PACKAGE LEAFLET: INFORMATION FOR THE USER

Flucloxacillin 250 mg, 500 mg and 1 g Powder for Solution for Injection or Infusion

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of your medicine is Flucloxacillin 250 mg, 500 mg and 1 g Powder for Solution for Injection or Infusion. In the rest of this leaflet it is called Flucloxacillin Injection.

What is in this leaflet:

1. What Flucloxacillin Injection is and what it is used for

Flucloxacillin belongs to a group of medicines called penicillins, which are antibiotics. These medicines work by killing bacteria that cause infections.

Flucloxacillin Injection is used for the treatment of a range of bacterial infections including bone infections (osteomyelitis) and infections within the lining of the heart (endocarditis). It is also used to prevent infections that can occur during major surgical operations such as heart and lung operations (cardiothoracic surgery) and bone, joint and muscle operations (orthopaedic surgery).

2. What you need to know before you use Flucloxacillin Injection

Do not use Flucloxacillin Injection:
- If you are allergic to flucloxacillin or any of the other ingredients of this medicine (listed in section 6)
- If you are allergic to cephalosporins, penicillin, or any other β-lactam antibiotic
- If you have had jaundice (yellow skin and whites of eyes) or other liver problems when you have been given flucloxacillin previously.

Warnings and precautions
Talk to your doctor before using Flucloxacillin Injection:

The use of flucloxacillin, especially in high doses, may reduce the potassium levels in the blood (hypokalaemia). Your doctor may measure your potassium levels regularly during the therapy with higher doses of flucloxacillin.

- If you have had any allergies especially to any other drugs (particularly penicillin)
- If you are suffering from liver or kidney problems
- If you have heart failure
- If you have syphilis (a sexually transmitted disease)
- If you have leptospirosis (Weil's disease)
- If you suffer from porphyria (an inherited blood disorder)
- If you are taking or will be taking paracetamol.

There is a risk of blood and fluid abnormality (high anion gap metabolic acidosis) which occurs when there is an increase in plasma acidity, when flucloxacillin is used concomitantly with paracetamol, particularly in certain groups of patients at risk, e.g. patients with severe renal impairment, sepsis or malnutrition, especially if the maximum daily doses of paracetamol are used. High anion gap metabolic acidosis is a serious disease that must have urgent treatment.

Special care should be taken in newborn babies to avoid overdose or high levels of a chemical in the blood which can lead to brain damage.

If any of the above statements apply to you, speak to your doctor or nurse before you are given Flucloxacillin Injection.

Other medicines and Flucloxacillin Injection
Taking other medicine while you are being given Flucloxacillin Injection can affect how it or the other medicine works. Tell your doctor if you are taking, have recently taken or might take any other medicines.

Please particularly check with your doctor if you are taking or need to take any of the following:
- oral contraceptives that contain oestrogen e.g. the combined pill. If you are using this type of medicine you should take additional precautions to prevent pregnancy while you are receiving Flucloxacillin Injection and for at least seven days afterwards. If these seven days run beyond the end of a packet of contraceptive pills you should start the next packet immediately without a break
- probenecid, a drug used for the treatment of gout
- methotrexate, a drug used in the treatment of cancer
- certain other "bacteriostatic" antibiotics (antibiotics that stop bacteria growing but do not kill them), such as chloramphenicol and tetracycline
- voriconazole (used against fungal infections).

Flucloxacillin Injection may interfere with various laboratory tests.

If you have any doubts about whether you should be given this medicine then talk to your doctor.

Pregnancy and breast-feeding
You should let your doctor know immediately if you are pregnant or trying for a baby before this medicine is administered.

You should not breast-feed whilst being given Flucloxacillin Injection. You should let your doctor know if you are breast-feeding while you are having treatment with Flucloxacillin Injection.

Driving and using machines
Flucloxacillin Injection is not known to affect your ability to drive or use machines.

Flucloxacillin Injection contains sodium
Flucloxacillin Injection 250 mg contains less than 1 mmol sodium (23 mg) per vial i.e. essentially sodium free.

Flucloxacillin Injection 500 mg and 1 g contain 1.13 mmol and 2.26 mmol of sodium per vial respectively. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Flucloxacillin Injection

Your doctor or nurse will prepare your injection by mixing the Flucloxacillin Injection powder with a liquid such as water for injections, either in the vial or in another container. The mixture is usually injected into a muscle, or into a vein when it will be given slowly over three to four minutes using a syringe or drip (infusion). In certain circumstances Flucloxacillin Injection can be injected directly into an infected joint or the chest wall, or breathed in as a mist.

Flucloxacillin is usually given as an intramuscular injection, slow intravenous injection and intravenous infusion. It may also be given by articular or intrapleural injection or inhaled. Flucloxacillin should not be given into the eye or the spine.

