Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 250mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted each 5ml contains 250mg flucloxacillin as flucloxacillin sodium.

Excipients with known effect:
Each 5ml dose contains 2.96g sucrose.
Each 5ml dose contains 24.09mg sodium.
Each 5ml dose contains 5mg sodium benzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Oral Solution.
Free flowing pink coloured powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of infections due to sensitive Gram-positive organisms, including infections caused by β-lactamase-producing *Staphylococci* and *Streptococci*.

Typical indications include:

Skin and soft tissue infections:

Boils	Infected burns
Impetigo	Furunculosis
Abscesses	Protection for skin grafts
Infected wounds	Cellulitis

Carbuncles
Infected skin conditions e.g. Ulcers, eczema and acne

Respiratory tract infections:

Pneumonia	Pharyngitis
Lung abscess	Tonsillitis
Empyema	Quinsy

Sinusitis
Otitis media and externa

Other infections caused by flucloxacillin-sensitive organisms:

Osteomyelitis	Septicaemia
Enteritis	Meningitis
Endocarditis	Urinary-tract infection

Flucloxacillin is also indicated for use as a prophylactic during major surgical procedures such as cardiothoracic and orthopaedic surgery. Parenteral usage is indicated where oral dosage is inappropriate.

Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

4.2 Posology and method of administration

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

Adults (including the elderly)
Oral: 250mg four times daily.
In serious infections, the dosage may be doubled.

Paediatric population

- Less than 2 years: 62.5 mg four times daily
- 2-10 years: 125mg four times daily
- 10-18 years: 250mg four times daily
- Premature infants, neonates, sucklings and infants. Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

Endocarditis or osteomyelitis
Up to 8g daily in divided doses six to eight hourly

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

Renal impairment
In common with other penicillins, Flucloxacillin usage in patients with renal impairment does not usually require dosage reduction. However, in cases of severe renal impairment (creatinine clearance < 10ml/min) a reduction in dosage may be necessary. 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. See Sections 4.3 and sections 4.4.

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

Flucloxacillin should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (e.g. penicillins, cephalosporins) or to any of the excipients listed in section 6.1.

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

As for other penicillins contact with the skin should be avoided as sensitisation may occur.

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

Prolonged use of an anti-infective agent may occasionally result in overgrowth of non-susceptible organisms.

Before initiating therapy with flucloxacillin, careful enquiry 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 anaphylaxis occurs flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine). Ensure adequate airway and ventilation and give 100% oxygen. IV crystalloids, hydrocortisone, antihistamine and nebulised bronchodilators may also be required.

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.

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 product contains 2.96g sucrose per 5ml dose. This should be taken into account in patients with diabetes mellitus. May be harmful to the teeth. Patients with hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not take this medicine.

This medicinal product contains 24.09mg sodium per 5ml dose, equivalent to 1.20% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This should be taken into consideration by patients on a controlled sodium diet.

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).

Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid and sulfinpyrazone slow down the renal excretion of flucloxacillin by decreasing tubular secretion.

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.

There are rare cases of altered 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.

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.)

Bacteriostatic drugs (chloramphenicol, erthromycins, sulphonamides, and tetracyclines) may interfere with the bactericidal action 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. Flucloxacillin preparations have been in use since 1970 and the limited numbers of reported cases of use in human pregnancy have shown no evidence of untoward effect.
Flucloxacillin should only be used in pregnancy when the potential benefits outweigh the risks associated with treatment.

Breast-feeding
Flucloxacillin is secreted into mother's milk and may occasionally cause sensitisation of the infant. The possibility of hypersensitivity reactions must be considered in breastfeeding 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

The most common adverse effects of flucloxacillin are hypersensitivity reactions especially skin rashes.

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. Haemolytic anaemia. Coagulation disorders. Eosinophilia.

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: Convulsions

Gastrointestinal disorders
*__Common:__ Minor gastrointestinal disturbances, diarrhoea, nausea
Uncommon: Sore mouth or tongue, black hairy tongue
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, serum sickness-like reaction 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 via 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

Pharmacotherapeuticgroup: Beta-lactamase resistant penicillins, ATC Code: J01CF05

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 bacterial 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 cefalosporins. Methicillin-resistant staphylococci generally have low susceptibility for all beta-lactam antibiotics.

Antimicrobial activity
Flucloxacillin is active against both -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 is 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)
Staphylococcus aureus	0.1 to 0.25
Staphylococcus aureus (beta-lactamase+)	0.25 to 0.5
Streptococcus pneumoniae	0.25
Streptococcus pyogenes (Group A beta-haemolytic)	0.1
Streptococcus viridans group	0.5
Clostridium tetani	0.25
Clostridium welchii	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 250mg by the oral route (in fasting subjects): Approximately 8.8mg/l.
- After 500mg by the oral route (in fasting subjects): Approximately 14.5mg/l.
- After 500mg by the IM route: Approximately 16.5mg/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: 11.6mg/l (compact bone) and 15.6mg/l (spongy bone), with a mean serum level of 8.9mg/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.

Metabolism:
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.

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.

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 creatinin 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 relevant information additional to that already contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)
Disodium edetate
Saccharin sodium
Ammonium glycyrrhizinate
Sodium citrate anhydrous
Pineapple flavour
Menthol flavour
Erythrosine (E127)
Sucrose

6.2 Incompatibilities

As for penicillins, incompatibilities with Colistin Polymyxin B sulphate. Loss of potency after mixing with streptomycin has also been reported.

6.3 Shelf life

Dry powder -
Bottle not placed in Aluminium pouch - 9 months
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.

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

150ml natural high density polyethylene (HDPE) bottle with tamper evident cap.
or
150ml natural high density polyethylene (HDPE) bottle with tamper evident/child resistant (CRC) cap.

Contents of the bottle after reconstitution: 100ml

Optional - Bottle placed in aluminium pouch.

5ml opaque spoon

6.6 Special precautions for disposal and other handling

To the pharmacist:
100ml: Add 58ml 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
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8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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