SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin Capsules BP 250 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg Flucloxacillin (as Flucloxacillin Sodium)

Excipient with known effect:
Each capsule contains approximately 12.6 mg of sodium. (See section 4.4).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule

Blue/Blue size 2 gelatin capsule, containing powder. Overprinted with “fluc” and “250”.

4.1 Therapeutic indications

Treatment of infections due to sensitive gram-positive organisms, including β-lactamase-producing *staphylococci* and *streptococci*.

Typical indications include:

Respiratory tract infections such as pneumonia, pharyngitis, tonsillitis, lung abscess, empyema, sinusitis, quinsy, otitis media and externa.

Skin and soft tissue infections such as boils, abscesses, carbuncles, infected skin infections (e.g. ulcers, eczema, and acne), furunculosis, cellulitis, infected wounds and burns, skin-graft protection, impetigo.

Other infections due to Flucloxacillin - sensitive organisms such as enteritis, endocarditis, meningitis, osteomyelitis, septicaemia and urinary tract infections.

Prophylaxis during major surgery, where 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 the elderly)

Oral - 250 mg four times a day.

In serious infections, the dosage may be doubled.

Osteomyelitis, endocarditis - 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.

Paediatric population

Under 2 years: 62.5mg four times daily
2-10 years: 125mg four times daily

Premature infants, neonates, sucklings and infants
Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

Renal impairment:

The use of Flucloxacillin (like other penicillins) in patients with renal impairment does not usually require dosage reduction. However, in the presence of severe renal failure (creatinine clearance less than 10ml/min), a reduction in dose or an extension of dose interval should be considered. 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. 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
For oral use only.
Flucloxacillin 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 capsules intake.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the ingredients listed in section 6.1, or to β-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 >50 years or patients 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 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.

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.

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 any previous hypersensitivity to β-lactams. Patients receiving β-lactam antibiotics have been reported to experience serious and occasionally fatal hypersensitivity reactions (anaphylaxis). Although anaphylaxis is more frequent

following parenteral therapy, it has occurred in patients on oral therapy. Patients with a history of β-lactam hypersensitivity are more likely to experience these reactions.

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.

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

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).

Excipient content

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid and sulfinpyrazone delays the renal tubular secretion of Flucloxacillin

upon concurrent administration.

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: The product has been in clinical use since 1970. Animal studies have shown no evidence of teratogenic effects. and the limited number of reports 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 breastfeeding 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

Flucloxacillin has no or negligible influence on the ability to drive and use machines.

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.

System Organ Class	Frequency	Adverse Events
Blood and lymphatic system disorders	Very rare:	Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued. Haemolytic anaemia, Eosinophilia.
Immune system disorders	Very rare:	Anaphylactic shock (exceptional with oral administration) (see section 4.4), angioneuroticoedema. 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[#]

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 $\geq$ 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).
	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.
Metabolism and nutrition disorders	Very rare:	Post marketing experience: 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

*The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.
#oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain.

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 website: 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.

5.1 Pharmacodynamic properties

ATC code: J01C F05

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.

Mechanism of Action: 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.
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 proportions into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mother's 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.

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: About 95% of Flucloxacillin in the circulation is bound to plasma proteins.

5.3 Preclinical safety data

No further information of relevance to add.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate

Capsule Shell:

Gelatin

Indigo Carmine (E132)

Titanium Dioxide (E171)

Printing ink:

Titanium Dioxide (E171)

Shellac

Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a dry place, below 25ºC. Store in the original pack.

6.5 Nature and contents of container

1. HDPE tablet containers with HDPE lids.
2. PVC/PVdC-Aluminium blister pack (250 micron PVC externally with 40 gsm PVdC, 20 micron hard tempered aluminium).
3. PVC/PVdC/Aluminium blister pack (250 micron PVC externally with 40 gsm PVdC, 20 micron hard tempered aluminium) - “Burgopak” packaging format.

Pack sizes: 4, 28, 100, 250, 500 and 1000 capsules.

Not all pack sizes may be marketed.

4. For bulk supply only, packs of 5,000 and 10,000 capsules will be available (supplied in polybags, free from additives, inside a cardboard outer container.

6.6 Special precautions for disposal

No special requirements for use/handling.

7 MARKETING AUTHORISATION HOLDER

Flamingo Pharma UK Ltd.
1st floor, Kirkland House,
11-15 Peterborough Road,
Harrow, Middlesex,
HA12AX, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 43461/0070

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/02/1999

10 DATE OF REVISION OF THE TEXT

23/12/2020