SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 125mg/5ml Powder for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flucloxacillin Powder Oral solution when reconstituted each 5 ml contains 136.000 mg of Flucloxacillin sodium is equivalent to 125mg of Flucloxacillin.

Excipient(s) with known effect:
Each 5ml of powder for oral solution contains 6.331 mg of Sodium and 2286.090 mg of Sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution

White granular powder, free from agglomerates and caking.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Flucloxacillin is an isoxazolyl penicillin of the β-lactam group of antibiotics which exerts a bactericidal effect on streptococci except those of group D (*Enterococcus faecalis*) staphylococci (see section 5.1).
Flucloxacillin oral solution 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,	Protection for skin grafts
Carbuncles	e.g. ulcer, eczema, and acne	
Furunculosis	Infected wounds	Impetigo

Respiratory tract infections:

Pneumonia	Lung abscess	Empyema
Sinusitis	Pharyngitis	Otitis media and externa
Tonsillitis	Quinsy	

Other infections caused by Flucloxacillin-sensitive organisms:

Urinary tract infection, Enteritis, Meningitis
Septicaemia

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 patients)
Oral - 250 mg four times a day.
In serious infections, the dosage may be doubled.

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

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

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 < 10 ml/min) a reduction in dose or an extension of dose interval should be considered. The maximum recommended dose in adults is 1 g every 8 to 12 hours.

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

Method of Administration
Oral: Oral doses should be administered at least one hour before or two hours after meals.
A full glass of water (250 ml) should be taken afterwards, to reduce the risk of oesophageal pain (see section 4.8). Patients should not lay down immediately after flucloxacillin oral solution intake.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Flucloxacillin should not be given to patients with a history of hypersensitivity 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 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.

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 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 sensitization 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. 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 discounted 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.

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

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).

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid and sulfinpyrazone slow down the excretion of flucloxacillin by decreasing tubular secretion. 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.

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.

Bacteriostatic drugs may interfere with the bactericidal action of flucloxacillin.

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.)

Flucloxacillin (CYP450 inducer) has been reported to significantly decrease plasma voriconazole concentrations. If concomitant administration of flucloxacillin with voriconazole cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g. by therapeutic drug monitoring); increasing the dose of voriconazole may be needed.

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.

Fertility
Information of effect on human fertility is not available.

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.

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.)

Frequency not known (cannot be estimated from the available data): Hypokalaemia.

Immune system disorders

Very rare: Anaphylactic shock (exceptional with oral administration) (see Item 4.4 Warnings), 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.

Frequency not known (cannot be estimated from the available data): Oesophageal pain and related events **

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice. (See Section 4.4 Special Warnings and Special 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.

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 patient's ≥ 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. (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.
**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 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.

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*) 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.

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.

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 further information of relevance to add.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sucralose (E 955)
Flavour Orange Powder (0473075)
Flavour Refreshing Powder (0479539) (Menthol)

6.2 Incompatibilities

As for Penicillin. Incompatible with Colistin Polymixin B Sulphate. Loss of potency after mixing with Streptomycin has also been reported.

6.3 Shelf life

Unopened	:	2 Years
After reconstitution	:	7 days at 2°C – 8°C

6.4 Special precautions for storage

Dry powder: Store in a dry place below 30°C, Store in original package. Protect from light.

Reconstituted solution: Store up to 7 days at 2°C–8°C in a refrigerator.

6.5 Nature and Contents of Container

Translucent HDPE round bottle with white round polypropylene CR Cap.
Pack size: 100ml

6.6 Special precautions for disposal and other handling

Add 68 ml of potable water for the 125mg/5ml strength of product and shake gently until all powder is dissolved.

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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 43461/0031

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

31/08/2023