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Front

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION, safely and effectively. See full prescribing information for AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION.

AMOXICILLIN and CLAVULANATE POTASSIUM for oral suspension, Initial U.S. Approval: 2001

INDICATIONS AND USAGE

Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL is a combination of amoxicillin, a penicillin-class antibacterial and clavulanate potassium, a beta-lactamase inhibitor, indicated for the treatment of pediatric patients with

- Recurrent or persistent acute otitis media due to *S. pneumoniae* (penicillin MICs less than or equal to 2 mcg/mL), *H. influenzae* (including β-lactamase-producing strains), or *M. catarrhalis* (including β-lactamase- producing strains) characterized by the following risk factors (1)
  - Antibacterial exposure for acute otitis media within the preceding 3 months, and either of the following: 1) age 2 years, or younger or 2) daycare attendance

Limitations of Use
Acute otitis media due to *S. pneumoniae* alone can be treated with amoxicillin. Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL is not indicated for the treatment of acute otitis media due to *S. pneumoniae* with penicillin MIC greater than or equal to 4 mcg/mL. Therapy may be instituted prior to obtaining the results from bacteriological studies when there is reason to believe the infection may involve both *S. pneumoniae* (penicillin MIC less than or equal to 2 mcg/mL) and the β-lactamase-producing organisms listed above. (1)

Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL and other antibacterial drugs, Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1)

DOSAGE AND ADMINISTRATION

- Pediatric Patients less than 40 kg: 90 mg/kg/day divided every 12 hours, administered for 10 days. (2)

DOSAGE FORMS AND STRENGTHS

Powder for Oral Suspension: 600 mg/42.9 mg per 5 mL. (3)

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction (e.g., anaphylaxis or Stevens-Johnson syndrome) to amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL or any other beta-lactams (e.g., penicillins or cephalosporins). (4.1)
- History of cholestatic jaundice/hepatic dysfunction associated with amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL. (4.2)

WARNINGS AND PRECAUTIONS

- Serious (including fatal) hypersensitivity reactions: Discontinue amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL if a reaction occurs. (5.1)
- Severe Cutaneous Adverse Reactions (SCAR): Monitor closely. Discontinue if rash progresses. (5.2)
- Drug-induced enterocolitis syndrome (DIES) has been reported with the use of amoxicillin, a component of Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL. If this occurs, discontinue Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL and institute appropriate therapy. (5.3)
- Hepatic dysfunction and cholestatic jaundice: Discontinue if signs/symptoms of hepatitis occur. Monitor liver function tests in patients with hepatic impairment. (5.4)
- *Clostridioides difficile*-associated diarrhea (CDAD) (ranging from mild diarrhea to fatal colitis): Evaluate patients if diarrhea occurs. (5.5)
- Patients with mononucleosis who receive amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL develop skin rash. Avoid amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL use in these patients. (5.6)

ADVERSE REACTIONS

The most frequently reported adverse reactions were diaper rash (4%), diarrhea (3%), vomiting (2%), candidiasis (1%), and rash (1%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Devatis, Inc. at 1-800-617-3238 or FDA at 1-800 -FDA-1088 or *www.fda.gov/medwatch*

DRUG INTERACTIONS

- Co-administration with probenecid is not recommended. (7.1)
- Concomitant use of amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL with oral anticoagulants may increase the prolongation of prothrombin time. (7.2)
- Co-administration with allopurinol increases the risk of rash. (7.3)
- Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL may reduce efficacy of oral contraceptives. (7.4)

USE IN SPECIFIC POPULATIONS

- Pediatric 3 months to 12 years old: Modify dose according to weight. (2.2, 8.4)
- Adults and pediatric patients weighing more than 40 kg: The safety and effectiveness of amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL has not been established. (8)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL is indicated for the treatment of pediatric patients with

- Recurrent or persistent acute otitis media due to *S. pneumoniae* (penicillin MICs less than or equal to 2 mcg/mL), *H. influenzae* (including β-lactamase-producing strains), or *M. catarrhalis* (including β-lactamase-producing strains) characterized by the following risk factors:
  - Antibacterial drug exposure for acute otitis media within the preceding 3 months, and either of the following: 1) age 2 years, or younger or 2) day care attendance *[see Microbiology (12.4)]*.

