Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 1g Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium flucloxacillin monohydrate equivalent to flucloxacillin 1g

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion (Powder for injection or infusion)

Flucloxacillin sodium is supplied as a white or almost white crystalline powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flucloxacillin is indicated for the treatment of infections due to penicillinase producing staphylococci and other gram positive organisms susceptible to this anti-infective (see Section 5.1).

Indications include: osteomyelitis and endocarditis.

Flucloxacillin is also indicated for use as a prophylactic agent during major surgical procedures when appropriate; for example cardiothoracic and orthopaedic surgery.

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

4.2 Posology and method of administration

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

Method of administration

The usual routes of administration for Flucloxacillin 250mg, 500mg and 1g Powder for Solution for Injection or Infusion are by slow intravenous injection and intravenous infusion.

Flucloxacillin 250mg and 500mg Powder for Solution for Injection or Infusion may also be administered by intramuscular, intra-articular or intrapleural injection. Flucloxacillin 250mg may also be inhaled by nebuliser.

The solutions must be prepared as follows:

Adults and the elderly

Intravenous: Dissolve 250 to 500mg in 5 to 10ml of water for injections or 1g in 15 to 20ml of water for injections. Administer by slow intravenous injection (over three to four minutes). Flucloxacillin may also be added to infusion fluids or injected (suitably diluted) into the drip tube over three to four minutes. Flucloxacillin may be added to most intravenous fluids (eg water for injections, sodium chloride 0.9%, glucose 5%, sodium chloride 0.18% with glucose 4%).

Intramuscular: Add 1.5ml of water for injections to 250mg vial contents or 2ml of water for injections to 500mg vial contents.

Intrapleural: Dissolve 250mg in 5 to 10ml of water for injections.

Intra-articular: Dissolve 250 to 500mg in up to 5ml of water for injections or 0.5% lignocaine hydrochloride solution for injection.

Nebuliser Solution: Dissolve 125mg to 250mg of the vial contents in 3ml of water for injections.

The usual adult dosage (including the elderly) is as follows:

By slow intravenous injection or by infusion: 250mg to 1g every six hours
These doses may be doubled in severe infections. Doses of up to 8g daily have been suggested for endocarditis or osteomyelitis.
During surgical prophylaxis, doses of 1 to 2g should be given intravenously at induction of anaesthesia followed by 500mg six hourly intravenously or intramuscularly.

By intramuscular injection: 250mg every six hours

By intrapleural injection: 250mg once daily

By intra-articular injection: 250mg to 500mg once daily

By nebuliser: 125mg to 250mg every six hours

Paediatric population
Any route of administration may be used. For children under two years old, a quarter of the adult dose should be administered. For children two to ten years old, half of the adult dose should be administered.

Renal impairment
Dosage reduction is not usually required. In severe renal failure, however, (creatinine clearance less than 10ml/min) a reduction in dose or extension of dose interval should be considered.

No supplementary dosages need be administered during or at the end of the dialysis period, as flucloxacillin is not significantly removed by dialysis.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Flucloxacillin should not be given to patients with a history of hypersensitivity to ß-lactam antibiotics (e.g. penicillins, cephalosporins).

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

Ocular or subconjunctival administration is contraindicated.

4.4 Special warnings and precautions for use

Flucloxacillin should be given with caution to patients with a history of allergy, especially to drugs. Before initiating therapy with flucloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to ß-lactams. Cross sensitivity between penicillins and cephalosporins is well documented. Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving ß-lactam antibiotics. These reactions are more likely to occur in individuals with a history of ß-lactam hypersensitivity. Desensitisation may be necessary if treatment is essential. If any hypersensitivity reaction occurs, the treatment should be discontinued.

Care is necessary if very high doses of flucloxacillin are given, especially if renal function is poor, because of the risk of nephrotoxicity and/or neurotoxicity. The intrathecal route should be avoided. Care is also necessary if large doses of sodium salts are given to patients with impaired renal function or heart failure. Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction (see section 4.8). Renal, hepatic and haematological status should be monitored during

prolonged and high-dose therapy (e.g. osteomyelitis, endocarditis). Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Care is required when treating some patients with spirochaete infections such assyphilis or leptospirosis because the Jarisch-Herxheimer reaction may occur shortly after treatment with a penicillin is started.

