SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 250 mg/5ml Granules for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flucloxacillin sodium 272.00 mg equivalent to 250 mg flucloxacillin per 5 ml of reconstituted product.

Excipients: Each 5 ml contains 3g of sucrose, 16mg of sodium, 5mg of aspartame, 0.4g of amaranth, 2mg of E217 & 6mg of E219.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Flucloxacillin granules for oral solution
Red granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flucloxacillin 250mg/5ml Granules for Oral Solution is indicated for the treatment of infections due to gram-positive organisms including infections caused by β-lactamase-producing staphylococci associated with:-

SKIN AND SOFT TISSUE: boils, abscesses, carbuncles, infected skin conditions e.g. ulcer, eczema, and acne, furunculosis, cellulitis, infected wounds and burns, protection for skin grafts and impetigo.

RESPIRATORY TRACT: pneumonia, lung abscess, empyema, sinusitis, pharyngitis, tonsillitis and quinsy.

OTHER INFECTIONS: otitis media and externa, osteomyelitis, enteritis, endocarditis, urinary tract infection, meningitis, septicaemia.

AS A PROPHYLACTIC: agent during major surgical procedures where appropriate e.g. cardiothoracic and orthopaedic surgery.

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

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

DOSAGE – Doses should be administered ½ - 1 hour before meals.

ADULTS (INCLUDING ELDERLY): 250 mg four times daily. The dose may be doubled where necessary.

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

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

CHILDREN: Over 10 years – as for adults
2 – 10 years - 125 mg every 6 hours
Under 2 years - 62.5 mg every 6 hours

ABNORMAL RENAL FUNCTION: Dose reduction is usually not required in patients with renal impairment. 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 1g 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.

Route of administration : Oral use

For instructions on dilution of the product before administration, see section 6.6.

4.3 Contraindications

Patients with a history of hypersensitivity to β-lactam antibiotics, (eg, penicillins, cephalosporins) or to any of the 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

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 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 the 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).

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

Before initiating therapy with flucloxacillin careful enquiry should be made concerning any previous hypersensitivity to β-lactams. Cross-sensitivity between penicillins and cephalosporins is well documented. 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. In cases of serious anaphylactic reactions immediate emergency treatment with adrenalin (epinephrine) may be required, as appropriate. Ensure adequate airway and ventilation and give 100% oxygen. IV crystalloids, hydrocortisone, antihistamine and nebulised bronchodilators may also be required.

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.

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.

Special caution is essential in the newborn because of the risk of hyperbilirubinemia. 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.

Overgrowth of non-susceptible organisms may occasionally result after prolonged use of an anti-infective agent.

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).

Sucrose: Each 5ml dose contains 3g sucrose; this should be taken into account in patients with diabetes. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium: Each 5ml dose contains 16mg of sodium. To be taken into consideration by patients on a controlled sodium diet.

Aspartame: Contains a source of phenylalanine. May be harmful for people with phenylketonuria.

Amaranth: May cause allergic reactions.

E217 & E219: May cause allergic reactions (possibly delayed).

4.5 Interactions with other medicinal products and other forms of interaction

Probenecid and sulfinpyrazone decreases the renal excretion of penicillins and serum concentrations of flucloxacillin are enhanced if probenecid is administered concurrently.

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

Oral courses of broad-spectrum anti-bacterials may affect the hypothrombinaemic response to oral anticoagulants.

Methotrexate excretion is reduced by penicillins. Patients should be monitored carefully for sign of methotrexate toxicity.

In common with other antibiotics, penicillins/flucloxacillin may affect the gut flora, leading to lower oestrogen reabsorption and may decrease the efficacy of combined oral contraceptives. Patients should be warned of this.

Bacteriostatic drugs may interfere with the bactericidal action of flucloxacillin.

Oral typhoid vaccine may be inactivated by flucloxacillin.

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 Pregnancy and lactation

Pregnancy: Studies conducted with animals 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 effect. 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.

Use in pregnancy should be reserved for cases considered essential by the clinician.

Lactation: Breast feeding is not contraindicated with flucloxacillin. Trace quantities of the drug are excreted in the breast milk. While adverse effects are apparently rare, three potential problems exist for the nursing infant: modification of bowel flora, direct effects on the infant such as allergy/sensitisation and interference with interpretation of culture results when pyrexia of unknown origin occurs. 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).

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 special 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

Post marketing experience: very rare cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generaly 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.

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. 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 necrolysis.

Frequency not known: AGEP acute generalised 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 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 is reported to be 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

Problems of overdosage are unlikely to occur; gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident, if encountered they should be treated symptomatically. More specific measures may be necessary in patients with impaired

renal function. Flucloxacillin is not significantly removed from the circulation by haemodialysis.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

J01CF05 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)* staphylococci. It is not active against methicillin-resistant staphylococci.

Bactericidal action of flucloxacillin depends on its ability to reach and bind. Penicillin binding proteins (PEP-1 and PBP-3) located in bacterial cytoplasmic membranes.

Flucloxacillin inhibits bacterial septum and cell wall synthesis probably by acylation of membrane bound transpeptidose enzymes; thus preventing cross linkage of peptidoglycan chains which are necessary for bacterial cell wall strength and rigidity.

Cell division and growth are also inhibited and lysis and elongation of susceptible bacteria frequently occur.

Rapidly dividing bacteria are the most susceptible to the action of flucloxacillin.

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 sodium is better absorbed from the gastro-intestinal tract than cloxacillin sodium. The absorption is decreased in the presence of food in the stomach and small intestine.

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 in common with other penicillins is widely distributed throughout the body. 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 mother's milk: Flucloxacillin is excreted in small quantities in mother's milk.
Therapeutic concentration persists for about 4 hours. Doubling the dose can double the plasma concentration. Serum concentrations are enhanced if probenecid is administered concomitantly.

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

There are no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Propyl Parahydroxybenzoate E217
Sodium Methyl Parahydroxybenzoate E219
Sodium Citrate
Citric Acid Anhydrous
Aspartame E951
Amaranth E123
Cherry Flavour
Sucrose

6.2 Incompatibilities

Incompatible with colistin sulphomethate sodium, gentamicin, kanemycin and Polymicin B Sulphate. Loss of potency after mixing with streptomycin has also been reported.

6.3 Shelf life

Before reconstitution: 2 years.
After reconstitution: 1 week

6.4 Special precautions for storage

In the form of dry granules: Do not store above 25°C. Keep the bottle tightly closed.
After reconstitution: Store in a refrigerator. Use within one week of preparation.

6.5 Nature and contents of container

Round, natural HDPE bottles with tamper evident polypropylene closure containing 66 gm of granules. The brimfill capacity of the bottle is 175 ml and the nominal working capacity is 150 ml.

6.6 Special precautions for disposal

To reconstitute the granules to make the solution, add 58 ml of water and shake well until the powder is dissolved. When reconstituted the solution produced is essentially a clear red cherry coloured solution.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
Units 3 & 4, Quidhampton Business Units
Polhampton Lane
Overton
Hampshire
RG25 3ED

8 MARKETING AUTHORISATION NUMBER

PL 20416/0077

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

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