1.17 Summary Product Characteristics (SPC)

Attached

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

FLOXAMED (FLUCLOXACILLIN SODIUM FOR INJECTION BP 500 MG)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each Vial contains:
Sterile Flucloxacillin Sodium BP
Eq. of Flucloxacillin.....500 mg

3 PHARMACEUTICAL FORM

Powder for injection

A fine white homogeneous sterile powder for solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

FLOXAMED is indicated for the treatment of infections due to β-lactamase-producing staphylococci and other sensitive Gram-positive organisms such as streptococci (see section 5.1 for details on sensitive strains). Typical indications include:

Skin and soft tissue infections:
- Boils, abscesses,carbuncles,furunculosis, cellulites, infected burns, infected wounds, impetigo, protection for skin grafts, infected skin conditions e.g. ulcer, eczema, and acne

Respiratory tract infections:
- Pneumonia, lung abscess, sinusitis, tonsillitis, quinsy, pharyngitis, empyema, otitis media and externa

Other infections caused by FLOXAMED-sensitive organisms:
- Osteomyelitis, arthritis, urinary tract infection, small intestine and colon infection, meningitis, endocarditis, septicaemia

FLOXAMED is also indicated for prophylaxis in cardiovascular surgery (valve prostheses, artery prostheses) and in orthopedic surgery (arthroplasty, osteosynthesis and arthrotomy) because of the dominant pathogenic potential of staphylococci during such surgical procedures.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

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

For instructions on the preparation of solution see section 6.6. For incompatibilities see section 6.2.

Intramuscular or intravenous

Adults and adolescents over 14 years of age
Total daily dosage of 1 g to 3 g, administered in three to four divided doses, by i.v. or i.m. injection.

In cases of severe infections: Up to 8 g per day administered in four infusions (over 20 to 30 min).

No single bolus injection or infusion should exceed 2 g.

The maximum dose of 12 g per day should not be exceeded.

In surgical prophylaxis: 2 g i.v. (bolus or infusion) upon induction of anaesthesia, to be repeated every 6 h for 24 h in cases of vascular and orthopaedic surgery, and for 48 h in cases of cardiac or coronary surgery.

Paediatric population
Children under 14 years of age
25 to 50 mg/kg/24 hours administered in three to four equally divided doses by i.m. or i.v. injection.

Children aged 10 to 14 years usually receive a daily dose of 1.5 g to 2 g and children aged 6 to 10 years 0.75 g to 1.5 g, divided into three to four equal doses.

In cases of severe infections: Up to 100 mg/kg/24 hours in three to four divided doses.

No single bolus injection or infusion should exceed 33 mg/kg.

Premature infants, neonates, sucklings and infants
Because of the possible induction of kernicterus, flucloxacillin should be used in premature infants and neonates only after a rigorous benefit-risk assessment (see section 4.4).

Premature infants and neonates as well as sucklings and infants are generally treated with 40 to 50 mg/kg/24 hours, divided into three equal doses. The daily dose may be increased to a maximum of 100 mg/kg.

Abnormal renal function
In common with other penicillins, FLOXAMED 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. In high dose regimens the maximum recommended dose is 1 g every 8 to 12 hours (in anuric patients, the maximum dosage is 1 g every 12 h).

FLOXAMED is not significantly removed by dialysis and hence no supplementary dosages need be administered either during, or at the end of the dialysis period.

An intravenous injection/infusion should be performed slowly.

Intrapleural and intra-articular
The usual maximum dose is 500 mg once daily.

Inhalation route
The usual maximum daily dose is 125 mg to 250 mg three times daily.

Method of administration

Parenteral therapy is indicated if the oral route is considered impracticable or unsuitable, as in the case of severe diarrhoea or vomiting, and particularly for the urgent treatment of severe infection.

Route of administration: Intramuscular, intravenous, intrapleural, intra-articular and aerosol.

4.3 Contraindications

Flucloxacillin should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (e.g. penicillins, cephalosporins) or excipients.

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

Ocular or subconjunctival administration.

