

AMOXICILLIN AND CLAVULANATE (Veterinary—Systemic)

A commonly used *brand name* for a veterinary-labeled product is *Clavamox*.

Note: For a listing of dosage forms and brand names by country availability, see the *Dosage Forms* sections(s).

Category: Antibacterial (systemic).

Indications

Note: Text between ^{EL,US} and ^{EL} describes uses not included in U.S. product labeling. Text between ^{EL,CAN} and ^{EL} describes uses not included in Canadian product labeling.

The ^{EL,US} or ^{EL,CAN} designation may signify a lack of product availability in the country indicated. See the *Dosage Forms* section of this monograph to confirm availability.

General considerations

Amoxicillin has activity against penicillin-sensitive gram-positive bacteria as well as some gram-negative bacteria. The gram-positive spectrum of activity includes alpha- and beta-hemolytic streptococci, some *Staphylococci* species, *Clostridia* species, and some *Bacillus anthracis*.^(R-2) Amoxicillin is also effective against gram-negative bacteria, including *Escherichia coli* (*E. coli*), many strains of *Salmonella*, and *Pasteurella multocida*.^(R-2) Amoxicillin is sensitive to destruction by beta-lactamases and therefore when administered by itself is not effective against bacteria, such as *Klebsiella* and *Proteus*, that produce these enzymes.^(R-2)

Clavulanate is a naturally occurring noncompetitive inhibitor of beta-lactamase produced by gram-positive, and also many gram-negative, bacteria.^(R-3; 4) Although it has a beta-lactam chemical structure, clavulanic acid has little antibacterial activity of its own. However, when clavulanic acid is administered concurrently with amoxicillin, it extends the activity of amoxicillin by preventing its destruction by bacterial enzymes. Beta-lactamase inhibitors will only assist in the destruction of bacteria that produce beta-lactamase enzymes; other forms of resistance, such as alteration of penicillin-binding protein, are not affected. Also, the beta-lactam structure of amoxicillin and clavulanate may stimulate some bacteria to produce more beta-lactamase; it is easier for clavulanate to protect amoxicillin against a small amount of enzyme than against a large amount.

Clavulanate extends the spectrum of activity of amoxicillin to include beta-lactamase producing *E. coli*, *Klebsiella*, *Proteus*, and *Staphylococcus* species.^(R-4; 6) Most anaerobes, including *Bacterioides fragilis*, are susceptible to the combination of clavulanic acid and amoxicillin.^(R-5) However, some beta-lactamase enzymes, including those produced by *Enterobacter* and *Pseudomonas*, are unaffected by clavulanate.^(R-6)

Accepted

Periodontal infections (treatment)—*Dogs*: Amoxicillin and clavulanate combination is indicated in the treatment of periodontal infections caused by susceptible strains of aerobic and anaerobic bacteria.^(R-1; 7-10; 31)

Skin and soft tissue infections (treatment)—*Cats and dogs*: Amoxicillin and clavulanate combination is indicated in the treatment of skin and soft tissue infections caused by susceptible *Staphylococcus* species, *E. coli*, *Pasteurella* species, and *Streptococcus* species.^(R-7-10)

Urinary tract infections, bacterial (treatment)—*Cats and dogs*^{EL}: Amoxicillin and clavulanate combination is indicated in the treatment of urinary tract infections, including those caused by susceptible *E. coli*.^(R-7-11)

Potentially effective

^{EL,US,CAN} Osteomyelitis (treatment)^{EL}—*Cats and dogs*: There are insufficient data to show that amoxicillin and clavulanate combination is effective in the treatment of osteomyelitis in cats and dogs; however, *in vitro* studies show that the bacteria causing this type of infection are often susceptible.^(R-32-34; 37)

Chemistry

Source:

Amoxicillin—Semisynthetic derivative of ampicillin.^(R-12)

Clavulanate—A fermentation product of the actinomycete *Streptomyces clavuligerus*.^(R-7; 8)

Chemical name:

Amoxicillin—4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, trihydrate[2*S*-[2α,3α,5β(5*S**)]]-.^(R-13)

Clavulanate potassium—4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt, [2*R*-(2α,3α,5α)]-.^(R-13)

Molecular formula:

Amoxicillin—C₁₆H₁₉N₃O₅S·3H₂O.^(R-13)

