1 PRODUCT NAME

FLUCLOXACILLIN KABI 500 mg powder for injection.

FLUCLOXACILLIN KABI 1000 mg powder for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FLUCLOXACILLIN KABI powder for injection is the sodium salt of flucloxacillin.

FLUCLOXACILLIN KABI 500 mg contains 500 mg flucloxacillin (as sodium monohydrate).

FLUCLOXACILLIN KABI 1000 mg contains 1000 mg flucloxacillin (as sodium monohydrate).

It should be recognised that each 1 gram of flucloxacillin sodium monohydrate contains 2.2 mmol (51 mg) of sodium.

This product contains no excipients.

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

FLUCLOXACILLIN KABI 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. Flucloxacillin Kabi 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

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.

Elderly population/Renal impairment
Dosage reduction is not usually required but is required in severe renal failure, creatinine clearance less than 10ml/min. In those instances, a reduction in dose or extension of dose.

Method of administration

For instructions on reconstitution of the medicinal product before administration, see **Section 6.6.**

Flucloxacillin Kabi 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

FLUCLOXACILLIN KABI is contraindicated in patients:

- who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.
- with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.
- with hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4 Special warnings and precautions for use

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, FLUCLOXACILLIN KABI 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 FLUCLOXACILLIN KABI 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 ratio 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

Oestrogen Containing Oral Contraceptives

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

Methotrexate

Penicillins may 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 (HAGMA), especially in patients with risk factors (see section 4.4.).

4.6 Fertility, pregnancy and lactation

Fertility

There are no data available on fertility.

Pregnancy

Safety for use of FLUCLOXACILLIN KABI 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 KABI is excreted in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidiasis) in the breast-fed infant. Consequently, breastfeeding might have to be discontinued.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Blood and lymphatic 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).

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

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, FLUCLOXACILLIN KABI 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://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.

Treatment

Treatment is symptomatic. 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

Mechanism of Action

Flucloxacillin is a semi-synthetic penicillin with a narrow spectrum of bacterial activity directed primarily against Gram-positive bacteria. Its mechanism of action is similar to that of benzyl penicillin in that it inhibits formation of the cell in susceptible species. FLUCLOXACILLIN KABI is resistant to hydrolysis by acid and penicillinase.

5.2 Pharmacokinetic properties

Absorption:

FLUCLOXACILLIN KABI is well absorbed following 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 KABI in the circulation is bound to plasma protein. FLUCLOXACILLIN KABI crosses the placental barrier and is excreted in breast milk, see section 4.6.

Biotransformation:

FLUCLOXACILLIN KABI is metabolised to a limited extent. *Elimination:*

The unchanged drug and metabolites are excreted by the kidneys by both tubular secretion and glomerular filtration. Approximately 90% of an intramuscular dose is excreted in the urine within 6 hours. The elimination half-life is short and variable having been measured in different studies between 0.5 – 1.5 h. The half-life is extended in neonates.

Special Populations:

Elimination of FLUCLOXACILLIN KABI is decreased in renal failure (see section 4.2)

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

No excipients.

6.2 Incompatibilities

FLUCLOXACILLIN KABI injections should not be mixed with blood products or other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions

FLUCLOXACILLIN KABI 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

24 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

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 1000mg flip-off cap is blue.

Products are supplied in packs of 5 or 10.

*Not all presentations or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Preparation
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.

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

FLUCLOXACILLIN KABI may be added to the following infusion fluids:
Water for Injections
Sodium chloride 0.9%
Glucose 5%

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.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Fresenius Kabi New Zealand Limited
c/o GNZCC
HSBC Tower, Level 14
188 Quay Street
Auckland 1010
Freecall: 0800 144 892

9 DATE OF FIRST APPROVAL

29 February 2024

10 DATE OF REVISION OF THE TEXT

Not applicable

SUMMARY TABLE OF CHANGES

XXXXXX