In case of severe and persistent diarrhoea, the possibility of pseudomembranous colitis should be considered; flucloxacillin therapy should be discontinued.

Contact with flucloxacillin should be avoided since skin sensitisation may occur.

Caution is advised in patients with porphyria.

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.

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.

Sodium content: Flucloxacillin for Injection 1g contains approximately 2.26mmol sodium per vial. This should be included in the daily allowance of patients on sodium restricted diets.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Other antibacterials: Since bacteriostatic drugs such as chloramphenicol and tetracycline may interfere with the bactericidal effect of penicillins in the treatment of meningitis or in other situations in which a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

Immunosuppressants: There is reduced excretion of methotrexate (increased risk of toxicity).

Oral contraceptives: Flucloxacillin may decrease the efficacy of oestrogen-containing oral contraceptives.

Uricosuric agents: Plasma concentrations of flucloxacillin are enhanced if probenecid is given concurrently.

Interference with diagnostic tests: 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

Pregnancy
There has been no evidence of a teratogenic effect in animals or untoward effect in humans. However, use in pregnancy should be reserved for essential cases.

Breastfeeding
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.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Blood and lymphatic system disorders: Transient leucopenia, thrombocytopenia, haemolytic anaemia, agranulocytosis and neutropenia (which might have some immunological basis); prolongation of bleeding time and defective platelet function are generally associated with large intravenous doses of flucloxacillin or impaired renal function.

Immune system disorders: The most common adverse effects are sensitivity reactions including urticaria, maculo-papular rashes, pruritus, fever, joint pains and angioedema.

Anaphylaxis occasionally occurs and has sometimes been fatal. Late sensitivity reactions may include serum sickness-like reactions (featuring symptoms such as arthralgia, rash, urticaria, fever, angioedema, lymphadenopathy), haemolytic anaemia, nephropathy and acute interstitial nephritis, which is reversible when treatment is discontinued.

Some patients with spirochaete infections such as syphilis or leptospirosis may experience a Jarisch-Herxheimer reaction shortly after treatment with a penicillin is started. Symptoms include fever, chills, headache and reaction at the site of lesions. The reaction can be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

Metabolism and nutrition disorders: Electrolyte disturbances, such as hypokalaemia, due to administration of large amounts of sodium (see Section 4.4), are generally associated with large intravenous doses of flucloxacillin or impaired renal function.

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.)

Psychiatric disorders: Hallucinations.

Nervous system disorders: Convulsions and other signs of central nervous system toxicity are generally associated with large intravenous doses of flucloxacillin or impaired renal function. Encephalopathy has been reported following intrathecal administration and can be fatal.
Coma may develop with high doses of flucloxacillin.

Respiratory, thoracic and mediastinal disorders: Acute, severe dyspnoea; bronchospasm.

Gastrointestinal disorders: Diarrhoea, nausea and vomiting, reported with flucloxacillin, commonly occur after oral or parenteral administration. Pseudomembranous colitis has been reported with most antibiotics. Prolonged use of penicillins may lead to the development of oral candidiasis.

Hepatobiliary disorders: Changes in liver function test results may occur, but are reversible when treatment is discontinued. Hepatitis and cholestatic jaundice have been reported. These reactions are related neither to the dose nor to the route of administration; administration for more than two weeks and increasing age are risk factors. 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. In very rare cases, a fatal outcome has been reported, almost always 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: Erythema multiforme; Stevens-Johnson syndrome; toxic epidermal necrolysis (Lyell's syndrome); erythema nodosum; pemphigoid reactions; non-thrombocytopenic purpura; vasculitis.
Frequency not known: AGEP - acute generalized exanthematous pustulosis (see section 4.4).

Congenital, familial and genetic disorders: Acute attacks of porphyria (refer to section 4.4).

General disorders and administration site conditions: Phlebitis has followed intravenous infusion.

