CALAMOX® (Co-amoxiclav)

Tablets
Suspension
Drops

کیلاموکس (کو۔اموکسی کلیو)

ٹیبلیٹس، سسپنشن، ڈراپس

QUALITATIVE AND QUANTITATIVE COMPOSITION
CALAMOX Tablets 375mg
Each film coated tablet contains:
Amoxicillin USP ..... 250mg (as amoxicillin trihydrate)
Clavulanic Acid ..... 125mg (as potassium clavulanate BP)
(Product Specs.: USP)

CALAMOX Tablets 625mg
Each film coated tablet contains:
Amoxicillin USP ..... 500mg (as amoxicillin trihydrate)
Clavulanic Acid ..... 125mg (as potassium clavulanate BP)
(Product Specs.: USP)

CALAMOX Tablets 1g
Each film coated tablet contains:
Amoxicillin USP ..... 875mg (as amoxicillin trihydrate)
Clavulanic Acid ..... 125mg (as potassium clavulanate BP)
(Product Specs.: USP)

CALAMOX for Oral Suspension 156.25mg/5mL
Each 5mL contains:
Amoxicillin Trihydrate eq. to 125mg Amoxicillin USP
Potassium Clavulanate BP eq. to 31.25mg Clavulanic acid.
(Product Specs.: BP)

CALAMOX for Oral Suspension 312.5mg/5mL
Each 5mL contains:
Amoxicillin Trihydrate eq. to 250mg Amoxicillin USP
Potassium Clavulanate BP eq. to 62.5mg Clavulanic acid
(Product Specs.: BP)

CALAMOX DUO for Oral Suspension 457mg/5mL
Each 5mL contains:
Amoxicillin Trihydrate eq. to 400mg Amoxicillin USP
Potassium Clavulanate BP eq. to 57mg Clavulanic acid
(Product Specs.: BP)

CALAMOX Drops 62.5mg/mL
Each mL contains:
Amoxicillin Trihydrate eq. to 50mg Amoxicillin USP
Potassium Clavulanate BP eq. to 12.5mg Clavulanic acid.
(Product Specs.: BP)

PHARMACEUTICAL FORM
Film coated tablets, Powder for Oral Suspension and Drops.
CLINICAL PARTICULARS
Therapeutic indications
Calamox is indicated for the treatment of the following infections in adults and children:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Posology and method of administration
Posology
For adults and children ≥ 40 kg: This formulation of Co-amoxiclav provides a total daily dose of 1500mg amoxicillin/375mg clavulanic acid, when administered as recommended below.

For children < 40 kg: This formulation of Co-amoxiclav provides a maximum daily dose of 2400mg amoxicillin/600mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Co-amoxiclav is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.
The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review.

Adults and children ≥ 40 kg: One 500mg/125mg dose taken three times a day.

Children < 40 kg: 20mg/5mg/kg/day to 60mg/15mg/kg/day given in three divided doses.
Children may be treated with Co-amoxiclav tablets, or suspensions. Children aged 6 years and below should preferably be treated with Co-amoxiclav suspension or oral drops.

FOR ORAL DROPS:
Calamox drops should be administered orally using the supplied doser. The doser is graduated to permit accurate and reproducible volumes to be dispensed. Children should be dosed according to body weight. A similar dose should be administered once every eight hours.

Weight of child (kg)	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
Volume (mL) of infant drops	0.13	0.20	0.27	0.33	0.40	0.47	0.53	0.60	0.67	0.73	0.80	0.87	0.93	1.00	1.07	1.14	1.20	1.27	1.34

Direction for Reconstitution (for Drops): Add a small quantity of pre-boiled cool water in the bottle and shake well, then add more water upto the mark given on the label and shake well to make suspension.

Elderly
No dose adjustment is considered necessary.

Renal impairment
Dose adjustments are based on the maximum recommended level of amoxicillin. No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30mL/min.

Adults and children ≥ 40 kg
CrCl: 10-30mL/min: 500mg/125mg twice daily
CrCl < 10mL /min: 500mg/125mg once daily
Hemodialysis: 500mg/125mg every 24 hours, plus 500mg/125mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg:
CrCl: 10-30mL/min: 15mg/3.75mg/kg twice daily (maximum 500mg/125mg twice daily).
CrCl < 10mL/min: 15mg/3.75mg/kg as a single daily dose (maximum 500mg/125mg).
Hemodialysis: 15mg/3.75mg/kg per day once daily.
Prior to hemodialysis 15mg/3.75mg/kg. In order to restore circulating drug levels, 15mg/3.75mg per kg should be administered after hemodialysis.