Limitations of Use
Acute otitis media due to *S. pneumoniae* alone can be treated with amoxicillin. Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL is not indicated for the treatment of acute otitis media due to *S. pneumoniae* with penicillin MIC greater than or equal to 4 mcg/mL. Therapy may be instituted prior to obtaining the results from bacteriological studies when there is reason to believe the infection may involve both *S. pneumoniae* (penicillin MIC less than or equal to 2 mcg/mL) and the β-lactamase-producing organisms listed above.

Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL and other antibacterial drugs, Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

To minimize the potential for gastrointestinal intolerance, Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL should be taken at the start of a meal. Absorption of clavulanate potassium may be enhanced when Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL is administered at the start of a meal.

2.2 Dosage in Pediatric Patients

Pediatric patients 3 months and older: Based on the amoxicillin component (600 mg/5 mL), the recommended dose of Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL is 90 mg/kg/day divided every 12 hours, administered for 10 days (see chart below). This dose provides 6.4 mg/kg/day of the clavulanic acid component.

Body Weight (kg)	Volume of Amoxicillin and Clavulanate Potassium for Oral Suspension, 600 mg /42.9 mg per 5 mL providing 90 mg/kg/day
8	3 mL twice daily
12	4.5 mL twice daily
16	6 mL twice daily
20	7.5 mL twice daily
24	9 mL twice daily
28	10.5 mL twice daily
32	12 mL twice daily
36	13.5 mL twice daily

Pediatric patients weighing 40 kg and more: Experience with amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL in this group is not available.

2.3 Dosage in Adult Patients

Experience with Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL in adults is not available and adults who have difficulty swallowing should not be given Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL in place of the 500 mg or 875 mg tablet of Amoxicillin and clavulanate potassium.

2.4 Dosage in Patients with Hepatic Impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals *[see Warnings and Precautions (5)]*.

2.5 Preparation of the Oral Suspension

Directions for Mixing Oral Suspension: Prepare a suspension at time of dispensing as follows: Tap bottle until all powder flows freely. Measure the total amount of water (see chart below) to be added in two parts. Add approximately 2/3 of the total amount of water for reconstitution, replace cap and shake vigorously to suspend powder. Add remainder of the water (that had been measured), replace cap and again shake vigorously.

Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL	
Bottle Size	Amount of Water Required for Reconstitution
75 mL	65 mL
125 mL	110 mL
200 mL	176 mL

Each teaspoonful (5 mL) will contain 600 mg of amoxicillin as the trihydrate, and 42.9 mg of clavulanic acid as the potassium salt.
Shake oral suspension well before each use. Suspension must be refrigerated. Discard after 10 days. Suspension is off-white at time of reconstitution; some color change is normal during the dosing period.

2.6 Switching between Dosage Forms and between Strengths

Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL does not contain the same amount of clavulanic acid (as the potassium salt) as any of the other suspensions of Amoxicillin and clavulanate potassium. Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL contains 42.9 mg of clavulanic acid per 5 mL, whereas the 200 mg/28.5 mg per 5 mL suspension of Amoxicillin and clavulanate potassium contains 28.5 mg clavulanic acid per 5 mL and the 400 mg/57 mg per 5 mL suspension of Amoxicillin and clavulanate potassium contains 57 mg clavulanic acid per 5 mL. Therefore, the 200 mg/28.5 mg per 5 mL and 400 mg/57 mg per 5 mL suspensions of Amoxicillin and clavulanate potassium should not be substituted for Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL as they are not interchangeable.

3 DOSAGE FORMS AND STRENGTHS

Amoxicillin and clavulanate potassium Powder for Oral Suspension, USP:
- **600 mg/42.9 mg per 5 mL:** Vanilla and tutti frutti-flavored for oral suspension (each 5 mL of reconstituted suspension contains 600 mg of amoxicillin as the trihydrate, and 42.9 mg of clavulanic acid as the potassium salt).

4 CONTRAINDICATIONS

4.1 Serious Hypersensitivity Reactions

Amoxicillin and clavulanate potassium is contraindicated in patients with a history of serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to amoxicillin, clavulanate or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins).

4.2 Cholestatic Jaundice/Hepatic Dysfunction

Amoxicillin and clavulanate potassium is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with treatment with amoxicillin and clavulanate potassium.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Allergic Reactions, Including Anaphylaxis

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterials, including amoxicillin and clavulanate potassium. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with amoxicillin and clavulanate potassium careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, discontinue amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL and institute appropriate therapy.

