New Zealand Data Sheet

1. PRODUCT NAME

Flucloxin® 250 mg powder for injection
Flucloxin® 500 mg powder for injection
Flucloxin® 1 g powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The flucloxacillin is present as flucloxacillin sodium monohydrate in Flucloxin®
(Each 1.088 g (1088 mg) of flucloxacillin sodium monohydrate is equivalent to approximately 1 g (1000 mg) of anhydrous flucloxacillin)

Flucloxin® 250 mg powder for injection/infusion contains 250mg flucloxacillin
Flucloxin® 500mg powder for injection/infusion contains 500 mg flucloxacillin
Flucloxin® 1 g powder for injection/infusion contains 1 g flucloxacillin

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Flucloxin® vials: Glass vials containing a white powder for reconstitution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Flucloxin® is indicated in adults and children for the following:

- The treatment of skin and soft tissue infections caused by susceptible organisms and infections due to penicillinase producing staphylococci and for mixed streptococcal and staphylococcal infections where the staphylococci are resistant to penicillin. For example, infections of the joints, respiratory tract and urinary tract, otitis media, endocarditis, septicaemia, and meningitis.
- Prophylaxis of staphylococcal infections during major surgical procedures, particularly in cardiothoracic or orthopaedic surgery.

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

4.2. Dose and method of administration

The dosage depends on the severity and nature of the infection.
The usual routes of administration are by intramuscular injection, slow intravenous injection and intravenous infusion. Flucloxin® may also be administered by intra-articular or intrapleural injection.

Dose

Adults

By intramuscular injection: Usual dosage 250 mg every 6 hours.
By injection or infusion: Usual dosage 250 mg to 1 g every 6 hours.
By intrapleural injection: Usual dosage 250 mg once daily.
By intra-articular injection: Usual dosage 250 mg to 500 mg once daily

Paediatric population

Children up to 2 years of age: One quarter of the adult dose.
Children 2 years to 10 years: Half the adult dose.

Elderly population/Renal impairment

Dosage reduction is not usually required but is required in severe renal failure, creatinine clearance less than 10ml/min. In those instances, a reduction in dose or extension of dose interval should be considered.

Method of Administration

For instructions on reconstitution of the medicinal product before administration, *see section 6.6*
Flucloxin® may be administered either by slow intravenous injection over a period of 3 to 4 minutes directly into a vein or injected, suitably diluted, into the drip tube.

4.3. Contraindications

Flucloxin® is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.

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

Flucloxin® is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4. Special warnings and precautions for use

Flucloxin® should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy.

Before commencing therapy with any penicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other

allergens. If an allergic reaction occurs; appropriate therapy should be instituted and Flucloxin® therapy discontinued.

Massive doses of Flucloxin® can cause hypokalaemia and sometimes hypernatraemia. Use of a potassium-sparing diuretic may be helpful. In patients undergoing high-dose treatment for more than 5 days, electrolyte balance, blood counts and renal functions should be monitored.

Care is necessary if prolonged doses of Flucloxin® are given and periodic assessment of renal, hepatic and haematopoietic function should be made. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Therefore the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Aerobacter, Pseudomonas or Candida), Flucloxin® should be discontinued and/or appropriate therapy instituted.

Hepatitis, predominantly of the cholestatic type has been reported to be associated with Flucloxin® therapy. Reports have been more frequent with increasing age or following prolonged treatment. Jaundice may first appear several weeks after therapy. Although resolution has occurred with time in most cases, hepatic dysfunction may be prolonged. Some patients have died of hepatitis associated with Flucloxin®.

Special caution is essential in the neonates and premature infants because of the risk of hyperbilirubinemia. Flucloxin® could potentially result in the reduction of albumin-bound bilirubin.

In case of diarrhoea, the possibility of pseudomembranous colitis due to Clostridium difficile should be considered. Such colitis may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to medicine discontinuance alone. In moderate to severe cases appropriate measures should be taken. Diarrhoea may also occur after the cessation of therapy.

4.5. Interaction with other medicines and other forms of interaction

<u>Oestrogen Containing Oral Contraceptives</u>

The efficacy of oral contraceptives may be impaired under concomitant administration of Flucloxin®, which may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

Methotrexate

Penicillins reduce the excretion of methotrexate thereby increasing the risk of methotrexate toxicity.

Interference with diagnostic tests

Penicillins may interfere with:

-Urinary glucose test

-Coomb's tests

-Tests for urinary or serum proteins

-Tests which use bacteria e.g.Guthrie test.

Probenecid

Probenecid decreases renal tubular secretion of penicillins when used concurrently, resulting in increased and more prolonged flucloxacillin serum concentrations and prolonged elimination half-life.

Bacteriostatic Antibiotics

Since bacteriostatic agents such as Chloramphenicol, Erythromycin, Sulfonamides or Tetracyclines may interfere with the bactericidal effect of penicillins in the treatment of meningitis or other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

4.6. Fertility, pregnancy and lactation

Pregnancy

Safety for use of Flucloxin® in the first trimester of pregnancy has not been established. Use in the second and third trimester of pregnancy has shown no significant risk to the neonate. Studies in animals have not shown evidence of fetal damage. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and fetus.

Breast-feeding

Flucloxin® is excreted in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidosis) in the breast-fed infant. Consequently, breastfeeding might have to be discontinued.

Fertility

There are no data available on fertility.

4.7. Effects ability to drive and use machines

During treatment with Flucloxin® Injection, undesirable effects may occur (e.g. allergic reactions and convulsions) which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

4.8. Undesirable effects

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena.

They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins. The following adverse reactions have been reported as associated with the use of flucloxacillin.