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals

Method of administration
Co-amoxiclav is for oral use.
Administer at the start of a meal to minimize potential gastrointestinal intolerance and optimize absorption of amoxicillin/clavulanic acid.

Contraindications
- Hypersensitivity to the active substances, to any of the penicillins.
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

Special warnings and precautions for use
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.
Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate. DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug use) in the absence of allergic skin or respiratory symptoms
In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with physician advice.
Convulsions may occur in patients with impaired renal function or in those receiving high doses.
Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.
Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.
Prolonged use may occasionally result in overgrowth of non-susceptible organisms.
The occurrence at the treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP). This reaction requires Co-amoxiclav discontinuation and contraindicates any subsequent administration of amoxicillin.
Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.
Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.
Periodic assessment of organ system functions, including renal, hepatic and hematopoietic function is advisable during prolonged therapy.
Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.
In patients with renal impairment, the dose should be adjusted according to the degree of impairment. In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.
The presence of Clavulanic acid in Co-amoxiclav may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Interaction with other medicinal products and other forms of interaction
Oral anticoagulants
If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Pregnancy and lactation
Pregnancy: Use should be avoided during pregnancy, unless considered essential by the physician.
Lactation: Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

Undesirable effects
The following terminologies have been used in order to classify the occurrence of undesirable effects. Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available patient)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leukopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time	Not known
Immune system disorders	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Cardiac disorders	
Kounis syndrome	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions	Not known
Aseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis	Not known
Black hairy tongue	Not known
Drug-induced enterocolitis syndrome	Not known
Tooth discoloration	Not known
Pancreatitis acute	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT	Uncommon
Hepatitis	Not known
Cholestatic jaundice	Not known
Skin and subcutaneous tissue disorders	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)	Not known
Linear IgA disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury)	Not known

Overdose

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxicillin/clavulanic acid can be removed from the circulation by hemodialysis

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties: Combinations of penicillins, incl. beta-lactamase inhibitors.

ATC code: J01CR02

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death. Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram negative bacteria.

Organism	**Susceptibility Breakpoints (µg /ml)**		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae	≤ 1	-	> 1
Moraxella catarrhalis	≤ 1	-	> 1
Staphylococcus aureus	≤ 2	-	> 2
Coagulase-negative staphylococci	≤ 0.25	-	> 0.25
Enterococcus	≤ 4	8	> 8
Streptococcus A, B, C, G	≤ 0.25	-	> 0.25
Streptococcus pneumoniae	≤ 0.5	1-2	> 2
Enterobacteriaceae	-	-	> 8
Gram-negative Anaerobes	≤ 4	8	> 8
Gram-positive Anaerobes	≤ 4	8	> 8
Non-species related breakpoints	≤ 2	4-8	> 8

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections.

Commonly susceptible species

Aerobic Gram-positive micro-organisms: *Enterococcus faecalis, Gardnerella vaginalis, Staphylococcus aureus (methicillin-susceptible), Coagulase-negative staphylococci (methicillin-susceptible), Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes and other beta-hemolytic streptococci, Streptococcus viridans* group

Aerobic Gram-negative micro-organisms: *Capnocytophaga spp., Eikenella corrodens, Haemophilus influenzae, Moraxella catarrhalis, Pasteurella multocida*

Anaerobic micro-organisms: *Bacteroides fragilis, Fusobacterium nucleatum, Prevotella spp.*

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms: *Enterococcus faecium*

Aerobic Gram-negative micro-organisms: *Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris*

Inherently resistant organisms

Aerobic Gram-negative micro-organisms: *Acinetobacter sp., Citrobacter freundii, Enterobacter sp., Legionella pneumophila, Morganella morganii, Providencia spp., Pseudomonas sp., Serratia sp., Stenotrophomonas maltophilia.*

Other micro-organisms: *Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetti, Mycoplasma pneumoniae.*

Pharmacokinetic properties

Absorption: Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimized when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

Distribution: About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid. Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

Amoxicillin, like most penicillins, and clavulanic acid can be detected in breast milk.

