1. NAME OF THE MEDICINAL PRODUCT

CLOXYPAK

(Ampicilin + Cloxacillin Capsules 500 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Ingredients	Spec.	Unit Formula (mg)	Batch Formula(kg) for 5,000 Capsule	Function
1	Ampicillin Trihydrate eq. to Ampicillin B.P	BP	250.0	1.472*	Active
2	Cloxacillin sodium eq. to Cloxacillin	BP	250.0	1.399*	Active
3	Talcum	BP	10.000	0.050	Diluent
4	Magnesium stearate BP	BP	8.000	0.040	Diluent
5	Silicon dioxide	BP	2.000	0.010	Diluent
6	E.H.G. Capsules, black/purple size "0" Printed with **"CLOXYPAK – 500"** on body and on cap	BP	NA	5,200	E.H.G. Capsules

* 2.5% overages added.

Net Content 594.2mg per Capsule

3. PHARMACEUTICAL FORM

Capsules for oral administration

Description: Black cap/Purple body Size '0' hard gelatin capsules printed with "**CLOXYPAK-500**" on body and on capsule containing white powder.

4. CLINICAL INFORMATION

4.1 Indications

Ampicillin - cloxacillin 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

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 ampicillin – cloxacillin. 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 ampicillin-cloxacillin is questionable (*see Clinical Pharmacology, Pharmacodynamic effects*).
Ampicillin - cloxacillin neonatal suspension and injection are indicated for the prophylaxis or treatment of bacterial infections in premature babies or neonates, caused by known susceptible strains of bacteria.

4.2 Dosage and Administration

Populations

• Adults

Oral:

Ampicillin - Cloxacillin 500 mg capsules (250 mg ampicillin and 250 mg cloxacillin per capsule): 2 to 4 capsules every 6 hours.

Renal impairment

In cases of renal failure, the dosage should be adapted in accordance with the following:
Creatinine clearance greater than 50 ml/minute: normal dose according to indication.

Creatinine clearance between 50 and 10 ml/minute:
Dosage (oral or parenteral administration) initial dose: normal dose (according to indication).
Dosage (oral or parenteral administration) maintenance dose: the normal unit dose (ampicillin - cloxacillin 500 mg orally, up to 1 g i.m. or i.v) three times daily.

Creatinine clearance below 10 ml/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 (ampicillin - cloxacillin 500 mg orally, up

to 1 g 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.

4.3. MODE OF ADMINISTRATION

Oral route:

Ampicillin - cloxacillin should be administered 0.5 to 1 hour before meals.

4.4 Contraindications

Ampicillin - cloxacillin should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (e.g. penicillins, cephalosporins) or excipients (*see Excipients*).

Ampicillin - cloxacillin is contraindicated for ocular administration.

4.5 Warnings and Precautions

Caution should be observed when administering ampicillin - cloxacillin neonatal suspension to babies whose mothers are hypersensitive to penicillin.

Before initiating therapy with ampicillin - cloxacillin, 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, ampicillin - cloxacillin should be discontinued and the appropriate alternative therapy instituted. All adverse reactions should be treated symptomatically.

Ampicillin - cloxacillin 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.

Ampicillin - cloxacillin neonatal suspension and syrup contain sodium benzoate which is a mild irritant to the skin, eyes and mucous membrane. It may increase the risk of jaundice in new born babies#.

#Statement to be included on paediatric presentations only.

Sodium content:

The sodium content of the formulation must be included in the daily allowance of patients on sodium restricted diets. One gram of the parenteral formulation contains [x#] mg of sodium. One gram of the oral formulation contains [x#] mg of sodium.

[x#]: please insert appropriate value.

Interactions

Probenecid decreases the renal tubular excretion of ampicillin **-** cloxacillin. Concurrent use with ampicillin – cloxacillin may result in increased and prolonged blood levels of ampicillin **-** cloxacillin.

In common with other antibiotics, ampicillin-cloxacillin 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 ampicillin **-** cloxacillin.

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

4.6 Pregnancy and Lactation

Fertility

No Text.

Pregnancy

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

Lactation

Adequate human and animal data on use during lactation are not available.

4.7 Ability to perform tasks that require judgement, motor or cognitive skills

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

4.8 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 ampicillin - cloxacillin. 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:	Haemolytic anaemia, 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:	Diarrhoea and nausea.
Uncommon:	Vomiting.
Very rare:	Pseudomembranous colitis (*See Warnings and Precautions*) and haemorrhagic colitis.

Hepato-biliary disorders

Very rare:	Hepatitis and cholestatic jaundice. A moderate and transient increase in transaminases.

Skin and subcutaneous tissue disorders

Common:	Skin rash, urticaria 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).*

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. Clinical Pharmacology

5.1 Pharmacodynamics

Ampicillin - cloxacillin 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.

ATC Code

No Text.

5.2 Mechanism of Action

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

5.3 Pharmacodynamic Effects

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.

Ampicillin - cloxacillin 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 ampicillin/cloxacillin. MRSA and MRCoNS are resistant to ampicillin/cloxacillin. For all other indicated bacterial species, the susceptibility of ampicillin/cloxacillin is similar to ampicillin including limited activity against Gram-negative organisms.

5.4 Pharmacokinetics

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 ampicillin - cloxacillin should therefore be taken 0.5 to 1 hour before meals.

Distribution

Ampicillin - cloxacillin 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: Ampicillin - cloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into breast milk: Ampicillin - cloxacillin is excreted in small quantities in breast milk.

Plasma half-life for cloxacillin is 0.5 to 1 hour and 1 to 1.5 hours 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.

Elimination

Ampicillin - cloxacillin is eliminated mainly through the kidney. Approximately 30% of the dose administered orally and over 60% of the ampicillin dose administered parenterally are 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.

Special Patient Populations

No Text.

Clinical Studies

No Text.

NON-CLINICAL INFORMATION

No further information of relevance to add.

PHARMACEUTICAL INFORMATION

Chemical Structure

No Text.

Shelf-Life

2 years

Storage

Ampicillin - cloxacillin should be stored in a dry place below 25°C.

Do not use after expiry date.

All medicines should be kept out of reach of children.

Reconstitution of ampicillin - cloxacillin injections and preparation of ampicillin - cloxacillin infusion solutions must be carried out under appropriate aseptic conditions if extended

storage periods are required.

Incompatibilities

Ampicillin - cloxacillin must not be dissolved in either protein or protein hydrolysate solutions or in lipid solutions, or in blood or plasma.

When ampicillin - cloxacillin 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. Pharmaceutical particulars

6.1 List of excipients

Each gelatin capsule contains:

Gelatin (capsule body and cap)

Magnesium stearate

Colloidal anhydrous silica

Purified Talcum

6.2 Nature and contents of container

Blister pack of 10 capsules.

6.3 Special precautions for disposal and other handling

No special instructions for use/handling.

7. APPLICANT/MANUFACTURER

Name: **Charles Mekus Pharmaceutical & Stores Nig. Ltd.**

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