

5.2 Summary of Product Characteristics:

1. Name of the Medicinal Product

1.1 Product Name: Fucanol – 500

1.2 Strength: Each hard gelatin capsule contains Flucloxacillin Sodium eq.to Flucloxacillin 500 mg

1.3 Pharmaceutical Dosage Form: Hard gelatin Capsules

2. Qualitative and Quantitative Composition:

Qualitative Declaration: Flucloxacillin Sodium eq.to Flucloxacillin

Each hard gelatin capsule contains:

Flucloxacillin Sodium	BP
Eq.to Flucloxacillin	500 mg
Excipients	Q.S

3. Pharmaceutical Form: Blue cap and White body, size ‘0’ hard gelatin capsule containing white to off white coloured granular powder.

4. Clinical Particulars:

4.1 Therapeutic indications

Flucloxacillin Sodium is indicated for the treatment of infections due to sensitive Gram-positive organisms, including β -lactamase producing staphylococci and streptococci. Typical indications include:

Skin and soft tissue infections:

Boils, cellulitis, infected burns, abscesses, infected skin conditions (e.g. ulcer, eczema, and acne), protection for skin grafts, carbuncles, furunculosis, infected wounds and impetigo

Respiratory tract infections:

Pneumonia, lung abscess, empyema, sinusitis, pharyngitis, otitis media and externa, tonsillitis and quinsy

Other infections caused by flucloxacillin-sensitive organisms:

Osteomyelitis, urinary tract infection, enteritis, meningitis, endocarditis and septicaemia.

Flucloxacillin Sodium is also indicated for use as a prophylactic agent during major surgical procedures when appropriate; for example, cardiothoracic and orthopaedic surgery.

Parenteral usage is indicated where oral dosage is inappropriate.

4.2 Posology and method of administration

Premature infants, neonates, suckling's and infants

Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

Depends on the age, weight and renal function of the patient, as well as on the severity of the infection.

Usual adult dosage (Including elderly patients)

Oral – 250mg four times a day

Osteomyelitis, endocarditis – Up to 8g daily, in divided doses six to eight hourly

Surgical prophylaxis – 1 to 2g IV at induction of anaesthesia followed by 500mg six hourly IV, IM or orally for up to 72hours

Usual children's dosage

2-10 years: half adult dose.

Under 2 years: quarter adult dose.

Abnormal renal function: In common with other penicillins, flucloxacillin usage in patients with renal impairment does not usually require dosage reduction. However, in the presence of severe renal failure (creatinine clearance <10ml/min) a reduction in dose or an extension of dose interval should be considered. Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need to be administered either during, or at the end of the dialysis period. The maximum recommended dose in adults is 1 g every 8 to 12 hours.

Hepatic impairment:

Dose reduction in patients with reduced hepatic function is not necessary.

Administration:

Oral: Oral doses should be administered half to one hour before meals.

4.3 Contraindications

Flucloxacillin should not be given to patients with a history of hypersensitivity to β -lactam antibiotics (e.g. penicillins, cephalosporins) or excipients.

Flucloxacillin is contra-indicated in patients with a previous history of flucloxacillin associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Before initiating therapy with flucloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to β -lactams.

As for other penicillin contact with the skin should be avoided as sensitization may occur. Patients with known history of allergy are more likely to develop a hypersensitivity reaction.

Cross-sensitivity between penicillin and cephalosporins is well documented.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving β -lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. These reactions are more likely to occur in individuals with a history of β -lactam hypersensitivity.

If anaphylaxis occurs flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine). Ensure adequate airway and ventilation and give 100% oxygen. IV crystalloids, hydrocortisone, antihistamine and nebulized bronchodilators may also be required.

Hepatitis and cholestatic jaundice have been reported. These reactions are related neither to the dose nor to the route of administration. Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, patients >50 years or patients with underlying disease all of whom are at increased risk of hepatic reactions. The onset of these hepatic effects may be delayed for up to two months post-treatment. In several cases, the course of the reactions has been protracted and lasted for some months. In very rare cases, a fatal outcome has been reported.

The use of flucloxacillin (like other penicillin) in patients with renal impairment does not usually require dosage reduction. In the presence of severe renal failure (creatinine clearance less than

10ml/min), however, a reduction in dose or an extension of dose interval should be considered because of the risk of neurotoxicity.

Special caution is essential in the newborn because of the risk of hyperbilirubinaemia. Studies have shown that, at high dose following parenteral administration, flucloxacillin can displace bilirubin from plasma protein binding sites, and may therefore predispose to kernicterus in a jaundiced baby. In addition, special caution is essential in the newborn because of the potential for high serum levels of flucloxacillin due to a reduced rate of renal excretion.

During prolonged treatments (e.g. osteomyelitis, endocarditis), regular monitoring of hepatic and renal functions is recommended.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Flucloxacillin oral solution contains approximately 10.72mg of sodium per 5ml.

The occurrence at the treatment initiation of a feverish generalized erythema associated with pustule may be a symptom of acute generalized exanthematous pustulosis (AGEP) . In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contra-indicated.

