AMPICLOX

Ampicillin sodium trihydrate – cloxacillin sodium monohydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules:

Capsules 250 mg (ampicillin sodium trihydrate - cloxacillin sodium monohydrate) contain 125 mg ampicillin and 125 mg cloxacillin.

Capsules 500 mg (ampicillin sodium trihydrate - cloxacillin sodium monohydrate) contain 250 mg ampicillin and 250 mg cloxacillin.

Neonatal Suspension:

Dry powder suspension 90 mg/0.6 ml (ampicillin sodium trihydrate - cloxacillin sodium monohydrate) contains 60 mg ampicillin and 30 mg cloxacillin.

Syrup:

Syrup 250 mg/5 ml (ampicillin sodium trihydrate - cloxacillin sodium monohydrate) contains 125 mg ampicillin and 125 mg cloxacillin.

Syrup 500 mg/5 ml (ampicillin sodium trihydrate - cloxacillin sodium monohydrate) contains 250 mg ampicillin and 250 mg cloxacillin.

Injection:

Vials 75 mg (ampicillin sodium trihydrate - cloxacillin sodium monohydrate) contain 50 mg ampicillin and 25 mg cloxacillin.

Vials 250 mg (ampicillin sodium trihydrate - cloxacillin sodium monohydrate) contain 125 mg ampicillin and 125 mg cloxacillin.

Vials 500 mg (ampicillin sodium trihydrate - cloxacillin sodium monohydrate) contain 250 mg ampicillin and 250 mg cloxacillin.

CLINICAL PARTICULARS

Indications

AMPICLOX 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 *AMPICLOX*. 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 *AMPICLOX* is questionable (*see Pharmacological properties, Pharmacodynamics*).

AMPICLOX neonatal suspension and injection are indicated for the prophylaxis or treatment of bacterial infections in premature babies or neonates, caused by known susceptibile strains of bacteria.

Dosage and Administration

Route	**Dosage**
Adults and Elderly	
Oral	1 to 2 g every 6 hours
Intramuscular (i.m.) injection	500 mg to 1g every 4 to 6 hours
Intravenous (i.v.) injection	500 mg to 1 g every 4 to 6 hours

The dose of *AMPICLOX* may be increased for the treatment of severe infections.

Children

2 to 12 years

Oral	Half adult dose: 5 to 10 ml syrup every 6 hours
Injectable	Half adult dose: 250 mg every 8 hours

Neonates to 2 years

Neonatal suspension	0.6 ml (90 mg) of reconstituted suspension every 4 hours. Administer 0/5 to 1 hour prior to feeding
Injection	One quarter adult dose: 75 mg every 8 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 *(AMPICLOX* 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 (*AMPICLOX* 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.

MODE OF ADMINISTRATION

Oral route:

AMPICLOX should be administered 0.5 to 1 hour before meals.

Parenteral route:

Administer by slow i.v. injection (3 to 4 minutes). *AMPICLOX* may also be added to infusion fluids (except for aminoglycosides, amino acid solutions, fat emulsions and blood), and can, therefore, be administered simultaneously with these forms of treatment or injected, suitably diluted, into the drug tube over a period of 3 to 4 minutes.

Contraindications

AMPICLOX 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*).

*AMPICLO*X is contraindicated for ocular administration.

Warnings and Precautions

Caution should be observed when administering *AMPICLOX* neonatal suspension to babies whose mothers are hypersensitive to penicillin.

Before initiating therapy with *AMPICLOX*, 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, *AMPICLOX* should be discontinued and the appropriate alternative therapy instituted. All adverse reactions should be treated symptomatically.

AMPICLOX 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.

AMPICLOX 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 newborn babies.

The sodium content of the formulation must be included in the daily allowance of patients on sodium restricted diets.

Each *AMPICLOX* 500 mg vial contains 30.4 mg of sodium.

Each *AMPICLOX* 250 mg vial contains 15.2 mg of sodium.