5.2 Severe Cutaneous Adverse Reactions

Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL may cause severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). If patients develop a skin rash, they should be monitored closely, and amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL discontinued if lesions progress.

5.3 Drug-Induced Enterocolitis Syndrome (DIES)

Drug-induced enterocolitis syndrome (DIES) has been reported with the use of amoxicillin, a component of Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL *[see Adverse Reactions (6.2)]*, with most cases occurring in pediatric patients ≤ 18 years of age. DIES is a non-IgE mediated hypersensitivity reaction characterized by protracted vomiting occurring 1 to 4 hours after drug ingestion in the absence of skin or respiratory symptoms. DIES may be associated with pallor, lethargy, hypotension, shock, diarrhea within 24 hours after ingesting amoxicillin, and leukocytosis with neutrophilia. If DIES occurs, discontinue Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL and institute appropriate therapy.

5.4 Hepatic Dysfunction

Use amoxicillin and clavulanate potassium with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin and clavulanate potassium is usually reversible. Deaths have been reported (fewer than one death reported per estimated four million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications *[see Contraindications (4.2) and Adverse Reactions (6.2)]*.

5.5 *Clostridioides difficile*-Associated Diarrhea (CDAD)

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including amoxicillin and clavulanate potassium and may range in severity from mild diarrhea 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 diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

5.6 Skin Rash in Patients with Mononucleosis

A high percentage of patients with mononucleosis who receive amoxicillin develop an erythematous skin rash. Thus, amoxicillin and clavulanate potassium should not be administered to patients with mononucleosis.

5.7 Potential for Microbial Overgrowth

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* spp. or *Candida* spp.), the drug should be discontinued, and appropriate therapy instituted.

5.9 Development of Drug-Resistant Bacteria

Prescribing amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL 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.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling *[see Warnings and Precautions (5)]:*
- Anaphylactic reactions *[see Warnings and Precautions (5.1)]*
- Severe Cutaneous Adverse Reactions (SCAR) *[see Warnings and Precautions (5.2)]*
- *Drug-Induced Enterocolitis Syndrome (DIES) [see Warnings and Precautions (5.3)]*
- Hepatic Dysfunction *[see Warnings and Precautions (5.4)]*
- Clostridioides difficile-Associated Diarrhea (CDAD) *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Two clinical trials evaluated the safety of a 10-day treatment course of amoxicillin and clavulanate potassium for oral suspension, 90/6.4 mg/kg/day, divided every 12 hours, in pediatric patients with acute otitis media *[see Clinical Studies (14)]*. The first trial involved 521 pediatric patients (3 months to 50 months) and the second trial involved 450 pediatric patients (3 months to 12 years). In the intent-to-treat population of the first trial of 521 patients, the most frequently reported adverse events were vomiting (7%), fever (6%), contact dermatitis (i.e., diaper rash) (6%), upper respiratory tract infection (4%), and diarrhea (4%). Protocol-defined diarrhea (i.e., 3 or more watery stools in one day or 2 watery stools per day for 2 consecutive days as recorded on diary cards) occurred in 13% of patients.

The primary objective of the second study was to compare the safety of amoxicillin and clavulanate potassium for oral suspension (90/6.4 mg/kg/day, divided every 12 hours) to amoxicillin and clavulanate potassium (45/6.4 mg/kg/day, divided every 12 hours) for ten days. There was no statistically significant difference between treatments in the proportion of patients with 1 or more adverse events. The most frequently reported adverse reactions for amoxicillin and clavulanate potassium for oral suspension and the comparator of amoxicillin and clavulanate potassium were coughing (12% versus 7%), vomiting (7% versus 8%), contact dermatitis (i.e., diaper rash, 6% versus 5%), fever (6% versus 4%), and upper respiratory infection (3% versus 9%), respectively. The frequencies of protocol-defined diarrhea with amoxicillin and clavulanate potassium for oral suspension (11%) and amoxicillin and clavulanate potassium (9%) were not statistically different. Two patients in the group treated with amoxicillin and clavulanate potassium for oral suspension and one patient in the group treated with amoxicillin and clavulanate potassium were withdrawn due to diarrhea.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following have been identified during postmarketing use of amoxicillin and clavulanate potassium products, including amoxicillin and clavulanate potassium for oral suspension. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to amoxicillin and clavulanate potassium.