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

Symptoms
With high parenteral doses of penicillins, neurotoxicity (e.g. convulsions, encephalopathy), blood disorders (e.g. neutropenia, haemolytic anaemia, prolongation of bleeding time, defective platelet function) or electrolyte disturbances may occur.

Treatment
Treatment is symptomatic. 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.

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.

Mechanism of action
Flucloxacillin is bactericidal with a similar mode of action to benzylpenicillin. It is resistant to staphylococcal penicillinase and therefore active against penicillinase-producing and non-penicillinase-producing staphylococci. It has minimum inhibitory concentrations in the range of 0.25 to 0.5µg per ml.

Pharmacodynamic effects
Its activity against streptococci such as *Streptococcus pneumoniae* and *Str. pyogenes* is less than that of benzylpenicillin but sufficient to be useful when these organisms are present with penicillin-resistant staphylococci. It is virtually ineffective against *Enterococcus faecalis*.

5.2 Pharmacokinetic properties

Absorption
After the intramuscular administration of a single 250 or 500mg dose of flucloxacillin to volunteers, mean peak concentrations of the drug in serum were approximately 10.5 and 16mg.l-1 respectively. Mean urinary excretion of flucloxacillin following its intramuscular use is 61% of the administered dose.

Flucloxacillin may also be administered by intravenous bolus injection or by slow intravenous infusion. High serum levels of the drug are achieved by these modes of administration: 30 minutes and 2 hours after a single 500mg intravenous bolus

injection of flucloxacillin the mean serum concentration of the drug was 38 and 7.5mg.l-1, respectively; 30 minutes and 3 hours after a single 1g intravenous bolus injection of flucloxacillin, the mean serum concentrations were 60 and 4mg.l-1 respectively. The administration of 2g flucloxacillin by intravenous infusion over 20 minutes resulted in mean serum concentrations of 244 and 27.7mg.l-1 15 minutes and 120 minutes respectively after the end of the infusion.

Elimination

The percentage of a dose of intravenous flucloxacillin recovered in urine in an 8 hour collection period varies from 60 to 76%.

About 95% of flucloxacillin in the circulation is bound to plasma proteins. Flucloxacillin has been reported to have a plasma half-life of approximately one hour. The half-life is prolonged in neonates.

The serum half-life of flucloxacillin in patients with severe kidney disease has been reported as 135 to 173 minutes. No significant difference in the half-life was found between patients on or off haemodialysis. Flucloxacillin is not removed by haemodialysis.

Flucloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. Up to 90% of an intramuscular dose is excreted in the urine within six hours. Only small amounts are excreted in the bile.

Flucloxacillin is unlikely to be excreted in breast milk to any significant extent. Similarly, placental transfer is unlikely to occur to any appreciable extent.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Flucloxacillin may be administered in combination with other antibiotics including ampicillin to produce a wider spectrum of antibacterial activity. If used concurrently with an aminoglycoside the two antibiotics should not be mixed in the syringe, container or giving set as precipitation may occur.

Flucloxacillin should not be mixed with blood products or other proteinaceous fluids (e.g. protein hydrolysates) or with intravenous lipid emulsions.

The following drugs are incompatible with flucloxacillin: amiodarone, atropine sulphate, buprenorphine, calcium gluconate, chlorpromazine hydrochloride, ciprofloxacin, clarithromycin, diazepam, dobutamine, hydrochloride, erythromycin lactobionate, gentamicin sulphate, metoclopramide hydrochloride, morphine sulphate, netilmicin sulphate, ofloxacin, papaveretum, pethidine hydrochloride, prochlorperazine edisylate, promethazine hydrochloride, tobramycin and verapamil hydrochloride.

6.3 Shelf life

3 years.

The unreconstituted dry powder is stable for 3 years. For the reconstituted solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, once opened, 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 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Flucloxacillin for Injection is supplied in Type II clear glass vials containing 1g of flucloxacillin equivalent. The vials are closed with a grey bromobutyl rubber stopper, sealed with an aluminium crimped blue flip-off ring.
The vials are packed in cartons of 10 vials.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/228/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2003
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10 DATE OF REVISION OF THE TEXT

June 2023