SUMMARY OF PRODUCT CHARACTERISTICS

Flucloxacillin Sodium for Injection 250 mg, 500 mg, 1 g.

1. Trade Name of Medicinal Product

Flucloxacillin Sodium for Injection 250 mg
Flucloxacillin Sodium for Injection 500 mg
Flucloxacillin Sodium for Injection 1 g

2. Qualitative and Quantitative Composition

Flucloxacillin sodium 250 mg per vial
Flucloxacillin sodium 500 mg per vial
Flucloxacillin sodium 1 g per vial

3. Pharmaceutical Form

Powder for solution for injection

4. Clinical Particulars

4.1 Therapeutic Indications

Flucloxacillin is indicated for the treatment of infections due to Gram-positive organisms, including infections caused by ß-lactamase-producing staphylococci and streptococci. Typical indications include:

Skin and soft tissue infections: boils, abscesses, carbuncles, furunculosis, cellulitis; infected skin conditions, e.g. ulcer, eczema and acne; infected wounds, infected burns, protection for skin grafts and impetigo.

Respiratory tract infections: pneumonia, lung abscess, empyema, sinusitis, pharyngitis, tonsillitis, quinsy, otitis media and externa.

Other infections caused by flucloxacillin-sensitive organisms: osteomyelitis, enteritis, endocarditis, urinary tract infection, meningitis, septicaemia.

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

Parental usage is indicated where oral dosage is inappropriate.

4.2 Posology and Method of Administration

Adults:

Usual adult dosage (including elderly patients)
Intramuscular – 250 mg four times a day.
Intravenous – 250 mg to 1g four times a day

The above systemic dosages may be doubled where necessary;
Treatment of osteomyelitis, endocarditis – Up to 8g daily in divided doses six to eight hourly.
Surgical prophylaxis – 1 to 2g IV at induction of anaesthesia followed by 500mg six hourly IV, or IM for up to 72 hours.

Flucloxacillin may be administered by other routes in conjunction with systemic therapy.
Intrapleural – 250 mg once daily
By nebuliser – 125 to 250 mg four times a day.
Intra-articular – 250 to 500 mg once daily.

Children*:*
Proportionately lower doses should be given in children.
Usual children's dosage
2-10 years: half adult dose
Under 2 years: quarter adult dose.

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 <10 ml/min) a reduction in dose or an extension of dose interval should be considered. 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.

Intramuscular Administration:
Add 1.5 ml Water for Injections to 250 mg vial contents or 2 ml Water for Injections to 500 mg vial contents.

Intravenous Administration*:*
Dissolve 250-500 mg in 5-10 ml Water for Injections or 1-2g in 15-20 ml Water for Injections.
Administer by slow intravenous injection (three to four minutes). Flucloxacillin may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of three to four minutes.

Intrapleural Administration*:*
Dissolve 250 mg in 5-10 ml Water for Injections.

Intraarticular Administration:
Dissolve 250-500 mg in up to 5ml Water for Injections or 0.5% lignocaine hydrochloride solution.

Nebuliser Solution Administration:
Dissolve 125-250 mg of the vial contents in 3 ml sterile water.

4.3 Contraindications
Flucloxacillin Sodium for Injection is contraindicated in patients with a penicillin or ß-lactam (e.g. cephalosporins) hypersensitivity. It is also contraindicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction. It is also contraindicated for ocular administration.

4.4 Special Warnings and Precautions for Use

Before initiating therapy with flucloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to ß-lactams. Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving ß-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 people with a history of ß-lactam hypersensitivity.

If anaphylaxis occurs flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine). Ensure adequate airway and ventilation and give 100% oxygen. IV crystalloids, hydrocortisone, antihistamine and nebulised bronchodilators 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 very rare circumstances, deaths have been reported (see section 4.8).

Special caution is essential in the newborn because of the risk of hyperbilirubinaemia. 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. Also, special caution is essential in the newborn because of the potential risk for high serum levels of flucloxacillin due to a reduced rate of renal excretion.

