AMOXICILLIN AND CLAVULANATE POTASSIUM - amoxicillin and clavulanate potassium tablet, film coated
State of Florida DOH Central Pharmacy

Amoxicillin and Clavulanate Potassium Tablets, USP

AMOXICILLIN, 500 mg, as the trihydrate and CLAVULANIC ACID, 125 mg, as clavulanate potassium; or

AMOXICILLIN, 875 mg, as the trihydrate and CLAVULANIC ACID, 125 mg, as clavulanate potassium

Rx only

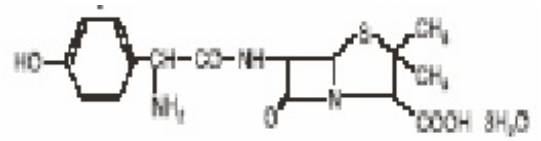
PRESCRIBING

INFORMATION

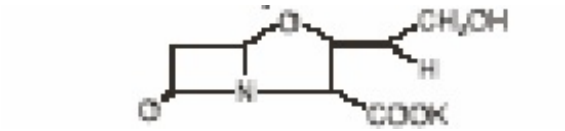
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Amoxicillin and Clavulanate Potassium Tablets, USP and other antibacterial drugs, Amoxicillin and Clavulanate Potassium Tablets, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Amoxicillin and Clavulanate Potassium Tablet USP is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ and the molecular weight is 419.46. Chemically, amoxicillin is *(2S, 5R, 6R)*-6-[(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate and may be represented structurally as:



Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$ and the molecular weight is 237.25. Chemically, clavulanate potassium is potassium (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate, and may be represented structurally as:



Each film coated tablet contains 500 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the

potassium salt or 875 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt. In addition, each 500 mg/125 mg and 875 mg/125 mg amoxicillin and clavulanate potassium tablet contains 0.63 mEq potassium.

Inactive Ingredients: Colloidal silicon dioxide, croscarmellose sodium dried, crospovidone dried, ethylcellulose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose dried, polysorbate 80, talc, titanium dioxide, triethyl citrat.

CLINICAL PHARMACOLOGY

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of amoxicillin/clavulanate potassium. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin/clavulanate potassium can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In 1 study, the relative bioavailability of clavulanate was reduced when amoxicillin/clavulanate potassium was dosed at 30 and 150 minutes after the start of a high-fat breakfast. The safety and efficacy of amoxicillin/clavulanate potassium have been established in clinical trials where amoxicillin/clavulanate potassium was taken without regard to meals.

Mean* amoxicillin and clavulanate potassium pharmacokinetic parameters are shown in the table below:

Dose† and regimen	AUC_{0-24} (mcg·hr/mL)		C_{max} (mcg/mL)	
amoxicillin/clavulanate potassium	amoxicillin (± S.D.)	clavulanate potassium (± S.D.)	amoxicillin (± S.D.)	clavulanate potassium (± S.D.)
250/125 mg q8h	26.7 ± 4.56	12.6 ±3.25	3.3 ± 1.12	1.5 ± 0.70
500/125 mg q12h	33.4 ± 6.76	8.6 ± 1.95	6.5 ± 1.41	1.8 ± 0.61
500/125 mg q8h	53.4 ± 8.87	15.7 ± 3.86	7.2 ± 2.26	2.4 ± 0.83
875/125 mg q12h	53.5 ± 12.31	10.2 ± 3.04	11.6 ± 2.78	2.2 ± 0.99

*Mean values of 14 normal volunteers (n=15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.

† Administered at the start of a light meal.

Amoxicillin serum concentrations achieved with amoxicillin/clavulanate potassium are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half-life of amoxicillin after the oral administration of amoxicillin/clavulanate potassium is 1.3 hours and that of clavulanic acid is 1.0 hour.

Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 250-mg or 500-mg tablet of amoxicillin/clavulanate potassium.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Neither component in amoxicillin/clavulanate potassium is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal

fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

Microbiology

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 β-lactamases and, therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance.

The formulation of amoxicillin and clavulanic acid in amoxicillin/clavulanate potassium protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics. Thus, amoxicillin/clavulanate potassium possesses the properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Gram-Positive Aerobes:

Staphylococcus aureus (β-lactamase and non-β-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 amoxicillin/clavulanate potassium in urinary tract infections caused by these organisms.)

