Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 2000 mg powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2000 mg flucloxacillin (as flucloxacillin sodium monohydrate).

Excipient with known effect
Each 2000 mg vial contains 4.4 mmol (101 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion.
White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flucloxacillin is indicated for the treatment of the following infections when caused by susceptible organisms, in particular Staphylococcus aureus (see sections 4.2 and 5.1):

- Skin and soft tissue infections: abscesses, cellulitis
- Respiratory tract infections: lung abscess, pneumonia, bronchopneumonia
- Bone and joint infections: arthritis, osteomyelitis
- Endocarditis

Flucloxacillin is also indicated for prophylaxis in cardiovascular surgery (valve prostheses, artery prostheses) and in orthopedic surgery (arthroplasty, osteosynthesis and arthrotomy) because of the dominant pathogenic potential of staphylococci during such surgical procedures.

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 patient's age, weight and kidney function as well as the severity and type of infection.

Adults and adolescents 12 years and older
Standard dose: total daily dosage of 1g – g administered in three to four divided doses, by intravenous or intramuscular injection.

In cases of severe infections: up to 8 g daily in the form of four infusions (over 20 to 30 min).

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

Methicillin-susceptible *Staphylococcus aureus.* Endocarditis: 2 g of flucloxacillin every 6 h, increasing to 2 g every 4 h in patients weighing >85 kg.

In surgical prophylaxis: 2 g intravenous (bolus or infusion) after induction of anaesthesia, to be repeated every 6 h for 24 h in cases of vascular and orthopaedic surgery, and for 48 h in cases of cardiac or coronary surgery.
A single bolus injection or infusion should not exceed 2 g.

Paediatric population

Children under 12 years
Standard dose for mild to moderate infections: 25 to 50 mg/kg/24 hours administered in three to four equally divided doses by intramuscular or intravenous injection.
In cases of severe infections: up to 100 mg/kg/24 hours in three to four divided doses.

A single bolus injection or infusion should not exceed 33 mg/kg.

Methicillin-susceptible *Staphylococcus aureus.* Endocarditis: 200 mg/kg/24 hours in three to four divided doses.

Premature newborns, neonates, infants and young children
Flucloxacillin should be administered to premature newborns and neonates only after careful risk-benefit assessment because of the possible triggering of kernicterus (see also section 4.4).

Premature newborns and infants generally receive 25 to 50 mg/kg body weight daily, divided into three to four equal doses. An increase in the daily dose to a maximum of 100 mg/kg body weight may be possible.

Renal impairment
In renal impairment, flucloxacillin is excreted with a delay. In the presence of severe renal impairment (creatinine clearance <10 ml/min) a reduction in dose or an extension of dose interval should be considered. The maximum recommended dose in adults is 1 g every 8 to 12 hours (n anuric patients, the maximum dosage is 1 g every 12 h).
Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need be administered either during, or after dialysis treatment..

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

Method of administration
The powder for solution for injection/infusion can be administered as intramuscular injection and intravenous injection or infusion.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance. Flucloxacillin must not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (e.g. penicillins, cephalosporins).
Flucloxacillin is contraindicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.
Ocular or subconjunctival administrationis contraindicated.

4.4 Special warnings and precautions for use

Before initiating therapy with flucloxacillin, careful inquiry 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, i.v. steroids, and airway management, including intubation, may also be required.

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.

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 hypokalemia-inducing diuretics or when other risk factors for the development of hypokalemia are present (e.g. malnutrition, renal tubule disfunction).

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, patients > 50 years of age, and those with serious underlying disease. In these patients, hepatic events may be severe, and in extremely rare circumstances, deaths have been reported (see section 4.8).

Special caution is advised regarding drug induces 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).

Special caution is essential in the newborn because of the risk of hyperbilirubinemia. 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.

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).

Important information about excipient
This medicinal product contains 101 mg sodium per vial, equivalent to 5.05% of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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

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

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

Flucloxacillin can influence the outcome of the **Guthrie-Test** (false-positive). Blood samples should be taken before the administration of Flucloxacillin.

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

There are case reports describing an altered (usually decreased) INR (International Normalised Ratio) in patients taking warfarin and receiving flucloxacillin concomitantly. Therefore, as a precaution, it is recommended to monitor prothrombin time or INR in patients taking warfarin regularly at the beginning, during and after discontinuation of flucloxacillin treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse effects of flucloxacillin on pregnancy or on the health of the foetus/new-born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.
Caution should be exercised when prescribing to pregnant women.

Breastfeeding
Flucloxacillin diffuses into breast milk in a limited amount and in rare cases this can lead to diarrhoea and/or fungal colonisation of the mucosa in the infant. The possibility of sensitisation of the infant to beta-lactam drugs should be considered.

Fertility
There are no data available on fertility.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). 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)
Not known (cannot be estimated from the available data)

Unless otherwise stated, the frequency of the adverse reactions has been derived from more than 30 years of post-marketing reports.

