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

Excipient(s) with known effect

Flucloxin contains only flucloxacillin sodium monohydrate, with no additional ingredients.
Each one gram of flucloxacillin sodium monohydrate contains approximately 2.2 mmol of sodium.

3. PHARMACEUTICAL FORM

Flucloxin powder for injection 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 intravenous 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

Note: Systemic doses may be doubled where necessary in severe infections.

Special populations

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.

Children have been given doses of 12.5 mg/kg body weight four times a day.

Renal impairment

As flucloxacillin is excreted to a large extent by the kidney, the dose or dose interval may need modification in patients with renal failure, as the half life in patients with renal failure is increased. However dosage recommendations for various plasma creatinine levels for patients with impaired renal function are not available.

Flucloxacillin is not significantly removed by haemodialysis.

Flucloxin may be used in combination with other antibiotics, particularly ampicillin, to product a wider spectrum of activity. If used concurrently with aminoglycosides, the two antibiotics should not be mixed.

Hepatic impairment

Adjustment of dosage may not be necessary as flucloxacillin is not metabolised in the liver to any appreciable extent. However, during prolonged treatment it is advisable to check periodically for hepatic dysfunction (see section 4.4 Special Warnings and Precautions for Use).

Method of Administration

For instructions on reconstitution of the medicinal product before administration, see section 6.6 Special Precautions for Disposal and Other Handling.

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.

Use in the eye.

4.4. Special warnings and precautions for use

Hepatic Toxicity
Flucloxacillin can cause severe hepatitis and cholestatic jaundice, which may be protracted. This reaction is more frequent in older patients and those who take the drug for prolonged periods (see section 4.8 Undesirable Effects).

Anaphylaxis
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 receiving beta-lactam antibiotics (e.g penicillins). Anaphylaxis is more frequent following parenteral therapy.

Before commencing therapy with any beta-lactam antibiotic, 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.

Serious anaphylactoid reactions require emergency treatment with adrenaline, oxygen, and intravenous steroids. Airway management including intubation, should also be administered as indicated.

As with any potent medicine, periodic assessment of renal, hepatic and haematopoetic function should be made during prolonged therapy. 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), the medicine should be discontinued and/or appropriate therapy instituted.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, Flucloxin should be discontinued immediately and an alternative treatment should be considered.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contraindicated (See section 4.8 Undesirable Effects).

Use in hepatic impairment
Flucloxin should be used with caution in patients with evidence of hepatic dysfunction even though the latter is not a recognised predisposing factor to hepatic reactions to the drug.

Prolonged use of flucloxacillin may occasionally result in an overgrowth of non-susceptible organisms or yeast and patients should be observed carefully for superinfections.

Hepatitis

Hepatitis, predominantly of the cholestatic type has been reported (see section 4.8 Undesirable Effects) to be associated with Flucloxin therapy. Reports have been more frequent with increasing age (particularly over 55 years of age) or following prolonged treatment (more than 14 days). Jaundice may first appear several weeks after therapy: in some cases the course of the reactions has been protracted and lasted for several months. Resolution has occurred with time in most cases. In rare cases, patients have died of hepatitis associated with flucloxacillin, nearly always in patients with serious underlying disease or receiving concomitant medication.

Use in renal impairment
The dose or dose interval may need modification in patients with renal failure as the half life in patients with renal failure is increased. As renal function is not fully developed in the neonate the risk/benefit ratio should be considered before administration to such patients.

Caution should be exercised in the treatment of patients with an allergic diathesis.

Very high doses of flucloxacillin can cause hypokalaemia and sometimes hypernatraemia. In patients undergoing high-dose treatment for more than 5 days, electrolyte balance, blood counts, and renal function should be monitored. Additionally, use of a potassium-sparing diuretic may be helpful.

Paediatric Use
Animal studies show that high doses of flucloxacillin reduce albumin-bound bilirubin to 50 to 70% of the base line concentration. Special caution is essential in jaundiced neonates and premature infants because of the risk of hyperbilirubinemia. Flucloxin could potentially result in the reduction of albumin-bound bilirubin.

Pseudomembranous Colitis
Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including flucloxacillin. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used. Diarrhoea may also occur after the cessation of therapy.

High anion gap metabolic acidosis
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 testing 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 Interactions with Other Medicines).

Use in the elderly
See Hepatitis

Effects on laboratory tests
No data available.

4.5. Interaction with other medicines and other forms of interaction

Aminoglycosides

It is recommended that flucloxacillin sodium for injection and aminoglycosides are not mixed together in the same solution for injection, due to possible precipitation and the gradual

inactivation of the aminoglycosides under these circumstances (See section 6.2 Incompatibilities).

Blood Products and Proteinases

Flucloxacillin sodium for injections should not be mixed with blood products or other proteinase fluids (e.g. protein hydrolysates).

Oestrogen Containing Oral Contraceptives

The efficacy of oral contraceptives may be impaired under concomitant administration of Flucloxin, which may result in unwanted pregnancy. Patients 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 the 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.

Paracetamol

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. Special Warnings and Precautions for Use)

Posaconazole and Voriconazole

Flucloxacillin (a CYP450 inducer) has been reported to significantly decrease plasma posaconazole and voriconazole concentrations. If concomitant administration of flucloxacillin

with either posaconazole or voriconazole cannot be avoided, monitor for potential loss of posaconazole or voriconazole effectiveness (e.g. by therapeutic drug monitoring); increasing the dose of posaconazole or voriconazole may be needed.

Warfarin

Cases have been reported in which the efficacy of warfarin decreased during concomitant oral treatment with flucloxacillin. If co-administration of warfarin with Flucloxin is necessary, the prothrombin time or international normalised ratio (INR) should be carefully monitored during addition or withdrawal of flucloxacillin.