Blood and Lymphatic Systems: Such reactions as anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia and agranulocytosis have been reported during therapy with other penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Immune system disorders: Anaphylactic, angioneurotic oedema. If any hypersensitivity reaction occurs, the treatment should be discontinued.

Gastrointestinal disorders: Nausea, vomiting, diarrhoea. Pseudomembranous colitis

Hepato-biliary disorders: A moderate rise in AST and cholestasis have been reported. Hepatitis and cholestatic jaundice (sometimes severe) have been reported.

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. Hepatic events may be severe and in very rare circumstances (patients over 50 years of age with serious underlying disease) a fatal outcome had been reported.

Skin and subcutaneous tissue disorders: Erythematous maculopapular rashes, urticaria. Whenever such reactions occur, Flucloxin® should be discontinued. Erythema multiforme; Stevens-Johnson syndrome; toxic epidermal necrolysis; cutaneous vasculitis.

Musculoskeletal and connective tissue disorders: arthralgia and myalgia sometimes develop more than 48 hours after the start of treatment.

Renal and Urinary disorders: Interstitial nephritis. This is reversible when treatment is discontinued.

General disorders and administration site conditions: Fever sometimes develops more than 48 hours after the start of the treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions https://nzphvc.otago.ac.nz/reporting/

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. Flucloxin® is not removed from the circulation by haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: BETA-LACTAM ANTIBACTERIALS, PENICILLINS- Beta-lactamase resistant penicillins

ATC code J01CF05

Mechanism of action

Flucloxin® is semi-synthetic penicillin with a narrow spectrum of bactericidal activity directed primarily against gram positive bacteria. Its mechanism of action is similar to that of benzyl penicillin in that it inhibits formation of the cell wall in susceptible species. Flucloxin® is resistant to hydrolysis by acid and penicillinase.

5.2. Pharmacokinetic properties

Absorption: Flucloxin® is well absorbed after an intramuscular administration. Peak serum concentrations after intramuscular administration of 250 mg-1 g may range from 5-15 mcg/mL after 30 minutes. Therapeutic concentrations persist for about 4 hours.

Distribution: Once absorbed, about 95% of Flucloxin® in the circulation is bound to plasma protein. Flucloxin® crosses the placental barrier and is excreted in breast milk, *see section 4.6*
Metabolism: Flucloxin® is metabolised to a limited extent
Elimination: The unchanged drug and metabolites are excreted by the kidneys by both tubular secretion and glomerular filtration. Approximately 90% of an intramuscular dose is excreted in the urine within 6 hours. The elimination half-life is short and variable having been measured in different studies between 0.5 – 1.5 h. The half-life is extended in neonates.

Renal impairment: Elimination of Flucloxin® is decreased in renal failure *(see section 4.2).*

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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Flucloxin® should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.

Flucloxin® may be used in combination with other antibiotics, particularly ampicillin, to produce a wider spectrum of activity. However, if prescribed concomitantly with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because of loss of activity of the aminoglycoside under these conditions.

6.3. Shelf life

Un-reconstituted dry powder Injection Vials 36 months
Reconstituted Flucloxin® injection in water or other compatible infusion fluid *(see section 6.6)* is stable for at least 72 hours when stored at 5°C or for a period not exceeding 1 hour at room temperature. However, microbiological point of view must be considered and the injection should be prepared immediately before use and any unused solution discarded.

6.4. Special precautions for storage

Store the unprepared Flucloxin® Vials in a cool, dry place protected from light. Store at or below 25°C

6.5. Nature and contents of container

Flucloxin® is supplied in glass vials containing 250mg or 500mg or 1 g of flucloxacillin for injection in packs of 5 or 10 vials

6.6. Special precautions for disposal and other handling

All prepared solutions should be checked for absence of particulate matter before use.

Since the dry powder in a vial displaces a set volume once it is in solution, this must be allowed for by calculating the volume of diluent to be added to ensure the correct dose is given.

250 mg of stated activity displaces 0.2 mL of diluent.
500 mg of stated activity displaces 0.4 mL of diluent.
1 g of stated activity displaces 0.8 mL of diluent.

Preparation:

Intravenous injection:
Reconstitute 250 mg to 500 mg in 10 ml of water for injection
Reconstitute 1 g in 15 ml to 20 ml of water for injection

Intravenous infusion:
Compatible infusion fluid: Flucloxin® injection is compatible with the following infusion fluids for a period not exceeding 1 hour at room temperature: Dextrose 5%, Dextrose/Saline, Hartman's Ringers, 0.9% sodium chloride, dextrans.

Intramuscular injection:
Reconstitute 250 mg in 1.5 ml of water for injection
Reconstitute 500 mg in 2 ml of water for injection
Reconstitute 1 g in 2.5 ml of water for injection

Intrapleural:
Reconstitute 250 mg in 5 to 10 ml of water for injection.

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

17 August 1983

10. DATE OF REVISION OF THE TEXT

18 May 2017

Summary table of changes

Section Changed	Summary of new information
4.3	Contraindications: previous experience of major allergy; hypersensitivity.
4.4	Special warnings and precautions for use: allergy associated with cephalosporin or penicillins; hypokalaemia.
4.5	Interactions with other medicines and other forms or interactions: oral contraceptives; methotrexate; interference with diagnostic tests.
4.6	Fertility, pregnancy and lactation: a benefit/risk statement
4.7	Effects on ability to drive and use machines: undesirable effects
4.8	Undesirable effects: cutaeneous vasculitis
4.9	Overdose: National Poisons Centre
5.1	Pharmacodynamic properties: Pharmacotherapeutic group and ATC code