Escherichia coli (β-lactamase and non-β-lactamase producing)

Haemophilus influenzae (β-lactamase and non-β-lactamase producing)

Klebsiella species (All known strains are β-lactamase producing.)

Moraxella catarrhalis (β-lactamase and non-β-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[II]

Staphylococcus epidermidis (β-lactamase and non-β-lactamase producing)

Staphylococcus saprophyticus (β-lactamase and non-β-lactamase producing)

Streptococcus pneumoniae [II¶] ,

Streptococcus pyogenes [II¶]

viridans group *Streptococcus* [II¶]

Gram-Negative Aerobes:

Eikenella corrodens (β-lactamase and non-β-lactamase producing)

Neisseria gonorrhoeae [II] (β-lactamase and non-β-lactamase producing)

Proteus mirabilis [II] (β-lactamase and non-β-lactamase producing)

Anaerobic Bacteria:

Bacteroides species, including *Bacteroides fragilis* (β-lactamase and non-β-lactamase producing)

Fusobacterium species (β-lactamase and non-β-lactamase producing)

Peptostreptococcus species[¶]

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

[¶] Those are non-β-lactamase-producing organisms and, therefore, are susceptible to amoxicillin alone.

Susceptibility Testing:

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). Those MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For Gram-Negative Enteric Aerobes:	
MIC (mcg/mL)	Interpretation
≤ 8/4	Susceptible (S)
16/8	Intermediate (I)
≥ 32/16	Resistant (R)
For *Staphylococcus* and *Haemophilus* species:**	
MIC (mcg/mL)	Interpretation
≤ 4/2	Susceptible (S)
≥ 8/4	Resistant (R)

**Staphylococci which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

For *Streptococcus pneumoniae* from non-meningitis sources:

Isolates should be tested using amoxicillin/clavulanic acid and the following criteria should be used:

MIC (mcg/mL)	Interpretation
≤ 2/1	Susceptible (S)
4/2	Intermediate (I)
≥ 8/4	Resistant (R)

Note: These interpretive criteria are based on the recommended doses for respiratory tract infections.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard amoxicillin/clavulanate potassium powder should provide the following MIC values:

Microorganism	MIC Range (mcg/mL) ††	
Escherichia coli	ATCC 25922	2 to 8
Escherichia coli	ATCC 35218	4 to 16
Enterococcus faecalis	ATCC 29212	0.25 to 1.0
Haemophilus influenzae	ATCC 49247	2 to 16
Staphylococcus aureus	ATCC 29213	0.12 to 0.5
Streptococcus pneumoniae	ATCC 49619	0.03 to 0.12

††Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) disk should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For *Staphylococcus*‡‡ species and *H.influenzae*[a]

Zone Diameter (mm)	Interpretation
≥ 20	Susceptible (S)
≤ 19	Resistant (R)

For Other Organisms Except *S. pneumoniae*[b] and *N. gonorrhoeae*[c]

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
14 to 17	Intermediate (I)
≤ 13	Resistant (R)

‡‡ Staphylococci which are resistant to methicillin/oxacillin must be considered as resistant to amoxicillin/clavulanic acid.

a A broth microdilution method should be used for testing *H. influenzae*. Beta-lactamase negative, ampicillin-resistant strains must be considered resistant to amoxicillin/clavulanic acid.

b Susceptibility of *S. pneumoniae* should be determined using a 1-mcg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin/clavulanic acid. An amoxicillin/clavulanic acid MIC should be determined on isolates of *S.pneumoniae* with oxacillin zone sizes of ≤19 mm.

c A broth microdilution method should be used for testing *N. gonorrhoeae* and interpreted according to penicillin breakpoints.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for amoxicillin/clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-mcg amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10-mcg clavulanate potassium) disk should provide the following zone diameters in these laboratory quality control strains.

