Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 1000 mg powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1000 mg flucloxacillin as flucloxacillin sodium and 2 mmol sodium per vial.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion

Flucloxacillin sodium is supplied as a white or almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Flucloxacillin is indicated for the treatment of the following infections in adults and children caused by flucloxacillin-sensitive gram positive organisms (see section 5.1.):

- Osteomyelitis
- Endocarditis

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Flucloxacillin may also be used in the peri-operative prophylaxis for surgical procedures when appropriate, for example cardiothoracic or orthopaedic surgery.

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

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 usual adult dosage (including the elderly) is as follows:

By slow intravenous injection or by infusion: 250 mg to 1 g every six hours. These doses may be doubled in severe infections. Doses of up to 8 g daily divided in 3 to 4 divided doses have been suggested for osteomyelitis; in endocarditis a dose of 8 g daily in four divided doses in patients weighing up to 85 kg, and 12 g daily in 6 divided doses may be used in those weighing more.

During surgical prophylaxis, 1 to 2 g intravenously at induction of anaesthesia followed by 500 mg six hourly intravenously or intramuscularly.

By intramuscular injection: 250 mg four times daily.

By intrapleural injection: 250 mg once daily.

By nebuliser: 125 to 250 mg four times daily.

By intra-articular injection: 250 to 500 mg once daily.

No single bolus injection or infusion should exceed 2 g.

The maximum dose of 12 g per day should not be exceeded.

Paediatric population

Children under 14 years of age
25 to 50 mg/kg/24 hours administered in three to four equally divided doses by i.m. or i.v. injection.

Children aged 10 to 14 years usually receive a daily dose of 1.5 g to 2 g and children aged 6 to 10 years 0.75 g to 1.5 g, divided into three to four equal doses.

In cases of severe infections: Up to 100 mg/kg/24 hours in three to four divided doses.

No single bolus injection or infusion should exceed 33 mg/kg.

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

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

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

Method of administration
Administer by slow intravenous injection (three to four minutes). Flucloxacillin may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of three to four minutes.
Flucloxacillin may also be administered by intra-articular, intrapleural or intramuscular injection or by nebuliser.

For instructions on reconstitution of flucloxacillin before administration, see section 6.6.

4.3 Contraindications

Flucloxacillin should not be given to patients with a history of hypersensitivity to β-lactam antibiotics (e.g. penicillins, cephalosporins).

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

Ocular or subconjunctival administration is contraindicated.

4.4 Special warnings and precautions for use

Flucloxacillin should be given with caution to patients with a history of allergy, especially to drugs. 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 anaphylaxis occurs, flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine). 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).
Care is necessary if very high doses of flucloxacillin are given, especially if renal function is poor, because of the risk of nephrotoxicity. Care is also necessary if large doses of sodium salts are given to patients with impaired renal function.

Caution is advised in patients with porphyria.

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.

In case of severe and persistent diarrhoea, the possibility of pseudomembranous colitis should be considered; flucloxacillin therapy should be discontinued.

Flucloxacillin injection contains approximately 51 mg sodium per g. This should be included in the daily allowance of patients on sodium restricted diets.

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.

Caution is advised when flucloxacillin is administered concomitantly with paracetamol due to the increased risk of high anion gap metabolic acidosis (HAGMA). Patients at high risk for HAGMA are in particular those with severe renal impairment, sepsis or malnutrition, especially if the maximum daily doses of paracetamol are used.

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

If flucloxacillin is continued after cessation of paracetamol, it is advisable to ensure that there are no signals of HAGMA, as there is a possibility of flucloxacillin maintaining the clinical picture of HAGMA (see section 4.5).

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

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

Probenecid decreases the renal tubular secretion of flucloxacillin. Concurrent administration of probenecid delays the renal excretion of flucloxacillin.

Bacteriostatic drugs (chloramphenicol, erthromycins, 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.

Caution should be taken when flucloxacillin is used concomitantly with paracetamol as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors. (see section 4.4.)

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies with flucloxacillin have shown no teratogenic effects. Limited information is available on the use of flucloxacillin in human pregnancy. Flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

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

Fertility
The impact on male or female fertility has not been investigated.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:- Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000),very rare (<1/10,000).

