Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 1000 mg powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flucloxacillin 1000 mg powder for solution for injection/infusion:
Each vial contains 1000 mg flucloxacillin as flucloxacillin sodium monohydrate.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion

White or almost white, crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flucloxacillin is indicated in all age groups 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 dose of 1000 mg to 4000 mg, administered in three to four divided doses, by intravenous or intramuscular injection. In cases of severe infections: up to 8000 mg per day administered in four infusions (over 20 to 30 min). No single bolus injection or infusion should exceed 2000 mg.
The maximum dose of 12000 mg per day should not be exceeded.

In surgical prophylaxis: 2000 mg 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: 2000 mg of flucloxacillin every 6 h, increasing to 2000 mg 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.

Renal impairment
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 1000 mg every 8 to 12 hours (in anuric patients, the maximum dosage is 1000 mg 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.

Flucloxacillin 1000 mg powder for solution for injection/infusion:
For intramuscular and intravenous use.

An intravenous injection/infusion should be performed slowly.

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

4.3 Contraindications

- Hypersensitivity to the active substance.
- Patients with a history of hypersensitivity to beta-lactam antibiotics (e.g. penicillins, cephalosporins).
- Patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.
- Ocular or subconjunctival administration.
- 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 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 is contra-indicated.

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).

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).

Sodium

Flucloxacillin 1000 mg powder for solution for injection/infusion:
This medicinal product contains 50.64 mg sodium per vial, equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Flucloxacillin is considered to be high in sodium. This should be taken into consideration if the patient is following a low-salt diet.

The maximum daily dose of this product is equivalent to 30.38 % of the maximum daily amount for an adult recommended by the WHO.

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.

In rare cases, an altered (usually decreased) International Normalised Ratio (INR) has been described in patients taking warfarin after initiation of therapy with flucloxacillin. Therefore, as a precautionary measure, it is recommended to monitor the prothrombin time or INR at the beginning, during and after the end of flucloxacillin treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Limited data is available on the use of flucloxacillin in pregnant women. Animal studies with flucloxacillin have shown no teratogenic effect. Flucloxacillin should be used during pregnancy only if the possible benefits outweigh the possible risks associated with treatment.

Breast-feeding
During breast-feeding, traceable amounts of penicillin can be detected in human milk. Flucloxacillin can be maintained during breast-feeding. With the exception of the possible risk of hypersensitivity reactions in newborn babies who are breast-fed or acute changes in their gut flora, resulting in diarrhoea or candidiasis, there are no other harmful effects for the baby.

Fertility
There are no data available on fertility in humans or animals.

4.7 Effects on ability to drive and use machines

Not relevant.

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/ 1000)
very rare (< 1/ 10,000)
not known (cannot be estimated from the available data).

Unless otherwise stated, the frequency of the undesirable effects 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 system disorders					neutropenia (including agranulocytosis)[1], thrombocytopenia[1] eosinophilia, haemolytic anaemia	
Immune system disorders					anaphylactic shock (exceptional with oral administration) (see section 4.4), angioneurotic 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.	
Gastrointestinal disorders		minor gastrointestinal disturbances[3]			pseudomembra-nous colitis[4]	
Hepatobiliary 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 exanthematous pustulosis (see section 4.4)
Musculoskeletal 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 via the 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: 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 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

Susceptibility testing breakpoints MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for flucloxacillin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx.

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 µg/ml ± 34.7 µg/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 are no preclinical data of relevance to the prescriber which are additional to those already included in other sections of the summary of product characteristics.

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 administration 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

3 years

Use immediately after first opening.

After reconstitution:
Intramuscular use
Chemical and physical in-use stability has been demonstrated for:
- 4 hours at 23-27°C in artificial light when reconstituted with water for injection and lidocaine solution 1 % w/v.
- 24 hours at 2-8°C protected from light when reconstituted with water for injection and lidocaine solution 1 % w/v.
Intravenous use
Chemical and physical in-use stability has been demonstrated for:
- 4 hours at 23-27°C in artificial light when reconstituted with water for injection and sodium chloride 9 mg/mL (0.9 %) solution.
- 24 hours at 2-8°C protected from light when reconstituted with water for injection and sodium chloride 9 mg/mL (0.9 %) solution.

