AUGMENTIN- amox/clav.pot.oral susp powder, for suspension
Direct_Rx

AMOXICILLIN AND CLAVULANATE POTASSIUM

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Amoxicillin and Clavulanate Potassium Powder for Oral Suspension, USP (amoxicillin/clavulanate potassium) and other antibacterial drugs, Amoxicillin and Clavulanate Potassium Powder for Oral Suspension, USP should be used only to treat 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.

Amoxicillin and Clavulanate Potassium Powder for Oral Suspension, USP is a combination penicillin-class antibacterial and beta-lactamase inhibitor indicated in the treatment of infections due to susceptible isolates of the designated bacteria in the conditions listed below*:

1.1 Lower Respiratory Tract Infections
- caused by beta-lactamase-producing isolates of Haemophilus influenzae and Moraxella catarrhalis.

1.2 Acute Bacterial Otitis Media
- caused by beta-lactamase-producing isolates of H. influenzae and M. catarrhalis.

1.3 Sinusitis
- caused by beta-lactamase-producing isolates of H. influenzae and M. catarrhalis.

1.4 Skin and Skin Structure Infections
- caused by beta-lactamase-producing isolates of Staphylococcus aureus, Escherichia coli, and Klebsiella species.

1.5 Urinary Tract Infections
- caused by beta-lactamase-producing isolates of E. coli, Klebsiella species, and Enterobacter species.

1.6 Limitations of Use
- When susceptibility test results show susceptibility to amoxicillin, indicating no beta-lactamase production, Amoxicillin and Clavulanate Potassium Powder for Oral Suspension, USP should not be used.

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1.6 Limitations of Use
- When susceptibility test results show susceptibility to amoxicillin, indicating no beta-lactamase production, Amoxicillin and Clavulanate Potassium Powder for Oral Suspension, USP should not be used.

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

2.1 Adults
The usual adult dose is one 500-mg tablet of amoxicillin and clavulanate potassium every 12 hours or one 250-mg tablet of amoxicillin and clavulanate potassium every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one 875-mg tablet of amoxicillin and clavulanate potassium every 12 hours or one 500-mg tablet of amoxicillin and clavulanate potassium every 8 hours. Adults who have difficulty swallowing may be given the 125 mg/5 mL or 250 mg/5 mL suspension in place of the 500-mg tablet. The 200 mg/5 mL suspension or the 400 mg/5 mL suspension may be used in place of the 875-mg tablet.

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

The 250-mg tablet of amoxicillin and clavulanate potassium and the 250-mg chewable tablet should not be substituted for each other, as they are not interchangeable. The 250-mg tablet of amoxicillin and clavulanate potassium and the 250-mg chewable tablet do not contain the same amount of clavulanic acid (as the potassium salt). The 250-mg tablet of amoxicillin and clavulanate potassium contains 125 mg of clavulanic acid, whereas the 250-mg chewable tablet contains 62.5 mg of clavulanic acid.

2.2 Pediatric Patients
Based on the amoxicillin component, amoxicillin and clavulanate potassium suspension should be dosed as follows:

Neonates and Infants Aged <12 weeks (<3 months): The recommended dose of amoxicillin and clavulanate potassium suspension 30 mg/kg/day divided every 12 hours, based on the amoxicillin component. Experience with the 200 mg/5 mL formulation in this age group is limited, and thus, use of the 125 mg/5 mL oral suspension is recommended.

Patients Aged 12 weeks (3 months) and Older: See dosing regimens provided in Table 1. The every 12 hours regimen is recommended as it is associated with significantly less diarrhea [see CLINICAL STUDIES (14.2)]. However, the every 12 hours suspension (200 mg/5 mL and 400 mg/5 mL) and chewable tablets (200 mg and 400 mg) contain aspartame and should not be used by phenylketonurics. [see WARNINGS AND PRECAUTIONS (5.6)]

Table 1: Dosing in Patients Aged 12 weeks (3 months) and Older

INFECTION	DOSING REGIMEN	
	Every 12 hours	Every 8 hours
	200 mg/5 mL or 400 mg/5 mL oral suspensiona	125 mg/5 mL or 250 mg/5 mL oral suspensiona

Otitis mediab, sinusitis, lower respiratory tract infections, and more severe infections 45 mg/kg/day every 12 hours 40 mg/kg/day every 8 hours
Less severe infections 25 mg/kg/day every 12 hours 20 mg/kg/day every 8 hours
a Each strength of suspension of amoxicillin and clavulanate potassium is available as a chewable tablet for use by older children.
b Duration of therapy studied and recommended for acute otitis media is 10 days.

