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. Ensure adequate airway and ventilation and give 100% oxygen. IV crystalloids, hydrocortisone, antihistamine and nebulised bronchodilators may also be required.

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, (patients ≥ 50 years and those with serious underlying disease. In these patients, hepatic events may be delayed for up to two months post-treatment, severe, and in very rare circumstances, deaths have been reported (see section 4.8).

Dosage should be adjusted in renal impairment (see section 4.2).

Special caution is essential in the newborn because of the risk of hyperbilirubinaemia. 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 (e.g. osteomyelitis, endocarditis), regular monitoring of hepatic and renal functions is recommended.

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

Benzoate: Flucloxacillin syrup contains sodium benzoate which is mild irritant to the skin, eyes and mucous membranes, so contact with the skin should be avoided

Patients with a known history of allergy are more likely to develop a hypersensitivity reaction.

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

If flucloxacillin 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 maintaining the clinical picture of HAGMA (see section 4.5).

Hypokalaemia (potentially life threatening) can occur with the use of flucloxacillin, especially in high doses. Hypokalaemia caused by flucloxacillin can be resistant to potassium supplementation. Regular measurements of potassium levels are recommended during the therapy with higher doses of flucloxacillin. Attention for this risk is warranted also when combining flucloxacillin with hypokalaemia-inducing diuretics or when other risk factors for the development of hypokalaemia are present (e.g. malnutrition, renal tubule dysfunction).

This medicinal product contains 18.05mg sodium per 5ml, equivalent to 0.90% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

To be taken into consideration by patients on a controlled sodium diet.

Contains 3.1 g sucrose per 5ml (6.2 g per 10ml dose). This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains 5mg benzoate salt in each dosage unit equivalent of 5ml volume.

Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid and sulfapyrazone decrease the renal tubular secretion of flucloxacillin. Concurrent administration of probenecid or sulfapyrazone delays the renal excretion of flucloxacillin.

Other drugs, such as piperacillin, which are excreted via renal tubular secretion, may interfere with flucloxacillin elimination.

Oral typhoid vaccine may be inactivated by flucloxacillin.

Flucloxacillin reduces the excretion of methotrexate which can cause methotrexate toxicity.

Flucloxacillin may reduce the response to sugammadex.

Bacteriostatic drugs (chloramphenicol, erythromycins, sulphonamides, and tetracyclines) may interfere with the bactericidal action of flucloxacillin.

Caution should be taken when flucloxacillin 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.) There are rare cases of decreased international normalised ratio (INR) in patients taking warfarin and prescribed a course of flucloxacillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored during addition or withdrawal of flucloxacillin.

Penicillins may produce false-positive results with the direct antiglobulin (Coombs') test, falsely high urinary glucose results with the copper sulphate test and falsely high urinary protein results, but glucose enzymatic tests (e.g. Clinistix) and bromophenol blue tests (e.g. Multistix or Albustix) are not affected.

Flucloxacillin (CYP450 inducer) has been reported to significantly decrease plasma voriconazole concentrations. If concomitant administration of flucloxacillin with voriconazole cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g. by therapeutic drug monitoring); increasing the dose of voriconazole may be needed.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 effects. The decision to administer any drug during pregnancy should be taken with the utmost care. Therefore flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breast-feeding

Trace quantities of flucloxacillin can be detected in breast milk. The possibility of hypersensitivity reactions must be considered in breast-feeding infants. Therefore flucloxacillin should only be administered to a breast-feeding mother when the potential benefits outweigh the potential risks associated with the treatment.

4.7 Effects on ability to drive and use machines

Flucloxacillin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

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 section 4.4), 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 IV injection of high doses.

Gastrointestinal disorders

***Common:** Minor gastrointestinal disturbances.

Very rare: Pseudomembranous colitis.

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

Not known: Oesophageal pain and related events #

oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain

Hepatobiliary disorders

Very rare: Hepatitis and cholestatic jaundice (see section 4.4). Changes in liver function laboratory test results (reversible when treatment is discontinued).

These reactions are related neither to the dose nor to the route of administration. The onset of these effects may be delayed for up to two months post-treatment; in several cases the course of the reactions has been protracted and lasted for some months. Hepatic events may be severe and in very rare circumstances a fatal outcome has been reported. Most reports of deaths have been in patients ≥ 50 years and in patients with serious underlying disease.

There is evidence that the risk of flucloxacillin-induced liver injury is increased in subjects carrying the HLA-B*5701 allele. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA-B*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended.

Skin and subcutaneous tissue disorders

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

Very rare: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

(See also Immune system disorders).

Not known: AGEP - acute generalized exanthematous pustulosis (see section 4.4)

Metabolism and nutrition disorders

Post marketing experience: very rare cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)

Not known: Hypokalaemia

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 to HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

With high doses (mainly parenteral) neurotoxicity may develop.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: Beta-lactamase resistant penicillins

ATC code: J01C F05

Properties

Flucloxacillin is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins; it is not inactivated by staphylococcal β -lactamases.

