Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains flucloxacillin sodium equivalent to flucloxacillin 500 mg.

Excipient with known effect
Flucloxacillin 500 mg Film-coated Tablets contains 29.33 mg of sodium, equivalent to 1.5% of the WHO's highest recommended daily intake (2 grams of sodium for adults).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet

White to off white capsule shaped film coated tablet debossed with 'FL|500' on one side and break line on other side.

The tablet can be divided into equal doses

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flucloxacillin is indicated in adults and children over the age of 10 years for the treatment of infections due to sensitive Gram-positive organisms, including β-lactamase-producing staphylococci and streptococci such as:
- Skin and soft tissue infections
- Respiratory tract infections
- Other infections caused by flucloxacillin-sensitive micro-organisms

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. The dosage may be increased if necessary.
Adults and children over 10 years of age: Total daily dosage of 1 g to 3 g, administered in three to four equally divided doses.

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

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

Method of Administration:
This medicine should be taken on an empty stomach. Flucloxacillin Tablets should be taken at least 1 hour before or 2 hours after meals. The tablets should be taken with a full glass of water (250 ml), to reduce the risk of oesophageal pain (see section 4.8). Patients should not lay down immediately after Flucloxacillin intake.

4.3 Contraindications

Hypersensitivity to the active substance, β-lactam antibiotics (e.g. penicillins, cephalosporins) or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

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.

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).

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

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

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Cross-allergy between penicillins and cephalosporins occurs. Diarrhea / pseudomembranous colitis caused by Clostridium difficile occurs. Patients with diarrhea should therefore be closely monitored.
There is a risk of liver damage when using flucloxacillin. This risk is rare but increases probably at older age and with longer-term treatment (see section 4.8).

The onset of a feverish generalized erythema associated with pustules at the start of treatment may be one symptoms of acute generalized exanthematous pustulosis (AGEP) (see section 4.8). At AGEP diagnosis should flucloxacillin is discontinued and any subsequent administration of flucloxacillin is contraindicated.

Caution is advised when flucloxacillin is co-administered with paracetamol due to of the increased risk of HAGMA (high anion gap metabolic acidosis). For patients at high risk for HAGMA belongs in particular to those with severe renal impairment, sepsis or malnutrition, especially in use of maximum daily doses of paracetamol.

After concomitant use of flucloxacillin and paracetamol, careful use is recommended monitoring to detect the occurrence of acid-base disorders, ie HAGMA, including searching for 5-oxoproline in the urine.

If treatment with flucloxacillin continues after discontinuation of paracetamol, it is advisable to make sure that there are no signals on HAGMA, as there is a possibility that flucloxacillin maintains 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 hypokalemia-inducing diuretics or when other risk factors for the development of hypokalemia are present (e.g. malnutrition, renal tubule disfunction).

The 500 mg tablet contains 29.33 mg of sodium, corresponding to 1.5% of the WHO's highest recommended daily intake (2 grams of sodium for adults).

This should be taken into consideration when treating patients on a low-salt diet.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid and sulfinpyrazone decrease the renal tubular secretion of flucloxacillin. Concurrent administration of probenecid delays the renal excretion of flucloxacillin.

Other substances, such as piperacillin, which are excreted via renal tubular secretion, may interfere with flucloxacillin elimination.

Oral typhoid vaccine may be inactivated by flucloxacillin.

Flucloxacillin reduces the excretion of methotrexate which can cause methotrexate toxicity. Flucloxacillin may reduce the response to sugammadex.

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

There are rare cases of decreased international normalised ratio (INR) in patients taking warfarin and prescribed a course of flucloxacillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored during addition or withdrawal 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 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

Pregnanacy
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
During lactation, trace quantities of penicillins can be detected in breast milk. Flucloxacillin may be administered during the period of lactation. With the exception of risk of sensitisation there are no other detrimental effects for the breast fed infant.

4.7 Effects on ability to drive and use machines

Flucloxacillin has no or negligible effect on the ability to drive and use machines.

4.8 Undesirable effects

The most common are gastrointestinal side effects, which occur in about 5% of treated patients.

Estimated adverse reaction rates are ranked as follows: Common (≥1/100, <1/10); Less common (≥1 / 1000, <1/100); Rare (≥1/10,000, <1/1000); Very rare (<1/10,000); No known frequency (cannot be calculated from the available data).

