Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 500 mg powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial contains 500 mg flucloxacillin (as flucloxacillin sodium).

Excipient with known effect:

Each 500 mg vial contains approximately 1.1 mmol sodium.
This medicine contains approximately 25.5 mg sodium per vial, equivalent to 1.275 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion
A fine white or almost white, hygroscopic, crystalline sterile powder for solution for injection/infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flucloxacillin is indicated for the treatment of the following infections due to beta-lactamase-producing staphylococci and other sensitive Gram-positive organisms such as streptococci (see section 4.2 and 5.1:

- Skin and soft tissue infections like abscesses, cellulitis, infected burns, impetigo
- Upper respiratory tract infections, like pharyngitis, tonsillitis, sinusitis
- Lower respiratory tract infections, like pneumonia, bronchopneumonia, pulmonary abscess, Bone and joint infections like osteomyelitis and arthritis

Endocarditis

- Prophylaxis in cardiovascular surgery (valve prostheses, artery prostheses) and in orthopedic surgery (arthroplasty, osteosynthesis and arthrotomy)

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

Adults and adolescents at and over 12 years of age

Total daily dosage of 1 g to 4 g, administered in three to four divided doses, by i.v. or i.m. injection.

In cases of severe infections: Up to 8 g per day administered in four infusions (over 20 to 30 min). No single bolus injection or infusion should exceed 2 g.

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

In surgical prophylaxis: 2 g i.v. (bolus or infusion) upon 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.

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

Paediatric population

Children under 12 years of age

In mild to moderate infections: 25 to 50 mg/kg/24 hours administered in three to four equally divided doses by i.m. or i.v. injection

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.

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

Premature infants, neonates, sucklings and infants

Because of the possible induction of kernicterus, flucloxacillin should be used in premature infants and neonates only after a rigorous benefit-risk assessment (see section 4.4).

Premature infants and neonates as well as sucklings and infants are generally treated with 25 mg to 50 mg/kg/24 hours, divided into three to four equal doses. The daily dose may be increased to a maximum of 100 mg/kg/24 hours.

Abnormal renal function

In patients with renal insufficiency, excretion of flucloxacillin is slowed. However, in the presence of severe renal insufficiency (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 (in 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 at the end of the dialysis period.

Hepatic impairment

Dose reduction in patients with reduced hepatic function is not necessary

Intrapleural and intraarticular
The usual dose is 250 mg to 500 mg once daily.

Method of administration
Parenteral therapy is indicated if the oral route is considered impracticable or unsuitable, as in the case of severe diarrhoea or vomiting, and particularly for the urgent treatment of severe infection.

Routes of administration for Flucloxacillin 500 mg powder for solution for injection/infusion:intramuscular, intravenous, intrapleural and intraarticular.

An intravenous injection/infusion should be performed slowly.

For instructions on the preparation of solution see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipents listed in section 6.1.
- Flucloxacillin should 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.
- Flucloxacillin is not suitable for ocular or subconjunctival administration.
- Flucloxacillin is not suitable for intrathecal injection.

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 betalactam 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 is contra-indicated.
Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, patients $\geq$ 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).

Flucloxacillin solutions reconstituted with local anesthetics (lidocaine) should not be given by intravenous administration (see section 6.6).

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 blood count, hepatic and renal functions is recommended.

Pseudomembranous colitis can occur while taking antibiotics. In case pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, such as oral administration of vancomycin, should be initiated.

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 are at high risk for HAGMA 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).

Particular caution is advised with respect to drug-induced liver injury in patients with the HLA-B * 5701 haplotype; indeed, the frequency of these disorders is currently increasing in HIV-infected patients, who may also be at increased risk of exposure to flucloxacillin (see section 5.1).

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).

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid, phenylbutazone, oxyphenbutazone, acetyl salicylic acid, indometacin and sulfinpyrazone decrease the renal tubular secretion of flucloxacillin. Concurrent administration of probenecid delays the renal excretion of flucloxacillin.