Activity

Flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on streptococci except those of group D (*Enterococcus faecalis*) and staphylococci. It is not active against methicillin-resistant staphylococci.

Risk of hepatic injury

There is evidence that the risk of flucloxacillin-induced liver injury is increased in subjects carrying the HLA-B*5701 allele. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA-B*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended.

Mode of action

Flucloxacillin inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

PK/PD relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for flucloxacillin.

Mechanism of resistance

Resistance to isoxazolylpenicillins (so-called methicillin-resistance) is caused by the bacteria producing an altered penicillin binding protein. Cross resistance may occur in the beta-lactam group with other penicillins and cephalosporins. Methicillin-resistant staphylococci generally have low susceptibility for all beta-lactam antibiotics.

Antimicrobial activity

Flucloxacillin is active against both β -lactamase-positive and -negative strains of *Staphylococcus aureus* and other aerobic Gram-positive cocci, with the exception of *Enterococcus faecalis*. Gram-positive anaerobes are generally susceptible (MIC 0.25-2 mg/l) but Gram-negative bacilli or anaerobes are moderately to fully resistant. Enterobacteria are fully resistant to flucloxacillin as well as 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 to 0.25
<i>Staphylococcus aureus</i> (beta-lactamase+)	0.25 to 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

Neisseria meningitides	0.1
Neisseria gonorrhoeae	0.1
Neisseria gonorrhoeae(beta-lactamase+)	2.5
The Group A beta-haemolytic streptococci are less sensitive to the isoxazolyl penicillins than to penicillin G or penicillin V	

5.2 Pharmacokinetic properties

Absorption

Flucloxacillin is stable in acid media and can therefore be administered either by the oral or parenteral route. The peak serum levels of flucloxacillin reached after one hour are as follows.

- After 250 mg by the oral route (in fasting subjects): Approximately 8.8 mg/l.
- After 500 mg by the oral route (in fasting subjects): Approximately 14.5 mg/l.
- After 500 mg by the IM route: Approximately 16.5 mg/l.

The total quantity absorbed by the oral route represents approximately 79% of the quantity administered.

Absorption is delayed by food, with peak serum levels being approximately halved compared with the fasting state. Therefore, it is recommended that flucloxacillin be taken 0.5 to 1 hour before meals.

Distribution

Flucloxacillin diffuses well into most tissue. 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 mothers' milk: Flucloxacillin is excreted in small quantities in mothers' milk.

Biotransformation

In normal subjects approximately 10% of the flucloxacillin administered is metabolised to penicilloic acid. The elimination half-life of flucloxacillin is in the order of 53 minutes.

Elimination

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.

Protein binding

The serum protein-binding rate is 95%.

Neonates and infants

The clearance of flucloxacillin is considerably slower in neonates compared with adults and a mean elimination half-life of approximately four and a half hours has been reported in neonates. Special care should be taken during administration of flucloxacillin to the newborn (see section 4.4). Younger infants (<6 months) achieve higher plasma concentrations of flucloxacillin than older children when given the same dose.

Patients with renal impairment

In patients with severe renal impairment the elimination half life of flucloxacillin increases to values of between 135- 173 min. Modified dosage is required if renal impairment is severe, with creatinine clearance <10ml/min (see section 4.2).

Patients with hepatic impairment

Hepatic disease is thought unlikely to influence the pharmacokinetics of flucloxacillin as the antibiotic is cleared primarily via the renal route.

5.3 Preclinical safety data

No further information of relevance to add.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate
Disodium edetate
Saccharin sodium
Ammonium glycyrrhizate
Anhydrous sodium citrate
Pineapple flavour
Menthol flavour
Erythrosine (E127)
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottle in Aluminium pouch - 24 months
Once removed from the pouch, reconstitute immediately

Once reconstituted the mixture may be stored for a maximum of 7 days when stored in the original container at 2°C-8°C in a refrigerator. Do not freeze.

6.4 Special precautions for storage

Dry powder: Do not store above 25°C. Store in the original container in order to protect from light and moisture.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

A high-density polyethylene (HDPE) bottle fitted with a tamper evident cap in an aluminium pouch, packed in an outer carton.
Each bottle is supplied with a 5ml opaque spoon.

When reconstituted as directed in section 6.6, each bottle contains 100 ml of oral solution.

6.6 Special precautions for disposal and other handling

Do not open the foil pouch until ready to reconstitute the product. Once opened the foil pouch may be discarded. Store the product in the original container.

To the pharmacist:
100ml: Add 58 ml of potable water and shake until all contents are dissolved.

To the patient:
Keep cap tightly closed. Shake well before use. Use within 7 days of preparation.

7 MARKETING AUTHORISATION HOLDER

Athlone Pharmaceuticals Limited
Connaught House
1 Burlington Road
Dublin 4
D04 C5Y6
Ireland

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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