4.6. Fertility, pregnancy and lactation

Pregnancy

Australian Pregnancy Category: B1
Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

The safety 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 foetal damage. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Breast-feeding

Flucloxacillin is excreted into breast milk in trace amounts. An alternative feeding method is recommended to avoid any possible sensitisation of the newborn.

Fertility

There are no data available on fertility.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, during treatment with Flucloxin Injection, undesirable effects may occur (e.g. allergic reactions, dizziness and convulsions) which may influence the ability to drive and use machines (see section 4.8 Undesirable Effects). Patients should be cautious when driving or operating machinery.

4.8. Undesirable effects

As with all penicillins, the possibility of hypersensitivity reactions should always be considered.

They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins. Anaphylactic shock is most likely to occur with injected penicillins.

The following adverse reactions have been reported as associated with the use of flucloxacillin:

Blood and lymphatic disorders: Haemolytic anaemia has been reported during therapy with flucloxacillin. Reactions such 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: Erythematous maculopapular rashes, urticaria, purpura, eosinophilia, angioneurotic oedema, erthyma nodosum, and cutaneous vasculitis. Anaphylaxis and erythema multiforme have been reported rarely. Certain reactions (fever, arthralgia and myalgia) sometimes develop more than 48 hours after the start of treatment. Whenever such reactions occur, the administration of Flucloxin should be discontinued. (Note: urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids).

Gastrointestinal disorders: Nausea, vomiting, diarrhoea, dyspepsia, constipation, abdominal pain, heart burn and loss of appetite. As with other antibiotics, pseudomembranous colitis has been reported rarely (see section 4.4 Special Warnings and Precautions for Use).

Hepatobiliary disorders: A moderate rise in SGOT and cholestasis have been reported. Hepatitis and cholestatic jaundice (sometimes severe) with a frequency of about 1 in 15,000 exposures have been reported (see section 4.4 Special Warnings and Precautions for Use).

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, erythema multiforme, cutaneous vasculitis. Whenever such reactions occur, Flucloxin should be discontinued.

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), a red, scaly rash with bumps under the skin and blisters, and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) have been reported in patients taking beta-lactam antibiotics.

Pruritus has been reported very rarely.

Musculoskeletal and connective tissue disorders: Arthralgia and myalgia sometimes develop

more than 48 hours after the start of treatment.

Renal and Urinary disorders: Isolated cases of nephritis, interstitial nephritis. This is reversible when treatment is discontinued. Frequency of micturition and haematuria.

General disorders and administration site conditions: Fever sometimes develops more than 48 hours after the start of the treatment. Pain may be experienced at the site of intramuscular injection and phlebitis at the site of intravenous injection.

Amongst the adverse events spontaneously reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC), 61% were dermatological effects, 17% were jaundice, 16% were gastrointestinal reactions and 2.5% were CNS related.

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 Special Warnings and Precautions for Use).

Nervous system disorders: Adverse effects have been reported rarely. They include aseptic meningitis, hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses. As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of flucloxacillin in patients with meningitis.

Respiratory, thoracic and mediastinal disorders: Bronchospasm.

Other: Malaise, bad taste, sore throat, sore tongue, pruritus vulvae, arthralgia, dizziness, depression and headache. Vaginal or oral moniliasis may occur following the use of antibiotics.

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 adverse reactions
https://pophealth.my.site.com/carmreportnz/s/

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. As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of flucloxacillin in patients with meningitis.

Treatment

Treatment is symptomatic. Flucloxacillin is not significantly removed from the circulation by haemodialysis. General supportive measures should be instituted.

For risk assessment and 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 a semi-synthetic penicillin with a narrow spectrum of bactericidal activity directed primarily against gram positive bacteria such as:
Beta-lactamase-producing *Staphylococcus aureus*
Penicillin sensitive *Staphylococcus aureus*
Streptococcus pyogenes
Streptococcus pneumoniae

It is less active than benzylpenicillin against organisms which are sensitive to benzylpenicillin and is not active against Gram-negative bacilli, methicillin resistant *Staphylococcus aureus* (MRSA), nor *Streptococcus faecalis.*

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 flucloxacillin in the circulation is bound to plasma protein. Flucloxacillin crosses the placental barrier and is excreted in breast milk, see section 4.6 Fertility, Pregnancy and Lactation.

Biotransformation

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, and high levels of active antibiotic are produced in the urine. 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. At least 10% of the dose is excreted as an active metabolite which can rise to as high as 50% in renal failure.

Special populations

Renal impairment

Elimination of Flucloxin is decreased in renal failure (see section 4.4 Special Warnings and Precautions for Use).

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 Special Precautions for Disposal and Other Handling.
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

Special Precautions for Disposal and Other Handling) 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.

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

Preparation for full vial doses

Intravenous injection

Reconstitute 250 mg and 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.

Preparation for part vial doses

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.

E.g. Add 4.8 mL of diluent to a 250 mg vial to produce:
250 mg in 5 mL, 200 mg in 4 mL, 150 mg in 3 mL, 100 mg in 2 mL, 50 mg in 1 mL.
Add 4.6 mL of diluent to a 500 mg vial to produce 500 mg in 5 mL.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
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New Zealand
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9. DATE OF FIRST APPROVAL

17 August 1983

10. DATE OF REVISION OF THE TEXT

29 January 2026

Summary table of changes

Section Changed	Summary of new information
4.8	Added: aseptic meningitis, hyperkinesia
4.9	Update to include: “risk assessment”