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.

Biotransformation: Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is eliminated in urine and faces and as carbon dioxide in expired air.

Elimination: The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms. Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Co-amoxiclav 250mg/125mg or 500mg/125mg tablets.

Age
For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
No significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

PHARMACEUTICAL PROPERTIES
Incompatibilities
Not applicable

Shelf life: 2 years

Storage and Instructions:
- Protect from heat, sunlight & moisture, store below 25°C.
- The expiration date refers to the product correctly stored at the required condition.
- Once reconstituted the suspension must be stored in a refrigerator, do not freeze and use within 7 days.

Special Precautions:
- Do not take if seal is broken.
- Close the bottle properly after use.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.
- Preparation contains a penicillin.

MARKETING AUTHORIZATION HOLDER
Head Office:
Bosch Pharmaceuticals (Pvt.) Ltd.,
8, Modern Society, Tipu Sultan Road, Karachi-75350 (Pakistan)

Manufacturer:
Bosch Pharmaceuticals (Pvt.) Ltd.
221-223, Sector 23, Korangi Industrial Area, Karachi - Pakistan.

PRESENTATION:
Calamox Tablets 375mg: 1x6's in Alu Alu Blister Pack.
Calamox Tablets 625mg: 1x6's & 2x6's in Alu Alu Blister Pack.
Calamox Tablets 1g: 1x6's & 2x6's in Alu Alu Blister Pack.
Calamox for Oral Suspension 156.25mg/5mL: 60ml (after reconstitution) in 90mL Amber Glass Bottle.
Calamox for Oral Suspension 156.25mg/5mL: 90ml (after reconstitution) in 120mL Amber Glass Bottle.
Calamox for Oral Suspension 312.5mg/5mL: 60mL (after reconstitution) in 90mL Amber Glass Bottle.
Calamox for Oral Suspension 312.5mg/5mL: 90mL (after reconstitution) in 120mL Amber Glass Bottle.
Calamox DUO for Oral Suspension 457mg/5mL: Available in 35mL & 70mL packaging
Calamox Drops 62.5mg/mL: 20ml (after reconstitution) in 30mL Amber Glass Bottle

REGISTRATION / MARKETING AUTHORIZATION NUMBER
Calamox Tablets 375mg: 021509
Calamox Tablets 625mg : 021510
Calamox Tablets 1g : 026198
Calamox for Oral Suspension 156.25mg/5mL: 022968
Calamox for Oral Suspension 312.5mg/5mL: 022969
Calamox DUO for Oral Suspension 457mg/5mL: 053118
Calamox Drops 62.5mg/mL: 058393

DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
Calamox Tablets 375mg: 16-05-1998 / 15-05-2023
Calamox Tablets 625mg: 16-05-1998 / 15-05-2023
Calamox Tablets 1g: 19-09-2000 / 18-09-2023
Calamox for Oral Suspension 156.25mg/5mL: 07-01-1998 / 06-01-2023
Calamox for Oral Suspension 312.5mg/5mL: 07-01-1998 / 06-01-2023
Calamox DUO for Oral Suspension 457mg/5mL: 11-11-2008 / 10-11-2023
Calamox Drops 62.5mg/mL: 26-08-2009 / 25-08-2019

DATE OF REVISION OF THE TEXT
31-01-2024

ہدایات:-

دھوپ، گرمی اور نمی سے محفوظ ۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

صرف سیل بند بوتل خریدیں۔

احتیاط: تیار شدہ شربت ریفریجریٹر میں رکھیں

منجمد ہونے سے بچائیں اور سات دن کے اندر استعمال کرلیں۔

بچّوں کی پہنچ سے دُور رکھیں۔

استعمال کے بعد ڈھکن کو اچھی طرح بند رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
Bosch Pharmaceuticals (Pvt.) Ltd.
221-223, Sector 23, Korangi Industrial Area,
Karachi - Pakistan

PNAC LAB 168 17025 | URAS ISO 9001 | ISO 14001 SGS | ISO 45001 SGS | ISO 22000 SGS | QSCert GMP | HALAAL | Pakistan's 1st Halaal Certified