4.4 Special warnings and precautions for use

Before initiating therapy with flucloxacillin, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactams. Cross-sensitivity between penicillins and cephalosporins is well documented.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving beta-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 beta-lactam hypersensitivity. If an allergic reaction occurs, flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions may require immediate emergency treatment with adrenaline. Oxygen, i.v. steroids, and airway management, including intubation, may also be required.

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 undesirable effects). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contra-indicated

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, patients $\geq$ 50 years of age, and those with serious underlying disease. In these patients, hepatic events may be severe, and in extremely rare circumstances, deaths have been reported (see section 4.8).

Dosage should be adjusted in renal impairment (see section 4.2).

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.

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

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

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 hypokalaemia-inducing diuretics or when other risk factors for the development of hypokalaemia are present (e.g. malnutrition, renal tubule dysfunction).

Sodium content:FLOXAMED injection contains approximately 51 mg sodium per g. This should be included in the daily allowance of patients on sodium restricted diets.

4.5 Interaction with other medicinal products and other forms of interactions

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

Bacteriostatic drugs (chloramphenicol, erthromycins, sulphonamides, and tetracyclines) may interfere with the bactericidal action of flucloxacillin.

Methotrexate, reduced excretion may occur with flucloxacillin (increased risk of toxicity).

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.)

Penicillins may produce false-positive results with the direct antiglobulin (Coombs') test, falsely high urinary glucose results with the copper sulphate test and falsely high urinary protein results, but glucose enzymatic tests (e.g. Clinistix) and bromophenol blue tests (e.g. Multistix or Albustix) are not affected.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies with flucloxacillin have shown no teratogenic effects. Limited information is available on the use of flucloxacillin in human pregnancy. Flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breast-feeding
During lactation, trace quantities of penicillins can be detected in breast milk. Flucloxacillin may be administered during the period of lactation. With the exception of risk of sensitisation there are no other detrimental effects for the breast fed infant.

4.7 Effects on ability to drive and use machines

None known.

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).

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

Nervous system disorders
Very rare: In patients suffering from renal failure, neurological disorders with convulsions are possible with the I.V. injection of high doses.

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). Changes in liver function laboratory test results (reversible when treatment is discontinued).
Hepatitis and cholestatic jaundice may be delayed for up to two months post-treatment. In some cases the course has been protracted and lasted for several months. Hepatic events may be severe, and in very rare circumstances, deaths have been reported. Most reports of deaths have been in patients ≥ 50 years of age 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 500-1,000 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).*
Not known: AGEP - acute generalized exanthematous pustulosis (see section special warnings and precautions for use)

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
Not known: Hypokalaemia

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.)

**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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

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: J01C F05.

Flucloxacillin is a semisynthetic penicillin (beta-lactam antibiotic; isoxazolylpenicillin) with a narrow spectrum of activity primarily against Gram-positive organisms, including β-lactamase-producing strains.

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 500-1,000 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 action
Flucloxacillin inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

PK/PD relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for flucloxacillin.

Mechanism of resistance
Resistance to isoxazolylpenicillins (so-called methicillin-resistance) is caused by the bacteria producing an altered penicillin binding protein. Cross resistance may occur in the beta-lactam group with other penicillins and cefalosporins. Methicillin-resistant staphylococci generally have low susceptibility for all beta-lactam antibiotics.

Antimicrobial activity
Flucloxacillin is active against both β-lactamase-positive and –negative strains of *Staphylococcus aureus* and other aerobic Gram-positive cocci, with the exception of *Enterococcus faecalis*. Gram-positive anaerobes are generally susceptible (MIC 0.25-2 mg/l) but Gram-negative bacilli or anaerobes are moderately to fully resistant. Enterobacteria is fully resistant to flucloxacillin as well as methicillin-resistant staphylococci.