Patients Weighing 40 kg or More: Pediatric patients weighing 40 kg or more should be dosed according to adult recommendations.

The 250-mg tablet of amoxicillin and clavulanate potassium should not be used until the child weighs at least 40 kg, due to the different amoxicillin to clavulanic acid ratios in the 250-mg tablet of amoxicillin and clavulanate potassium (250/125) versus the 250-mg chewable tablet of amoxicillin and clavulanate potassium (250/62.5).

2.3 Patients with Renal Impairment
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Renal impairment patients with a glomerular filtration rate of <30 mL/min should not receive the 875-mg dose. Patients with a glomerular filtration rate of 10 to 30 mL/min should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a glomerular filtration rate less than 10 mL/min should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

2.4 Directions for Mixing Oral Suspension
Prepare a suspension at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see Table 2 below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

Table 2: Amount of Water for Mixing Oral Suspension
Strength Bottle Size Amount of Water for Reconstitution Contents of Each Teaspoonful (5 mL)
200 mg/5 mL 50 mL
75 mL
100 mL 48 mL
71 mL
95 mL 200 mg amoxicillin and 28.5 mg of clavulanic acid as the potassium salt
400 mg/5 mL 50 mL
75 mL
100 mL 45 mL
68 mL
90 mL 400 mg amoxicillin and 57.0 mg of clavulanic acid as the potassium salt
Note: Shake oral suspension well before using. Reconstituted suspension must be stored under refrigeration and discarded after 10 days.

200 mg/28.5 mg per 5 mL: The dry powder is white to off white with fruity flavor. Each 5 mL of reconstituted creamy suspension contains 200 mg amoxicillin and 28.5 mg clavulanic acid as the potassium salt.
400 mg/57 mg per 5 mL: The dry powder is white to off white with fruity flavor. Each 5 ml of reconstituted creamy suspension contains 400 mg amoxicillin and 57 mg clavulanic acid as the potassium salt.

5.1 Hypersensitivity Reactions
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterials, including amoxicillin and clavulanate potassium suspension. 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 suspension, careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, amoxicillin and clavulanate potassium suspension should be discontinued and appropriate therapy instituted.

5.2 Hepatic Dysfunction
Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of amoxicillin and clavulanate potassium suspension. Hepatic toxicity is usually reversible; however, deaths have been reported. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.

5.3 Clostridium difficile Associated Diarrhea (CDAD)
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including amoxicillin and clavulanate potassium suspension, 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 use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial 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.

5.4 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 suspension should not be administered to patients with mononucleosis.

5.5 Potential for Microbial Overgrowth
The possibility of superinfections with fungal or bacterial pathogens should be considered during therapy. If superinfection occurs, amoxicillin/clavulanate potassium suspension should be discontinued and appropriate therapy instituted.

5.6 Phenylketonurics
Amoxicillin and clavulanate potassium for oral suspension contains aspartame which contains phenylalanine. Each 5 mL of either the 200 mg/5 mL or 400 mg/5 mL suspension contains 7 mg phenylalanine.

5.7 Development of Drug-Resistant Bacteria
Prescribing amoxicillin and clavulanate potassium suspension in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient, and increases the risk of the development of drug-resistant bacteria.

The following are discussed in more detail in other sections of the labeling:

Anaphylactic reactions [see WARNINGS AND PRECAUTIONS (5.1)]
Hepatic Dysfunction [see WARNINGS AND PRECAUTIONS (5.2)]
CDAD [see WARNINGS AND PRECAUTIONS (5.3)]
6.1 Clinical Trials 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.

The most frequently reported adverse reactions were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). Less than 3% of patients discontinued

therapy because of drug-related adverse reactions. The overall incidence of adverse reactions, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported adverse reactions (<1%) include: Abdominal discomfort, flatulence, and headache.

In pediatric patients (aged 2 months to 12 years), 1 US/Canadian clinical trial was conducted which compared 45/6.4 mg/kg/day (divided every 12 hours) of amoxicillin and clavulanate potassium for 10 days versus 40/10 mg/kg/day (divided every 8 hours) of amoxicillin and clavulanate potassium for 10 days in the treatment of acute otitis media. A total of 575 patients were enrolled, and only the suspension formulations were used in this trial. Overall, the adverse reactions seen were comparable to that noted above; however, there were differences in the rates of diarrhea, skin rashes/urticaria, and diaper area rashes. [See CLINICAL STUDIES (14.2)]

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. 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: 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 AND PRECAUTIONS (5.3)]

Hypersensitivity Reactions: Pruritus, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, hypersensitivity vasculitis, and cases of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. [see WARNINGS AND PRECAUTIONS (5.1)]

