

NOVACLOX Capsules (Amoxicillin + Dicloxacillin)

Composition

NOVACLOX Capsule

Each capsule contains

Amoxicillin Trihydrate IP equivalent to Amoxicillin250 mg

Dicloxacillin sodium IP equivalent to Dicloxacillin.....250 mg

Dosage Form

Capsules

Pharmacology

NOVACLOX is a combination of two beta-lactam antibiotics, amoxicillin and dicloxacillin, and lactobacillus. They exert their bactericidal action by inhibition of cell wall synthesis. Amoxicillin is active against a wide range of Gram-positive and Gram-negative pathogens, and dicloxacillin acts against penicillinase-producing Gram-positive pathogens.

Microbiology

Amoxicillin is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections:

Aerobic Gram-positive Microorganisms

Enterococcus faecalis

*Staphylococcus spp.** (beta-lactamase-negative strains only)

Streptococcus pneumoniae

Streptococcus spp. (alpha- and beta-haemolytic strains only)

* Staphylococci that are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

Aerobic Gram-negative Microorganisms

Escherichia coli (beta-lactamase-negative strains only)

Haemophilus influenzae (beta-lactamase-negative strains only)

Neisseria gonorrhoeae (beta-lactamase-negative strains only)

Proteus mirabilis (beta-lactamase-negative strains only)

Helicobacter

Helicobacter pylori

Lactobacillus acidophilus therapy in the prevention and adjuvant therapy of certain infectious diseases, especially gastrointestinal disorders in children and adults, is advocated in many parts of the world. The recent emphasis on supplementation with lactobacilli is largely attributed to information obtained regarding the beneficial effects of lactobacilli in preventing or minimizing the severity of antibiotic-associated diarrhoeal episodes. Most probiotics have been designated as "generally recognized as safe" (GRAS).

Pharmacokinetics

Amoxicillin

Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. The effect of food on the absorption of amoxicillin from amoxicillin tablets and amoxicillin suspension has been partially investigated. The 400 mg and 875 mg formulations have been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 200 mg and 500 mg formulations. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. In blood serum, amoxicillin is approximately 20% protein-bound.

Orally administered doses of 250 mg and 500 mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 3.5 mcg/mL to 5 mcg/mL and 5.5 mcg/mL to 7.5 mcg/mL, respectively.

Mean amoxicillin pharmacokinetic parameters from an open, two-part, single-dose crossover bioequivalence study in 27 adults comparing 875 mg of amoxicillin with 875 mg of amoxicillin/clavulanate potassium showed that the 875 mg tablet of amoxicillin produces an $AUC_{0-\infty}$ of 35.4 ± 8.1 mcg•hr/mL and a C_{max} of 13.8 ± 4.1 mcg/mL. Dosing was at the start of a light meal following an overnight fast.

Orally administered doses of amoxicillin suspension, 125 mg/5 mL and 250 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 1.5 mcg/mL to 3 mcg/mL and 3.5 mcg/mL to 5 mcg/mL, respectively.

Oral administration of single doses of 400 mg amoxicillin chewable tablets and 400 mg/5 mL suspension to 24 adult volunteers yielded comparable pharmacokinetic data:

Dose†	$AUC_{0-\infty}$ (mcg•hr/mL)	C_{max} (mcg/mL)‡
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Amoxycillin	Amoxycillin (± S.D.)	Amoxycillin (±S.D.)
400 mg (5 mL of suspension)	17.1 (3.1)	5.92 (1.62)
400 mg (1 chewable tablet)	17.9 (2.4)	5.18 (1.64)

†Administered at the start of a light meal.

‡Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxycillin. Following a 1-gram dose and utilizing a special skin window technique to determine levels of the antibiotic, it was noted that therapeutic levels were found in the interstitial fluid. Approximately 60% of an orally administered dose of amoxycillin is excreted in the urine within 6 to 8 hours.

Dicloxacillin

Absorption ranges from 35 to 76%; rate and extent is reduced by food. It is distributed throughout the body, with the highest concentrations in the kidneys and liver; cerebrospinal fluid (CSF) penetration is low; it crosses the placenta, and also enters breast milk. Protein binding is 96%. Half-life elimination is 0.6 to 0.8 hours; this is slightly prolonged with renal impairment. Time to peak, serum is 0.5 to 2 hours. It is excreted in the faeces and urine (56 to 70% as unchanged drug).

Indications

Respiratory Tract Infections

Tonsillar abscess, otitis media, suppurative sinus infection, acute chronic bronchitis, bronchiectasis, bronchopneumonia, pleurisy, empyema, lung abscess, emphysema, bronchiolitis.

Urinary Tract Infections

Acute and chronic pyelonephritis, cystitis, urethritis.

Skin and Soft Tissue Infections

Recurrent boils, carbuncles, impetigo, cellulitis and other infected dermatoses.

Bone Infections

Osteomyelitis and septic arthritis.

Serious Infections

Septicaemia, bacterial endocarditis, brain abscess and bacterial meningitis.

Dosage And Administration

The dosage differs depending on the type, site and severity of infections. It is usually given as one capsule three to four times daily.