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

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

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 can influence the outcome of the Guthrie-Test (false-positive). Blood samples should be taken before the administration 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 test (e.g. Clinistix) and bromophenol blue tests (e.g. Multistix or Albustix) are not affected.

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

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

Breast-feeding

Flucloxacillin may be administered during the period of lactation. Trace quantities of penicillin can be detected in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) in the breast-fed neonate or acute alterations in the neonatal bowel flora with resultant diarrhoea.

Fertility

There is no data on human fertility, but available data on animal reveals no identifiable risks.

4.7 Effects on ability to drive and use machines

None known.

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 (≥1/1,000, ≤1/100)
rare (≥1/10,000, ≤1/1,000)
very rare (<1/10,000)
not known (cannot be estimated from available data).

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

System Organ Class	**Frequency**					
	Very common	***common***	***uncommon***	***rare***	***Very rare***	***Not known***
Blood and lymphatic disorders					neutropenia (including agranulocytosis)[1], thrombocytopenia[1] eosino-philia, haemolytic anaemia	
Immune system disorders					anaphylac-tic shock (exceptional with oral administration) (see section 4.4), angioneuro-tic oedema[2]	
Metabolism and nutrition disorders					high anion gap metabolic acidosis[9]	hypokalaemia
Nervous system disorders					In patients suffering from renal failure, neurological disorders with convulsions are possible with the i.v. injection of high doses.	
Gastrointesti-nal disorders		minor gastro-intestinal distur-bances[3]			pseudo-membra-nous colitis[4]	
Hepato-biliary disorders					Hepatitis, cholestatic jaundice (see section 4.4)[5], changes in liver function laboratory test results[6]	
Skin and subcutaneous tissue disorders			rash, urticaria, purpura[3]		erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis	acute generalized exanthema-tous pustulosis (see section 4.4)
Musculo-skeletal and connective tissue disorders					arthralgia[7], myalgia[7]	
Renal and urinary disorders					interstitial nephritis[8]	
General disorders and administration site conditions					Fever sometimes develops more than 48 hours after the start of the treatment.	phlebitis

[1] These events are reversible when treatment is discontinued.
[2] If any hypersensitivity reaction occurs, the treatment should be discontinued.
[3] The incidence of these adverse events (AEs) was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.

[4] If pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.
5 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 500-1,000 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.
[6] reversible when treatment is discontinued.
[7] Sometimes develops more than 48 hours after the start of the treatment.
[8] This is reversible when treatment is discontinued.
[9] 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.).

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. Website: www.hpra.ie

4.9 Overdose

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident, which may lead to fluid and electrolyte disturbance and should be treated symptomatically.

In case of neurological disorders with convulsions, symptomatic treatment is essential (rehydration and diazepam).

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.

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 beta-lactamase-positive and –negative strains of *Staphylococcus aureus* and other aerobic Gram-positive cocci, with the exception of *Enterococcus faecalis*. Gram-negative bacilli or anaerobes are moderately to fully resistant. Enterobacteria are fully resistant to flucloxacillin as well as methicillin-resistant staphylococci.

Breakpoints

EUCAST breakpoints, V10.0 valid from 2020-01-01 are as follows:

Micro-organisms	**MIC (mg/l)**
Staphylococcus spp.	Note[1)]
Streptococcus spp.(Groups A, C and G)	Note[2)]
[1)] Most staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to 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. Staphylococci that test resistant to cefoxitin are resistant to all penicillins. [2)] The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for streptococcus group B.	

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 500-1,000 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

After intramuscular administration of 500 mg flucloxacillin, maximal plasma concentrations of 16 µg/ml are reached after 30 minutes.
After a 20-minute infusion of 2 g flucloxacillin, plasma concentrations of about 244 micrograms/ml ± 34.7 micrograms/ml are reached 15 minutes after the start of the infusion. Maximal plasma concentrations are depending on duration and rate of infusion.

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's 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 53 min.

