DGF Drugfield **PHARMACEUTICALS LIMITED**

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Compi-clox® Capsule

(Ampicillin 250mg + Cloxacillin 250mg)

1. Name of the medicinal product

Compi-clox® (Ampicillin Trihydrate 250mg, Cloxacillin Sodium 250mg) Capsules (DGF COMPI-CLOX)

2. Qualitative and quantitative composition

Each tablet contains Ampicillin Trihydrate 250mg, Cloxacillin Sodium 250mg.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

SSolid-Capsules.

Hard Gelatin Capsules filled with almost white granular powder.

4.1 Therapeutic indications

Compi-clox is indicated for the treatment of the following infections including mixed Gram-positive (except methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant coagulase-negative staphylococcus (MRCoNS)) and Gram-negative infections: Surgery: post-operative wound infections, post-operative pulmonary infections.

2 Respiratory infections: bronchopneumonia, acute exacerbations of chronic bronchitis. Obstetrics: puerperal fever. Other infections such as septicaemia, bone infections e.g., osteomyelitis, ear, nose and throat infections. Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to **Compi-clox**. Where treatment is initiated before results are available expert advice should be sought when the local prevalence of resistance is such that the utility of **Compi-clox** is questionable (see Pharmacological properties, Pharmacodynamics). **Compi-clox** neonatal oral drops are indicated for the prophylaxis or treatment of bacterial infections in premature babies or neonates, caused by known susceptibile strains of bacteria.

4.2 Posology and method of administration

Adults and Elderly
Dosage: Oral

One or Two Capsules 4 times daily or as directed by physician

<u>Posology</u>

Renal impairmentIn cases of renal failure, the dosage should be adapted in accordance with the following:

Creatinine clearance greater than 50mL/minute: normal dose according to indication.

Creatinine clearance between 50 and 10mL/minute:

- Dosage (oral or parenteral administration) initial dose: normal dose (according to indication).

- Dosage (oral or parenteral administration) maintenance dose: the normal unit dose (Compi-clox 500mg orally) three times daily.

Creatinine clearance below 10mL/minute:

- Dosage (oral or parenteral administration) initial dose: normal dose (according to indication).

- Dosage (oral or parenteral administration) maintenance dose: the normal unit dose twice or once daily.

In cases of dialysis, an additional normal unit dose (Compi-clox 500mg orally, up to 1g i.m. or i.v) is to be administered after the procedure.

Hepatic impairment
Reduce frequency of administration depending on the severity of the condition.

Method of administration
Oral use.
Compi-clox should be administered 0.5 to 1 hour before meals.

4.3 Contraindications
Compi-clox should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (e.g., penicillins, cephalosporins) or excipients (See List of Excipients).

- Compi-clox is contraindicated for ocular administration.

4.4 Special warnings and precautions for use
Caution should be observed when administering Compi-clox neonatal oral drops to babies whose mothers are hypersensitive to penicillin.Before initiating therapy with Compi-clox, 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 penicillins. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity.
If an allergic reaction occurs, Compi-clox should be discontinued and the appropriate alternative therapy instituted. All adverse reactions should be treated symptomatically.

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

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Dosage should be adjusted in patients with renal impairment (See Dosage and Administration, Renal impairment). Cloxacillin can displace bilirubin from protein-binding sites. Normal caution should therefore be exercised in the treatment of jaundiced neonates.

Compi-clox neonatal oral suspension and suspension contain sodium benzoate which is a mild irritant to the skin, eyes, and mucous membrane. It may increase the risk of jaundice in newborn babies.The sodium content of the formulation must be included in the daily allowance of patients on sodium restricted diets.
Each Compi-clox 500mg vial contains 29.63mg of sodium. EachCompi-clox 500mg capsule contains 13.17mg of sodium.
Compi-clox suspension 250mg contains 12.14mg sodium per 5 mL dose. Compi-clox Neonatal oral drops contains 2.46 mg sodium per 0.6mL dose.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid decreases the renal tubular excretion of Compi-Clox. Concurrent use with Compi-clox may result in increased and prolonged blood levels of Compi-Clox.

In common with other antibiotics, Compi-clox may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Sulphonamides and acetylsalicylic acid inhibit serum protein binding of cloxacillin in vitro. This may result in increased levels of free cloxacillin in serum in vivo. Bacteriostatic drugs may interfere with the bactericidal action of Compi-clox. Concurrent administration of allopurinol during treatment with Compi-clox can increase the likelihood of allergic skin reactions.

4.6 Fertility, pregnancy and lactation

Pregnancy and Lactation
Adequate human data on use during pregnancy are not available. However, animal studies have not identified any risk to pregnancy or embryo-foetal development.

Adequate human and animal data on use during lactation are not available.
Ability to perform tasks that require judgment, motor or cognitive skills

4.7 Effects on ability to drive and use machines

No adverse effects on the ability to drive or operate machinery have been observed.

4.8 Undesirable effects
Adverse Reactions
The following statements reflect the information available on the adverse reaction profile of the individual constituents (ampicillin and cloxacillin) and/or the combination in Compi-clox. The

majority of the adverse reactions listed below are not unique to ampicillin - cloxacillin and may occur when using other penicillins.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: 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), including isolated reports. Common and uncommon adverse reactions were generally determined from pooled safety data from a clinical trial population of 1210 treated patients. Rare and very rare adverse reactions were generally determined from more than 32 years of post-marketing experience data and refer to reporting rate rather than true frequency.