Adults
The recommended dose by intramuscular injection or infusion is 250 mg every six hours. The recommended adult dose by intravenous injection is 250 mg to 1 g every six hours. These doses may be doubled in severe infections. Doses of up to 8 g a day may be required for osteomyelitis or endocarditis. To prevent surgical infections you will be given 1 to 2 g with your anaesthetic followed by 500 mg every six hours.

Use in children
The recommended dose for children aged two to ten years is half the adult dose. The recommended dose for children under two years old is a quarter of the adult dose.

Special care should be taken in newborn babies to prevent the risk of overdosing.

Injections into joints or the chest, or inhalation of Flucloxacillin Injection
The usual doses are:

- into infected joint – 250 to 500 mg once a day
- into chest – 250 mg once daily
- by inhaler – 125 to 250 mg every six hours.

Severe kidney disease
If you have severe kidney failure you may be given a lower dose or you may receive your doses less frequently.

Your doctor will decide the dose that is best for you. If you do not understand, or are in any doubt, ask your doctor or nurse.

If you are given more Flucloxacillin Injection than you should
A doctor or nurse will give you this medicine. If you think you may have received too much Flucloxacillin Injection, please tell your doctor or nurse immediately. Symptoms of an overdose may include fits, behaviour disorders, fever, weakness, breathlessness, bleeding more easily and longer than usual, or changes to the salt levels in the blood.

If you think you have missed a dose of Flucloxacillin Injection
A doctor or a nurse will give you this medicine. If you think you have missed a dose, please tell your doctor or nurse.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you notice any of the following side effects as they may be a sign of an allergic or sensitivity reaction:
- rash
- itching
- redness and blistering of the skin
- fever
- aching joints
- swelling of the face, throat or hands
- difficulty breathing
- anaemia
- kidney problems
- blood problems (causing a sore throat, mouth ulcers, repeated infections or a tendency to bleed easily)
- fits (convulsions) and other problems affecting the nervous system
- Serious skin reactions
- A red, scaly rash with bumps under the skin and blisters (exanthematous pustulosis).

Also tell your doctor immediately if you develop any of the following:
- tenderness of the upper abdomen which may indicate inflammation of the liver or jaundice (yellow skin and whites of eyes)
- severe diarrhoea. Treatment with Flucloxacillin can affect the normal bacteria in the gut, causing a new infection (pseudomembranous colitis)

Hepatitis (inflammation of the liver) and jaundice may be long lasting. They are more likely in the elderly or patients who have been given flucloxacillin for more than two weeks.

You should tell your doctor if you develop any of the symptoms above, even if they occur some weeks after you have stopped having the injections.

Other side effects include:
- shortness of breath
- difficulty in breathing or wheezing
- tender red lumps under the skin
- blistering of the skin
- red or purple skin discolouration
- inflammation of blood vessels, often with skin rash
- severe attacks of porphyria (an inherited blood disorder)
- hallucinations

- feeling sick
- being sick
- thrush in the mouth
- coma
- high salt levels in the blood
- redness and pain around the area of infusion.

Very rare (may affect up to 1 in 10,000 people):

Very rare cases of blood and fluid abnormality (high anion gap metabolic acidosis) which occurs when there is an increase in plasma acidity, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 2).

Not known (cannot be estimated from the available data):
- Low potassium levels in the blood (hypokalaemia), which can cause muscle weakness, twitching or abnormal heart rhythm.

If you have syphilis
Patients who have syphilis or leptospirosis (Weil's disease) have occasionally suffered from a type of reaction (Jarisch-Herxheimer reaction) shortly after their injection, with fever, chills, headache and sometimes heart or eye problems.

If you receive high doses or a long course of treatment
Your doctor may take blood tests during your treatment to check your liver, kidneys and blood, particularly if you receive high doses or a long course of treatment.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Flucloxacillin Injection

Keep this medicine out of the sight and reach of children.
- Flucloxacillin Injection should not be used after the expiry date given on the vial. The expiry date refers to the last day of that month
- Your doctor, nurse or pharmacist will be responsible for storing and preparing Flucloxacillin Injection before use and for checking that the vials have not passed their expiry date
- The medicine should not be used if it shows any signs of deterioration such as going cloudy
- Do not store above 25^{o}C
- Once the solution has been diluted the product should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Flucloxacillin Injection contains
The active substance is flucloxacillin as sodium flucloxacillin monohydrate.
There are no other ingredients.

What Flucloxacillin Injection looks like and contents of the pack
Flucloxacillin Injection is a white or almost white powder for solution for injection/infusion. Flucloxacillin Injection is supplied in glass vials fitted with a grey bromobutyl rubber stopper.
Flucloxacillin 250 mg Injection: The vials are sealed with an aluminium crimped green flip-off cap.
Flucloxacillin 500 mg Injection: The vials are sealed with an aluminium crimped red flip-off cap.
Flucloxacillin 1000 mg Injection: The vials are sealed with an aluminium crimped blue flip-off cap.