Liver: Hepatic dysfunction, including hepatitis and cholestatic jaundice, increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been reported with amoxicillin and clavulanate potassium. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. Deaths have been reported. [see CONTRAINDICATIONS (4.2), WARNINGS AND PRECAUTIONS (5.2)]

Renal: Interstitial nephritis, hematuria, and crystalluria have been reported. [see OVERDOSAGE (10)]

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Thrombocytosis was noted in less than 1% of the patients treated with amoxicillin and clavulanate potassium. There have been reports of increased prothrombin time in patients receiving amoxicillin and clavulanate potassium and anticoagulant therapy concomitantly. [see DRUG INTERACTIONS (7.2)]

Central Nervous System: Agitation, anxiety, behavioral changes, 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.

7.1 Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin but does not delay renal excretion of

clavulanic acid. Concurrent use with amoxicillin and clavulanate potassium may result in increased and prolonged blood concentrations of amoxicillin. Coadministration 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 with amoxicillin and clavulanate potassium. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

7.3 Allopurinol

The concurrent administration of allopurinol and amoxicillin increases 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.

7.4 Oral Contraceptives

Amoxicillin and clavulanate potassium 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, 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.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B. Reproduction studies performed in pregnant rats and mice given amoxicillin and clavulanate potassium (2:1 ratio formulation of amoxicillin:clavulanate) at oral doses up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to amoxicillin and clavulanate potassium. The amoxicillin doses in rats and mice (based on body surface area) were approximately 4 and 2 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, these dose multiples were approximately 9 and 4 times the maximum recommended adult human oral dose (125 mg every 8 hours). 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.

8.2 Labor and Delivery

Oral ampicillin-class antibiotics are poorly absorbed during labor. It is not known whether 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 of the necessity for an obstetrical intervention.

8.3 Nursing Mothers

Amoxicillin has been shown to be excreted in human milk. Amoxicillin/clavulanate potassium use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin/clavulanate potassium is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of amoxicillin and clavulanate potassium for oral suspension has been established in pediatric patients. Use of amoxicillin and clavulanate potassium in pediatric patients is supported by evidence from studies of amoxicillin and clavulanate potassium tablets in adults with additional data from a study of amoxicillin and clavulanate potassium powder for oral suspension in pediatric patients aged 2 months to 12 years with acute otitis media. [see CLINICAL STUDIES (14.2)]

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed; clavulanate elimination is unaltered in this age group. Dosing of amoxicillin and clavulanate potassium should be modified in pediatric patients aged <12 weeks (<3 months). [see DOSAGE AND ADMINISTRATION (2.2)]

8.5 Geriatric Use

Of the 3,119 patients in an analysis of clinical studies of amoxicillin and clavulanate potassium, 32% were ≥65 years old, and 14% were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but 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 adverse 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.

8.6 Dosing in Renal Impairment

Amoxicillin is primarily eliminated by the kidney and dosage adjustment is usually required in patients with severe renal impairment (GFR <30 mL/min). See Patients with Renal Impairment (2.3) for specific recommendations in patients with renal impairment.

Amoxicillin and Clavulanate Potassium Powder for Oral Suspension, USP is an oral antibacterial combination consisting of amoxicillin and the beta-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:

The structural formula for Amoxicillin.

Clavulanic acid is produced by the fermentation of Streptomyces clavuligerus. It is a beta-lactam structurally related to the penicillins and possesses the ability to inactivate some beta-lactamases by blocking the active sites of these enzymes. The clavulanate potassium molecular formula is $C_8H_8KNO_5$, and the molecular weight is 237.25. Chemically, clavulanate potassium is potassium (Z)(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate and may be represented structurally as:

The structural formula for Clavulanic acid.

Inactive Ingredients:

Aspartame, colloidal silicon dioxide, HPMC 2910/ hypromellose 5 cP, silicon dioxide, succinic acid, xanthan gum, golden syrup flavor, orange flavor.

• See PRECAUTIONS - Information for the Patient.

Each 5 mL of reconstituted amoxicillin and clavulanate potassium 400 mg/57 mg per 5 mL suspension contains 0.268 mEq of potassium.

Each 5 mL of reconstituted amoxicillin and clavulanate potassium 200 mg/28.5 mg per 5 mL suspension contains 0.143 mEq of potassium

12.1 Mechanism of Action

Amoxicillin and clavulanate potassium for oral suspension is an antibacterial drug. [see MICROBIOLOGY 12.4]

12.3 Pharmacokinetics

Mean amoxicillin and clavulanate potassium pharmacokinetic parameters in normal adults following administration of amoxicillin and clavulanate potassium tablets are shown in Table 3 and following administration of amoxicillin and clavulanate potassium powder for oral suspension and chewable tablets are shown in Table 4.