Intravenous infusion
Chemical and physical in-use stability has been demonstrated for:
- 2 hours at 23-27°C in artificial light when reconstituted with water for injection, sodium chloride 9 mg/mL (0.9 %) solution, glucose 5 % w/v solution or sodium chloride 1.8 mg/mL (0.18 %) solution for injection with glucose 4 % w/v solution.
- 24 hours at 2-8°C protected from light when reconstituted with water for injection, sodium chloride 9 mg/mL (0.9 %) solution, glucose 5 % w/v solution or sodium chloride 1.8 mg/mL (0.18 %) solution for injection with glucose 4 % w/v solution.

From a microbiological point of view, 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 normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Reconstitution using Hartmann solution:
- at 23-27°C: use immediately
- at 2-8°C: 2 hours protected from light.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Flucloxacillin 1000 mg powder for solution for injection/infusion:
20 ml Type III clear glass vial sealed with chlorobutyl rubber stoppers and aluminum caps, with red plastic flip off cap.

Pack sizes: cartons of 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use only undamaged containers.
Do not use if the vial is damaged or broken.

Flucloxacillin can be added to the following solutions for infusion:

- Water for injection
- Sodium chloride 9 mg/mL (0.9 %) solution for injection
- Glucose 5 % w/v solution
- Sodium chloride 1.8 mg/mL (0.18 %) solution for injection and glucose 4 % w/v solution
- Hartmann solution

Route of administration	**Solvent**		**Stability of the solution at room temperature**
	Volume to be added	**Type**	
Intramuscular use Flucloxacillin 2000 mg Flucloxacillin 1000 mg Flucloxacillin 2000 mg	2 mL 3 mL 4 mL	Water for injection Lidocaine 1 % w/v solution	4 hours in artificial light (24 hours in the refrigerator)
Intravenous use as an injection Flucloxacillin 500 mg Flucloxacillin 1000 mg Flucloxacillin 2000 mg	10 mL 20 mL 40 mL	Water for injection Sodium chloride 9 mg/mL (0.9 %) solution for injection	4 hours in artificial light (24 hours in the refrigerator)
Intravenous use as an infusion Flucloxacillin 500 mg Flucloxacillin 1000 mg Flucloxacillin 2000 mg	Volume equivalent to a concentration of 1 % w/v	Water for injection Sodium chloride 9 mg/mL (0.9 %) solution for injection Glucose 5% solution Sodium chloride 1.8 mg/mL (0.18 %) solution for injection and glucose 4% w/v solution	2 hours in artificial light (24 hours in the refrigerator)
		Hartmann solution	Use immediately (2 hours in refrigerator)
Intrapleural	5 mL	Water for	4 hours in artificial light

use Flucloxacillin 500 mg		injections Sodium chloride 9 mg/mL (0.9 %) solution for injection	(24 hours in the refrigerator)
	10 mL	Water for injections Sodium chloride 9 mg/mL (0.9 %) solution for injection	4 hours in artificial light (24 hours in the refrigerator)
Intraarticular use Flucloxacillin 500 mg	5 mL	Water for injections Sodium chloride 9 mg/mL (0.9 %) solution for injection	4 hours in artificial light (24 hours in the refrigerator)

Administer via a slow intravenous injection.

Appearance of the solution
Clear, colourless or pale yellow,particle-free solution.

Only clear solutions practically free from particles should be used.

For single use only.

Any unused solution should be discarded.

Flucloxacillin may also be added to infusion fluids or injected, suitably diluted, into the drip tube.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Noridem Enterprises Limited
Evagorou & Makariou
Mitsi Building 3, Office 115
1065 Nicosia
Cyprus

8 MARKETING AUTHORISATION NUMBER

PA1122/036/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th November 2024

10 DATE OF REVISION OF THE TEXT