Clavulanate potassium—C₈H₈KNO₅.^(R-13)

Molecular weight:

Amoxicillin—419.45.^(R-13)

Clavulanate potassium—237.25.^(R-13)

Description:

Amoxicillin USP—White, practically odorless, crystalline powder.^(R-14)

Clavulanate Potassium USP—White to off-white powder. Is moisture-sensitive.^(R-14)

pKa:

Amoxicillin—2.8 and 7.2.^(R-16)

Clavulanate—2.7.^(R-17)

Solubility:

Amoxicillin USP—Slightly soluble in water and in methanol; insoluble in carbon tetrachloride, and in chloroform.^(R-14)

Clavulanate Potassium USP—Freely soluble in water, but stability in aqueous solution is not good; optimum stability at a pH of 6.0 to 6.3; soluble in methanol, with decomposition.^(R-14)

Pharmacology/Pharmacokinetics

Note: There is evidence that giving amoxicillin with clavulanate has little effect on the pharmacokinetics of either medication.^(R-17; 24)

Mechanism of action/Effect:

Amoxicillin—Bactericidal. Amoxicillin must reach and bind to the penicillin-binding proteins on the inner membrane of the bacterial cell wall. In actively growing cells, the binding of amoxicillin within the cell wall leads to interference with production of cell wall peptidoglycans and subsequent lysis of the cell in an iso-osmotic environment.^(R-18-20)

Clavulanate—Binds irreversibly to susceptible beta-lactamase enzymes, preventing hydrolysis of the amoxicillin beta-lactam ring. When clavulanate binds with the enzyme, a chemical complex is formed, which destroys the clavulanate and inactivates the beta-lactamase.^(R-3; 4; 6)

Absorption:

Cats and dogs—Both amoxicillin and clavulanate are stable in gastric fluid and, therefore, are well absorbed after oral administration.^(R-6; 7; 21-23)

Calves—

Preruminant calves (2 weeks old): Absorption of amoxicillin when administered in combination with clavulanate at doses of 10 to 20 mg per kg of body weight (mg/kg) is 34

to 36%.

Early ruminant calves (6 weeks old): Absorption of amoxicillin and clavulanate combination is much poorer than in preruminant calves given the same dose; early ruminant calves do not develop therapeutic serum amoxicillin concentrations.^[R-26]

Horses—Orally administered amoxicillin is only 10% absorbed in adult horses.^[R-36]

Peak serum concentration: Amoxicillin—

Calves, preruminant:

Oral, 10 mg/kg dose—2 mcg per mL (mcg/mL) at 78 minutes.^[R-26]

Oral, 20 mg/kg dose—3.3 mcg/mL at 64 minutes.^[R-26]

Dogs: Oral, 12.5 mg/kg dose—5 to 6 mcg/mL at 60 minutes.^[R-38]

Distribution: *Cats* and *dogs*—Amoxicillin and clavulanate diffuse into most body tissues and fluids; however, distribution of amoxicillin into cerebrospinal fluid is low unless the meninges are inflamed and the penetration of clavulanic acid into spinal fluid is unknown.^[R-7; 8]

Elimination: Amoxicillin—Primarily excreted unchanged in the urine; 10 to 25% is excreted in the form of penicilloic acid.^[R-25]

Precautions to Consider

Cross-sensitivity and/or related problems

Animals allergic to one penicillin or cephalosporin may also be allergic to amoxicillin or clavulanate.^[R-9]

Species sensitivity

Horses and *rabbits*—This medication is generally contraindicated in these species because of the potential for disturbance of the normal gastrointestinal microflora.^[R-6]

Pregnancy/Reproduction

The safety of administration of amoxicillin and clavulanate to pregnant or breeding animals is unknown.^[R-8; 9] Penicillins have been shown to cross the placenta; however, laboratory animal reproduction studies have shown no evidence of adverse effects on the fetus.^[R-17]

Lactation

In humans, penicillins are distributed into milk, and the same is true for many animals.^[R-27; 28]

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Probenecid

(probenecid decreases tubular secretion and slows the body clearance of amoxicillin, resulting in increased serum concentrations and longer elimination half-lives in many species;^[R-24; 29] however, clavulanic acid is unlikely to be affected because it is cleared primarily by glomerular filtration^[R-17])

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Laboratory value alterations relating specifically to use of amoxicillin and clavulanate in animals appear to be rare. Human

laboratory value alterations have been reported and are included in this section.

