1. NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 250mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg flucloxacillin as flucloxacillin sodium.
For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Capsules

Blue cap/blue body capsule printed with "F 250" and containing a white, free flowing powder.

4.1 Therapeutic indications

Flucloxacillin is an isoxazolyl penicillin of the β-lactam group of antibiotics which exerts a bactericidal effect upon many Gram-positive organisms including β-lactamase-producing staphylococci and streptococci.
Flucloxacillin Capsules are indicated for the treatment of infections due to flucloxacillin sensitive gram-positive organisms, including β-lactamase-producing staphyloccoci and streptococci. Typical indications include:

Skin and soft tissue infections:		
Boils Abscesses	Cellulitis Infected skin conditions, e.g. ulcer, eczema, and acne	Infected burns Protection for skin grafts
Carbuncles	Impetigo	
Furunculosis	Infected wounds	
Respiratory tract infections:		
Pneumonia Sinusitis Tonsillitis	Lung abscess Pharyngitis Quinsy	Empyema Otitis media and externa

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

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 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

Premature infants, neonates, sucklings 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 the severity of the infection.

Usual adult dosage (including elderly patients)

Oral - 250 mg four times a day.

In serious infections, the above systemic dosage may be doubled.

Endocarditis or osteomyelitis
Up to 8 g daily in divided doses six to eight hourly.

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

Usual children's dosage

2-10 years: half the adult dose

Under 2 years: quarter the 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 case of severe renal impairment (creatinine clearance <10 ml/min) a reduction in dosage or an extension of dose interval 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. 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.

Method of 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 flucloxacillin, other β-lactam antibiotics (e.g. penicillins, cephalosporins) or any of the excipients listed in section 6.1.

Flucloxacillin is contraindicated 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 (see section 4.2).

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 ≥ 50 years of age and those with serious 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 reactions has been protracted and lasted for some months. In these patients, hepatic events may be severe, and in very rare circumstances, deaths have been reported (see section 4.8).

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

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

Prolonged use 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. Cross-sensitivity between penicillins 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 nebulised bronchodilators may also be required.

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

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.

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.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid decreases the renal tubular secretion of flucloxacillin. Concurrent administration of probenecid and sulfinpyrazone delay/slow down the renal excretion of flucloxacillin.

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

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.

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. (see section 4.4.)

4.6 Fertility, 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.

Breast feeding: 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 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, <1/1000), 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. Eosinophilia, Haemolytic anaemia.

Immune system disorders

Very rare:	Anaphylactic shock (exceptional with oral administration) (see section 4.4 special warnings and precautions for use), angioneurotic oedema.

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

Metabolism and nutrition disorders

Very rare:	**Post marketing experience:** high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)

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.

Hepatobiliary disorders

Very rare:	Hepatitis and cholestatic jaundice. (see section 4.4 special warnings and precautions for use). 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 cases, 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.
Not known:	AGEP – acute generalized exanthematous pustulosis (see section 4.4)

(See also Immune system disorders).

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 usually reversible when treatment is discontinued, but in rare situations can lead to renal failure.

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.

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.

4.9 Overdose

With high doses (mainly parenteral), neurotoxicity may develop.

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

Flucloxacillin is not removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Beta-lactamase resistant penicillins

ATC code: J01CF05

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). 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 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.
- After 500 mg by the IM route: Approximately 16.5 mg/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: 11.6 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 mothers' milk: flucloxacillin is excreted in small quantities in mothers' milk.

Metabolism: 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.

Excretion: excretion occurs mainly through the kidney. About 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 additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate

Capsule Shell

Titanium dioxide (E171)

Indigo carmine (E132)

Gelatin

Methyl hydroxybenzoate (E218)

Propyl hydroxybenzoate (E216)

Printing ink

Shellac

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/PVDC/Aluminium foil blisters, packs of 28 and 56 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd,

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HP4 1EG

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