Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flucloxacillin 250 mg Capsules BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains flucloxacillin 250 mg as flucloxacillin sodium.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard (capsule).
Size 2, hard gelatin, opaque blue capsule printed 'FXN 250' and twin triangle logo.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Flucloxacillin is also indicated for use as a prophylactic agent during major surgical procedures when appropriate; for example cardiothoracic and orthopaedic surgery.

4.2 Posology and method of administration

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

The dosage may be increased if necessary.

Maximum daily dose is 8 g per day.

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

Usual children's dosage:
2-10 years: One-half adult dose.
Under 2 years: One-quarter adult dose.

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

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

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. 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.

Administration: The oral dosage should be administered one-half to one hour before meals.

4.3 Contraindications

Flucloxacillin is contraindicated in patients with a history of hypersensitivity to flucloxacillin or other beta-lactams or to any of the excipients of the product.

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.

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.

Dosage should be adjusted in renal impairment (see Posology and Method of Administration).

Special caution is essential in the newborn because of the risk of hyperbilirubinemia. Studies have shown that, at high doses 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.

Sodium Content: Flucloxacillin Capsules contain 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 interaction

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

Bacteriostatic drugs may interfere with the bactericidal action 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.

4.6 Fertility, 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

Not 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 item 4.4 Warnings), 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 Warnings and Precautions). 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.

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.

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: http://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 classification: Beta lactamase resistant penicillins
ATC Code: J01 F05

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

5.2 Pharmacokinetic properties

Peak serum concentrations are reached after one hour following an oral dose of 250mg to 500mg in fasting subjects. Peak serum concentration range from about 3 to 27 micrograms/ml with a mean peak of 11 to 15 micrograms/ml. Therapeutic concentrations persist for about 4 hours.
Following oral administration, flucloxacillin is almost completely absorbed achieving blood levels comparable to those achieved after intramuscular injection.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Gelatin
Titanium dioxide (E171)
Patent blue V (E131)
Erythrosine (E127)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original container.

6.5 Nature and contents of container

Polypropylene tubular tablet container equipped with an open end to accept a polyethylene closure with a tamper-evident tear strip, and is of the appropriate size to accommodate 100, 250, 500 or 1000 capsules.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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Date of last renewal: 13 March 2007

10 DATE OF REVISION OF THE TEXT

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