Gastrointestinal: Drug-induced enterocolitis syndrome (DIES), 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 antibacterial treatment *[see Warnings and Precautions (5)]*.

Immune: Hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock), angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), hypersensitivity vasculitis *[see Warnings and Precautions (5.1)]*.

Skin and Appendages: Rashes, pruritus, urticaria, erythema multiforme, SJS, TEN, DRESS, AGEP, exfoliative dermatitis, and linear IgA bullous dermatosis.

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibacterials. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been infrequently reported with amoxicillin and clavulanate potassium or amoxicillin and clavulanate potassium for oral suspension. 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 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. Deaths have been reported *[see Contraindications (4.2), Warnings and Precautions (5.4)]*.

Renal: Interstitial nephritis and hematuria have been reported. Crystalluria has also been reported *[see Overdosage (10)]*.

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. There have been reports of increased prothrombin time in patients receiving amoxicillin and clavulanate potassium and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, aseptic meningitis, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

7 DRUG INTERACTIONS

7.1 Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin and clavulanate potassium for oral suspension may result in increased and prolonged blood levels of amoxicillin. Co- administration of probenecid is not recommended.

7.2 Oral Anticoagulants

Abnormal prolongation of prothrombin time (increased international normalized ratio [INR]) has been reported in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

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7.3 Allopurinol

The concurrent administration of allopurinol and amoxicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving amoxicillin alone. It is not known whether this potentiation of amoxicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with amoxicillin and clavulanate potassium for oral suspension and allopurinol administered concurrently.

7.4 Oral Contraceptives

Amoxicillin and clavulanate potassium for oral suspension may affect intestinal flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

7.5 Effects on Laboratory Tests

High urine concentrations of amoxicillin 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 clavulanate potassium for oral suspension, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

Following administration of amoxicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

There are 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.

Reproduction studies performed in pregnant rats and mice given amoxicillin and clavulanate potassium (2:1 ratio formulation of amoxicillin: clavulanate) at oral dosages up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to amoxicillin and clavulanate potassium. The amoxicillin doses in rodents (based on body surface area and assuming a 20 kg child) were approximately 2 times (rats) or equal to (mice) the recommended clinical amoxicillin and clavulanate potassium for oral suspension dose of 90/6.4 mg/kg/day. For clavulanate, these dose multiples were approximately 15 times and 7.5 times the recommended daily dose of amoxicillin and clavulanate potassium for oral suspension.

8.2 Labor and Delivery

Oral ampicillin-class antibacterial drugs 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 and 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 and clavulanate potassium may be associated with an increased risk of necrotizing enterocolitis in neonates.

8.3 Nursing Mothers

Ampicillin-class antibacterial drugs are excreted in human milk; therefore, caution should be exercised when amoxicillin and clavulanate potassium is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy of amoxicillin and clavulanate potassium for oral suspension in infants younger than 3 months have not been established. Safety and efficacy of amoxicillin and clavulanate potassium for oral suspension have been demonstrated for treatment of acute otitis media in infants and children 3 months to 12 years *[see Clinical Studies (14)]*.

The safety and effectiveness of amoxicillin and clavulanate potassium for oral suspension have been established for the treatment of pediatric patients (3 months to 12 years) with acute bacterial sinusitis. This use is supported by evidence from adequate and well-controlled studies of amoxicillin and clavulanate potassium extended-release tablets in adults with acute bacterial sinusitis, studies of amoxicillin and clavulanate potassium for oral suspension in pediatric patients with acute otitis media, and by similar pharmacokinetics of amoxicillin and clavulanate in pediatric patients taking amoxicillin and clavulanate potassium for oral suspension *[see Clinical Pharmacology (12)]* and adults taking amoxicillin and clavulanate potassium extended-release tablets.

10 OVERDOSAGE

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

In case of overdosage, discontinue amoxicillin and clavulanate potassium for oral suspension, 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 control 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.[1]

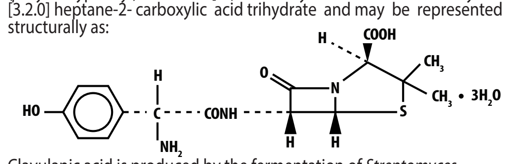
Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

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.

