SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 500 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg flucloxacillin as Flucloxacillin Sodium.

For the full list of excipients see section 6.1.

3 PHARMACEUT ICAL FORM

Capsules, hard

Gelatin capsules, size 0, with caramel body and black cap, printed with FLU500 MIL, containing white to almost white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of infections due to sensitive Gram-positive organisms, including infections caused by β-lactamase-producing *Staphylococci* and *Streptococci.*

Typical indications include:

Skin and soft tissue infections:
Boils
Abscesses
Carbuncles
Furunculosis
Cellulitis
Infected skin conditions e.g. ulcers, eczema and acne
Infected wounds
Infected burns
Protection for Skin grafts
Impetigo

Respiratory tract infections:
Pneumonia
Pharyngitis
Tonsillitis
Quinsy
Empyema
Lung abscess
Sinusitis
Otitis media and externa

Other infections caused by Flucloxacillin-sensitive organisms:
Osteomyelitis
Enteritis
Meningitis
Septicaemia
Urinary tract infections
Endocarditis

Flucloxacillin 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.

Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

4.2 Posology and method of administration

Posology
The dosage depends on the age, weight and renal function of the patient, as well as the severity of the infection.

Adults (including elderly people):
Oral - 250mg four times a day.
In serious infections, the dosage may be doubled.

Paediatric population
The capsule formulation of Flucloxacillin 250mg and 500mg may not be suitable for children. In such cases a syrup formulation should be used.

Usual children's dosage:

- 2-10 years: half adult dose (125mg four times daily).
- Under 2 years: quarter adult dose (62.5mg four times daily).

Renal impairment
In cases of severe renal impairment (creatinine clearance <10mL/min) a reduction in dosage may be necessary. 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.

Hepatic impairment
Use with caution in patients with hepatic dysfunction (see section 4.4).

Endocarditis or osteomyelitis
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 72 hours.

Method of administration

Oral: Flucloxacillin 500 mg Capsules should be taken at least 1 hour before or 2 hours after meals.

The capsules should be taken with a full glass of water (250 ml), to reduce the risk of oesophageal pain (see section 4.8).

Patients should not lay down immediately after Flucloxacillin 500 mg Capsules intake.

4.3 Contraindications

Flucloxacillin should not be given to patients with a history of hypersensitivity to the active substance, to any of the excipients listed in section 6.1, or to ß-lactam antibiotics (e.g. penicillins, cephalosporins).

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

4.4 Special warnings and precautions for use

The use of Flucloxacillin (like other penicillins) 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.

Flucloxacillin is not significantly removed by dialysis and so no supplementary dosages need to be administered either during or at the end of the dialysis period.

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 over 50 years or those 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 (see section 4.8).

As for other penicillins contact with the skin should be avoided as sensitisation may occur.

Patients with a known history of allergy are more likely to develop a hypersensitivity reaction.

Prolonged use of an anti-infective agent may occasionally result in overgrowth of non-susceptible organisms.

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

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.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contra-indicated.

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

Flucloxacillin capsules contain approximately 51mg sodium per g. This should be included in the daily allowance of patients on sodium restricted diets.

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 (see section 4.5).

Hypokalaemia (potentially life threatening) can occur with the use of flucloxacillin, especially in high doses. Hypokalaemia caused by flucloxacillin can be resistant to potassium supplementation. Regular measurements of potassium levels are recommended during the therapy with higher doses of flucloxacillin. Attention for this risk is warranted also when combining flucloxacillin with hypokalemia-inducing diuretics or when other risk factors for the development of hypokalemia are present (e.g. malnutrition, renal tubule disfunction).

4.5 Interaction with other medicinal products and other forms of interaction

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

Other drugs, such as piperacillin, which are excreted via renal tubular secretion, may interfere with flucloxacillin elimination.

In common with other antibiotics, flucloxacillin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Oral typhoid vaccine may be inactivated by Flucloxacillin.

Flucloxacillin reduces the excretion of methotrexate which can cause methotrexate toxicity.

Flucloxacillin may reduce the response to sugammadex.

There are rare cases of altered international normalised ratio (INR) in patients taking warfarin and prescribed a course of flucloxacillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored during addition or withdrawal 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. (See section 4.4.)

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with flucloxacillin have shown no teratogenic effects. The Flucloxacillin preparations have 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. Therefore flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breast-feeding

Flucloxacillin is secreted into mother's milk and may occasionally cause sensitisation of the infant. 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 utilised 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), not known (cannot be estimated from the available data).

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) (see section 4.4), angioneurotic oedema.

If any hypersensitivity reaction occurs, the treatment should be discontinued (see also skin and subcutaneous tissue disorders).

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.

Not known: Oesophageal pain and related events *

* oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain.

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice (see section 4.4). Changes in liver function laboratory test results (reversible when treatment is discontinued).

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; 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 necroylsis.

(See also Immune system disorders).

Frequency not known: AGEP - acute generalized exanthematous pustulosis (see section 4.4).

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.

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

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.).

Not known: Hypokalaemia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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, at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

With high doses (mainly parenteral) neurotoxicity may develop.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J01CF05

Pharmacotherapeutic group - Beta-lactamase resistant penicillins

Properties: Flucloxacillin is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins. 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*), and staphylococci. It is not active against methicillin-resistant staphylococci.

Risk of hepatic injury
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.

Mechanism of resistance
Bacterial resistance to flucloxacillin may occur because of:

- Inactivation of flucloxacillin by bacterial enzymes
- Alteration in the properties of bacterial penicillin-binding protein
- Failure of flucloxacillin to gain access to transpeptidase

Breakpoints
The minimum inhibitory concentration (MIC) breakpoints separating susceptible and resistant organisms have been defined as follows (classification from the British Society for Antimicrobial Chemotherapy):

Organism	**S ≤ (mg/L)**	**R ≥ (mg/L)**
Haemolytic streptococci	4	8
Staphylococci	4	8
Moraxella catarrhalis	4	8
Haemophilus influenza	4	8

S=Susceptible, R=Resistant

EUCAST has published the following information for flucloxacillin (ver.1.2, 2008):

Staphylococci: Most staphylococci are penicillinase-producers. Penicillinase-producing strains are resistant to benzylpenicillin, phenoxymethylpenicillin, amino-, carboxy- and ureidopenicillins. The benzylpenicillin breakpoint will mostly, but not unequivocally, separate beta-lactamase producers from non-producers.

Streptococci: The beta-lactam susceptibility of beta-haemolytic groups A, B, C and G is inferred from the penicillin susceptibility. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant *breakpoint* they should be reported resistant. *Streptococci* groups A, B, C and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.

Non-species related breakpoints: There is insufficient evidence that the species in question is a good target for therapy with the drug.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable

Sensitive organisms

Staphylococcus aureus

Streptococcus pyogenes

beta-haemolytic *streptococci* groups C and G

Acquired resistance

Staphylococcus aureus, methicillin-resistant

Inherently resistant organisms

All Gram-negative organisms, all Anaerobic organisms and most Gram-positive organisms are inherently resistant.

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 proportions 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.

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

Elimination
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 relevant information additional to that already contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Magnesium stearate
Gelatin
Black iron oxide (E172)
Titanium dioxide (E171)
Iron Oxide Red (E172)
Iron Oxide Yellow (E172)

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original pack.

6.5 Nature and contents of container

PVC/Aluminium blister pack containing 14’s capsules

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

SK MEDICINES LIMITED

Lagos, Nigeria

8 MARKETING AUTHORISATION NUMBER(S)

Not Applicable

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable

10 DATE OF REVISION OF THE TEXT

Not Applicable