Unless otherwise stated, the frequency of theadverse 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 Item 4.4 Warnings), 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.	
Metabolism and nutrition disorders	
Frequency not known (cannot be estimated fromthe available data):	Hypokalaemia
Post marketing experience: very rare cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)	
Hepato-biliary disorders	
Very rare:	Hepatitis and cholestatic jaundice. (See Section 4.4 Special Warnings and Special Precautions for Use). Changes in liver function laboratory test results (reversible when treatment is discontinued).
Hepatitis and cholestatic jaundice may be delayed for up to two months post-treatment. In some cases the course has been protracted and lasted for several months. Hepatic events may be severe, and in very rare circumstances, deaths have been reported. Most reports of deaths have been in patients > 50 years of age 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.
Not known:	AGEP – acute generalized exanthematous pustulosis (see section 4.4)
(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 treatment.
Renal and urinary disorders	
Very rare:	Interstitial nephritis.
This is reversible when treatment is discontinued.	
General disorders and administration site conditions	
Very rare:	Fever sometimes develops more than 48 hours after the start of the treatment.

*The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, 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 group: β-lactamase resistant penicillins, ATC code: J01 CF05.

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

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

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

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

Antimicrobial activity
Flucloxacillin is active against both β-lactamase-positive and –negative strains of *Staphylococcus aureus* and other aerobic Gram-positive cocci, with the exception of *Enterococcus faecalis*. Gram-positive anaerobes are generally susceptible (MIC 0.25-2 mg/l) but Gram-negative bacilli or anaerobes are moderately to fully resistant. Enterobacteria is fully resistant to flucloxacillin as well as methicillin-resistant staphylococci.
Strains of the following organisms are generally sensitive to the bactericidal action of flucloxacillin *in vitro*.

The minimal inhibitory concentrations (MIC) of flucloxacillin are quoted below:

Micro-organisms	**MIC (mg/l)**
Staphylococcus aureus	0.1 to 0.25
Staphylococcus aureus (beta-lactamase +)	0.25 to 0.5
Streptococcus pneumoniae	0.25
Streptococcus pyogenes (Group A beta-haemolytic) (*)	0.1
Streptococcus viridans group	0.5
Clostridium tetani	0.25
Clostridium welchii	0.25
Neisseria meningitidis	0.1
Neisseria gonorrhoeae	0.1
Neisseria gonorrhoeae(beta-lactamase +)	2.5

(*) The Group A beta-haemolytic streptococci are less sensitive to the isoxazolyl penicillins than to penicillin G or penicillin V.

5.2 Pharmacokinetic properties

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

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

Paediatric population
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 are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Flucloxacillin should not be mixed with blood products or other proteinaceous fluids (e.g. protein hydrolysates) or with intravenous lipid emulsions.

If flucloxacillin is prescribed concurrently with an aminoglycoside, the two antibiotics should not be mixed in the syringe, intravenous fluid container or giving set; precipitation may occur.

This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

Unopened product: 3 years

Reconstituted solutions for IM or direct IV injection should normally be administered within 30 minutes of preparation.

6.4 Special precautions for storage

Do not store above 25^{o}C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The product is presented in colourless glass vials sealed with a bromobutyl rubber stopper and aluminium cap with plastic lid.

Pack size: 10 vials/carton

6.6 Special precautions for disposal and other handling

Instructions for preparation of reconstituted solutions:
Flucloxacillin may be added to most intravenous fluids (e.g. Water for Injections, sodium chloride 0.9%, glucose 5%, sodium chloride 0.18% with glucose 4%, Hartmann's solution, Dextran 40 (10%) Intravenous Infusion in NaCl (0.9%) intravenous infusion, Dextran 40 (10%) Intravenous Infusion in glucose (5%) intravenous infusion).

Intramuscular: Add 2 ml Water for Injections to 500 mg vial contents. Add 3.0 ml Water for Injections to 1 g vial contents

Intravenous: Dissolve 250-500 mg in 5-10 ml Water for Injections. Dissolve 1g in 20 ml Water for Injections. Administer by slow intravenous injection (three to four minutes). Flucloxacillin may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of three to four minutes.

Intrapleural: Dissolve 250 mg in 5-10 ml Water for Injections.

Intra-articular: Dissolve 250-500 mg in up to 5 ml Water for Injections or 1.0% lidocaine hydrochloride solution.

Nebuliser solution: Dissolve 125-250 mg of the vial contents in 3 ml sterile water.

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

7 MARKETING AUTHORISATION HOLDER

Esteve Pharmaceuticals GmbH
Hohenzollerndamm 150-151
Schmargendorf
Berlin
14199

Germany

8 MARKETING AUTHORISATION NUMBER

PA22709/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th August 2019
Date of last renewal: 12th August 2024

10 DATE OF REVISION OF THE TEXT

July 2023