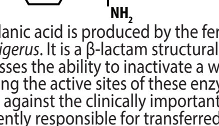
Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis *[see Dosage and Administration (2)]*.

11 DESCRIPTION

Amoxicillin and clavulanate potassium for oral suspension USP, is an oral antibacterial combination consisting of the semisynthetic antibacterial 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 (2*S*,5*R*,6*R*)-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:



Following constitution, each 5 mL of oral suspension contains 600 mg of amoxicillin as the trihydrate and 42.9 mg of clavulanic acid (equivalent to 51.1 mg of clavulanate potassium).

Inactive Ingredients: Powder for oral suspension - carboxymethylcellulose sodium, sucralose, sodium citrate, anhydrous citric acid, silicon dioxide, colloidal silicon dioxide, xanthan gum, vanilla flavor (maltodextrin, glyceryl triacetate, corn starch, flavoring components), tutti frutti flavor (maltodextrin, propylene glycol, alpha tocopherol, flavoring components).

Each 5 mL of reconstituted amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL contains 0.23 mEq potassium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amoxicillin and clavulanate potassium is an antibacterial drug *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

The pharmacokinetics of amoxicillin and clavulanate were determined in a study of 19 pediatric patients, 8 months to 11 years, given amoxicillin and clavulanate potassium for oral suspension at an amoxicillin dose of 45 mg/kg q12h with a snack or meal. The mean plasma amoxicillin and clavulanate pharmacokinetic parameter values are listed in the following table.

Table 1. Mean (± SD) Plasma Amoxicillin and Clavulanate Pharmacokinetic Parameter Values Following Administration of 45 mg/kg of Amoxicillin and Clavulanate Potassium for Oral Suspension Every 12 Hours to Pediatric Patients

PARAMETER	AMOXICILLIN	CLAVULANATE
C_{max} (mcg/mL)	15.7 ± 7.7	1.7 ± 0.9
T_{max} (hr)	2.0 (1.0 to 4.0)	1.1 (1.0 to 4.0)
AUC_{0-T} (mcg*hr /mL)	59.8 ± 20.0	4.0 ± 1.9
$T_{1/2}$ (hr)	1.4 ± 0.3	1.1 ± 0.3
CL/F (L/hr/kg)	0.9± 0.4	1.1 ± 1.1

*Arithmetic mean ± standard deviation, except T_{max} values which are medians (ranges).

The effect of food on the oral absorption of amoxicillin and clavulanate potassium for oral suspension has not been studied.

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 10 mL of amoxicillin and clavulanate potassium, 250 mg/62.5 mg per 5 mL suspension.

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

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

Oral administration of a single dose of amoxicillin and clavulanate potassium for oral suspension at 45 mg/kg (based on the amoxicillin component) to pediatric patients, 9 months to 8 years, yielded the following pharmacokinetic data for amoxicillin in plasma and middle ear fluid (MEF):

Table 2. Amoxicillin Concentrations in Plasma and Middle Ear Fluid Following Administration of 45 mg/kg of Amoxicillin and Clavulanate Potassium for Oral Suspension to Pediatric Patients

Timepoint		Amoxicillin concentration in plasma (mcg/mL)	Amoxicillin concentration in MEF (mcg/mL)
1 hour	mean	7.7	3.2
	median	9.3	3.5
	range	1.5 to 14.0 (n equals 5)	0.2 to 5.5 (n equals 4)
2 hour	mean	15.7	3.3
	median	13.0	2.4
	range	11.0 to 25.0 (n equals 7)	1.9 to 6 (n equals 5)
3 hour	mean	13.0	5.8
	median	12.0	6.5
	range	5.5 to 21.0 (n equals 5)	3.9 to 7.4 (n equals 5)

Dose administered immediately prior to eating.

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.

12.4 Microbiology

Amoxicillin is a semisynthetic antibacterial 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, its spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to penicillin, 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 found responsible for transferred drug resistance. The clavulanic acid component of Amoxicillin and clavulanate potassium for oral suspension protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibacterials. Thus, Amoxicillin and clavulanate potassium for oral suspension possesses the distinctive properties of a broad spectrum antibacterial and a β-lactamase inhibitor. Amoxicillin/clavulanic acid has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections *[see Indications and Usage (1)]*.