During prolonged treatments (eg osteomyelitis, endocarditis), regular monitoring of hepatic and renal function is recommended.

Flucloxacillin injection contains approximately 51 mg sodium per g. This should be included in the daily allowance of patients on sodium restricted diets.

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

Care is necessary if very high doses of flucloxacillin are given, especially if renal function is poor, because of the risk of nephrotoxicity. Care is also necessary if large doses of sodium salts are given to patients with impaired renal function.

The occurrence at the treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalized 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).

4.5 Interactions with other medicinal products and other forms of Interaction

The plasma concentration is enhanced if probenecid is given concurrently; probenecid decreases the renal tubular secretion of flucloxacillin. There is decreased excretion of methotrexate (increased risk of toxicity).

Please see section 6.2.

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.)

4.6 Fertility, pregnancy and lactation

Pregnancy: Animal studies with flucloxacillin have shown no teratogenic effects. The product has been in clinical use since 1970 and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effect. The decision to administer any drug 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: During lactation, trace quantities of penicillins can be detected in breast milk. Consequently, 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

None

4.8 Undesirable Effects

The following convention has been utilised for the classification of the 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).

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. 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.

Gastro-intestinal disorders

***Common**: minor gastro-intestinal disturbances (eg nausea, diarrhoea)

Very rare: pseudomembranous colitis.

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

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice

(See Section 4.4 Special Warnings and Special Precautions for Use). 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.

Skin and subcutaneous 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 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 > 48 hours after the start of the treatment.

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.)

*The incidence of these AEs 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose
Problems of overdosage with flucloxacillin are unlikely to occur; nausea, vomiting and diarrhoea may be seen; if encountered they may be treated symptomatically. Flucloxacillin is not removed from the circulation by haemodialysis.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties
Flucloxacillin is a bactericidal antibiotic that is particularly useful against penicillinase-producing staphylococci. Flucloxacillin is a semisynthetic member of the penicillin family. The penicillin nucleus consists of a thiazolidine ring fused with a β-lactam ring to which is attached a side chain. The side chain determines most of the antibacterial properties of the penicillin in question. Flucloxacillin kills bacteria by interfering in the synthesis of the bacterial cell wall.

Flucloxacillin resists the action of bacterial penicillinase probably because of the steric hindrance induced by the acyl side chain which prevents the opening of the β-lactam ring.

Flucloxacillin is active against Gram-positive organisms with the exception of Streptococcus faecalis. In general, it is not active against Gram-negative bacilli or anerobes. It is also regarded as not being effective against methicillin resistant staphylococcus aureus.

5.2 Pharmacokinetic Properties
Flucloxacillin has been reported to have a plasma half-life of approximately 1 hour. The half-life is prolonged in neonates. About 95% of flucloxacillin in the circulation is bound to plasma proteins.
Flucloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and the renal tubular secretion. About 50% of a dose by mouth and up to 90% of an intramuscular dose is excreted in the urine within 6 hours. Only small amounts are excreted in the bile. Flucloxacillin is not removed by haemodialysis.

5.3 Preclinical Safety Data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars

6.1 List of Excipients
None

6.2 Incompatibilities
Flucloxacillin should not be mixed with blood products or other proteinaceous fluids (eg protein hydrolysates) or with intravenous lipid emulsions.
It is advisable not to combine flucloxacillin with other drugs in solution for parenteral administration.
If flucloxacillin is prescribed concurrently with an aminoglycoside, the two antibiotics should not be mixed in the syringe, intravenous fluid container or giving set as precipitation may occur.

6.3 Shelf Life
36 months

6.4 Special Precautions for Storage
Do not store above 25°C. Keep container in outer carton.

From a microbiological point of view, 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 re-constitution / dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and Contents of Container
Type III uncoloured glass vials with rubber stoppers.
Packs of 5, 10, 50, 100

6.6 Special precautions for disposal
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%).

Reconstitution of flucloxacillin injections and preparation of flucloxacillin infusion solutions must be carried out under appropriate aseptic conditions if the extended storage periods are required.