Microorganism	Zone Diameter (mm)
Escherichia coli	
ATCC 25922	19 to 25
Escherichia coli	
ATCC 35218	18 to 22
Staphylococcus aureus	
ATCC 25923	28 to 36

INDICATIONS AND USAGE

Amoxicillin/clavulanate potassium 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 β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis.*

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

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

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

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

While amoxicillin/clavulanate potassium is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to amoxicillin/clavulanate potassium treatment due to its amoxicillin content, therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to amoxicillin/clavulanate potassium should not require the addition of another antibiotic. 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 and amoxicillin/clavulanate potassium. (See **Microbiology.**)

To reduce the development of drug-resistant bacteria and maintain the effectivness of amoxicillin/clavulanate potassium and other antibacterial drugs, amoxicillin/clavulanate potassium should be used only to treat or prevent infections, that are proven or strongly suspected to be caused by susceptible bacteria.When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Bacteriological studies, to determine the causative organisms and their susceptibility to amoxicillin/clavulanate potassium, should be performed together with any indicated surgical procedures.

CONTRAINDICATIONS

Amoxicillin/clavulanate potassium 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 amoxicillin/clavulanate potassium.

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 AMOXICILLIN/CLAVULANATE POTASSIUM, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN/CLAVULANATE POTASSIUM 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 amoxicillin/clavulanate potassium, 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 “antibiotic 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.

Amoxicillin/clavulanate potassium should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin/clavulanate potassium is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See **CONTRAINDICATIONS and ADVERSE REACTIONS -*Liver***.)

PRECAUTIONS

General

While amoxicillin/clavulanate potassium 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 amoxicillin/clavulanate potassium 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 resistance bacteria.

Drug Interactions

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin/clavulanate potassium 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 amoxicillin/clavulanate potassium and allopurinol administered concurrently.

In common with other broad-spectrum antibiotics, amoxicillin/clavulanate potassium may reduce the efficacy of oral contraceptives.

Drug/Laboratory Test Interactions

Oral administration of amoxicillin/clavulanate potassium will result in high urine concentrations of amoxicillin. 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 and therefore amoxicillin/clavulanate potassium, 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 estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This

effect may also occur with amoxicillin and therefore amoxicillin/clavulanate potassium.

Information for Patients:

Patients should be counseled that antibacterial drugs including amoxicillin/clavulanate potassium, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When amoxicillin/clavulanate potassium is 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 effectivness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by amoxicillin/clavulanate potassium or other antibacterial drugs in the future.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis:

The mutagenic potential of amoxicillin/clavulanate potassium was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.

Impairment of Fertility:

Amoxicillin/clavulanate potassium at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m^2/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Teratogenic effects. *Pregnancy (Category B):*

Reproduction studies performed in pregnant rats and mice given amoxicillin/clavulanate potassium at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m^2/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to amoxicillin/clavulanate potassium. 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.

Labor and Delivery:

Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions; however, it is not known whether the use of amoxicillin/clavulanate potassium in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with amoxicillin/clavulanate potassium may be associated with an increased risk of necrotizing enterocolitis in neonates.

Nursing Mothers:

Ampicillin-class antibiotics are excreted in the milk; therefore, caution should be exercised when amoxicillin/clavulanate potassium is administered to a nursing woman.

Pediatric Use:

Pediatric patients weighing 40 Kg or more should be dosed according to the adult recommendations (see **DOSAGE AND ADMINISTRATION: Pediatric Patients**). Safety and effectiveness of Amoxicillin and Clavulanate Potassium Tablets in pediatric patients weighing less than 40 kg have not

been established. (See prescribing information for Amoxicillin and Clavulanate Powder for Oral Suspension and Chewable Tablets).

Geriatric Use:

An analysis of clinical studies of Amoxicillin and Clavulanate Potassium Tablets was conducted to determine whether subjects aged 65 and over respond differently from younger subjects. Of the 3,119 patients in this analysis, 68% were < 65 years old, 32% were ≥ 65 years old and 14% were ≥ 75 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 kidney, 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.

ADVERSE REACTIONS

Amoxicillin/clavulanate potassium 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 “hairy” tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See **WARNINGS**.)

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. (See WARNINGS.)

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 amoxicillin/clavulanate potassium. It has been reported more commonly in 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. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions

worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal

Interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported (see **OVERDOSAGE**).

