# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 250mg Capsules

Flucloxin 250mg Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg of flucloxacillin as flucloxacillin sodium Ph. Eur.

Excipients with known effect:

Each capsule has a sodium content of 52.3 mg per gram.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsules

## 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 | Impetigo |
| Abscesses | Infected wounds |
| Carbuncles | Infected burns |
| Furunculosis | Protection for skin grafts |
| Cellulitis | |

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 the 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

2 – 10 years: 125mg four times daily

Under 2 years: 62.5mg four times daily

In cases of severe renal impairment (creatinine clearance < 10ml/min) a reduction in dosage may be necessary. 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.

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.

Method of administration

Oral. This medicine should be taken on an empty stomach. This means an hour before food or two hours after food.

## 4.3 Contraindications

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

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 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 all of whom are at increased risk of hepatic reactions. The onset of these hepatic 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. In very rare cases, a fatal outcome has 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 β-lactams. 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 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.

This medicinal product contains approximately 52.3 mg sodium per g. To be taken into consideration by patients on a controlled sodium diet.

## 4.5 Interaction with other medicinal products and other forms of interaction

Probenecid and sulfinpyrazone slow down the 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.

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.

## 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 number 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 potential risks associated with treatment.

Breastfeeding

Flucloxacillin is secreted into mother's milk and may occasionally cause sensitisation of the infant. Therefore flucloxacillin should 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 (≥1/1,000 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).

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.

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).

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.

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).

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 the yellow card scheme at www.mhra.gov.uk/yellowcard.

### 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

**ATC Code : J01CF05**

Pharmacotherapeutic group – Beta-lactamase resistant penicillins

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.

### 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 8.8 mg/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.

**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 proportions into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mother's 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%.

## 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

Magnesium stearate

Sodium starch glycolate

Red iron oxide

Yellow iron oxide

Black iron oxide

Titanium dioxide

Gelatin

## 6.2 Incompatibilities

None known.

## 6.3 Shelf life

3 years in securitainers

12 months in PVC/PE/PVDC and PVDC/PVC blister packs.

2 years in PVC/PE/PVDC blister packs in aluminium pouch.

## 6.4 Special precautions for storage

Securitainers: Do not store above 25$^{o}$C. Keep the container tightly closed in order to protect from light and moisture. Store in the original container.

Blister packs: Do not store above 25$^{o}$C. Store in the original package. Keep the container in the outer carton in order to protect from light and moisture.

Blister packs in aluminium pouch: Do not store above 25$^{o}$C. Store in the original package. Keep the container in the outer carton in order to protect from light and moisture.

## 6.5 Nature and contents of container

Polypropylene securitainers with polyethylene air-proof cap, with jayfilla containing 15, 18, 20, 21, 28, 30, 50, 100, 250 or 500 capsules

Opaque PVC/ PVDC blister 250/40 with an aluminium lidding foil 20 micron containing 15, 18, 20, 21, 28, 30, 50, 100, 250 or 500 capsules

Opaque PVC/PE/PVDC blister 250/25/90 with an aluminium lidding foil 20 micron containing 15, 18, 20, 21, 28, 30, 50, 100, 250 or 500 capsules.

Opaque PVC/PE/PVDC blister 250/25/90 with an aluminium lidding foil 20 micron containing 15, 18, 20, 21, 28, 30, 50, 100, 250 or 500 capsules in aluminium pouch.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

ATHLONE LABORATORIES LIMITED,

BALLYMURRAY,

CO. ROSCOMMON,

IRELAND.

## 8 MARKETING AUTHORISATION NUMBER

PL 06453/0015

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 03/12/1992

Renewal: 05/02/1998

## 10 DATE OF REVISION OF THE TEXT

November 2015

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 250mg Capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains flucloxacillin 250 mg as flucloxacillin sodium.

Excipient with known effect:
Contains 13.2 mg of sodium per capsule.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard.

hard gelatin capsule approximately 1.8 cm in length having an opaque caramel body and opaque grey cap each printed ‘FXN 250' in black ink.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

F Flucloxacillin capsules are indicated for the treatment of infections due to sensitive Gram-positive organisms, including β-lactamase-producing *staphylococci* and *streptococci* (see section 5.1) such as:
- Skin and soft tissue infections
- Respiratory tract infections
- Other infections caused by flucloxacillin-sensitive micro-organisms, *e.g.* enteritis, urinary tract infections.

Parenteral use is indicated where oral dosage is inappropriate.

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

### 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.

For doses not practicable with this product, other strengths and pharmaceutical forms are available.

*Usual dosage (adults including elderly patients and children over 10 years of age)*
*Oral* - 1-3 g daily in 3-4 equally divided doses.

