IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0282/041/003
Case No: 2061679

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Norton Healthcare Limited T/A IVAX Pharmaceuticals UK

Regent House, 5-7 Broadhurst Gardens, **Swiss Cottages**, **London NW6 3RZ**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Flucloxacillin Oral Solution BP 125 mg/5 ml

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/02/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin Oral Solution BP 125 mg/5 ml.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted as directed, each 5 ml contains 125 mg flucloxacillin, as flucloxacillin sodium.

Excipients: Each 5ml contains 3093.65 mg of Sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.
A pink, pineapple-flavoured granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of infections due to penicillinase producing staphylococci and other gram-positive organisms susceptible to this anti-infective.

4.2 Posology and method of administration

The dosage depends upon the severity and nature of the infection.

Usual adult (and children over 10 years of age) dosage:
250-500mg three times a day.

Usual children's dosage:
2 – 10 years: ½ adult dose.
Under 2 years: ¼ adult dose.

The dosage may be increased if necessary.

Maximum daily dose is 8g per day.

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 extension of the dose interval should be considered. In high dose regimens the maximum recommended dose is 1 g every 8 to 12 hours.

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

4.3 Contraindications

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

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, Undesirable effects*).

Dosage should be adjusted in renal impairment (*see section 4.2, Posology and method of administration*).

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 over-growth of non-susceptible organisms.

Benzoate: Flucloxacillin Oral Solution contains sodium benzoate which is a mild irritant to the skin, eyes and mucous membranes. It may cause jaundice in newborn babies.

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

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.

Flucloxacillin, like other penicillins, may reduce the excretion of methotrexate, thereby increasing the risk of methotrexate toxicity.

There have been isolated reports of increased anticoagulant effects when penicillins and oral anticoagulants are administered concurrently.

In common with other antibiotics, flucloxacillin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Bacteriostatic drugs may interfere with the bactericidal action of flucloxacillin.

4.6 Pregnancy and lactation

Pregnancy:
Animal studies with flucloxacillin have shown no teratogenic effects. The decision to administer any drug during pregnancy should be taken with the utmost care. Limited information is available on the use of flucloxacillin in human pregnancy. Therefore flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Lactation:
During lactation, trace quantities of pencillins 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 effects 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 precautions for use*), 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, Special warnings and precautions for use*). 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**.**

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).*

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.

Investigations
Very rare:
Liver function tests abnormal.

**The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.*

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

Flucloxacillin has the same spectrum of activity as the earlier antistaphylococcal penicillins methicillin and cloxacillin against Gram-positive organisms, including penicillinase-producing strains.

5.2 Pharmacokinetic properties

Absorption
Flucloxacillin is stable in acid media and can therefore be administered by the 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.

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.

Metabolism
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.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)
Disodium edetate
Saccharin sodium
Mono-ammonium glycrrhizinate
Sodium citrate
Flavour menthol (contains Sulphur Dioxide (E220))
Flavour pineapple (contains Sulphur Dioxide (E220))
Erythrosine (E 127)
Sucrose

6.2 Incompatibilities

None known.

6.3 Shelf Life

Product in unopened state
18 months from the date of manufacture.

Reconstituted product
7 days from the date of reconstitution.

6.4 Special precautions for storage

Powder
Do not store above 25°C.

Reconstituted product
Store in a refrigerator (at 2-8°C).

6.5 Nature and contents of container

150 ml amber glass bottles with polypropylene screw cap or 150 ml high-density polyethylene bottles with tamper evident and child resistant closures - Polypropylene caps with uni-foam wad/liner - expanded polyethylene liner (Extruded closed cell foam produced from Low density Polyethylene) (LDPE) not faced with aluminium.
Each bottle contains sufficient powder to produce 100 ml Flucloxacillin Oral Solution BP 125 mg/5 ml.

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 prepare add 58 mls of potable water and shake until all powder is dispersed. This product may be diluted with sorbitol solution BP or potable water.
The appearance of the product after reconstitution is a clear pink solution.

7 MARKETING AUTHORISATION HOLDER

Norton Healthcare Ltd
T/A IVAX Pharmaceuticals UK
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5-7 Broadhurst Gardens
Swiss Cottage
London, NW6 3RZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0282/041/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th March 1987

Date of last renewal: 13th March 2007

10 DATE OF REVISION OF THE TEXT

February 2009