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 of 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.

4.5 Interaction with other medicinal products and other forms of Interactions

Probenecid decreases the renal tubular secretion of flucloxacillin. Concurrent administration of probenecid delays the renal excretion of flucloxacillin.

Bacteriostatic drugs may interfere with the bactericidal action of flucloxacillin.

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.

4.6 Pregnancy and Lactation

Pregnancy: 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 effects. The decision to administer any drug during pregnancy should be taken with the utmost care. Therefore, flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Lactation: Trace quantities of flucloxacillin can be detected in breast milk. The possibility of hypersensitivity reactions must be considered in breast-feeding infants. Therefore, flucloxacillin should only be administered to a breast-feeding mother when the potential benefits outweigh the potential risks associated with the treatment.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

The following convention has been utilized for the classification of undesirable effects: Very common ($>1/10$), common ($>1/100$, $<1/10$), uncommon ($>1/1000$, $<1/100$), rare ($>1/10,000$, $<1/1,000$), very rare ($<1/10,000$).

Unless otherwise stated, the frequency of the adverse events has been derived from more than 30 years of post-marketing reports.

Blood and lymphatic system disorders

Very rare: Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued. Haemolytic anaemia.

Immune system disorders

Very rare: Anaphylactic shock (exceptional with oral administration), angioneurotic oedema.

If any hypersensitivity reaction occurs, the treatment should be discontinued

Gastrointestinal disorders

***Common:** Minor gastrointestinal disturbances.

Very rare: Pseudomembranous colitis.

If pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice. Changes in liver function laboratory test results (reversible when treatment is discontinued).

Hepatitis and cholestatic jaundice may be delayed for up to two months post-treatment; in several cases the course of the reactions has been protracted and lasted for some months. Hepatic events may be severe and in very rare circumstances a fatal outcome has been reported. Most reports of deaths have been in patients ≥ 50 years and in patients with serious underlying disease.

There is evidence that the risk of flucloxacillin induced liver injury is increased in subjects carrying the HLA-B*5701 allele. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA-B*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended.

Skin and subcutaneous tissue disorders

***Uncommon:** Rash, urticaria and purpura.

Very rare: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Frequency not known: AGEP – acute generalized exanthematous pustulosis.

Musculoskeletal and connective tissue disorders

Very rare: Arthralgia and myalgia sometimes develop more than 48 hours after the start of the treatment.

Renal and urinary disorders

Very rare: Interstitial nephritis.

This is reversible when treatment is discontinued.

General disorders and administration site conditions

Very rare: Fever sometimes develops more than 48 hours after the start of the treatment.

Metabolism and nutrition disorders

Post marketing experience: very rare case of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors

*The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and pediatric patients taking flucloxacillin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Flucloxacillin is not removed from the circulation by hemodialysis.

5 Pharmacological Properties:

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Beta-Lactamase Resistant Penicillin

ATC code: J01CF05

Properties: Flucloxacillin is a narrow-spectrum antibiotic of the group of is oxazolyl penicillin; it is not inactivated by staphylococcal β -lactamases.

Activity: Flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on streptococci except those of group D (*Enterococcus faecalis*) staphylococci. It is not active against methicillin-resistant staphylococci.

There is evidence that the risk of flucloxacillin induced liver injury is increased in subjects carrying the HLA-B*5701 allele. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA-B*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended.

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 one hour are as follows.

- After 250mg by the oral route (in fasting subjects): Approximately 8.8mg/l
- After 500mg by the oral route (in fasting subjects): Approximately 14.5mg/l
- After 500mg by the IM route: Approximately 16.5mg/l

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

Distribution:

Flucloxacillin diffuses well into most tissue. Specifically, active concentrations of flucloxacillin have been recovered in bones: 11.6mg/l (compact bone) and 15.6mg/l (spongy bone), with a mean serum level of 8.9mg/l.

Crossing the meningeal barrier: Flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed. Crossing into mothers' milk: flucloxacillin is excreted in small quantities in mothers' milk

Metabolism:

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

Excretion:

Excretion occurs mainly through the kidney. 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.

Protein binding: The serum protein-binding rate is 95%.

5.3 Preclinical safety Data

No further information of relevance to add

6.0 Pharmaceutical Particulars

6.1 List of excipients

- Sodium Starch glycolate
- Colloidal anhydrous silica
- Magnesium Stearate
- Ehg. Cap '0' Blue/White

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C temperature in tightly closed container, protected from light.

6.5 Nature and contents of container

3 x 4's Alu/Alu blister packed in carton along with leaflet.

2 x 4's Alu/Alu blister packed in carton along with leaflet.

7.0 Marketing Authorization Holder

BEKRA PHARMA UK LTD.

13/091, Lavington Road,

Beddington,

LONDON.

UNITED KINGDOM

8.0 Marketing Authorization Number

9.0 Date of first authorization/renewal of the authorization

10.0 Date of revision of the text

January 15th, 2019