In impaired renal function, the dosage should be modified in patients with severe renal impairment, by increasing the intervals between doses. With a creatinine clearance between 10 and 50 ml/min, the dosing interval can be up to 12 hours. If the clearance is less than 10 ml/min, the interval can be 16 hours.

Contraindications

A history of allergic reaction to any of the penicillins is a contraindication.

Warnings And Precautions

Serious, and occasionally fatal, hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. 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 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 amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and 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.

Clostridium difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including amoxicillin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of "*C. difficile*" cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against "*C. difficile*" may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of "*C. difficile*", and surgical evaluation should be instituted as clinically indicated.

General

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If super infections occur, amoxycillin should be discontinued and appropriate therapy instituted.

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.

Prescribing amoxycillin capsules, amoxycillin tablets, and amoxycillin for oral suspension 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.

Laboratory Tests

As with any potent drug, periodic assessment of renal, hepatic and haematopoietic function should be made during prolonged therapy.

All patients with gonorrhoea should have a serologic test for syphilis at the time of diagnosis. Patients treated with amoxycillin should have a follow-up serologic test for syphilis after 3 months.

Information for Patients

Amoxycillin may be taken every 8 hours or every 12 hours, depending on the strength of the product prescribed.

Patients should be counselled that antibacterial drugs, including amoxycillin capsules, amoxycillin tablets, and amoxycillin for oral suspension should only be used to treat bacterial infections. They do not treat viral infections (e.g. the common cold). When amoxycillin capsules, amoxycillin tablets, and amoxycillin for oral suspension are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by amoxycillin capsules, amoxycillin tablets, and amoxycillin for oral suspension or other antibacterial drugs in the future.

Diarrhoea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes, after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions

Probenecid decreases the renal tubular secretion of amoxycillin. Concurrent use of amoxycillin and probenecid may result in increased and prolonged blood levels of amoxycillin.

Chloramphenicol, macrolides, sulphonamides and tetracyclines may interfere with the bactericidal effects of penicillin. This has been demonstrated *in vitro*; however, the clinical significance of this interaction is not well documented.

In common with other antibiotics, amoxicillin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral oestrogen/progesterone contraceptives.

Drug/Laboratory Test Interactions

High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using CLINITEST[®], Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX[®]) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone, and oestradiol has been noted. This effect may also occur with amoxicillin.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in mice and rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of the infants. Caution should be exercised when amoxicillin is administered to a nursing mother.

Pediatric Use

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of amoxicillin should be modified in paediatric patients 12 weeks or younger (≤ 3 months).

Geriatric Use

An analysis of clinical studies of amoxicillin was conducted to determine whether subjects aged ≥ 65 years and over respond differently from younger subjects. Of the 1,811 subjects treated with capsules of amoxicillin, 85% were < 60 years old, 15% were ≥ 61 years old and 7% were ≥ 71 years old. This analysis and other reported clinical experience have not identified differences in responses between the elderly and younger patients, but a greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. 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.

Undesirable Effects

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of penicillins:

Infections and Infestations:Mucocutaneous candidiasis.

Gastrointestinal: Nausea, vomiting, diarrhoea, black hairy tongue, and haemorrhagic/pseudomembranous colitis.

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

Hypersensitivity Reactions:Anaphylaxis Serum sickness-like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematouspustulosis, hypersensitivity vasculitis and urticaria have been reported.

Note: These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to amoxicillin therapy.

Liver:A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction, including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis,hasbeen reported.

Renal:Crystalluria has also been reported

Haemic and Lymphatic Systems:Anaemia, including haemolytic anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia, and agranulocytosishave been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System:Reversible hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness have been reported rarely.

Miscellaneous:Tooth discolouration (brown, yellow, or grey staining) has been rarely reported. Most reports occurred in paediatric patients. Discolouration was reduced or eliminated with brushing or dental cleaning in most cases.

Combination Therapy with Clarithromycin and Lansoprazole:In clinical trials using combination therapy with amoxicillin plus clarithromycin and lansoprazole, and amoxicillin plus lansoprazole, no adverse reactions

peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with amoxicillin, clarithromycin, or lansoprazole.

Triple Therapy:Amoxicillin/Clarithromycin/Lansoprazole: The most frequently reported adverse events for patients who received triple therapy were diarrhoea (7%), headache (6%), and taste perversion (5%). No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy:Amoxicillin/Lansoprazole:The most frequently reported adverse events for patients who received amoxicillin three times daily plus lansoprazole three times daily dual therapy were diarrhoea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with amoxicillin three times daily plus lansoprazole three times daily dual therapy than with lansoprazole alone.

For more information on adverse reactions with clarithromycin or lansoprazole, refer to the ADVERSE REACTIONS section in their package inserts.

Overdosage

In case of overdosage, discontinue medication, 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 paediatric patients at a poison-control centre 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 paediatric 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 amoxicillin. Amoxicillin may be removed from circulation by haemodialysis.

Storage And Handling Instructions

Store in a cool dry place

Packaging Information

NOVACLOX: Strip pack of 9 capsules

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NOVACLOX Capsules

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