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 amoxicillin/clavulanate potassium. There have been rare reports of increased prothrombin time in patients receiving amoxicillin/clavulanate potassium 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 occured in pediatric patients. Discolorations 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 amoxicillin/clavulanate potassium, 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.[3] 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. (See **DOSAGE AND ADMINISTRATION** for recommended dosing for patients with impaired renal function.)

DOSAGE AND ADMINISTRATION

Since both the Amoxicillin and Clavulanate Potassium Tablets, 250 mg/125 mg and 500 mg/125 mg contain the same amount of clavulanic acid (125 mg, as the potassium salt), two Amoxicillin and Clavulanate Potassium Tablets 250 mg/125 mg are not equivalent to one Amoxicillin and

Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium); therefore, two Amoxicillin and Clavulanate Potassium Tablets 250 mg/125 mg should not be substituted for one Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as thetrihydrate and clavulanic acid, 125 mg, as clavulanate potassium)
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Dosage

Adults

The usual adult dose is one Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium) every 12 hours or one Amoxicillin and Clavulanate Potassium Tablet 250 mg/125 mg every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 875 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium) every 12 hours or one Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium) 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/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg/125 mg or 250 mg/125 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg/125 mg or 250 mg/125 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg/125 mg or 250 mg/125 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. (See **WARNINGS**.)

Pediatric Patients

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

Due to the different amoxicillin to clavulanic acid ratios in the Amoxicillin and Clavulanate Potassium Tablet 250 mg/125 mg versus the Amoxicillin and Clavulanate Potassium Chewable Tablet 250 mg/62.5, the Amoxicillin and Clavulanate Potassium Tablet 250 mg/125 mg should not be used until the pediatric patient weighs at least 40 kg or more.

Administration

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

HOW SUPPLIED

Amoxicillin and Clavulanate Potassium Tablets, USP 500/125 mg are white to off-white, oblong film coated tablets with beveled edges, debossed with 500/125 on one side and AMC on the other side.

Amoxicillin and Clavulanate Potassium Tablets, USP 875/125 mg are white to off-white, oblong film coated tablets with beveled edges, scored and debossed with 875/125 on one side and AMC on the other side.

They are supplied by **State of Florida DOH Central Pharmacy** as follows:

NDC	Strength	Quantity/Form	Color	Source Prod. Code
53808-0740-1	875 mg / 125 mg	1 Tablet in a Dose Pack, 30 Dose Packs in a Carton	WHITE	66685-1001

Store tablets at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature]. Dispense in tightly closed, moisture-proof containers.

CLINICAL STUDIES

Data from 2 pivotal studies in 1.191 patients treated for either lower respiratory tract infections or complicated urinary tract infections compared a regimen of 875 mg/125 mg amoxicillin/clavulanate potassium tablets q12h to 500 mg/125 mg amoxicillin/clavulanate potassium tablets dosed q8h (584 and 607 patients, respectively). Comparable efficacy was demonstrated between the q12h and q8h dosing regimens. There was no significant difference in the percentage of adverse events in each group. The most frequently reported adverse event was diarrhea; incidence rates were similar for the 875 mg/125 mg q12h and 500 mg/125 mg q8h dosing regimens (14.9% and 14.3%, respectively); however, there was a statistically significant difference ($p<0.05$) in rates of severe diarrhea or withdrawals with diarrhea between the regimens: 1.0% for 875 mg/125 mg q12h dosing versus 2.5% for the 500 mg/125 mg q8h dosing.

In one of these pivotal studies, 629 patients with either pyelonephritis or a complicated urinary tract infection (*i.e.*, patients with abnormalities of the urinary tract that predispose to relapse of bacteriuria following eradication) were randomized to receive either 875 mg/125 mg amoxicillin/clavulanate potassium tablets q12h or 500 mg/125 mg amoxicillin/clavulanate potassium tablets q8h in the following distribution:

	875 mg/125 mg q12 h	**500 mg/125 mg q8h**
Pyelonephritis	173 patients	188 patients
Complicated UTI	135 patients	133 patients
Total patients	308	321

The number of bacteriologically evaluable patients was comparable between the two dosing regimens. Amoxicillin/clavulanate potassium produced comparable bacteriological success rates in patients assessed 2 to 4 days immediately following end of therapy. The bacteriologic efficacy rates were comparable at one of the follow-up visits (5 to 9 days post-therapy) and at a late post-therapy visit (in the majority of cases, this was 2 to 4 weeks post-therapy), as seen in the table below:

	875 mg/125 mg q12h	**500 mg/125 mg q8h**
2 to 4 days	81%, n=58	80%, n=54
5 to 9 days	58.5%, n=41	51.9%, n=52
2 to 4 weeks	52.5%, n=101	54.8%, n=104

As noted before, though there was no significant difference in the percentage of adverse events in each group, there was a statistically significant difference in rates of severe diarrhea or withdrawals with diarrhea between the regimens.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25. NCCLS, Villanova, PA, December 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24. NCCLS, Villanova, PA, December 1993.

3. Swanson-Biearman B, Dean BS, Lopez G, Krenzelok EP. The effects of penicillin and cephalosporin ingestions in children less than six years of age. *Vet Hum Toxicol* 1988;30:66-67.

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Manufactured in Slovenia

By Lek Pharmaceuticals d.d.

Distributed by Lek Pharmaceuticals Inc.

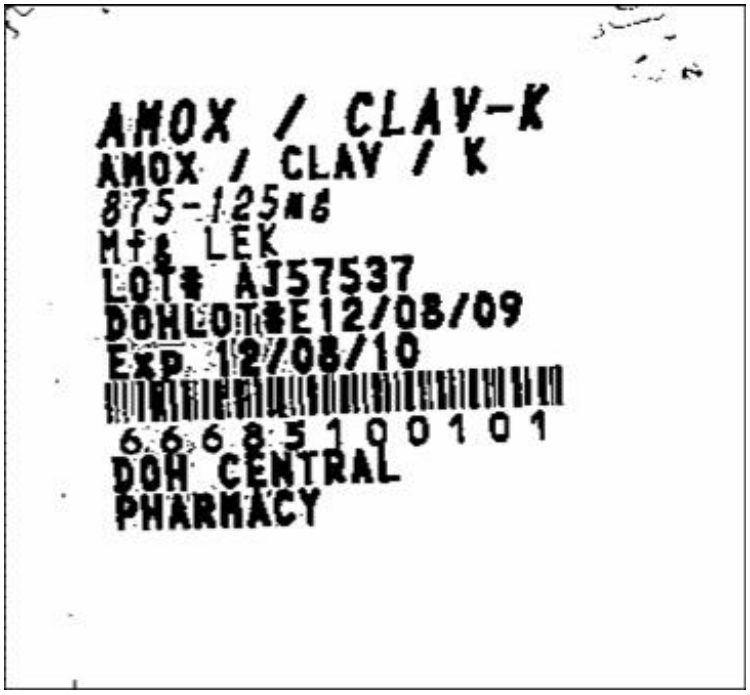
An affiliate of Sandoz Inc.,

Princeton, NJ 08540

This Product was Repackaged By:

State of Florida DOH Central Pharmacy
104-2 Hamilton Park Drive
Tallahassee, FL 32304
United States

Label Image for 875/125mg



AMOXICILLIN AND CLAVULANATE POTASSIUM

amoxicillin and clavulanate potassium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:53808-0740(NDC:66685-1001)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMOXICILLIN (UNII: 804826J2HU) (AMOXICILLIN - UNII:804826J2HU)	AMOXICILLIN	875 mg
CLAVULANATE POTASSIUM (UNII: Q42OMW3AT8) (CLAVULANIC ACID - UNII:23521W1S24)	CLAVULANATE POTASSIUM	125 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
CROSPOVIDONE (UNII: 68401960MK)	
ETHYLCELLULOSE (UNII: 7Z8S9VYZ4B)	
HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	

Product Characteristics

Color	white (WHITE)	**Score**	no score
Shape	OVAL (OVAL)	**Size**	13mm
Flavor		**Imprint Code**	875;125;AMC
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:53808-0740-1	30 in 1 CARTON		
1		1 in 1 DOSE PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065093	07/01/2009	

Labeler - State of Florida DOH Central Pharmacy (829348114)

Establishment

Name	Address	ID/FEI	Business Operations
State of Florida DOH Central Pharmacy		829348114	repack

Revised: 6/2010

State of Florida DOH Central Pharmacy