AUSTRALIAN PRODUCT INFORMATION – FLUCLOXACILLIN KABI (FLUCLOXACILLIN AS SODIUM MONOHYDRATE)

1. NAME OF THE MEDICINE

Flucloxacillin (as sodium monohydrate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg or 1000 mg of flucloxacillin (as sodium monohydrate).

Each gram of flucloxacillin sodium monohydrate contains approximately 2.2 mmol (51 mg) sodium.

This product contains no excipients.

3. PHARMACEUTICAL FORM

Flucloxacillin sodium is white or almost white, hygroscopic, crystalline powder. The substance is freely soluble in water and in methanol and soluble in ethanol (96 %).

Flucloxacillin Kabi is provided as a powder for Injection, for Intraarticular, Intramuscular, Intrapleural or Intravenous use.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Usual Adult Dosage

Intramuscular:	250 mg 6 hourly.
IV injection/infusion:	250 mg to 1000 mg 6 hourly.
Intrapleural:	250 mg once daily.
Intra-articular:	250 to 500 mg once daily.

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

Children's Dosage

2 to 10 years:	half adult dose.
Under 2 years:	quarter adult dose.

Note: In severe infections dosage may be increased.

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.

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.

Directions for Use:

500 mg and 1000 mg vials:

Intramuscular: dissolve the contents of the 500 mg and 1000 mg vials in, respectively, 2 and 2.5 mL of Water for Injections B.P.

Intravenous: dissolve the contents of the 500 mg and 1000 mg vials in, respectively, 10 and 20 mL of Water for Injections B.P., and administer by slow i.v. injection over 3 to 4 minutes.

Flucloxacillin sodium may also be added to infusion fluids or injected, suitably diluted, into drip tube over a period of 3 to 4 minutes.

Intrapleural: dissolve 250 mg in 5 to 10 mL of Water for Injections B.P.

Intra-articular: dissolve 250 mg to 500 mg in up to 5 mL Water for Injections B.P., or in 0.5% lignocaine hydrochloride solution.

Flucloxacillin Injection may be added to the following infusion fluids:

- Water for Injections
- Sodium chloride 0.9%
- Glucose 5%
- Sodium chloride 0.18% with glucose 4%
- Compound Sodium Lactate Intravenous Infusion (Ringer-Lactate solution; Hartmann's Solution).

Stability in solution:

Solutions of Flucloxacillin sodium in Water for Injections should be freshly prepared.

The maximum period that solutions of flucloxacillin (500 mg) in intravenous fluids (500 mL) of normal saline, glucose saline or 5% glucose are stable when stored at 2°C - 8°C (under refrigeration) is 24 hours. However, to reduce microbiological hazards, the solution should be used as soon as practicable after preparation.

For intramuscular use, dissolve 500 mg vial content in 2.0 mL Water for Injections BP or 1000 mg vial content in 2.5 mL Water for Injections BP.

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

Flucloxacillin sodium contains no antimicrobial preservative. Product is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

History of flucloxacillin associated jaundice or hepatic dysfunction.

History of a hypersensitivity reaction to beta-lactam antibiotics, e.g. penicillins.

Use in the eye.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warning:

Hepatic Toxicity: Flucloxacillin sodium 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS))

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY REACTIONS (ANAPHYLAXIS) 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 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.

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.

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 (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, 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 AND OTHER FORMS OF INTERACTIONS**)

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

Flucloxacillin Kabi 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.

Hepatitis

Hepatitis predominantly of a cholestatic type, has been reported (see **Section 4.8 ADVERSE EFFECTS (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 first appear several weeks after therapy: in several 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.

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

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.

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.

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

It should be recognised that each 1g of flucloxacillin sodium contains 2.0 mmol of sodium.

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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

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**).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in 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.

Use in lactation.

Flucloxacillin sodium is excreted in breastmilk 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

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (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 (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

The following adverse reactions have been reported as associated with the use of Flucloxacillin sodium for injection.

- **Hepatic**: 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**)

- **Gastro-intestinal disorders**: Nausea, vomiting, diarrhoea and dyspepsia. As with other antibiotics, pseudomembranous 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 and erythema nodosum. 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, flucloxacillin sodium 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).

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

- **Pulmonary**: bronchospasm.

- **Blood and lymphatic systems**: 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.

- **Nervous system disorders**: Adverse effects have been reported rarely. They include 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.

- **Skin and subcutaneous tissue disorders**: A red, scaly rash with bumps under the skin and blisters - AGEP - acute generalized exanthematous pustulosis

  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.

- **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**).

- **Infections and infestations**: Vaginal or oral moniliasis may occur following the use of antibiotics.

- **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 the Therapeutic Goods Administration (TGA), 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, dizziness, depression and headache.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No information is available, but it could be anticipated that overdosage with flucloxacillin would cause gastrointestinal and CNS symptoms (see **Section 4.8 ADVERSE EFFECTS (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.

Treatment: The drug should be withdrawn and general supportive measures of symptomatic treatment instituted.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Refer to the Microbiology and Susceptibility of tests below.

Microbiology

Flucloxacillin sodium is a narrow spectrum antibiotic belonging to the isoxazolyl group of semi-synthetic penicillins which characteristically combine resistance to penicillinase with gastric acid stability and activity against Gram-positive organisms. It is not active against Gram-negative bacilli, methicillin resistant staphylococcus, 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 (eg. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical 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 usually 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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The pharmacokinetics of flucloxacillin sodium follow a similar pattern for both oral and intramuscular (i.m.) administration, however, since oral absorption is incomplete, higher peak plasma concentrations are achieved after i.m. injection.

Distribution

Peak plasma concentrations occur approximately 30 minutes after i.m. injection with therapeutic concentrations persisting for about four hours. Doubling the dose can double the plasma concentration.

Metabolism

Flucloxacillin sodium is approximately 93% protein bound and has been reported to have a plasma half-life of about one hour. The half-life is prolonged in neonates. Metabolism occurs to a limited extent with the unchanged drug.

Excretion

The metabolites are excreted in the urine. Up to 90% of an i.m. dose is excreted within 6 hours. Flucloxacillin sodium is not removed from the circulation by dialysis.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

This product contains no excipients.

6.2 INCOMPATIBILITIES

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.

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

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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

FLUCLOXACILLIN KABI is supplied in clear glass vials (type II) closed with bromobutyl rubber stoppers and covered with aluminium/plastic flip-off caps. The 500 mg flip-off cap is green and the 1000 mg flip-off cap is blue.

FLUCLOXACILLIN KABI 500 mg (AUST R 340130) & 1000 mg (AUST R 340131) are supplied in packs of 5 or 10 vials.

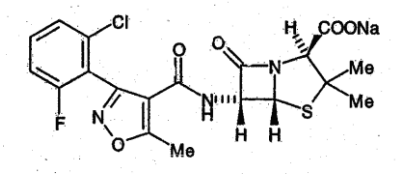
*Not all presentations or pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical name: (2S, 5R, 6R)-6-[[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Molecular formula: $C_{19}H_{16}ClFN_3NaO_5SH_2O$

Molecular Weight: 493.9

CAS number

34214-51-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

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9. DATE OF FIRST APPROVAL

07 Jun 2021

10. DATE OF REVISION

12 October 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Minor editorial changes
4.4	Addition of use in renal impairment Deletion of subtitle use in neonates
4.6	Additional safety information of flucloxacillin in the first trimester of pregnancy
4.8	Addition of micturition