NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Flucloxacillin Sodium 1g Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Flucloxacillin Sodium Powder for Injection is the sodium salt of flucloxacillin.

DBL Flucloxacillin Sodium Powder for Injection contains 1 g of flucloxacillin as flucloxacillin sodium.

It should be recognised that each 1 gram of flucloxacillin sodium monohydrate contains 2.2 mmol of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for injection.

Flucloxacillin sodium is a white or almost white, crystalline powder, hygroscopic, freely soluble in water and in methanol, soluble in alcohol.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of confirmed or suspected staphylococcal and other Gram-positive coccal infections. Indications include pneumonia, osteomyelitis and skin and skin structure infections, such as wound infections, infected burns and cellulitis.

4.2 Dose and method of administration

Dose

Usual adult dosage

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.

Special populations

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.

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.

Paediatric population

2 to 10 years	1/2 adult dose
Under 2 years	1/4 adult dose

Note: In severe infections the dosage may be increased.

Method of administration

*Intramuscular***:** Dissolve 1 g vial content in 2.5 mL Water for Injections BP.

Intravenous: Dissolve 1 g in 15 to 20 mL Water for Injections BP. Administer by slow IV injection (3 to 4 minutes).

DBL Flucloxacillin Sodium Powder for Injection may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of 3 to 4 minutes.

4.3 Contraindications

Patients with a previous history of flucloxacillin associated jaundice or hepatic dysfunction.

DBL Flucloxacillin Sodium Powder for Injection should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (eg penicillins, cephalosporins).

DBL Flucloxacillin Sodium Powder for Injection should not be used in the eye, either conjunctively or locally.

4.4 Special warnings and precautions for use

WARNING
Liver 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).

Anaphylaxis

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY REACTIONS (ANAPHYLAXIS) HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAM ANTIBIOTICS. 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. FLUCLOXACILLIN SHOULD BE GIVEN WITH CAUTION TO PATIENTS WHO HAVE PREVIOUSLY EXPERIENCED SIGNS AND SYMPTOMS OF ALLERGY ASSOCIATED WITH A CEPHALOSPORIN OR PENICILLIN TREATMENT. IF AN ALLERGIC REACTION OCCURS, APPROPRIATE THERAPY SHOULD BE INSTITUTED AND FLUCLOXACILLIN THERAPY DISCONTINUED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous Colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including flucloxacillin. A toxin produced with *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.

Hepatitis, predominantly of a cholestatic type, has been reported (see section 4.8). 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.

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.

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, DBL Flucloxacillin Sodium Powder for Injection should be discontinued immediately and an alternative treatment should be considered.

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 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.

Use in hepatic impairment

During prolonged treatment it is advisable to check periodically for hepatic dysfunction in patients with impaired hepatic function.

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

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 ration should be considered before administration to such patients.

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

Massive 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.

4.5 Interaction with other medicines and other forms of interaction

Probenecid decreases the renal tubular secretion of flucloxacillin. Concurrent use with DBL Flucloxacillin Sodium Powder for Injection may result in increased and prolonged blood levels of flucloxacillin.

It is recommended that DBL Flucloxacillin Sodium Powder for Injection and aminoglycosides not be mixed together in the same solution for injection due to possible precipitation and the gradual inactivation of the aminoglycosides under these circumstances.

DBL Flucloxacillin Sodium Powder for Injection injections should not be mixed with blood products or other proteinaceous fluids (e.g. protein hydrolysates).

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

Penicillins may interfere with:
-Urinary glucose test
-Coomb's tests
-Tests for urinary or serum proteins
-Tests which use bacteria e.g.Guthrie test.

Caution should be taken when flucloxacillin is used concomitantly with paracetamol as concurrent intake has been associated with high anion gap metabolic acidosis (HAGMA), especially in patients with risk factors.

4.6 Fertility, pregnancy and lactation

Fertility

Refer to Pregnancy section

Pregnancy

Category B1
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 DBL Flucloxacillin Sodium Powder for Injection 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.

Lactation

Low quantities of penicillin can be detected 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.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive or use machines have been performed.

4.8 Undesirable effects

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

Blood and lymphatic system disorders
Haemolytic anaemia has been reported during therapy with flucloxacillin. Reactions such as anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopoenia 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.

Metabolism and nutrition disorders
Post marketing experience: very rare cases of high anion gap metabolic acidosis (HAGMA), when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors.

Nervous system disorders
In patients suffering from renal failure, neurological disorders with convulsions are possible with the I.V. injection of high doses.

Respiratory, thoracic and mediastinal disorders
Bronchospasm

Gastrointestinal disorders
Nausea, vomiting, diarrhoea, dyspepsia, constipation, abdominal pain, heart burn, loss of appetite. As with other antibiotics, pseudomembraneous colitis has been reported rarely (see section 4.4).

Hepatobiliary disorders
Hepatitis and cholestatic jaundice (occasionally severe) have been reported with a frequency of about 1 in 15 000 exposures (see section 4.4).