*Paediatric population under 10 years of age*
25-50 mg/kg/24 hours in three to four equally divided doses.

Example of posology:

| Weight | Daily dose (mg/24 hours) | Daily dosing regimen |
|---|---|---|
| 22 kg | 550 – 1,100 | 250 mg x 3-4 |
| 25 kg | 625 – 1,250 | 250 mg x 3-4 |
| 27 kg | 675 – 1,350 | 250 mg x 3-4 |
| 30 kg | 750 – 1,500 | 250 mg x 4 or 500 mg x 3 |
| 35 kg | 875 – 1,750 | 250 mg x 4 or 500 mg x 3 |

*Renal impairment*:
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. In high dose regimens the maximum recommended dose is 1 g every 8 – 12 hours. Flucloxacillin is not significantly removed by dialysis and hence no supplementary doses need to be administered either during, or at the end of the dialysis period.

Method of administration

*Oral:* Oral doses should be administered half to one hour before meals.

## 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

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. Oxygen, i.v. steroids, and airway management, including intubation, 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 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).

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

During prolonged treatments, regular monitoring of hepatic and renal functions is recommended.

This medicinal product contains 13.2 mg sodium per capsule. To be taken into consideration by patients on a controlled sodium diet.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

Other substances, 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 substances may interfere with the bactericidal action of flucloxacillin.

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.

## 4.6 Fertility, pregnancy and lactation

Pregnancy: Animal studies with flucloxacillin have shown no teratogenic effects. Limited data is available on the use of flucloxacillin in pregnancy. The decision to administer any medicinal product 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 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).

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 I.V. 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.

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).

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 adverse events 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
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517

Website: www.hpra.ie
e-mail: medsafety@hpra.ie

### 4.9 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: Antibacterials for systemic use, beta-lactamase resistant penicillins
ATC code: J01C F05

Flucloxacillin is a semi-synthetic penicillin (beta-lactam antibiotic; isoxazolylpenicillin) with a narrow spectrum of activity primarily against Gram-positive organisms, including β-lactamase-producing strains.

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.

Pharmacokinetic/pharmacodynamic relationship

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

Mechanisms of resistance

Resistance to isoxazolylpenicillins (so-called meticillin-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. Meticillin-resistant *staphylococci* generally have low susceptibility for all beta-lactam antibiotics.

Antimicrobial activity

Flucloxacillin is active against both beta-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 meticillin-resistant *staphylococci*.

Strains of the following organisms are generally sensitive to the bactericidal action of flucloxacillin *in vitro*. The minimal inhibitory concentrations ($MIC_{90}$) of flucloxacillin are quoted below:

| **Micro-organisms** | **$MIC_{90}$ (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 |

| **Micro-organisms** | **$MIC_{90}$ (mg/l)** |
|---|---|
| *Clostridium tetani* | 0.25 |
| *Clostridium welchii* | 0.25 |
| *Neisseria meningitidis* | 0.1 |
| *Neisseria gonorrhoeae* | 0.1 |
| *Neisseria gonorrhoeae* (beta-lactamase +) | 2.5 |

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

*Breakpoints*
Flucloxacillin sensitivity testing may be carried out with cefoxitin or oxacillin using the standard dilution series. The following minimum inhibitory concentrations for sensitive and resistant strains have been determined:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints

| **Species** | **Sensitive** | **Resistant** |
|---|---|---|
| For oxacillin: | | |
| *Staphylococcus aureus* and *S. lugdunensis* | - | >2 mg/l |
| Coagulase-negative *staphylococci* except *S. lugdunensis* | - | > 0.25 mg/l |
| For cefoxitin: | | |
| *Staphylococcus aureus* and *S. lugdunensis* | - | >4 mg/l |

Prevalence of resistance

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

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.

## 5.2 Pharmacokinetic properties

Absorption:
Flucloxacillin is stable in acid media and can therefore be administered either orally or parenterally. The peak serum levels of flucloxacillin reached after one hour are as follows:

*Oral use:* after 250 mg (in fasting subjects): Approximately 8.8 mg/l.
after 500 mg (in fasting subjects): Approximately 14.5mg/l.
Intramuscular use: after 500 mg Approximately 16.5 mg/l.

The total quantity absorbed after oral administration represents approximately 79% of the quantity administered.

Distribution:
Serum protein binding rate is 95%. Flucloxacillin diffuses well into most tissue.

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.

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 use) and 76.1% (parenteral use) 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.

Following oral administration flucloxacillin is almost completely absorbed achieving blood levels comparable to those achieved after intramuscular injection.