Blood and lymphatic system disorders
Very rare: Hemolytic anemia, leucopenia, thrombocytopenia,agranulocytosis

Immune system disorders

Very rare: Anaphylaxis

(See Warnings and Precautions) and other hypersensitivity reactions

Skin disorders and interstitial nephritis have been reported as hypersensitivity reactions. (See also Skin and subcutaneous tissue disorders and Renal and urinary disorders).

If any hypersensitivity reaction occurs, the treatment should be discontinued.

Nervous system disorders
Very rare: Myoclonus and convulsions

Gastrointestinal disorders
Common: Diarrhoeaand nausea
Uncommon: Vomiting
Very rare: Pseudomembranouscolitis

(See Warnings and Precautions) and haemorrhagic colitis

Hepatobiliary disorders
Very rare: Hepatitisandcholestatic jaundice. A moderate and transient increase in transaminases
Skin and subcutaneous tissue disorders
Common: Skin rash, urticarial and pruritus

The incidence of skin rash, pruritus and urticaria is higher in patients suffering from infectious mononucleosis and acute or chronic leukaemia of lymphoid origin.

Very rare: Bullous reactions(including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), exfoliative dermatitis and purpura

Skin disorders have also been reported as hypersensitivity reactions
(See Immune system disorders).

Renal and urinary disorders

Very rare: Interstitial nephritis

Interstitial nephritis has also been reported as a hypersensitivity reaction (See also Immune system disorders).

4.9 Overdose
Overdosage with oral Compi-clox is unlikely to cause serious reactions if renal function is normal. Very high dosage of i.v. administered ampicillin and/or high dosage of cloxacillin in renal failure may provoke neurotoxic reactions similar to those seen with benzylpenicillin in excess.

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

5. Pharmacological properties
5.1 Pharmacodynamic properties

Compi-clox is a combination of ampicillin and cloxacillin. Cloxacillin is a narrow-spectrum antibiotic of the isoxazolyl penicillin group; it is not inactivated by staphylococcal beta-lactamases. Ampicillin is a broad-spectrum antibiotic of the aminopenicillin group; it is not resistant to beta-lactamases.

Both ampicillin and cloxacillin are bactericidal antibiotics and act by interfering with the formation of new bacterial cell wall by dividing organisms.

The prevalence of acquired resistance is geographically variable and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

Compi-clox susceptibility rates are higher than ampicillin rates due to the cloxacillin activity against β-lactamase producing staphylococci. Methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin-susceptible coagulase-negative staphylococcus (MSCoNS) are commonly susceptible to Compi-clox. MRSA and MRCoNS are resistant to Compi-clox. For all other indicated bacterial species, the susceptibility of Compi-clox is similar to ampicillin including limited activity against Gram-negative organisms.

5.2 Pharmacokinetic properties

Absorption
Both ampicillin and cloxacillin are stable in the gastric environment resulting in good absorption. Neither component of the combination of ampicillin and cloxacillin interferes with the absorption or excretion of the other.

The total quantity absorbed by the oral route represents 50% (cloxacillin) and 40% (ampicillin) of the quantity administered.

The presence of food in the stomach may depress oral absorption and Compi-clox should therefore be taken 0.5 to 1 hour before meals.

Distribution
Compi-clox diffuses well into most tissues and body fluids including, among others, bronchial secretions, sinuses, saliva, cerebrospinal fluid (variable percentage depending on the degree of meningeal inflammation), bile, serous membranes and middle ear.

Crossing the meningeal barrier: Compi-clox diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into breast milk: Compi-clox is excreted in small quantities in breast milk.

Plasma half-life for cloxacillin is 0.5 to 1 hour and 1 to 1.5 hour for ampicillin. Protein binding: the serum protein binding proportion is approximately 94% for cloxacillin and 18% for ampicillin.

Metabolism
In normal subjects approximately 20% (cloxacillin) and 40% (ampicillin) of the dose administered is metabolised.

Excretion
Compi-clox is eliminated mainly through the kidney. Approximately 30% of the dose administered orally and over 60% of the ampicillin dose administered parenterally is eliminated in active form in the urine within 24 hours. The equivalent percentages for cloxacillin are approximately 20% and 30% respectively. A small proportion (10%) of the dose administered is excreted in bile.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Talcum powder
Magnessium stearate
Aerosil 200

6.2 Incompatibilities

Compi-clox must not be dissolved in either protein or protein hydrolysate solutions or in lipid solutions, or in blood or plasma. When Compi-clox is prescribed together with an aminoglycoside, the two antibiotics should not be mixed in the same container as the one containing the infusion solution because a loss of activity may occur.

6.3 Shelf life

48 Months

6.4 Special precautions for storage

Store below 30°C in tight container protected from light and moisture.

6.5 Nature and contents of container

500mg: 250mg Ampicillin as Ampicillin Trihydrate BP and 250mg Cloxacillin as Cloxacillin Sodium BP in Blister and 500's packs.

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.

7.0 APPLICANT/MANUFACTURER

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