Table 3: Mean (±S.D.) Amoxicillin and Clavulanate Potassium Pharmacokinetic Parametersa,b with Amoxicillin and Clavulanate Potassium Tablets

Dose and Regimen	Cmax (mcg/mL)		AUC0-24 (mcg*h/mL)	
Amoxicillin/Clavulanate potassium	Amoxicillin	Clavulanate potassium	Amoxicillin	Clavulanate potassium
250/125 mg every 8 hours	3.3 ± 1.12	1.5 ± 0.70	26.7 ± 4.56	12.6 ± 3.25
500/125 mg every 12 hours	6.5 ± 1.41	1.8 ± 0.61	33.4 ± 6.76	8.6 ± 1.95
500 125 mg every 8 hours	7.2 ± 2.26	2.4 ± 0.83	53.4 ± 8.87	15.7 ± 3.86
875/125 mg every 12 hours	11.6 ± 2.78	2.2 ± 0.99	53.5 ± 12.31	10.2 ± 3.04

a Mean (± standard deviation) values of 14 normal adults (N=15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.

b Amoxicillin/clavulanate potassium administered at the start of a light meal.

Table 4: Mean (±S.D.) Amoxicillin and Clavulanate Potassium Pharmacokinetic Parametersa,b with Amoxicillin and Clavulanate Potassium Powder for Oral Suspension and Chewable Tablets

Dose	Cmax (mcg/mL)		AUC0-24 (mcg*h/mL)	
Amoxicillin/Clavulanate potassium	Amoxicillin	Clavulanate potassium	Amoxicillin	Clavulanate potassium
400/57 mg (5 mL of suspension)	6.94 ± 1.24	1.10 ± 0.42	17.29 ± 2.28	2.34 ± 0.94
400/57 mg (1 chewable tablet)	6.67 ± 1.37	1.03 ± 0.33	17.24 ± 2.64	2.17 ± 0.73

a Mean (± standard deviation) values of 28 normal adults. Peak concentrations occurred approximately 1 hour after the dose.
b Amoxicillin/clavulanate potassium administered at the start of a light meal.

Oral administration of 5 mL of 250 mg/62.5 mg per 5 mL suspension of amoxicillin and clavulanate potassium or the equivalent dose of 10 mL of 125 mg/31.25 mg per 5 mL suspension of amoxicillin and clavulanate potassium provides average peak serum concentrations approximately 1 hour after dosing of 6.9 mcg/mL for amoxicillin and 1.6 mcg/mL for clavulanic acid. The areas under the serum concentration curves obtained during the first 4 hours after dosing were 12.6 mcg*h/mL for amoxicillin and 2.9 mcg*h/mL for clavulanic acid when 5 mL of 250 mg/62.5 mg per 5 mL suspension of amoxicillin and clavulanate potassium or equivalent dose of 10 mL of 125 mg/31.25 mg per 5 mL suspension of amoxicillin and clavulanate potassium were administered to normal adults. One 250 mg/62.5 mg chewable tablet of amoxicillin and clavulanate potassium or two 125 mg/31.25 mg chewable tablets of amoxicillin and clavulanate potassium are equivalent to 5 mL of 250 mg/ 62.5 mg per 5 mL suspension of amoxicillin and clavulanate potassium and provide similar serum concentrations of amoxicillin and clavulanic acid.

Amoxicillin serum concentrations achieved with amoxicillin and clavulanate potassium suspension are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. Time above the minimum inhibitory concentration of 1 mcg/mL for amoxicillin has been shown to be similar after corresponding every 12 hour and every 8 hour dosing regimens of amoxicillin and clavulanate potassium suspension in adults and children.

Absorption: Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin and clavulanate potassium suspension can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In one study, the relative bioavailability of clavulanate was reduced when amoxicillin and clavulanate potassium suspension was dosed at 30 and 150 minutes after the start of a high-fat breakfast.

Distribution: Neither component in amoxicillin and clavulanate potassium suspension is highly protein-bound; clavulanic acid is 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.

Two hours after oral administration of a single 35 mg/kg dose of suspension of amoxicillin and clavulanate potassium to fasting children, average concentrations of 3 mcg/mL of amoxicillin and 0.5 mcg/mL of clavulanic acid were detected in middle ear effusions.

Metabolism and Excretion: The half-life of amoxicillin after the oral administration of amoxicillin and clavulanate potassium suspension is 1.3 hours and that of clavulanic acid is 1 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 and clavulanate potassium.