Gram-Positive bacteria:
Streptococcus pneumoniae (including isolates with penicillin MICs less than or equal to 2 mcg/mL)

Gram-Negative bacteria:
Haemophilus influenzae (including β-lactamase–producing isolates)
Moraxella catarrhalis (including β-lactamase–producing isolates)

The following in vitro data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit in vitro minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for amoxicillin/clavulanic acid. However, the safety and efficacy of amoxicillin/clavulanic acid in treating infections due to these microorganisms have not been established in adequate and well-controlled trials.

Gram-Positive bacteria:
Staphylococcus aureus (including β-lactamase-producing isolates)
Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.
Streptococcus pyogenes
S. pyogenes do not produce β-lactamase, and therefore, are susceptible to amoxicillin alone. Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to *S. pyogenes*

Susceptibility Test Methods:
For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Amoxicillin and clavulanate potassium (4:1 ratio formulation of amoxicillin:clavulanate) was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Amoxicillin and clavulanate potassium was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at concentrations that were also associated with decreased cell survival. Amoxicillin and clavulanate potassium was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test and was negative in each of these assays.

Amoxicillin and clavulanate potassium (2:1 ratio formulation of amoxicillin:clavulanate) at oral doses of up to 1,200 mg/kg/day was found to have no effect on fertility and reproductive performance in rats. Based on body surface area (assuming a 20 kg child), this dose of amoxicillin is approximately 2 times the recommended clinical amoxicillin and clavulanate potassium for oral suspension dose of 90/6.4 mg/kg/day. For clavulanate, the dose multiple is approximately 15 times higher than the recommended clinical daily dose, also based on body surface area.

14 CLINICAL STUDIES

Two clinical studies were conducted in pediatric patients with acute otitis media. A non-comparative, open-label study assessed the bacteriologic and clinical efficacy of amoxicillin and clavulanate potassium for oral suspension (90 mg/6.4 mg/kg/day, divided every 12 hours) for 10 days in 521 pediatric patients (3 to 50 months) with acute otitis media. The primary objective was to assess bacteriological response in children with acute otitis media due to *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4 mcg/mL. The study sought the enrollment of patients with the following risk factors: Failure of antibacterial therapy for acute otitis media in the previous 3 months, history of recurrent episodes of acute otitis media, 2 years or younger, or daycare attendance. Prior to receiving amoxicillin and clavulanate potassium for oral suspension, all patients had tympanocentesis to obtain middle ear fluid for bacteriological evaluation. Patients from whom *S. pneumoniae* (alone or in combination with other bacteria) was isolated had a second tympanocentesis 4 to 6 days after the start of therapy. Clinical assessments were planned for all patients during treatment (4 to 6 days after starting therapy), as well as 2 to 4 days post-treatment and 15 to 18 days post-treatment. Bacteriological success was defined as the absence of the pretreatment pathogen from the on-therapy tympanocentesis specimen. Clinical success was defined as improvement or resolution of signs and symptoms. Clinical failure was defined as lack of improvement or worsening of signs and/or symptoms at any time following at least 72 hours of amoxicillin and clavulanate potassium for oral suspension; patients who received an additional systemic antibacterial drug for otitis media after 3 days of therapy were considered clinical failures. Bacteriological eradication on therapy (day 4 to 6 visit) in the per protocol population is summarized in the following table:

Table 3. Bacteriologic Eradication Rates in the Per Protocol Population

Pathogen	Bacteriologic Eradication on Therapy		
	n/N	%	95% CI*
All *S. pneumoniae*	121/123	98	(94.3, 99.8)
S. pneumoniae with penicillin MIC equal to 2 mcg/mL	19/19	100	(82.4, 100.0)
S. pneumoniae with penicillin MIC equal to 4 mcg/mL	12/14	86	(57.2, 98.2)
H. influenzae	75/81	93	(84.6, 97.2)
M. catarrhalis	11/11	100	(71.5, 100.0)

* CI equals confidence intervals; 95% CIs are not adjusted for multiple comparisons.