Flucloxacillin Injection is available in packs of 10 vials.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Pinewood Laboratories Limited, Ballymacarbry, Clonmel, Co. Tipperary, Ireland

Manufacturer:
CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK

This leaflet was last revised in 05/2023.

1. NAME OF THE MEDICINAL PRODUCT
Flucloxacillin 250 mg Powder for Solution for Injection or Infusion
Flucloxacillin 500 mg Powder for Solution for Injection or Infusion
Flucloxacillin 1 g Powder for Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Sodium flucloxacillin monohydrate equivalent to flucloxacillin 250 mg
Sodium flucloxacillin monohydrate equivalent to flucloxacillin 500 mg
Sodium flucloxacillin monohydrate equivalent to flucloxacillin 1 g

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

CLINICAL PARTICULARS
4.1 Therapeutic indications
Flucloxacillin is indicated for the treatment of infections due to pencillinase 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 for administration
The dosage depends on the severity and nature of the infection.

Method of administration
The usual routes of administration for Flucloxacillin 250 mg, 500 mg and 1 g Powder for Solution for Injection or Infusion are by slow intravenous injection and intravenous infusion. Flucloxacillin 250 mg and 500 mg Powder for Solution for Injection or Infusion may also be administered by intramuscular, intra-articular or intrapleural injection. Flucloxacillin 250 mg may also be inhaled by nebuliser. The solutions must be prepared as follows:

Adults and the elderly

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

Intravenous: Dissolve 250 to 500 mg in 5 to 10 ml of water for injections or 1 g in 15 to 20 ml 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 (e.g. water for injections, sodium chloride 0.9%, glucose 5%, sodium chloride 0.18% with glucose 4%).

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

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

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

The usual adult dosage (including the elderly) is as follows:
By intramuscular injection 250 mg every six hours
By slow intravenous injection or by infusion
250 mg to 1 g every six hours

These doses may be doubled in severe infections. Doses of up to 8 g daily have been suggested for endocarditis or osteomyelitis.

During surgical prophylaxis, doses of 1 to 2 g should be given intravenously at induction of anaesthesia followed by 500 mg six hourly intravenously or intramuscularly.

By intrapleural injection 250 mg once daily
By intra-articular injection 250 mg to 500 mg once daily
By nebuliser 125 mg to 250 mg 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 10 ml/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 s-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 warning 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 s-lactams. Cross sensitivity between penicillins and cephalosporins is well documented. Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving s-lactam antibiotics. These reactions are more likely to occur in individuals with a history of s-lactam hypersensitivity. Desensitisation may be necessary if treatment is essential.
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 as syphilis 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 250 mg, 500 mg and 1 g contains approximately 0.57 mmol, 1.13 mmol and 2.26 mmol of sodium respectively 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 penicillinaseproducing and non-penicillinase-producing staphylococci. It has minimum inhibitory concentrations in the range of 0.25 to 0.5 µg 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 500 mg dose of flucloxacillin to volunteers, mean peak concentrations of the drug in serum were approximately 10.5 and 16 mg.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 500 mg intravenous bolus injection of flucloxacillin the mean serum concentration of the drug was 38 and 7.5 mg.l-1, respectively; 30 minutes and 3 hours after a single 1 g intravenous bolus injection of flucloxacillin, the mean serum concentrations were 60 and 4 mg.l-1 respectively. The administration of 2 g flucloxacillin by intravenous infusion over 20 minutes resulted in mean serum concentrations of 244 and 27.7 mg.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.

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°C

6.5 Nature and contents of container

Flucloxacillin for Injection is supplied in Type II clear glass vials containing 250 mg, 500 mg or 1 g of flucloxacillin equivalent. The vials are closed with a grey bromobutyl rubber stopper.

Flucloxacillin 250 mg Injection: The vials are sealed with an aluminium crimped green flip-off cap.
Flucloxacillin 500 mg Injection: The vials are sealed with an aluminium crimped red flip-off cap.
Flucloxacillin 1000 mg Injection: The vials are sealed with an aluminium crimped blue flip-off cap.

The vials are packed in cartons of 10 vials.

6.6 Special precautions for disposal. None.

7. MARKETING AUTHORISATION HOLDER
Pinewood Laboratories Limited, Ballymacarbry, Clonmel, Co. Tipperary, Ireland

8. MARKETING AUTHORISATION NUMBER(S)
Flucloxacillin for Injection 250 mg
- PA 0281/228/001
Flucloxacillin for Injection 500 mg
- PA 0281/228/002
Flucloxacillin for Injection 1 g
- PA 0281/228/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 13 June 2008 (Ireland)

10. DATE OF REVISION OF THE TEXT
May 2023