Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Floxapen Syrup 125mg/5ml Powder for Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted as directed each 5 ml contains 125 mg flucloxacillin as Flucloxacillin Magnesium.
Excipients with known effect:
Contains sucrose 2.9g/5ml
This medicinal product contains 10.3mg sodium per dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral suspension
A white free flowing powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Floxapen 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 Floxapen-sensitive organisms:
- Urinary tract infection, small intestine and colon infection, meningitis

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.

Adults and children over 10 years of age:
Total daily dosage of 1 g to 3 g, administered in three to four equally divided doses.

Children under 10 years of age:
25-50 mg/kg/24 hours in three to four equally divided doses.

The dosage may be increased if necessary.

Example of dosages (1 ml reconstituted suspension contains 25 mg flucloxacillin):

Weight		Daily dose (mg/24hours)	Daily dosing regimen		
5 kg		125 - 250	2 ml x 4	or	3 ml x 3
10 kg		250 - 500	4 ml x 4	or	6 ml x 3
15 kg		375 - 750	6 ml x 4	or	8 ml x 3
20 kg		500 - 1000	8 ml x 4	or	11 ml x 3
25 kg		625 - 1250	10 ml x 4	or	14 ml x 3
30 kg		750 - 1500	12 ml x 4	or	16 ml x 3
35 kg		875 - 1750	15 ml x 4	or	20 ml x 3

Abnormal renal function: In common with other penicillins, Floxapen 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 does regimens the maximum recommended dose is 1 g every 8 to 12 hours.

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

Method of administration
Oral forms of flucloxacillin should be taken half to one hour before meals

To the Pharmacist: Do not store above 25 C. Add 61ml of water to reconstitute.
To Dispense: Check cap seal is intact before using. Unscrew cap to break seal.
Loosen powder, add approximately half the water, invert bottle and shake well. Add the remaining water. Shake to complete the suspension which will take 2-5 minutes.

4.3 Contraindications

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

Before initiating therapy with flucloxacillin, careful enquiry 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 betalactam 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 ≥ 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).

Benzoate: Floxapen Syrup contains sodium benzoate which is a mild irritant to the skin, eyes and mucous membranes.

Contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine. Contains 2.9 g of sucrose per 5 ml dose of Floxapen Syrup 125 mg. This should be taken into account in patients with diabetes mellitus. May be harmful to the teeth.

Contains sodium: This medicinal product contains 10.3 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid decreases the renal 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.

Breastfeeding
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 postmarketing reports.

Blood and lymphatic systems 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 500-1000 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).
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
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 adverse events (AEs) was derived from clinical studies involving a total of the 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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@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: J01CF05.

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 500-1000 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.

Mode 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
Floxapen is stable in acid media and can therefore be administered by oral route. The peak serum levels of flucloxacillin reached after 1h 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

The total quantity absorbed by the oral route represents approximately 79% of the quantity administered.
Absorption is delayed by food, with peak serum levels being approximately halved compared with the fasting state. Therefore, it is recommended that flucloxacillin be taken 0.5 to 1 hour before meals.

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.

Neonates and infants
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

Saccharin sodium
Xanthan gum (E415)
Citric acid anhydrous
Sodium citrate
Sodium benzoate (E211)
Blood orange
Tutti frutti flavour
Menthol dry flavours
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened Dry Powder: 2 years.
Following reconstitution: 14 days.

6.4 Special precautions for storage

Unopened Dry Powder: Do not store above 25°C.
Following reconstitution: Once reconstituted, Floxapen Syrup remains stable for 14 days stored in a refrigerator at 2-8° C. Do not freeze.

6.5 Nature and contents of container

Clear glass bottles, reconstituted volume of 100 ml (nominal size). Closure: 28mm aluminium roll-on pilfer proof (ROPP) cap.

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

To the Pharmacist: Do not store above 25 C. Add 61ml of water to reconstitute.
To Dispense: Check cap seal is intact before using. Unscrew cap to break seal.
Loosen powder, add approximately half the water, invert bottle and shake well. Add the remaining water. Shake to complete the suspension which will take 2-5 minutes.

If a dilution of the reconstituted suspension is required, Syrup BP should be used.

If any medicine is left after two weeks, it should be returned to the pharmacist.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavíkurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/011/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 May 1985

Date of last renewal: 06 May 2010

10 DATE OF REVISION OF THE TEXT

April 2018