Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucillin – Flucloxacillin Capsules 500 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg flucloxacillin as flucloxacillin sodium.
Sodium content: 25.370 mg or 1.103 mmol of sodium per capsule.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard
Capsules with caramel – coloured bodies and grey caps, printed 'FXN 500' in black and containing a white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of infections due to penicillinase producing staphylococci and other Gram-positive organism susceptible to this anti-infective.

4.2 Posology and method of administration

The dosage depends on the severity and nature of the infection.

The dosage may be increased if necessary

Usual adult (and children over 10 years of age) dosage:
Oral: 250-500 mg three times a day.

Usual children's dosage:
2-10 years: one-half adult dose.
Under 2 years: one quarter adult dose.
Osteomyelitis, endocarditis: Up to 8 g daily in divided doses six to eight-hourly.
Surgical prophylaxis: 1 to 2 g IV at induction of anaesthesia followed 500 mg six-hourly IV, IM, or orally at six-hourly intervals for up to 72 hours.

Abnormal renal function:
In common with other penicillin, Flucloxacillin usage in patients with renal impairment does not usually require dose 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 dosages need to be administered either during, or at the end of the dialysis period.

Administration:
Flucillin – Flucloxacillin capsule should be taken at least 1 hour before or 2 hours after meals.
The capsule 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

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

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

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.

Flucloxacillin has been associated with cholestatic jaundice.

Flucloxacillin appears to be excreted in a manner similar to that for benzyl penicillin i.e. by glomerular filtration and tubular secretion. This should be borne in mind when prescribing therapy.

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, those with serious underlying disease, and the elderly. In these patients, hepatic events may be severe, and in extremely rare circumstances, deaths have been reported (*see Undesirable Effects*).

Dosage should be adjusted in renal impairment (*see Posology and Method of Administration*)

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.

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.

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).

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 content: Flucillin capsules contain approximately 51 mg sodium per g. This should be included in the daily allowance of patients on sodium restricted diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

Bacteriostatic drugs may interfere with the bactericidal action of flucloxacillin.

In common with other antiobiotics, flucloxacillin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

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

The product should not be used during pregnancy unless considered essential by the physician. Flucloxacillin is excreted in breast milk, presenting the risk of candidiasis and also central nervous system toxicity due to prematurity of the blood brain barrier. There is a theoretical possibility of later sensitisation.

4.7 Effects on ability to drive and use machines

Patients receiving this medication should not drive or operate machinery unless the drug has been shown not to interfere with physical or mental ability.

4.8 Undesirable effects

The following convention has been utilized for the classification of undesirable effects: 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 events has been derived from more than 30 years of post-marketing reports.

Blood and lymphatic system disorders

Very rare: Neutropenia (including agranulcytosis) and thrombocytopenia. These are reversible when treatment is discontinued. Eospinphilia, haemolytic anaemia.

Immune system disorders

Very rare: Anaphylactic shock (exceptional with oral administration) (see Item 4.4 Warnings), 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 (such as nausea and diarrhoea).

Very rare: Pseudomembranous colitis.

If pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.

Not known: Oesophageal pain and related events **

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice (see Warnings and Precautions). 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)*.

Frequency 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.

Metabolism and nutrition disorders

Not known: Hypokalaemia

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.)

**The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.*
** oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain

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 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 classification: Beta-lactamase resistant penicillins.
ATC code: J01C F05

Flucloxacillin is a semisynthetic penicillin which is not decomposed by staphylococcal penicillinase but is destroyed by penicillinase produced by Gram-negative bacteria.

Flucloxacillin has the same spectrum of activity as the earlier antistaphylococcal penicillins methicillin and cloxacillin against Gram-positive organisms, including pencillinase-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.

5.2 Pharmacokinetic properties

It is well absorbed after oral administration. In unfasted subjects the absorption is reduced by 50 % compared to fasted subjects. Plasma half-life is 40 to 45 minutes. It does not enter the cerebrospinal fluid: 90 to 95 % bound to plasma proteins; 20 to 50 % of an oral dose is excreted in the urine.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents
Magnesium stearate
Colloidal anhydrous silica

Capsule Shell Body
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Capsule Shell Cap
Black iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Capsule Ink
Shellac Glaze
Iron Oxide Black (E172)
Propylene Glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polypropylene tablet containers with polyethylene lids or high density polyethylene containers with low density polyethylene caps in packs of 20, 40, 100 or 500 capsules , with or without a Jayfilla.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/031/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 May 1995

Date of last renewal: 03 May 2010

10 DATE OF REVISION OF THE TEXT

May 2023