SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Fluampicil 125/125 mg/5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml reconstituted suspension contains Flucloxacillin Sodium equivalent to 125 mg Flucloxacillin and Ampicillin Trihydrate equivalent to 125 mg Ampicillin

Excipients with known effect

Sucrose 3.03 mg per 5 ml of Oral Suspension.
Sodium Content: 12.3 mg Sodium per 5 ml of Oral Suspension.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Oral Suspension.

A free flowing powder in two layers the top layer being white, the bottom layer being off-white. Orange coloured suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-fluampicil is indicated for the treatment of severe infections where the causative organism is unknown, and for mixed infections involving β-lactamase-producing staphylococci.

In general practice: Chest infections, ENT infections, skin and soft tissue infections and patients with an underlying pathology which makes them more susceptible to infections.

In hospital use (if laboratory tests are not yet available): severe respiratory infections, post-operative chest and wound infections, septic abortion, puerperal fever, septicaemia, prophylaxis in major surgery and infections in patients receiving immunosuppressive therapy.

The spectrum of activity of co-fluampicil also makes it suitable for the treatment of many mixed infections, particularly those where β-lactamase-producing staphylococci are suspected or confirmed.

4.2 Posology and method of administration

Posology
Adults (including elderly patients and children over 10 years)
10 ml four times a day;

Paediatric population (under 10 years)
5 ml four times a day;

The above dosages may be doubled where necessary and should be administered half an hour to one hour before meals.

Method of administration
Co-Fluampicil oral suspension should be taken at least 1 hour before or 2 hours after meals.

A full glass of water (250 ml) should be taken afterwards, to reduce the risk of oesophageal pain (see section 4.8). Patients should not lay down immediately after Co-Fluampicil intake.

4.3 Contraindications

Co-fluampicil contains ampicillin and flucloxacillin which are penicillins and should not be given to patients with a history of hypersensitivity to β-lactam antibiotics (e.g. penicillins, cephalosporins) or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

Before initiating therapy with co-fluampicil careful enquiries should be made concerning previous hypersensitivity reactions to β-lactam antibiotics.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving β-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 hypersensitivity to β-lactam antibiotics.

Co-fluampicil contains ampicillin and should be avoided if infectious mononucleosis and/or acute or chronic leukaemia of lymphoid origin are suspected. The occurrence of a skin rash has been associated with these conditions following the administration of ampicillin.

In case of severe and persistent diarrhoea, the possibility of pseudomembranous colitis should be considered; flucloxacillin therapy should be discontinued.

Care is required when treating some patients with spirochaete infections such as syphilis or leptospirosis because the Jarisch-Herxheimer reaction may occur shortly after treatment with a penicillin is started.

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).

Co-fluampicil should be used with caution in patients with evidence of hepatic dysfunction (see section 4.8).

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.

Care is necessary if very high doses of flucloxacillin are given, especially if renal function is poor, because of the risk of nephrotoxicity and/or neurotoxicity. Care is also necessary if large doses of sodium (salts) are given to patients with impaired renal function or heart failure. Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction (see section 4.8). Renal, hepatic and haematological status should be monitored during prolonged and high-dose therapy (e.g. osteomyelitis, endocarditis). Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

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 hypokalemia are present (e.g. malnutrition, renal tubule dysfunction).

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.

Excipients with known effect
Co-Fluampicil contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Co-Fluampicil contains 12.3mg sodium per 5ml of oral suspension. 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

Other antibacterials: There may be antagonism between penicillins, including ampicillin and bacteriostatic agents such as chloramphenicol, erythromycins or tetracyclines. This may reduce the effectiveness of penicillins particularly in the treatment of infections such as pneumococcal meningitis and scarlet fever.

Cytotoxics: Penicillins reduce the excretion of methotrexate (increased risk of toxicity).

Bacteriostatic drugs may interfere with the bactericidal action of ampicillin and flucloxacillin.

In common with other oral broad-spectrum antibiotics, co-fluampicil may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Probenecid decreases the renal tubular secretion of co-fluampicil. Concurrent use with co-fluampicil may result in increased and prolonged blood levels of both ampicillin and flucloxacillin.

Concurrent administration of all allopurinol during treatment with ampicillin can increase the likelihood of allergic skin reactions.

Interference with diagnostic tests: 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.

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 Fertility, pregnancy and lactation

Pregnancy
Animal studies with co-fluampicil have shown no teratogenic effects. The product has been in clinical use since 1971 and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effects. The decision to administer any drug during pregnancy should be taken with the utmost care. Therefore co-fluampicil should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breast-feeding
Trace quantities of penicillin, ampicillin and flucloxacillin can be detected in breast milk. The possibility of hypersensitivity reactions must be considered in breast-fed infants. Therefore co-fluampicil should only be administered to a breast-feeding mother when the potential benefit outweigh the potential risks associated with treatment.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

Blood and lymphatic system disorders:
As with other b-lactam antibiotics, haematological effects including reversible leucopenia, reversible thrombocytopenia and haemolytic anaemia have been reported rarely.