Each *AMPICLOX* 75 mg vial contains 4.73 mg of sodium.

Each *AMPICLOX* 500 mg capsule contains 13.2 mg of sodium.

Each *AMPICLOX* 250 mg capsule contains 6.6 mg of sodium.

AMPICLOX syrup 500 mg contains 26.4 mg sodium per 5 ml dose.

AMPICLOX syrup 250 mg contains 13.2 mg sodium per 5 ml dose.

AMPICLOX Neonatal Suspension contains 2.5 mg sodium per 0.6 ml dose.

Interactions

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

In common with other antibiotics, *AMPICLOX* 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 *AMPICLOX*.

Concurrent administration of allopurinol during treatment with *AMPICLOX* can increase the likelihood of allergic skin reactions.

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 judgement, motor or cognitive skills

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

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 *AMPICLOX*. 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).*

Overdose

Overdosage with oral *AMPICLOX* 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

AMPICLOX 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.

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

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 *AMPICLOX* should therefore be taken 0.5 to 1 hour before meals.

Distribution

AMPICLOX 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: *AMPICLOX* diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into breast milk: *AMPICLOX* 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.

Excretion

AMPICLOX 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

List of Excipients

Capsules:

Magnesium stearate.

Neonatal Suspension:

Sodium benzoate

Xanthan gum

Sodium citrate anhydrous

Saccharin sodium.

Syrup:

Sodium benzoate

Disodium edetate

Methyl polysiloxane

Sodium citrate anhydrous

Saccharin sodium

Monoammonium glycyrrhizinate

Menthol dry flavour

Tutee Fruity dry flavour

Blood orange dry flavour

Sucrose.

Injection:

None.

Incompatibilities

AMPICLOX must not be dissolved in either protein or protein hydrolysate solutions or in lipid solutions, or in blood or plasma.

When *AMPICLOX* 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.

Shelf-Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

AMPICLOX should be stored in a dry place below 25°C.

Do not use after the expiry date.

All medicines should be kept out of reach of children.

Reconstitution of *AMPICLOX* injections and preparation of *AMPICLOX* infusion solutions must be carried out under appropriate aseptic conditions if extended storage periods are required.

Nature and Contents of Container

Capsules:

250 mg: black and amethyst capsules

500 mg: black and amethyst capsules

Neonatal Suspension:

Neonatal drops: clear, glass bottles containing powder for reconstitution to 8 ml of 90 mg/0.6 ml

Syrup:

Clear, glass bottles containing powder for reconstitution to 100 ml of 250 mg/5 ml syrup

Injection:

1 g; 500 mg; 75 mg: white powder in clear, glass vials.

Instructions for Use/Handling

Neonatal Suspension:

Preparation of the suspension: Before dispensing this drug, add 7 ml of distilled water to the powder and shake well. Before each use, shake the bottle containing the reconstituted mixture thoroughly.

Injection:

Any residual antibiotic solution should be discarded.

AMPICLOX vials are not suitable for multidose use.

Solutions should be administered immediately after reconstitution.

Intramuscular route: *AMPICLOX* 500 mg, 250 mg and 75 mg.

Solvent volume: 1.5 ml, 1 ml and 0.5 ml.

Solvent type: Water for injection.

Stability of the solution at room temperature: 30 minutes.

Intravenous route: infusion *AMPICLOX* 500 mg, 250 mg and 75 mg.

Solvent volume: 10 ml, 5 ml and 2 ml.

Solvent type: Water for injection.

Stability of the solution at room temperature: 30 minutes.

Not all presentations are available in every country.

GSK is committed to the effective collection and management of human safety information relating to our products and we encourage healthcare professionals to report adverse events to us on +254 20 693 3200 or email us on ke.safety@gsk.com

Full Prescribing Information is available on request from GlaxoSmithKline Pharmaceutical Kenya Limited, P.O. Box 78392-00507, 23 Likoni Road, Nairobi, Kenya.

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