### 5.3 Preclinical safety data

No further information of relevance to add

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Capsule content:*
Sodium starch glycolate (Type A)
Magnesium stearate

*Capsule shell:*
Gelatin
Black iron oxide (E172)
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

*Printing ink:*
Shellac
Propylene glycol
Black iron oxide (E172)

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

3 years in securitainers
2 years in PVC/PE/PVDC blister packs in aluminium pouch. Use within 3 months of opening the foil pouch.

### 6.4 Special precautions for storage

Securitainers: Do not store above 25ºC. Keep the container tightly closed. Store in the original container to protect from light and moisture.

Blister packs in aluminium pouch: Do not store above 25ºC. Keep the blister in the outer carton in order to protect from light and moisture. Do not open the foil pouch until ready to use the product. Once opened the foil pouch may be discarded.

### 6.5 Nature and contents of container

Polypropylene securitainers with polyethylene air-proof security caps.

Securitainers are available in pack sizes of 40, 100 & 500 capsules.

Opaque PVC/PE/PVDC blister with an aluminium lidding foil containing 10, 16, 20, 24 or 28 capsules in an aluminium pouch.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Athlone Laboratories Limited
Ballymurray
Co. Roscommon
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

PA 298/17/1

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th October 2011

## 10. DATE OF REVISION OF THE TEXT

November 2015.

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 125mg/5ml Oral Solution

Flucloxin 125mg/5ml Oral Solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flucloxacillin as flucloxacillin sodium Ph. Eur.

125.0mg/5ml of flucloxacillin when reconstituted

Excipients with known effect:

Each 5ml dose contains 3.09g of sucrose and 18.05mg of sodium.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for oral solution

Free-flowing pink-coloured powder for reconstitution.

## 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

Abscesses

Carbuncles

Furunculosis

Cellulitis

Impetigo

Infected wounds

Infected burns

Protection for skin grafts

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 the age, weight and renal function of the patient, as well as the severity of the infection.

Adults (including the elderly)

Oral: - 250mg every 6 hours

In serious infections, the dosage may be doubled.

Paediatric population

2 - 10 years: 125mg every 6 hours

Under 2 years: 62.5mg every 6 hours

In cases of severe renal impairment (creatinine clearance < 10ml/min) a reduction in dosage may

be necessary. 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.

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.

Method of administration

Oral. To be administered ½ - 1 hour before meals.

## 4.3 Contraindications

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

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 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 all of whom are at increased risk of hepatic reactions. The onset of these hepatic 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. In very rare cases, a fatal outcome has 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 β-lactams. 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 anaphylaxis occurs, flucloxacillin should be discounted 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.

Sodium content: this medicinal product contains 18.05mg sodium per 5ml. To be taken into consideration by patients on a controlled sodium diet.

This product contains up to 3.09g sucrose per 5ml dose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption syndrome or sucrase-isomaltase deficiency should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

Probenecid and sulfinpyrazone slow down the 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.

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.

## 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 number of reported cases of use in human pregnancy has shown no evidence of untoward effect. The use of flucloxacillin in pregnancy should be reserved for cases considered essential by the clinician. Flucloxacillin should only be used in pregnancy when the potential benefits outweigh the risks associated with treatment.

Breastfeeding

Flucloxacillin is secreted into mother's milk and may occasionally cause sensitisation of the infant. 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 (≥1/1,000 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).

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.

**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).

**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.

**Hepato-biliary 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).

**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 the yellow card scheme at www.mhra.gov.uk/yellowcard

## 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

**ATC Code: J01CF05**

Pharmacotherapeutic group – Beta-lactamase resistant penicillins

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.

## 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.

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 in to 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.

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%.

### 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

Disodium edetate

Saccharin sodium

Ammonium-glycyrrhizate

Sodium citrate (dried)

Flavour pineapple

Flavour menthol

Red FD & C No.3 (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 in an aluminium pouch - 9 months.

Bottle in an aluminium pouch – 2 years.

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 polypropylene cap, R4 Flexband with blue tamper evident band.

OR

150ml natural high density polyethylene (HDPE) bottle with polypropylene cap, PP28 Mediloc tamper evident closure.

Contents of the bottle after constitution: 100ml

Optional – Bottle placed in Aluminium pouch.

Hugo Meding – polypropylene spoon –article number 7229.

5ml Medispoon.

### 6.6 Special precautions for disposal

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 preparation

## 7. MARKETING AUTHORISATION HOLDER

Athlone Pharmaceuticals Limited

Ballymurray

Co. Roscommon

Ireland

## 8. MARKETING AUTHORISATION NUMBER

PL 30464/0167

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14th September 1995 / 22nd Oct 2009

## 10. DATE OF REVISION OF THE TEXT

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