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
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
Metabolism and nutrition disorders	Very rare	Cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)
	Not known	Hypokalaemia
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). 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 *(See also Immune system disorders)*
	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 adverse events (AEs) was derived from clinical studies involving 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 Health Products Regulatory Authority (HPRA) at HPRA Pharmacovigilance, Website: www.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: Antibacterials for systemic use; 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 β-lactamase-producing strains.
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.

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.

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 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)**	
	S ≤	**R >**
Staphylococcus spp.	Note [1,2]	Note [1,2]
Streptococcus (Groups A, C and G)	Note[3]	Note[3]

[1] Most *S. aureus* are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Isolates that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Isolates that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β-lactam β-lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Isolates that test resistant to cefoxitin are resistant to all penicillins.
[2] Most coagulase-negative staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. No currently available method can reliably detect penicillinase production in coagulase-negative staphylococci but

methicillin resistance can be detected with cefoxitin as described.
[3] The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility (indications other than meningitis) with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for streptococcus group B.

5.2 Pharmacokinetic properties

Absorption
The peak serum levels of flucloxacillin reached after 1h are as follows:
- After 500mg by the i.m. route: approximately 16.5 mg/l.

Distribution
Protein binding: the serum protein binding rate is 95%. Flucloxacillin diffuses well into most tissues.
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 milk.

Biotransformation
In normal subjects approximately 10% of the flucloxacillin administered is metabolised to penicilloic acid. The elimination half life of flucloxacillin is on the order of 53min.

Elimination
Excretion occurs mainly through the kidney. Sixty-five per cent of the dose administered orally is recovered in unaltered active form in the urine within 8h. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

Neonates and infants
The clearance of flucloxacillin is considerably slower in neonates compared with adults and a mean elimination half life of approximately four and a half hours has been reported in neonates. Special care should be taken during administration of flucloxacillin to the newborn (see section 4.4).
Younger infants (<6 months) achieve higher plasma concentrations of flucloxacillin than older children when given the same dose.

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

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

5.3 Preclinical safety data

There is no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the SmPC.

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 same syringe, intravenous fluid container or giving set; precipitation may occur.
Ringer's solution is not compatible with Flucloxacillin for injection/infusion.

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

6.3 Shelf life

3 years.
Reconstituted/diluted solution: Chemical and physical in-use stability has been demonstrated for 1 hour at 25°C and for 24 hours at 2-8°C. From a microbiological point of view, unless the method of opening/ reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than the times stated above for the chemical and physical in-use stability.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I transparent, clear, glass vials, 50 ml, 32 mm closed with a 20 mm bromobutylic rubber stoppers and an aluminium sealing ring with a flip-off cap. The vials are placed into carton box.

Packs sizes: Packs of 1, 5, 10, 20 and 50 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Flucloxacillin may be added to the following infusion fluids:
- Water for injections
- Sodium chloride 9 mg/ml (0.9%) solution for injection
- Dextrose 50 mg/ml (5%) solution for injection
- Sodiumchloride 1.8 mg/ml(0.18%) with glucose 40mg/ml (4%) solution for injection

Intramuscular use
Add 4.0 ml water for injections to 2000 mg vial contents.

Intravenous use
Dissolve Flucloxacillin 2000 mg in 40 ml Water for Injections.
Administer by slow intravenous injection. Flucloxacillin may also be added slowly to infusion fluids or injected, suitably diluted, into the drip tube over a period of three to four minutes.

Flucloxacillin reconstitution volumes
After reconstitution with water for injection, as above reported, the vials can be further added to 50, 100, 125, 200, 250 and 500 ml of the compatible infusion fluids.
The powder volume leads to a volume dilatation, according to the below table:

Strength	Reconstitution with water for injection	Obtained volume water for injection	Displacement value
Flucloxacillin 250 mg	5.0 ml	5.2 ml	0.2 ml
Flucloxacillin 500 mg	10.0 ml	10.3 ml	0.3 ml
Flucloxacillin 1000 mg	20.0 ml	20.6 ml	0.6 ml
Flucloxacillin 2000 mg	40.0 ml	41.2 ml	1.2 ml

Consequently, the final concentrations of the reconstituted solution are as so calculated.

Added volume	50 ml	100 ml	125 ml	200 ml	250 ml	500 ml
	Concentration (mg/ml)					
Flucloxacillin 250 mg	4.5	2.4	1.9	1.2	1.0	0.5
Flucloxacillin 500 mg	8.3	4.5	3.7	2.4	1.9	1.0
Flucloxacillin 1000 mg	14.2	8.3	6.9	4.5	3.7	1.9
Flucloxacillin 2000 mg	21.9	14.2	12.0	8.3	6.9	3.7

Appearance of the solution
Clear colourless or pale yellow particle free solution.
After reconstitution/dilution, the medicinal product should be visually inspected prior to use. Only clear solutions practically free from particles should be used.

For single use only. Any unused solution should be discarded.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1862/003/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th August 2016
Date of last renewal: 8th June 2021

10 DATE OF REVISION OF THE TEXT

July 2023