Human laboratory value alterations^[R-15]

The following laboratory value alterations have been reported in humans, and are included in the human monograph *Penicillins and Beta-lactamase Inhibitors (Systemic)* in *USP DI Volume I*; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of amoxicillin and clavulanate combination in the treatment of animals:

With diagnostic test results

Glucose, urine

(high urinary concentrations of a penicillin may produce false-positive or falsely elevated test results with copper-reduction tests [Benedict's, *Clinitest*, or Fehling's]; glucose enzymatic tests [*Clinistix* or *Testape*] are not affected)

Direct antiglobulin (Coombs') tests

(false-positive result may occur during therapy with any penicillin)

With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) and

Alkaline phosphatase and

Aspartate aminotransferase (AST [SGOT]) and

Lactate dehydrogenase (LDH), serum

(values may be increased)

Bilirubin, serum

(concentrations may be increased)

Estradiol or

Estriol-glucuronide or

Estriol, total conjugated, or

Estrone, conjugated

(concentrations may be transiently decreased in pregnant women following administration of amoxicillin)

White blood count

(leukopenia or neutropenia is associated with the use of all penicillins; the effect is more likely to occur with prolonged therapy and severe hepatic function impairment)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

Culture and susceptibility, *in vitro*, and

Minimum inhibitory concentration (MIC)

(*in vitro* cultures and MIC test should be done on samples collected prior to amoxicillin and clavulanate administration to determine pathogen susceptibility)^[R-7; 8]

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

Those indicating need for medical attention

Incidence unknown

All species^[R-7; 8; 25]

Hypersensitivity reactions, specifically acute anaphylaxis, fever, or urticaria

Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

Cats and *dogs*^[R-6; 17]

Anorexia; diarrhea; vomiting

Human side/adverse effects^[R-15]

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph *Penicillins and Beta-lactamase Inhibitors (Systemic)* in *USP DI Volume I*; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of amoxicillin and clavulanate in the treatment of animals:

Incidence more frequent

Gastrointestinal reactions

Incidence less frequent

Allergic reactions, specifically anaphylaxis; oral candidiasis; serum sickness-like reactions; skin rash, hives, or itching; vaginal candidiasis

Incidence rare

Chills; Clostridium difficile colitis; dysuria or urinary retention; edema; epistaxis; erythema multiforma; glossitis; hepatic dysfunction, including cholestatic hepatitis; leukopenia or neutropenia; platelet dysfunction; proteinuria or pyuria; seizures; toxic epidermal necrolysis

Note: *Clostridium difficile colitis* may occur up to several weeks after discontinuation of these medications.

Seizures are more likely to occur in patients receiving high doses of a penicillin and/or patients with severe renal function impairment.

Overdose

For information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

General Dosing Information

In *cats* and *dogs*, the therapeutic efficacy of amoxicillin and clavulanate is not significantly affected by administration with food.^[R-21]

For treatment of adverse effects

For anaphylaxis

- Parenteral epinephrine.^[R-25]
- Oxygen administration and breathing support.

Oral Dosage Forms

Note: The dosing and strengths of the dosage forms available are expressed in terms of clavulanic acid (not the potassium salt).

AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP

Usual dose: Antibacterial—*Cats* and *dogs*: Oral, 11 to 20 mg of amoxicillin and 2.75 to 5 mg of clavulanic acid per kg of body weight every eight to twelve hours.^[R-32-34]

Note: Urinary tract infections should be treated for fourteen days or longer. Deep pyoderma may require treatment for twenty-one days. Treatment for any indication should not exceed thirty days.^[R-8]

Strength(s) usually available:^[R-8; 9; 30] When reconstituted according to manufacturer's instructions—

U.S.:

Veterinary-labeled product(s)—
50 mg of amoxicillin and 12.5 mg clavulanic acid per mL (Rx) [*Clavamox*].

Canada:

Veterinary-labeled product(s)—
50 mg of amoxicillin and 12.5 mg of clavulanic acid per mL (Rx) [*Clavamox*].