Flucloxacillin vials are not suitable for multidose use. Any residual flucloxacillin should be discarded.

PACKAGE LEAFLET: INFORMATION FOR THE USER
Flucloxacillin Sodium for Injection 250 mg, 500 mg, 1 g.

The name of your medicine is Flucloxacillin Sodium for Injection 250 mg, 500 mg, 1 g, which will be referred to as Flucloxacillin throughout this leaflet.

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 your nurse.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

What is in this leaflet:
1. What Flucloxacillin is and what it is used for
2. What you need to know before you use Flucloxacillin
3. How to use Flucloxacillin
4. Possible side effects
5. How to store Flucloxacillin
6. Contents of the pack and other information

1. What Flucloxacillin is and what it is used for

Flucloxacillin is an antibiotic belonging to the group known as penicillins. Antibiotics are used to kill the bacteria or "germs" which cause infections. Flucloxacillin can be given as an injection or breathed-in using a nebulizer (a device used to give a medicine as a liquid mist).

Flucloxacillin is given to treat:
• skin and soft tissue infections, e.g. boils and abscesses
• infected wounds and burns
• protection for skin grafts
• infections of the inner and outer ear (Otitis media and externa)
• infected skin conditions, e.g. ulcers, eczema and acne and infection of the skin, usually affecting the face and scalp (Impetigo)
• chest infections such as pneumonia and lung abscess
• infection of the sinuses (Sinusitis)
• infection of the pharynx, which is found at the back of the mouth (Pharyngitis)
• infection of the tonsils which are found at the back of the mouth (Tonsillitis)
Flucloxacillin may also be used to treat other infections:
• inside bones (Osteomyelitis)
• within the bowels (Enteritis)
• within the lining of the heart (Endocarditis)
• that cause pain when passing water (Urinary tract infections)
• within the lining of the brain (Meningitis)
• within the blood (Septicaemia)

Flucloxacillin may also be used to prevent infections during major operations such as heart and lung operations or bone and muscle operations.

2. What you need to know before you use Flucloxacillin

Do not use Flucloxacillin:
• if you are allergic (hypersensitive) to flucloxacillin
• if you have ever had an allergic (hypersensitive) reaction to penicillin or any other similar antibiotics (called "beta-lactams")
• if you have a history of liver problems related to the use of flucloxacillin

Warning and Precautions
Tell your doctor before taking this medicine:

• if you have liver problems
• if you are on a sodium restricted diet
• if you are 50 years or over
• if you have a serious illness, other than this infection
• you might need regular checks of your liver and kidneys if you take flucloxacillin for a long period of time.
• If you take flucloxacillin for a long time, it may become less effective against some bacteria and you may develop other infections (known as super-infections)
• newborn babies receiving flucloxacillin may be at a greater risk of jaundice (yellowing of the skin and whites of the eyes).
• <u>If you are taking or will be taking paracetamol</u>

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.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription.

Flucloxacillin should not be given with:
• blood products such as plasma
• nutritional fluids which are given through a drip

It is especially important to tell your doctor if you are taking:
• probenecid, a drug used for the treatment of gout
• methotrexate, a drug used in the treatment of cancer
Flucloxacillin may reduce the effectiveness of oral contraceptives that contain oestrogen.

Pregnancy and Breast-feeding:
Inform your doctor if you are pregnant, planning to become pregnant or if you are breast-feeding. Your doctor will decide if you may be given Flucloxacillin.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
There should be no effect on the ability to drive and operate machinery.

Important information about some of the ingredients of Flucloxacillin:
Flucloxacillin contains sodium (51 mg per gram). This should be taken into consideration if you are on a low sodium diet.

