# AMOCLAN®

(Amoxicillin and Clavulanic acid)

## ACTION

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by ß-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a ß-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of ß-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated ß-lactamases frequently responsible for transferred drug resistance. The formulation of amoxicillin and clavulanic acid in Amoclan protects amoxicillin from degradation by ß-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other ß-lactam antibiotics. Thus, Amoclan possesses the properties of a broad-spectrum antibiotic and a ß-lactamase inhibitor.

## INDICATIONS

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections:

*Gram-Positive Aerobes:*

Staphylococcus aureus (ß-lactamase and non ß-lactamase producing), Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

*Gram-Negative Aerobes:*

Enterobacter species (Although most strains of Enterobacter species are resistant in vitro, clinical efficacy has been demonstrated with Amoclan in urinary tract infections caused by these organisms.

Escherichia coli (ß-lactamase and non ß-lactamase producing), Haemophilus influenzae (ß-lactamase and non ß-lactamase producing), Klebsiella species (All known strains are ß-lactamase producing.)

Moraxella catarrhalis (ß-lactamase and non ß-lactamase producing)

The following in vitro data are available, but their clinical significance is unknown.

Amoxicillin/clavulanic acid exhibits in vitro minimal inhibitory concentrations (MICs) of 2 mcg/ml or less against most (≥90%) strains of Streptococcus pneumoniae; MICs of 0.06 mcg/ml or less against most (≥90%) strains of Neisseria gonorrhoeae; MICs of 4 mcg/ml or less against most (≥90%) strains of staphylococci and anaerobic bacteria; and MICs of 8 mcg/ml or less against most (≥90%) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials. Because amoxicillin has greater in vitro activity against S. pneumoniae than does ampicillin or penicillin, the majority of S. pneumoniae strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin.

*Gram-Positive Aerobes:*

Enterococcus faecalis, Staphylococcus epidermidis (ß-lactamase and non ß-lactamase producing), Staphylococcus saprophyticus (ß-lactamase and non ß-lactamase producing), Streptococcus pneumoniae, Streptococcus pyogenes, viridans group Streptococcus

*Gram-Negative Aerobes:*

Eikenella corrodens (ß-lactamase and non ß-lactamase producing), Neisseria gonorrhoeae (ß-lactamase and non ß-lactamase producing), Proteus mirabilis (ß-lactamase and non ß-lactamase producing)

*Anaerobic Bacteria:*

Bacteroides species, including Bacteroides fragilis (ß-lactamase and non ß-lactamase producing), Fusobacterium species (ß-lactamase and non ß-lactamase producing), Peptostreptococcus specie

Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to these organisms.

These are non ß-lactamase producing organisms, and therefore, are susceptible to amoxicillin alone.

**Amoclan is indicated** in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

*Lower Respiratory Tract Infections* caused by ß-lactamase producing strains of H. influenzae and M. catarrhalis.

*Otitis Media* caused by ß-lactamase producing strains of H. influenzae and M. catarrhalis.

*Sinusitis* caused by ß-lactamase producing strains of H. influenzae and M. catarrhalis.

*Skin and Skin Structure Infections* caused by ß-lactamase producing strains of S. aureus, E. coli, and Klebsiella spp.

*Urinary Tract Infections* caused by ß-lactamase producing strains of E. coli, Klebsiella spp., and Enterobacter spp.

## DOSAGE AND ADMINISTRATION

Since both the 250 mg and 500 mg tablets of Amoclan contain the same amount of clavulanic acid (125 mg, as the potassium salt), two 250 mg tablets of Amoclan are not equivalent to one 500 mg tablet of Amoclan; therefore, two 250 mg tablets of Amoclan should not be substituted for one 500 mg tablet of Amoclan.