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.

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 new-born (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 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.

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

6.3 Shelf life

Shelf life of the medicinal product in its original package before opening:
2 years

Shelf life after first opening:
Medicinal product must be used immediately after first opening.

Shelf life after reconstitution:
The medicinal product must be used immediately after reconstitution.

Chemical and physical in-use stability of reconstituted or further diluted product has been demonstrated for 2 hours at 20-25 °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.
For reconstitution of Flucloxacillin solution for injection/infusion see section 6.6.

6.4 Special precautions for storage

For single use only. Discard any unused solution.

This medicinal product does not require any specific storage conditions.

For storage conditions of the opened/reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Flucloxacillin 500 mg powder for solution for injection/infusion:
10 mL Type II glass vial closed with halobutyl stoppers and yellow (250 mg) or green (500 mg) aluminium/plastic flip-off caps.

Pack sizes:
500 mg: 10 mL vials in pack of 10 or 50.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use immediately after opening and only undamaged containers. For single use only.
Do not use if the vial is damaged or broken.

Flucloxacillin 500 mg powder for solution for injection/infusion may be added to the following infusion fluids for reconstitution:
- water for injections
- sodium chloride 9 mg/mL (0.9%)
- glucose 50 mg/mL (5%)
- lidocaine hydrochloride 5 mg/mL (0.5 %)

Instruction for reconstitution

Route of Administration	Strengths [mg]	Infusion fluids/ solvents	Volume to be added [mL]	Approximate available volume per flask (mL)	Approximate flucloxacillin concentration per flask (mg/mL)
intramuscular	250	Water for injections	1.5	1.6	155
		Sodium chloride 0.9%	1.5	1.7	145
		Lidocaine hydrochloride 0.5%			
	500	Water for injections	2	2.2	225
		Sodium chloride 0.9%	2	2.3	215

		Lidocaine hydrochloride 0.5%			
	1000	Water for injections	3	3.6	280
		Sodium chloride 0.9%			
		Lidocaine hydrochloride 0.5%	3	3.7	270
		Lidocaine hydrochloride 1.0%			
	2000	Water for injections	4	5.2	385
		Sodium chloride 0.9%	4	5.3	375
		Lidocaine hydrochloride 0.5%	4	5.4	370
		Lidocaine hydrochloride 1.0%	4	5.2	385
intravenous	250	Water for injections	5	5.1	50
		Sodium chloride 0.9%			
		Glucose 5%			
	500	Water for injections	10	10.3	50
		Sodium chloride 0.9%			
		Glucose 5%			
	1000	Water for injections	20	21	45
		Sodium chloride 0.9%	20	20.5	50
		Glucose 5%			
	2000	Water for injections	40	41	50
		Sodium chloride 0.9%			
		Glucose 5%			
intrapleural	250	Water for injections	5	5.1	50
		Sodium chloride 0.9%			
		Water for injections	10	10.2	25
		Sodium chloride 0.9%			
	500	Water for injections	5	5.4	95
		Sodium chloride 0.9%			
		Water for injections	10	10.3	50
		Sodium chloride 0.9%			
intraarticular	250	Water for Injections	5	5.1	50
		Sodium chloride 0.9%			
	500	Water for injections	5	5.4	95
		Sodium chloride 0.9%			

The reconstituted solution can be diluted with:

- water for injections
- sodium chloride 9 mg/mL (0.9%)
- glucose 50 mg/mL (5%)

The compatibility of flucloxacillin with diluents other than described above or in section 6.2 is unknown.

The reconstituted solution should be visually inspected and should not be used in the presence of opalescence, visible particles or precipitate.

In case precipitations are seen after the reconstitution, shake well before use.

Any antibiotic residual solution as well as all materials that have been used for administration should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
Germany

8 MARKETING AUTHORISATION NUMBER

PA2059/069/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th November 2020
Date of last renewal: 3rd September 2025

10 DATE OF REVISION OF THE TEXT

January 2025