

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

Geriflox 250mg Capsules, Hard

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains flucloxacillin sodium equivalent to 250 mg of flucloxacillin.

#### Excipient(s) with known effect:

Each capsule contains approximately 13mg sodium.

For the full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Capsule, hard

Grey and brown, size 2, hard gelatin capsules marked with a 'G' and 'FN 250' in black, containing a white to off-white powder.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

Geriflox 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:*

Urinary tract infection, enteritis, meningitis

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

Parenteral usage is indicated where oral dosage is inappropriate.

#### 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 and nature of the infection.

The dosage may be increased if necessary.

##### **Adults and children over 10 years of age**

Total daily dosage of 1 g to 3 g, administered in three to four equally divided doses.

**Paediatric population**

Children up to 10 years of age: 25-50 mg/kg/24 hours in three to four equally divided doses. If the posology cannot be achieved using this medicine, alternate pharmaceutical forms may be more appropriate.

*Example of dosages*

<b>Weight</b>	<b>Daily dose (mg/24 hours)</b>	<b>Daily dosing regimen</b>
22 kg	550-1100	250 mg x 3-4
25 kg	625-1250	250 mg x 3-4
27 kg	675-1350	250 mg x 3-4
30 kg	750-1500	250 mg x 4 or 500 mg x 3
35 kg	875-1750	250 mg x 4 or 500 mg x 3

*Patients with 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 to 12 hours. Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosage need to be administered either during, or at the end of the dialysis period.

Method of administration

Oral administration. To be taken 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 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.

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, 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  $\geq$  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).

Special caution is advised regarding drug induced liver injury in subjects harbouring the HLA-B\*5701 haplotype, as this is currently evaluated in a growing number of subjects with HIV-infection whom may also be at increased risk for exposure to flucloxacillin.

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

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

Prolonged use of an anti-infective agent may result in the development of superinfection due to organisms resistant to that anti-infective.

This medicinal product contains 52 mg sodium per g. To be taken into consideration by patients on a controlled sodium diet.

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.

#### Paediatric population

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.

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

Concurrent administration of probenecid slows down the renal excretion of flucloxacillin.

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

Methotrexate, reduced excretion may occur with flucloxacillin (increased risk of toxicity).

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. Limited information is available on the use of flucloxacillin in human pregnancy. The product should not be used during pregnancy unless considered essential by the physician. Flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment

#### Breast-feeding

The product is excreted in breast milk, presenting risk of sensitisation, candidiasis and also of central nervous system toxicity due to prematurity of the blood brain barrier. 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 known 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 ( $< 1/10,000$ ).

*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  $\geq 50$  years and in patients with serious underlying disease.

#### 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).

*Frequency not known:* AGEP - acute generalized exanthematous pustulosis (See section 4.4)

#### 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 adults 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 HPRC 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 group: beta-lactamase resistant penicillins, ATC code: J01CF05

Flucloxacillin is a semisynthetic penicillin (beta-lactam antibiotic; isoxazolylpenicillin) with a narrow spectrum of activity primarily against Gram-positive organisms, including-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.

#### PK/PD relationship

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

#### Mechanism of resistance

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

#### Antimicrobial activity

Flucloxacillin is active against both-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)
<i>Staphylococcus aureus</i>	0.1 to 0.25
<i>Staphylococcus aureus</i> (beta-lactamase +)	0.25 to 0.5
<i>Streptococcus pneumoniae</i>	0.25
<i>Streptococcus pyogenes</i> (Group A beta-haemolytic)	0.1
<i>Streptococcus viridans</i> group	0.5
<i>Clostridium tetani</i>	0.25
<i>Clostridium welchii</i>	0.25
<i>Neisseria meningitidis</i>	0.1
<i>Neisseria gonorrhoeae</i>	0.1
<i>Neisseria gonorrhoeae</i> (beta-lactamase +)	2.5
The Group A beta-haemolytic streptococci are less sensitive to the isoxazolyl penicillins than to penicillin G or penicillin V.	

## 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

The serum protein-binding rate is 95 %. 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 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.

### 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. The elimination half-life of flucloxacillin is in the order of 53 minutes.

### Neonates and infants

The clearance of flucloxacillin is considerably slower in neonates compared with adults and a mean elimination half life of approximately four and a half hours has been reported in neonates. Special care should be taken during administration of flucloxacillin to the newborn (see section 4.4).

Younger infants (< 6 months) achieve higher plasma concentrations of flucloxacillin than older children when given the same dose.

### Patients with renal impairment

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

There is no additional data of relevance to the prescriber.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule contents:

Magnesium stearate.

The capsule shell contains:

Body:

Gelatin  
Black iron oxide (E172)  
Yellow iron oxide (E172)  
Red iron oxide (E172)  
Titanium dioxide (E171)

Cap:

Gelatin  
Black iron oxide (E172)  
Titanium dioxide (E171)

Printing ink contains:

Shellac  
Black iron oxide (E172)  
N-butyl alcohol  
Macrogol  
Isopropyl alcohol  
Ammonium hydroxide

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

3 years in securitainers, 2 years in blister packs.

### 6.4 Special precautions for storage

Do not store above 25°C.

Blisters: Store in the original package.

Securitainers: Keep the container tightly closed.

### 6.5 Nature and contents of container

Polypropylene containers with polyethylene caps (with optional polyethylene ullage filler) of 15, 100, 250, 500 or 1000 capsules.

PVC/Aluminium foil blister packs of 15, 100, 250, 500 or 1000 capsules.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Generics (UK) Limited  
12 Station Close  
Potters Bar  
Hertfordshire EN6 1TL  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA0405/010/001

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

Date of first authorisation: 25<sup>th</sup> July 1988

Date of last renewal: 25<sup>th</sup> July 2008

## **10 DATE OF REVISION OF THE TEXT**

March 2017