

# 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  $\beta$ -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 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  $\beta$ -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  $\beta$ -lactams. 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.

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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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  $\geq 50$  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](http://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  $\beta$ -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 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 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**

14<sup>th</sup> September 1995 / 22<sup>nd</sup> Oct 2009

**10. DATE OF REVISION OF THE TEXT**

08 Jan 2016

## 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 and 3.1 g of sucrose 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  $\beta$ -lactam group of antibiotics which exerts a bactericidal effect upon many Gram-positive organisms including  $\beta$ -lactamase-producing staphylococci and streptococci.

#### 4.1 Therapeutic indications

Flucloxacillin is indicated for the treatment of infections due to sensitive Gram-positive organisms, including  $\beta$ -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.

*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. 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.

### Method of administration

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

## 4.3 Contraindications

Hypersensitivity to the active substance,  $\beta$ -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  $\beta$ -lactams. Cross sensitivity between penicillins and cephalosporins is well documented.

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

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, (patients  $\geq 50$  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).

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.

Contains 18.05mg sodium per 5ml. 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.

#### **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 or sulfinpyrazone 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 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.

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.

#### **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. 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.

#### 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  $\geq 50$  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 to

HPRA Pharmacovigilance  
Earlsfort Terrace  
IRL - Dublin 2  
Tel: +353 1 6764971  
Fax: +353 1 6762517  
Website: [www.hpra.ie](http://www.hpra.ie)  
e-mail: [medsafety@hpra.ie](mailto: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: 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  $\beta$ -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 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.

### 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%.

## **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 glycyrrhizinate  
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 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 Laboratories Limited  
Ballymurray  
Co. Roscommon  
Ireland

## **8. MARKETING AUTHORISATION NUMBER(S)**

PA 298/17/3

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

Date of first authorisation: 14<sup>th</sup> October 2011

**10. DATE OF REVISION OF THE TEXT**

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