Strains of the following organisms are generally sensitive to the bactericidal action of flucloxacillin *in vitro*.
The minimal inhibitory concentrations (MIC) of flucloxacillin are quoted below:

Micro-organisms	**MIC (mg/l)**
Staphylococcus aureus	0.1 to 0.25
Staphylococcus aureus (beta-lactamase +)	0.25 to 0.5
Streptococcus pneumoniae	0.25
Streptococcus pyogenes (Group A beta-haemolytic)	0.1
Streptococcus viridans group	0.5
Clostridium tetani	0.25
Clostridium welchii	0.25
Neisseria meningitidis	0.1
Neisseria gonorrhoeae	0.1
Neisseria gonorrhoeae(beta-lactamase +)	2.5
The Group A beta-haemolytic streptococci are less sensitive to the isoxazolyl penicillins than to penicillin G or penicillin V.	

5.2 Pharmacokinetic properties

Absorption
The peak serum levels of flucloxacillin reached after 1h are as follows:
- After 500mg by the i.m. route: approximately 16.5 mg/l

Distribution
Protein binding: the serum protein binding rate is 95%.

Flucloxacillin diffuses well into most tissues.

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 mothers milk.

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

Elimination
Excretion occurs mainly through the kidney. Sixty five per cent of the dose administered orally is recovered in unaltered active form in the urine within 8h. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

Paediatric population

The clearance of flucloxacillin is considerably slower in neonates compared with adults and a mean elimination half life of approximately four and a half hours has been reported in neonates. Special care should be taken during administration of flucloxacillin to the newborn (see section 4.4).
Younger infants (<6 months) achieve higher plasma concentrations of flucloxacillin than older children when given the same dose.

Patients with renal impairment
In patients with severe renal impairment the elimination half life of flucloxacillin increases to values of between 135-173 min. Modified dosage is required if renal impairment is severe, with creatinin clearance <10 ml/min (see section 4.2).

Patients with hepatic impairment
Hepatic disease is thought unlikely to influence the pharmacokinetics of flucloxacillin as the antibiotic is cleared primarily via the renal route.

5.3 Preclinical safety data

Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

FLOXAMED should not be mixed with blood products or other proteinaceous fluids (e.g. protein hydrolysates) or with intravenous lipid emulsions.

If FLOXAMED is prescribed concurrently with an aminoglycoside, the two antibiotics should not be mixed in the same syringe, intravenous fluid container or giving set; precipitation may occur.

This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

As packaged for sale: 2 years

From a microbiological point of view, the product should be administered within 30 minutes of preparation. However chemical and physical in-use stability of aqueous solutions of FLOXAMED has been demonstrated for 24 hours at 2-8°C. Reconstitution of the injection and preparation of the infusion solutions must be carried out under the appropriate aseptic conditions if these extended storage periods are required.

6.4 Special precautions for storage

Unopened product: Do not store above 30°C.

Aqueous solutions of FLOXAMED may be stored for 24 hours at 2-8°C if prepared under the appropriate aseptic conditions (refer to section 6.3).

6.5 Nature and contents of container

10 ml Glass Vial

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

FLOXAMED may be added to most intravenous fluids (e.g. Water for Injections, sodium chloride 0.9%, glucose 5%, sodium chloride 0.18% with glucose 4%).

Intramuscular: Add 1.5 ml Water for Injections BP to 250 mg vial contents.

Intravenous: Dissolve 250-500 mg in 5-10 ml Water for Injections BP. Administer by slow intravenous injection (three to four minutes). FLOXAMED may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of three to four minutes.

Intrapleural: Dissolve 250 mg in 5-10 ml Water for Injections BP.

Intra-articular: Dissolve 250-500 mg in up to 5 ml Water for Injections BP or 0.5% lignocaine hydrochloride solution.

Nebuliser solution: Dissolve 125-250 mg of the vial contents in 3 ml sterile water.

Appearance of the solution
Clear, colourless or pale yellow, particle-free solution.

Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Applicant:
PROMED INDUSTRIES LIMITED
West lands Avenue David Osieri
Road, Off Waiyaki Way, Nairobi,
00200 Kenya

Manufacturer:
Systochem Laboratories Ltd.
B-75, Roop Nagar, Industrial Area, Loni-
201 102 (UP) (India)

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

March 2021