***Dosage:***

*Adults:* The usual adult dose is one 500 mg tablet of Amoclan every 12 hours or one 250 mg tablet of Amoclan every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one 875 mg tablet of Amoclan every 12 hours or one 500 mg tablet of Amoclan every 8 hours. Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 ml/min. should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 ml/min. should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 ml/min. glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis. Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

*Pediatric Patients:*

| Infections | Dosing regimen | |
|---|---|---|
| | Amoclan BID (q 12h) | Amoclan (q 8hr) |
| | 200 mg/5ml or 400 mg/5ml oral suspension | 125 mg/5ml (156 mg) or 250 mg/5ml (312 mg) oral suspension |
| Otitis media, sinusitis, lower respiratory tract infections and more severe infections | 22.5 mg/kg q12h | 13.3 mg/kg q8h |
| Less severe infections: strep throat, uncomplicated UTI skin & soft tissue infections | 12.5 mg/kg q12h | 6.7 mg/kg q 8h |

Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

***Administration:***

Amoclan may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when Amoclan is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, Amoclan should be taken at the start of a meal.

## CONTRAINDICATIONS

Amoclan is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Amoclan.

## WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy.

These reactions are more likely to occur in individuals with a History of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins.

Before initiating therapy with Amoclan, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, Amoclan should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Amoclan, and has ranged in severity from mild to life-threatening; therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of lantibiotic-associated colitis. After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone.

In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C. difficile colitis. Amoclan should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of Amoclan is usually reversible.

## PRECAUTIONS

*General:* While Amoclan possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas or Candida*), the drug should be discontinued and/or appropriate therapy instituted. Prescribing Amoclan in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

**Drug Interactions:**

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with Amoclan may result in increased and prolonged blood levels of amoxicillin. Coadministration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with Amoclan and allopurinol administered concurrently. In common with other broad-spectrum antibiotics, Amoclan may reduce the efficacy of oral contraceptives.

## SIDE EFFECTS

Amoclan is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose.

Other less frequently reported reactions include: abdominal discomfort, flatulence, and headache.

The following adverse reactions have been reported for ampicillin-class antibiotics:

*Gastrointestinal:* diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

*Hypersensitivity Reactions:* skin rashes, pruritus, urticaria, angioedema, serum sickness like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized exanthematous pustulosis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise.

Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin.

*Liver:* a moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been infrequently reported with Amoclan. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible.

*Renal:* interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported

*Hemic and Lymphatic Systems:* anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with Amoclan. There have been reports of increased prothrombin time in patients receiving Amoclan and anticoagulant therapy concomitantly.

*Central Nervous System:* agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

*Miscellaneous:* tooth discoloration (brown, yellow, or gray staining) has been rarely reported.

Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

## OVERDOSAGE

Following overdosage, patients have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity, or drowsiness have also been observed in a small number of patients.

In the case of overdosage, discontinue Amoclan, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adult and pediatric patients. In case of overdosage, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin crystalluria.

Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis

## STORAGE

***Tablets:*** Store in a dry place, between 15-25°C.

***Suspension:*** Store the powder in a dry place between 15-25°C. After reconstitution, keep in refrigerator and use within seven days.

## PRESENTATIONS

***Tablets***

| | |
|---|---|
| Amoclan BID (1g): | Amoxicillin (as trihydrate) USP 875 mg and Clavulanic acid (as potassium) USP 125 mg |
| Amoclan FORTE (625 mg): | Amoxicillin (as trihydrate)USP 500 mg and Clavulanic acid (as potassium) USP 125 mg |
| Amoclan (375 mg): | Amoxicillin (as trihydrate) USP 250 mg and Clavulanic acid (as potassium) USP 125 mg |

***Suspension***

| | |
|---|---|
| Amoclan BID (400 mg/5 ml): | Amoxicillin (as trihydrate) USP 400 mg and Clavulanic acid (as potassium) USP 57.1 mg* |
| Amoclan BID (200 mg/5 ml): | Amoxicillin (as trihydrate) USP 200 mg and Clavulanic acid (as potassium) USP 28.5 mg* |
| Amoclan FORTE (312 mg/5ml): | Amoxicillin (as trihydrate) USP 250 mg and Clavulanic acid (as potassium) USP 62.5 mg* |
| Amoclan (156 mg/5ml): | Amoxicillin (as trihydrate) USP 125 mg and Clavulanic acid (as potassium) USP 31.25 mg* |

** per 5 ml (after reconstitution)*

**THIS IS A MEDICAMENT**

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

HIKMA Pharmaceuticals, Amman-Jordan

Keep medicament out of the reach of children

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