3. How to use Flucloxacillin.

Flucloxacillin is usually given in a hospital by a doctor or nurse as an injection. Your doctor will decide how you are given Flucloxacillin and your dose. The dose you will receive depends upon how you are given flucloxacillin and the condition being treated. Flucloxacillin should not becombined with other drugs in the same syringe.

It is important to tell the doctor about any of your medical conditions, so that your doctor can ensure that the injection is administered properly.

The usual dose is:

Adults and elderly
Injections into the muscle (Intramuscular)
• 250 mg of Flucloxacillin four times a day

Injections into a vein (Intravenous)
• 250 mg to 1g of Flucloxacillin four times a day

The dose may be doubled for certain serious infections, when necessary.

For treatment of infections inside the bones (osteomyelitis) or infections inside the heart (endocarditis) the amount of flucloxacillin may be increased up to 8 g each day, and given in equal doses every six to eight hours.

Prevention of infection during operations
• between 1 g to 2 g, given into a vein, just as you receive your anaesthetic. A further dose of 500 mg every six hours will be given for up to 72 hours.

Flucloxacillin may be given in other ways when you are receiving other treatments at the same time. These are:
• into the lining of the lung (intrapleural injections) – 250 mg once daily.
• breathing the drug in through a mask (by nebuliser) – 125 to 250 mg four times a day.
• into an artery (intra-articular injections) – 250 to 500 mg once daily.
Flucloxacillin should not be given into the eye

Children aged 2-10 years
• half the adult dose

Children under 2 years
• one quarter of the adult dose

If you use more Flucloxacillin than you should
Your doctor or nurse will know how much to give you. If you think you have been given too much Flucloxacillin you should talk to your nurse or doctor.

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

4. Possible side effects

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

If the following happen tell your doctor or nurse immediately:
• an allergic reaction e.g. if you have difficulty in breathing, swelling of the eyelids, face or lips, rash or itching especially affecting your whole body (angioedema and anaphylaxis)
• yellowing of the skin or whites of the eyes (jaundice or hepatitis)
These are very serious side effects and may occur up to 48 hours after treatment. Treatment should be stopped and you may need urgent medical attention.

Tell your doctor if you experience any of the following as treatment may be discontinued:
• fever
• joint pain
• aching muscles, muscle tenderness or weakness, not caused by exercise
• convulsions
• problems with your blood, which may cause you to bruise or bleed easily
• severe diarrhoea, which may also be bloody

The following side effects have also been reported:
• nausea
• diarrhoea

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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).

Other side effects (frequency not known)

Serious skin reactions

A red, scaly rash with bumps under the skin and blisters (exanthematous pustulosis).

Contact a doctor immediately if you get any of these symptoms.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Flucloxacillin

Your doctor or pharmacist will know how to store Flucloxacillin.

Flucloxacillin must be stored below 25°C and kept in the original carton.

Keep this medicine out of the sight and reach of children.

Do not use Flucloxacillin after the expiry date, which is stated on the label. The expiry date refers to the last day of that month.

6. Contents of the pack and other information

What Flucloxacillin contains:
The active substance is Flucloxacillin Sodium.

What Flucloxacillin Injection looks like and contents of the pack
• Flucloxacillin Injection comes in Type III uncoloured glass vials with rubber stoppers.
• It is available in pack sizes of 5, 10, 50 and 100 vials.

Marketing Authorisation Holder and Manufacturer:
Marketing Authorisation Holder:
Villerton Invest S.A.
Rue Edward Steichen 14
2540 Luxembourg

Manufacturer:
Mitim S.r.l
Via Cacciamali 34-36-38
25125 Brescia
and
IBI Istituto Biochimico Italiano G. Lorenzini S.p.A.,
Via di Fossignano, 2
Italy 04011 Aprilia (LT) – Italy

Distributor in the UK:
Actavis, Barnstaple, EX32 8NS, UK

This leaflet was last updated in January 2018
PL 24780/0013-0015