Clinical assessments were made in the per protocol population 2 to 4 days post-therapy and 15 to 18 days post-therapy. Patients who responded to therapy 2 to 4 days post-therapy were followed for 15 to 18 days post- therapy to assess them for acute otitis media. Non-responders at 2 to 4 days post-therapy were considered failures at the latter timepoint.

Table 4. Clinical Assessments in the Per Protocol Population (Includes *S. pneumoniae* Patients with Penicillin MICs equal to 2 or 4 mcg/mL*)

Pathogen	2 to 4 Days Post-Therapy (Primary Endpoint)		
	n/N	%	95% CI[1]
All *S. pneumoniae*	122/137	89	(82.6, 93.7)
S. pneumoniae with penicillin MIC equal to 2 mcg/mL	17/20	85	(62.1, 96.8)
S. pneumoniae with penicillin MIC equal to 4 mcg/mL	11/14	79	(49.2, 95.3)
H. influenzae	141/162	87	(80.9, 91.8)
M. catarrhalis	22/26	85	(65.1, 95.6)

Pathogen	15 to 18 Days Post-Therapy[2] (Secondary Endpoint)		
	n/N	%	95% CI[1]
All *S. pneumoniae*	95/136	70	(61.4, 77.4)
S. pneumoniae with penicillin MIC equal to 2 mcg/mL	11/20	55	(31.5, 76.9)
S. pneumoniae with penicillin MIC equal to 4 mcg/mL	5/14	36	(12.8, 64.9)
H. influenzae	106/156	68	(60.0, 75.2)
M. catarrhalis	14/25	56	(34.9, 75.6)

* *S. pneumoniae* strains with penicillin MICs of 2 or 4 mcg/mL are considered resistant to penicillin.
[1] CI equals confidence intervals; 95% CIs are not adjusted for multiple comparisons.
[2] Clinical assessments at 15 to 18 days post-therapy may have been confounded by viral infections and new episodes of acute otitis media with time elapsed post-treatment.

In the intent-to-treat analysis, overall clinical outcomes at 2 to 4 days and 15 to 18 days post-treatment in patients with *S. pneumoniae* with penicillin MIC equal to 2 mcg/mL and 4 mcg/mL were 29/41 (71%) and 17/41 (42%), respectively.

15 REFERENCES

1. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
The color of the dry powder for amoxicillin and clavulanate potassium for oral suspension USP, 600 mg/42.9 mg/5 mL is white to creamy white powder.

Vanilla and tutti frutti-flavored powder for oral suspension. Following constitution, each 5 mL of oral suspension contains 600 mg of amoxicillin as the trihydrate and 42.9 mg of clavulanic acid as the potassium salt (equivalent to 51.1 mg of clavulanate potassium).

NDC 73043 008 01, 75 mL bottle

NDC 73043 008 02, 125 mL bottle

NDC 73043 008 03, 200 mL bottle.

Storage
Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days. Store dry powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Dispense in original container. Keep tightly closed.

Keep this and all medications out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Administration Instructions
Inform patients to take Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL every 12 hours with a meal or snack to reduce the possibility of gastrointestinal upset. If diarrhea develops and is severe or lasts more than 2 or 3 days, call your doctor.

Allergic Reactions
Counsel patients that Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL contains a penicillin class drug product that can cause allergic reactions in some individuals.

Severe Cutaneous Adverse Reactions (SCAR)
Advise patients about the signs and symptoms of serious skin manifestations. Instruct patients to stop taking Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL immediately and promptly report the first signs or symptoms of skin rash, mucosal lesions, or any other sign of hypersensitivity *[see Warnings and Precautions (5.2)]*.

Diarrhea
Counsel patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterial drugs, 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 antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

Antibacterial Resistance
Patients should be counseled that antibacterial drugs, including Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL, should only be used to treat bacterial infections. Antibacterial drugs do not treat viral infections (e.g., the common cold). When Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL 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 effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL or other antibacterial drugs in the future.

Storage Instructions
Keep suspension refrigerated. Shake well before using. When dosing a child with the suspension (liquid) of Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL, use a dosing spoon or medicine dropper. Be sure to rinse the spoon or dropper after each use. Bottles of suspension of Amoxicillin and clavulanate potassium for oral suspension, 600 mg/42.9 mg per 5 mL may contain more liquid than required. Follow your doctor's instructions about the amount to use and the days of treatment your child requires. Discard any unused medicine.

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