Packaging and storage: Store below 40 °C (104 °F), preferably

between 15 and 30 °C (59 and 86 °F). Store in a tight container.

Stability: After reconstitution, suspensions retain their potency for ten days if refrigerated.^[R-8]

Auxiliary labeling:

- Refrigerate.
- Shake well.

USP requirements: Preserve in tight containers, at controlled room temperature. Contains the labeled amount of amoxicillin, within –10% to +20%, and an amount of clavulanate potassium equivalent to the labeled amount of clavulanic acid, within –10% to +25%. Contains one or more suitable buffers, colors, flavors, preservatives, stabilizers, sweeteners, and suspending agents. Meets the requirements for Identification, Uniformity of dosage units (for powder packaged in single-unit containers), Deliverable volume (for powder packaged in multiple-unit containers), pH (3.8–6.6, in the suspension constituted as directed in the labeling, the test being performed immediately after constitution), and Water (not more than 7.5%, where the label indicates that after constitution as directed, the suspension contains an amount of amoxicillin that is less than 40 mg per mL; not more than 8.5% where the label indicates that after constitution as directed the suspension contains an amount of amoxicillin that is equal to or more than 40 mg per mL and is less than or equal to 50 mg per mL; not more than 11.0% where the label indicates that after constitution as directed the suspension contains an amount of amoxicillin that is more than 50 mg per mL and is less than or equal to 80 mg per mL; and not more than 12.0% where the label indicates that after constitution as directed the suspension contains an amount of amoxicillin that is more than 80 mg per mL).^[R-14]

AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP

Usual dose: See *Amoxicillin and Clavulanate Potassium for Oral Suspension USP*.

Strength(s) usually available:^[R-7; 10; 30]

U.S.—

Veterinary-labeled product(s):

- 50 mg of amoxicillin and 12.5 mg of clavulanic acid (Rx) [*Clavamox*].
- 100 mg of amoxicillin and 25 mg of clavulanic acid (Rx) [*Clavamox*].
- 200 mg of amoxicillin and 50 mg of clavulanic acid (Rx) [*Clavamox*].
- 300 mg of amoxicillin and 75 mg of clavulanic acid (Rx) [*Clavamox*].

Canada—

Veterinary-labeled product(s):

- 50 mg of amoxicillin and 12.5 mg of clavulanic acid (Rx) [*Clavamox*].
- 100 mg of amoxicillin and 25 mg of clavulanic acid (Rx) [*Clavamox*].
- 200 mg of amoxicillin and 50 mg of clavulanic acid (Rx) [*Clavamox*].
- 300 mg of amoxicillin and 75 mg of clavulanic acid (Rx) [*Clavamox*].

Packaging and storage: Store below 25 °C (77 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling: • Do not remove from foil strip until ready to use.

USP requirements: Preserve in tight containers. Label chewable Tablets to include the word “chewable” in juxtaposition to the official name. The labeling indicates that chewable Tablets may

be chewed before being swallowed or may be swallowed whole. Tablets intended for veterinary use only are so labeled. Contain the labeled amount of amoxicillin, within -10% to +20%, and an amount of clavulanate potassium equivalent to the labeled amount of clavulanic acid, within -10% to +20%. Meet the requirements for Identification, Disintegration (for Tablets labeled for veterinary use only, 30 minutes, in simulated gastric fluid TS), Dissolution (85% of amoxicillin and 80% of clavulanic acid in 30 minutes [or 80% of each amoxicillin and clavulanic acid in 45 minutes where the Tablets are labeled as chewable] in water in Apparatus 2 at 75 rpm [Note: Tablets labeled for veterinary use only are exempt from this requirement]), Uniformity of dosage units, and Water (not more than 7.5% where the labeled amount of amoxicillin in each Tablet is 250 mg or less; not more than 10.0% where the labeled amount of amoxicillin in each Tablet is more than 250 mg but less than or equal to 500 mg; not more than 11.0% where the labeled amount of amoxicillin in each Tablet is more than 500 mg. Where Tablets are labeled as chewable, not more than 6.0% where the labeled amount of amoxicillin in each Tablet is 125 mg or less; not more than 8.0% where the labeled amount of amoxicillin in each Tablet is more than 125 mg. Where the Tablets are labeled for veterinary use only, not more than 10.0%).^(R-14)

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