NEW ZEALAND DATA SHEET

1 PRODUCT NAME

FLUCIL Powder for Injection 500 mg & 1 g

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FLUCIL Powder for Injection 500 mg vials contain flucloxacillin sodium monohydrate equivalent to 500 mg of flucloxacillin.

FLUCIL Powder for Injection 1 g vials contain flucloxacillin sodium monohydrate equivalent to 1 g of flucloxacillin.

Each vial contains 95.0 to 105.0% of the stated amount of flucloxacillin. Each one gram of monograph substance represents 2 mmol of sodium.

3 PHARMACEUTICAL FORM

FLUCIL Powder for Injection is a fine white to off-white homogeneous powder, soluble in water. The injection is prepared by the addition of the appropriate volume of Water for Injections to give the desired concentration of flucloxacillin.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

FLUCIL is indicated for 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.

FLUCIL is also used in the prophylaxis of staphylococcal infections during major surgical procedures, particularly in cardiothoracic or orthopaedic surgery.

4.2 Dose and Method of Administration

Usual adult dose

Intramuscular	250 mg, 6-hourly
Intravenous	250 mg to 1 g, 6-hourly
Intrapleural	250 mg once daily
Intra-articular	250 mg to 500 mg once daily

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

Usual children's dose

2 to 10 years	Half of the adult dose
under 2 years	Quarter of the adult dose

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

Dosage in patients with impaired liver function
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**).

Dosage in patients with impaired renal function
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.

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

Preparation of Injections
INTRAMUSCULAR: Dissolve the 500 mg vial contents in 2.0 mL Water for Injections, or the 1 g vial contents in 2.5 mL Water for Injections.

INTRAVENOUS: Dissolve the 500 mg vial contents in 10 mL Water for Injections, or the 1 g vial contents in 15 mL to 20 mL Water for Injections. Administer by slow intravenous injection (3 to 4 minutes). FLUCIL may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of 3 to 4 minutes.

INTRAPLEURAL: Dissolve the 500 mg vial contents in 10 mL Water for Injections.

INTRA-ARTICULAR: Dissolve the 500 mg vial contents in up to 5 mL Water for Injections or in 0.5% lignocaine hydrochloride solution.

The following tables (Tables 1 and 2) may be used as a guide to assist in the preparation of fractional doses of FLUCIL.

Table 1: 500 mg Powder for Injection

For concentration of:	**100**	**125**	**200**	**250**	**mg per mL**
Add to 500 mg powder:	4.6	3.6	2.1	1.6	mL Water for Injections

Table 2: 1 g Powder for Injection

For concentration of:	**100**	**200**	**250**	**500**	**mg per mL**
Add to 1 g powder:	9.3	4.3	3.3	1.3	mL Water for Injections

When FLUCIL is reconstituted with Water for Injections, it must be used immediately to reduce microbiological hazard. FLUCIL is for one dose in one patient only. Discard any remaining contents.

4.3 Contraindications
The use of this agent is contraindicated in individuals with a history of an allergic reaction to the penicillins and in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.

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

Serious, and occasionally fatal, hypersensitivity reactions (anaphyloactoid) have been reported in patients receiving beta-lactam antibiotics, e.g. penicillins. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral 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 a hypersensitivity reaction occurs, appropriate therapy should be instituted and FLUCIL 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 haematopoietic 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.

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.

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

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 (HAGMAl. 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, 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)

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, flucloxacillin 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 contra-indicated.

Use in hepatic impairment

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

Hepatitis

Hepatitis, predominantly of a cholestatic type, has been reported (see **Section 4.8 Undesirable Effects**). Reports have been more frequent with increasing age (particularly over 55 years of age) or following prolonged treatment (more than 14 days). Jaundice may 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, deaths have been reported, 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.

Use in the elderly

See Hepatitis.

Paediatric use

Animal studies show that high doses of flucloxacillin reduce albumin-bound bilirubin to 50 to 70% of the base line concentration. The drug should therefore be used with extreme caution in jaundiced neonates or premature infants.

Effects on laboratory tests
No data available.

4.5 Interaction with other medicines and other forms of interaction

Probenecid
Probenecid decreases the renal tubular secretion of flucloxacillin. Concurrent use with FLUCIL may result in increased and prolonged blood levels of flucloxacillin.

Oral contraceptives
In common with other antibiotics, patients should be warned that FLUCIL may reduce the effectiveness of oral contraceptives.

Aminoglycosides
It is recommended that flucloxacillin sodium for injection and aminoglycosides are not to be mixed together in the same solution for injection, due to possible precipitation and the gradual inactivation of the aminoglycosides under these circumstances.

Blood products and proteinases
Flucloxacillin sodium for injections should not be mixed with blood products or other proteinases fluids (e.g. Protein hydrolysates).

Bacteriostatic antibiotics
Chloramphenicol, Erythromycin, Sulfonamides or Tetracyclines: Since bacteriostatic agents 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.