Immune System Disorders:
Anaphylaxis (see section 4.4) has been reported rarely.
If any hypersensitivity reaction (e.g skin rash) occurs, the treatment should be discontinued.
Late sensitivity reactions may include serum sickness-like reactions (featuring symptoms such as arthralgia, rash, urticaria, fever, angioedema, lymphadenopathy), haemolytic anaemia and acute interstitial nephritis.

Metabolism and nutrition disorders:
Frequency not known (cannot be estimated from the available data):

Electrolyte disturbances, such as hypokalaemia, due to administration of large amounts of sodium.
Post marketing experience: very rare cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4).

Psychiatric disorders:
There is a potential for hallucinations to occur rarely with flucloxacillin.

Nervous System Disorders:
Coma may develop with high doses of Flucloxacillin.

Respiratory, thoracic and mediastinal disorders:
Bronchospasm may occur as a result of penicillin allergy.
There is a potential for acute, severe dyspnoea to occur with flucloxacillin.

Gastrointestinal disorders:
Minor gastrointestinal disturbances, including occasionally nausea, vomiting and diarrhoea may occur during treatment. Pseudomembranous colitis has been reported rarely.

Oesophageal pain and related events*
Frequency not known (cannot be estimated from the available data):
*oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain.

Hepatobiliary disorders:
Hepatitis and cholestatic jaundice have been reported rarely. These may be delayed for up to two months after withdrawal of treatment. In some cases the course of these conditions has been protracted and lasted for several months. Very rarely deaths have been reported from hepatic effects but are mostly limited to patients with serious underlying disease.

As with most other antibiotics, a moderate transient increase in transaminases has been reported.

Skin and subcutaneous tissue disorders:
Skin rash, pruritis and urticaria have been reported. The incidence of rash is higher in patients suffering from infectious mononucleosis and acute or chronic leukaemia of lymphoid origin. Purpura, fever, eosinophilia and sometimes angioneurotic oedema have also been reported. Rarely, skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Reactions such as fever, arthralgia, and myalgia can develop more than 48 hours after the start of the treatment.

Erythema nodosum may occur rarely with flucloxacillin.
Potential for pemphigoid reactions to occur rarely with flucloxacillin.
There is potential for non-thrombocytopenic purpura to occur rarely with flucloxacillin.
Vasculitis may occur rarely with flucloxacillin.

AGEP - Acute Generalized Exanthematous Pustulosis (see section 4.4).

Renal and urinary disorders:
Interstitial nephritis can occur rarely but it is reversible when treatment is discontinued.

Congenital, familial and genetic disorders:
Potential for acute attacks of porphyria to occur with flucloxacillin.

General disorders and administration site conditions:
Some patients with spirochaete infections such as syphilis or leptospirosis may experience a Jarisch-Herxheimer reaction shortly after treatment with a penicillin is started. Symptoms include fever, chills, headache and reaction at the site of lesions. The reaction can be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically.

Co-fluampicil contains flucloxacillin. Haemodialysis does not lower the serum levels of flucloxacillin.

Co-fluampicil contains ampicillin, which may be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Beta-Lactam Antibacterials,
ATC code: J01D

Flucloxacillin is used for the treatment of infections due to staphylococci resistant to
benzylpenicillin. It is also used for the mixed streptococcal infections when the staphylococci are penicillin-resistant.

Ampicillin is a broad spectrum antibiotic which is bactericidal for both gram positive and gram negative bacteria.

5.2 Pharmacokinetic properties

Both ampicillin and flucloxacillin have been shown to attain therapeutic serum levels following oral administration of co-fluampicil and the serum levels achieved are comparable with those which could be expected as a result of administering each antibiotic separately.

Flucloxacillin after an oral dose of 250 to 500 mg in fasting subjects shows peak serum concentrations at one hour ranging from 3-27 mcg/ml with a mean peak 11-15 mcg/ml. Therapeutic concentrations persist for about four hours. Doubling the dose can double the plasma concentrations. About 95% of flucoxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine.

Ampicillin is relatively stable in gastric secretion and is well absorbed from the gastro-intestinal tract producing peak concentrations in about two hours. Doubling the dose can produce double the concentration. Ampicillin diffuses across the placenta and the foetal circulation and concentrations can persist in amniotic fluid. Concentrations can be detected in the milk of nursing mothers.

There is little diffusion into the cerebro-spinal fluid except when the meninges are infected, when high concentrations are achieved. Concentrations of ampicillin are found in ascetic, pleural, joint and ocular fluids. 30% of the orally administered dose is excreted unchanged in the urine in about six hours.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate
Disodium edetate
Saccharin sodium

Mono-ammonium glycyrrhizinate
Sodium citrate (dried)
Flavour apricot
Flavour menthol
Yellow F.D. & C.No:6 (E110)
Sucrose (Caster)

6.2 Incompatibilities

None known

6.3 Shelf life

2 years unopened.
7 days after reconstitution.

6.4 Special precautions for storage

Store in a cool dry place. Store below 25°C.

6.5 Nature and contents of container

High density polyethylene bottles with tamper-evident and child-resistant cap or Amber Beatson Clark Winchester with polypropylene screw cap. Each pack contains 100ml when reconstituted.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0524

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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