Skin and subcutaneous tissue disorders
Hypersensitivity reactions**:** Erythematous maculopapular rashes, urticaria, purpura, eosinophilia, angioneurotic oedema, erythema nodosum, 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, DBL Flucloxacillin Sodium Powder for Injection should be discontinued. (Note: Urticaria, other skin rashes and serum sickness like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids).

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) have been reported in beta-lactam antibiotics.

Renal and urinary disorders
Isolated cases of nephritis, interstitial nephritis, frequency of micturation and haematuria have been reported. Interstitial nephritis may occur but is reversible when treatment is discontinued.

General disorders and administration site conditions
Pain may be experienced at the site of intramuscular injection, and phlebitis may occur at the site of intravenous injection.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically.

Flucloxacillin 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

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

Beta-lactamase-producing *Staphylococcus aureus*
Penicillin sensitive *Staphylococcus aureus*
Beta-haemolytic streptococci *(Streptococcus pyogenes)*
Streptococcus pneumoniae *(Diplococcus pneumoniae)*

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

5.2 Pharmacokinetic properties

Absorption: Flucloxacillin is stable in acid media and can therefore be administered either by the oral or parenteral route. The peak serum levels of flucloxacillin reached after 1 hour are as follows.
- After 500 mg by the I.M. route: approximately 16.5 mg/L.
- After 250 mg by the oral route (in fasting subjects): approximately 8.8 mg/L.
- After 500 mg by the oral route (in fasting subjects): approximately 14.5 mg/L.

The total quantity absorbed by the oral route represents approximately 79% of the quantity administered.

DBL Flucloxacillin Sodium Powder for Injection is well absorbed following intramuscular administration.

Distribution: Flucloxacillin diffuses well into most tissues. Specifically, active concentrations of flucloxacillin have been recovered in bones: 11.6 mg/L (compact bone) and 15.6 mg/L (spongy bone), with a mean serum level of 8.9 mg/L.
Crossing the meningeal barrier: flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.
Crossing into mother's milk: flucloxacillin is excreted in small quantities in mother's milk.
Protein Binding: flucloxacillin, in common with other isoxazolylpenicillins, is highly bound to serum proteins. The low MICs of flucloxacillin against Gram-positive cocci and the free antibiotic levels achieved however ensure that the preparation is fully active against susceptible pathogens.

Biotransformation: In normal subjects approximately 10% of the flucloxacillin administered is metabolized to penicilloic acid. The elimination half-life of flucloxacillin is on the order of 53 minutes.

Elimination: 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. Between 65.5% (oral route) and 76.1% (parenteral route) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

The concurrent administration of probenecid delays the excretion of DBL Flucloxacillin Sodium Powder for Injection resulting in higher and more prolonged blood levels of the antibiotic.

5.3 Preclinical safety data

Not known

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

No excipients

6.2 Incompatibilities

Not known

6.3 Shelf life

36 months from date of manufacture stored at or below 25°C

6.4 Special precautions for storage

DBL Flucloxacillin Sodium Powder for Injection should be stored in a dry place at less than 25^{O}C. Protect from light and moisture.

6.5 Nature and contents of container

Vials containing flucloxacillin sodium equivalent to 1.0 g of flucloxacillin in cartons of 5 and 10.

6.6 Special precautions for disposal and other handling

Stability in solution
All injections should be reconstituted from the injection presentations under appropriate aseptic conditions and the solutions prepared should be used as soon as practicable after preparation to reduce microbiological hazards. If storage is necessary, hold at 2 to 8°C for not more than 24 hours. The solutions should be used in one patient on one occasion only and any residue discarded as the solutions do not contain an antimicrobial preservative.

Solutions of flucloxacillin in water for injections (500 mg/mL), 0.5% lignocaine hydrochloride solution (500 mg/mL), 0.9% sodium chloride solution (1 mg/mL), 2.5% glucose in 0.45% sodium chloride solution (1 mg/mL), 5% glucose in water (1 mg/mL) and 1/6 M sodium lactate solution (1 mg/mL) have been shown to be stable for 24 hours when stored at 2 to 8°C.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Pfizer New Zealand Limited,
PO Box 3998
Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

13 July 1995

10. DATE OF REVISION OF THE TEXT

24 May 2019

Summary table of changes

Section	Update
All sections	Deleted trademark symbol from repeated tradename.
2.	Relocated statement of sodium content
4.4	Added subheadings Add safety information of Severe cutaneous adverse reactions (SCAR) and acute generalised exanthematous pustulosis (AGEP). Add safety information of high anion gap metabolic acidosis (HAGMA) associated with the concomitant administration of flucloxacillin and paracetamol. Relocated sodium content statement to section 2.
4.5	Add safety information of high anion gap metabolic acidosis (HAGMA) associated with the concomitant administration of flucloxacillin and paracetamol.
4.8	Added System Organ Class (SOC) 'Metabolism and nutrition disorders' and undesirable effect information of high anion gap metabolic acidosis (HAGMA) associated with the concomitant administration of flucloxacillin and paracetamol.

	Added undesirable effect of information on Severe cutaneous adverse reactions (SCAR) and acute generalised exanthematous pustulosis (AGEP) under the SOC 'Skin and subcutaneous tissue disorders'.
9	Minor editorial changes to the Date of First Approval