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

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

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). An increased dose of posaconazole or voriconazole may be needed.

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**).

Interference with diagnostic tests
Penicillins may interfere with:
- Urinary glucose test
- Commbs tests
- Tests for urinary or serum proteins
- Test which use bacteria e.g. Guthrie test.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy
Australian Pregnancy Category: B1

The safety of flucloxacillin in the first trimester of pregnancy has not yet been established.

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 use of flucloxacillin in pregnancy should be reserved for cases considered essential by the clinician.

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

Australian categorisation definition of:
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.

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

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, adverse effects of FLUCIL include dizziness which could affect the ability to drive or use machines (see **Section 4.8 Undersirable Effects**).

4.8 Undesirable effects

As with all penicillins, the possibility of hypersensitivity reactions should always be considered. Reactions are more likely to occur in those with an allergic diathesis. Anaphylactic shock is most likely to occur with injected penicillins.

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

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

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

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 FLUCIL should be discontinued. (Note: urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids).

Renal and urinary disorders*:* Isolated cases of nephritis, interstitial nephritis, frequency of micturation and haematuria have been reported.

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 penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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.

Skin and subcutaneous tissue disorders: Erythematous maculopapular rashes, urticaria, erythema multiforme, cutaneous vasculitis. Whenever such reactions occur, flucloxacillin should be discontinued.

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

Pruritus has been reported very rarely.

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**).

General disorders and administration site conditions: 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 ADRAC, 61% were dermatological effects, 17% were jaundice, 16% were gastrointestinal reactions and 2.5% were CNS related.

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 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

No information is available, but it could be anticipated that overdosage with FLUCIL would cause gastrointestinal and CNS symptoms (see **Section 4.8 Undesirable Effects**). As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower levels of flucloxacillin in patients with meningitis.

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

FLUCIL is a narrow spectrum antibiotic with considerable activity against the following Gram-positive organisms:

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.

It is not active against Gram-negative bacilli, methicillin resistant *Staphylococcus aureus* (MRSA), nor *Streptococcus faecalis.*

Susceptibility tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technique aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in

interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

5.2 Pharmacokinetic properties

Flucloxacillin is well absorbed following intramuscular injection. The major route of excretion is renal (by both glomerular filtration and tubular secretion) and high levels of active antibiotic are produced in the urine. At least 10% of the dose is excreted as an active metabolite which can rise to as high as 50% in renal failure.

The concurrent administration of probenecid delays the excretion of flucloxacillin resulting in higher and more prolonged blood levels of the antibiotic.

Flucloxacillin, in common with other isoxazolylpenicillins, is highly bound to serum proteins. However, the low minimum inhibitory concentrations of flucloxacillin against Gram-positive cocci and the free antibiotic levels achieved ensure that the preparation is fully active against susceptible pathogens.

5.3 Preclinical safety data

Not included.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

FLUCIL Powder for Injection contains no antiseptics or buffering agents nor are there any excipients.

6.2 Incompatibilities

Flucloxacillin sodium for injection is incompatible with aminoglycosides, amiodarone, atropine, buprenorphine, calcium gluconate, chlorpromazine, ciprofloxacin, diazepam, dobutamine, erythromycin lactobionate, metoclopramide, morphine sulphate, pefloxacin, pethidine, prochlorperazine edisylate and verapamil.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

FLUCIL Powder for Injection should be stored in a dry place, protected from light, at less than 25°C.

FLUCIL Powder for Injection should be used immediately following reconstitution.

Stability in Solution

FLUCIL Powder for Injection 500 mg, after reconstitution in different infusion liquids to a final concentration of 1 mg/mL, retained the flucloxacillin content reported in Table 3. However, to avoid microbiological hazards, FLUCIL Powder for Injection should be used immediately following reconstitution. As FLUCIL Powder for Injection does not contain an antimicrobial preservative, the reconstituted injection solution should be used only once and any residue discarded.

Table 3: Stability of FLUCIL Powder for Injection 500 mg in 500 mL of different infusion fluids at 2-8°C

Intravenous Fluid	Residual Potency after 24 hours (% of initial value)
Normal saline	97
Glucose saline	94
5% Glucose	99
M/6 Sodium lactate	96

If up to 24 hour storage of FLUCIL at 2-8°C is required in one of the above intravenous fluids at a concentration of 1 mg/mL, reconstitution should be carried out under appropriate aseptic conditions to avoid microbiological hazards.

6.5 Nature and contents of container

FLUCIL Powder for Injection 500 mg or 1 g vials are stored in cartons of 5.

Glass vials with rubber stopper and aluminium seal.

6.6 Special precautions for disposal

Not included.

7 MEDICINE SCHEDULE

Prescription medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

23 July 2013

10 DATE OF REVISION OF THE TEXT

25 November 2025

SUMMARY TABLE OF CHANGES

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