Infections and Infestations	Rare	Pseudomembranous colitis

The blood and lymphatic system	Less common	Eosinophilia.
	Rare	Agranulocytosis
Immune system disorders	Rare	Anaphylactic reactions
Central and peripheral nervous system	No known frequency	Dizziness
The gastrointestinal tract	Common	Nausea, diarrhoea
	No known frequency	Abdominal pain, vomiting
	No known frequency	Oesophageal pain and related events **
Liver and biliary tract *	Rare	Liver effects of usually mixed cholestatic-hepatocellular type.
Skin and subcutaneous tissue disorders	common	Exanthema
	Less common	Urticaria
	Very rare	Itching
	No known frequency	AGEP - acute generalized exanthematous pustulosis (see section 4.4)

Fungal overgrowth in the oral cavity and abdomen may occur.
**Oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain.

* Liver and bile ducts
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 (see Section 4.4).
There is evidence that the risk of flucloxacillin-induced liver damage increases in people who carry it allele HLA-B * 5701. Despite this strong association, only 1 in 500-1000 carriers will develop liver damage. Consequently, the positive predictive value of testing for allele HLA-B * 5701 with regarding liver damage very low (0.12%) and routine screening for this allele not recommended.

Metabolism and nutrition disorders
Post-market experience: very rare cases of HAGMA (high anion gap metabolic acidosis) with concomitant use of flucloxacillin and paracetamol, usually in the presence of risk factors (see section 4.4.)

Hypokalaemia also reported with frequency not known.

Reporting of suspected side effects:
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, 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: Beta-lactam-resistant penicillins.
ATC code: J01CF05.

Flucloxacillin belongs to the group of isoxazolylpenicillins, which combine high activity against beta-lactamase-producing staphylococci with good acid stability. Flucloxacillin works by inhibit the bacterial cell wall synthesis and the effect is bactericidal. The antibacterial effect is best correlated to the time that the antibiotic concentration exceeds the MIC.

Antibacterial spectrum

Sensitive	Staphylococcus aureus and coagulase-negative staphylococci included beta-lactamase-producing strains Streptococci and pneumococci
Resistant	Methicillin-resistant staphylococci Enterococci Gram-negative bacteria Clostridium difficile

Resistance is common (approximately 40%) in coagulase-negative staphylococci due to methicillin resistance. Streptococci and pneumococci are more sensitive to benzylpenicillin and penicillin V than to flucloxacillin.

Mechanism of resistance: Resistance to isoxazolylpenicillins (so-called methicillin resistance) is caused by the bacterium produces an altered penicillin-binding protein. Cross-resistance occurs within the beta-lactam group (penicillins and cephalosporins). Methicillin-resistant staphylococci generally have low sensitivity to all beta-lactam antibiotics.

Development of resistance: In Sweden, resistance to isoxazolylpenicillins is rare in Staphylococcus aureus but common in coagulase-negative staphylococci. Methicillin-resistant Staphylococcus aureus (MRSA) are common in some parts of Europe.

Penicillin-resistant pneumococci are uncommon in Sweden. Such strains are resistant to cloxacillin. The resistance situation varies geographically and information about the locals resistance conditions should be obtained through a local microbiological laboratory.

Liver damage
There is evidence that the risk of flucloxacillin-induced liver damage increases in people who carry it allele HLA-B * 5701. Despite this strong association, only 1 in 500 -1000 carriers will develop liver damage. Consequently, the positive predictive value of testing for allele HLA-B * 5701 with regarding liver damage very low (0.12%) and routine screening for this allele not recommended.

5.2 Pharmacokinetic properties

Flucloxacillin has good absorption after oral administration. Administration in connection with a meal adversely affects absorption. The biological half-life in serum is about 80-90 minutes and binding to serum proteins amounts to 94-95%. Of the various isoxazolyl penicillins Flucloxacillin the highest percentage of free (non-protein bound) penicillin in serum. The elimination of flucloxacillin occurs mainly in the kidneys via tubular secretion and glomerular filtration. Within 6 hours, about 50-55% of an oral dose is excreted in the urine.

5.3 Preclinical safety data

There are no preclinical data relevant to the safety assessment beyond what has already been considered in the product summary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose, Povidone K-30, Croscarmellose Sodium, Silica Hydrophobic Colloid, Magnesium stearate, Ethyl cellulose, HPMC 2910/Hypromellose, Titanium Dioxide, Macrogol/PEG and Paraffin.

6.2 Incompatibilities

Not relevant

6.3 Shelf life

Strip pack - 3 Years
Blister pack - 3 Years
HDPE bottle - 2 Years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Strip of 10 tablets per pack
Blister of 10 tablets per pack
HDPE bottle of 100 tablets per container

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Azure Pharmaceuticals Ltd
12 Hamilton Drive
The Rock Road
Blackrock
Co. Louth
A91 T997
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22871/026/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th March 2023

10 DATE OF REVISION OF THE TEXT

July 2023