Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 500 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains flucloxacillin 500 mg as flucloxacillin sodium.

Excipient with known effect:
Contains 26.4 mg of sodium per 500mg capsule.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Elongated hard gelatin capsule approximately 2 cm in length having an opaque caramel body and opaque grey cap each printed ‘FXN 500’ in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Flucloxacillin 500 mg capsules are 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* (see section 5.1) such as:

- Skin and soft tissue infections
- Respiratory tract infections
- Other infections caused by flucloxacillin-sensitive micro-organisms, *e.g.* enteritis, urinary tract infections.

Parenteral use is indicated where oral dosage is inappropriate.

Consideration should be given to official guidance on the appropriate use of antibacterial substances.

4.2 Posology and method of administration

Posology

The dosage depends on the age, weight and renal function of the patient, as well as the severity of the infection.

This medicinal product should not be administered to children under 10 years of age.

For doses not practicable with this product, other strengths and pharmaceutical forms are available.

Usual dosage (adults including elderly patients and children over 10 years of age)
Oral - 1-3 g daily in 3-4 equally divided doses.

Renal impairment
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 < 10 ml/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 – 12 hours. Flucloxacillin is not significantly removed by dialysis and hence no supplementary doses need to be administered either during, or at the end of the dialysis period.

Method of administration

Oral: Oral doses should be administered half to one hour before meals.

4.3 Contraindications

Flucloxacillin should not be given to patients with a history of hypersensitivity to β-lactam antibiotics (e.g. penicillins, cephalosporins) or to any excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

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.

Before initiating therapy with flucloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to β-lactams. Cross sensitivity between penicillins and cephalosporins is well documented.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving β-lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. These reactions are more likely to occur in individuals with a history of β-lactam hypersensitivity. If an allergic reaction occurs, flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions may require immediate emergency treatment with adrenaline. Oxygen, IV steroids, and airway management, including intubation, may also be required.

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

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

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

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

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).

This medicinal product contains 26.4 mg sodium per 500 mg capsule. To be taken into consideration by patients on a controlled sodium diet.

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.

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.)

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with flucloxacillin have shown no teratogenic effects. Limited data is available on the use of flucloxacillin in pregnancy. The decision to administer any medicinal product during pregnancy should be taken with the utmost care. Therefore flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:- Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

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

Blood and lymphatic system disorders
Very rare: Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued. Eosinophilia. Haemolytic anaemia.

Immune system disorders
Very rare: Anaphylactic shock (exceptional with oral administration) (see 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 IV 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.

Hepatobiliary disorders
Very rare: Hepatitis and cholestatic jaundice. (See section 4.4). Changes in liver function laboratory test results (reversible when treatment is discontinued).

These reactions are related neither to the dose nor to the route of administration. The onset of these effects may be delayed for up to two months post-treatment; in several cases the course of the reactions has been protracted and lasted for some months. Hepatic events may be severe and in very rare circumstances a fatal outcome has been reported. Most reports of deaths have been in patients ≥ 50 years 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).

Metabolism and nutrition disorders

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.)

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 was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2 Tel: +353 1 6764971, Fax: +353 1 6762517 Website: www.hpra.ie, e-mail: medsafety@hpra.ie

4.9 Overdose

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically. Flucloxacillin is not removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: Antibacterials for systemic use, beta-lactamase resistant penicillins
ATC code: J01C F05

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

Mode 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.

Pharmacokinetic/pharmacodynamic relationship

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

Mechanisms of resistance

Resistance to isoxazolylpenicillins (so-called meticillin-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. Meticillin-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-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 meticillin-resistant *staphylococci*.

Strains of the following organisms are generally sensitive to the bactericidal action of flucloxacillin *in vitro*. The

minimal inhibitory concentrations (MIC_{90}) of flucloxacillin are quoted below:

Micro-organisms	**MIC_{90} (mg/l)**
Staphylococcus aureus	0.1 to 0.25
Staphylococcus aureus (beta-lactamase +)	0.25 to 0.5
Streptococcus pneumoniae	0.25
Streptococcus pyogenes (Group A beta-haemolytic)	0.1
Streptococcus viridans group	0.5
Clostridium tetani	0.25
Clostridium welchii	0.25
Neisseria meningitidis	0.1
Neisseria gonorrhoeae	0.1
Neisseria gonorrhoeae (beta-lactamase +)	2.5

The Group A beta-haemolytic *streptococci* are less sensitive to the isoxazolylpenicillins than to penicillin G or penicillin V.

Breakpoints
Flucloxacillin sensitivity testing may be carried out with cefoxitin or oxacillin using the standard dilution series. The following minimum inhibitory concentrations for sensitive and resistant strains have been determined:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints

Species	**Sensitive**	**Resistant**
For oxacillin:		
Staphylococcus aureus and *S. lugdunensis*	-	>2 mg/l
Coagulase-negative *staphylococci* except *S. lugdunensis*	-	> 0.25 mg/l
For cefoxitin:		
Staphylococcus aureus and *S. lugdunensis*	-	>4 mg/l

Prevalence of resistance

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

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 500-1000 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.

5.2 Pharmacokinetic properties

Absorption

Flucloxacillin is stable in acid media and can therefore be administered either orally or parenterally. The peak serum levels of flucloxacillin reached after one hour are as follows:

Oral use: after 250 mg (in fasting subjects): Approximately 8.8 mg/l.
after 500 mg (in fasting subjects): Approximately 14.5mg/l.
Intramuscular use: after 500 mg: Approximately 16.5 mg/l.

The total quantity absorbed after oral administration represents approximately 79% of the quantity administered.

Absorption is delayed by food, with peak serum levels being approximately halved compared with the fasting state. Therefore, it is recommended that flucloxacillin be taken 0.5 to 1 hour before meals.

Distribution

Serum protein binding rate is 95%. Flucloxacillin diffuses well into most tissue.

Crossing the meningeal barrier: Flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mother's milk: Flucloxacillin is excreted in small quantities in mother's milk.

Biotransformation

In normal subjects approximately 10% of the flucloxacillin administered is metabolised to penicilloic acid. The elimination half-life of flucloxacillin is in the order of 53 minutes.

Elimination

Excretion occurs mainly through the kidney. Between 65.5% (oral use) and 76.1% (parenteral use) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

Following oral administration flucloxacillin is almost completely absorbed achieving blood levels comparable to those achieved after intramuscular injection.

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 impairement 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

No further information of relevance to add.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Sodium starch glycolate (type A)
Magnesium stearate

Capsule shell:
Gelatin
Black iron oxide (E172)
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink:
Shellac
Propylene glycol
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
Use within 3 months of opening the foil pouch.

6.4 Special precautions for storage

Do not store above 25° C. Keep the blister in the outer carton in order to protect from light and moisture. Do not open the foil pouch until ready to use the product. Once opened the foil pouch may be discarded.

6.5 Nature and contents of container

Opaque PVC/PE/PVDC blister with an aluminium lidding foil containing 10, 16, 20, 24 or 28 capsules in an alumimium pouch. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Athlone Laboratories Limited
Ballymurray
Co. Roscommon
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0298/016/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th October 2011
Date of last renewal: 13th October 2016

10 DATE OF REVISION OF THE TEXT

April 2018