12.4 Microbiology
Amoxicillin is a semisynthetic antibiotic with in vitro bactericidal activity against Gram-positive and Gram-negative bacteria. Amoxicillin is, however, susceptible to degradation by beta-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate some beta-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated beta-lactamases frequently responsible for transferred drug resistance.

The formulation of amoxicillin and clavulanic acid in amoxicillin and clavulanate potassium for oral suspension protects amoxicillin from degradation by some beta-lactamase enzymes and extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin.

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

Gram-positive bacteria

Staphylococcus aureus

Gram-negative bacteria

Enterobacter species

Escherichia coli

Haemophilus influenzae

Klebsiella species

Moraxella catarrhalis

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

Gram-positive bacteria

Enterococcus faecalis Staphylococcus epidermidis Staphylococcus saprophyticus Streptococcus pneumoniae Streptococcus pyogenes Viridans group Streptococcus

Gram-negative Bacteria

Eikenella corrodens

Proteus mirabilis

Anaerobic Bacteria

Bacteroides species including Bacteroides fragilis

Fusobacterium species

Peptostreptococcus species

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method2, 3 (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 5.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method3,4. This procedure uses paper disks impregnated with 30 mcg amoxicillin/clavulanic acid (20 mcg amoxicillin plus 10 mcg clavulanic acid) to test the susceptibility of bacteria to amoxicillin/clavulanic acid. The disc diffusion interpretive criteria are provided in Table 5.

Table 5: Susceptibility Test Interpretive Criteria for Amoxicillin Clavulanic Acid

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae	8/4	16/8	32/16	≥18	14-17	≤13
Haemophilus influenzae and Staphylococcus aureus	4/2	--	8/4	≥20	--	≤19

Quality Control:

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test2,3,4. Standard amoxicillin/clavulanic acid powder should provide the following range of MIC values noted in Table 6 for the diffusion technique using the 30 mcg amoxicillin/clavulanic acid (20 mcg amoxicillin plus 10 mcg clavulanic acid) disk, the criteria in Table 6 should be achieved.

Table 6: Acceptable Quality Control Ranges for Amoxicillin/Clavulanic Acid

QC Strain	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion (zone diameter in mm)
Escherichia coli ATCC 25922	2/1 to 8/4	18 to 24
Escherichia coli ATCC 35218	4/2 to 16/8	17 to 22
Haemophilus influenzae ATCC 49247	2/1 to 16/8	15 to 23
Staphylococcus aureus ATCC 29213	0.12/0.06 to 0.5/0.25	-
Staphylococcus aureus ATCC 29523	-	28 to 36

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 doses that were also associated with decreased cell survival.
Amoxicillin and clavulanate potassium suspension 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 suspension (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, this dose of amoxicillin is approximately 4 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, the dose multiple is approximately 9 times higher than the maximum recommended adult human oral dose (125 mg every 8 hours), also based on body surface area.

14.1 Lower Respiratory Tract and Complicated Urinary Tract Infections
Data from 2 pivotal trials in 1,191 patients treated for either lower respiratory tract infections or complicated urinary tract infections compared a regimen of 875-mg tablets of amoxicillin and clavulanate potassium every 12 hours to 500-mg tablets of amoxicillin and clavulanate potassium dosed every 8 hours (584 and 607 patients, respectively). Comparable efficacy was demonstrated between the every 12 hours and every 8 hours 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 every 12 hours and 500-mg every 8 hours dosing regimens (15% and 14%, respectively); however, there was a statistically significant difference ($p < 0.05$) in rates of severe diarrhea or withdrawals with diarrhea between the regimens: 1% for 875-mg every 12 hours regimen versus 2% for the 500-mg every 8 hours regimen.

In one of these pivotal trials, patients with either pyelonephritis (n = 361) or a complicated urinary tract infection (i.e., patients with abnormalities of the urinary tract that predispose to relapse of bacteriuria following eradication, n = 268) were randomized (1:1) to receive either 875-mg tablets of amoxicillin and clavulanate potassium every 12 hours (n=308) or 500-mg tablets of amoxicillin and clavulanate potassium every 8 hours (n=321).

The number of bacteriologically evaluable patients was comparable between the two dosing regimens. Amoxicillin and 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 Table 7.

Table 7: Bacteriologic efficacy rates for Amoxicillin and Clavulanate Potassium

Time Post Therapy	875 mg every 12 hours % (n)	500 mg every 8 hours % (n)
2 to 4 days	81% (58)	80% (54)
5 to 9 days	58% (41)	52% (52)
2 to 4 weeks	52% (101)	55% (104)

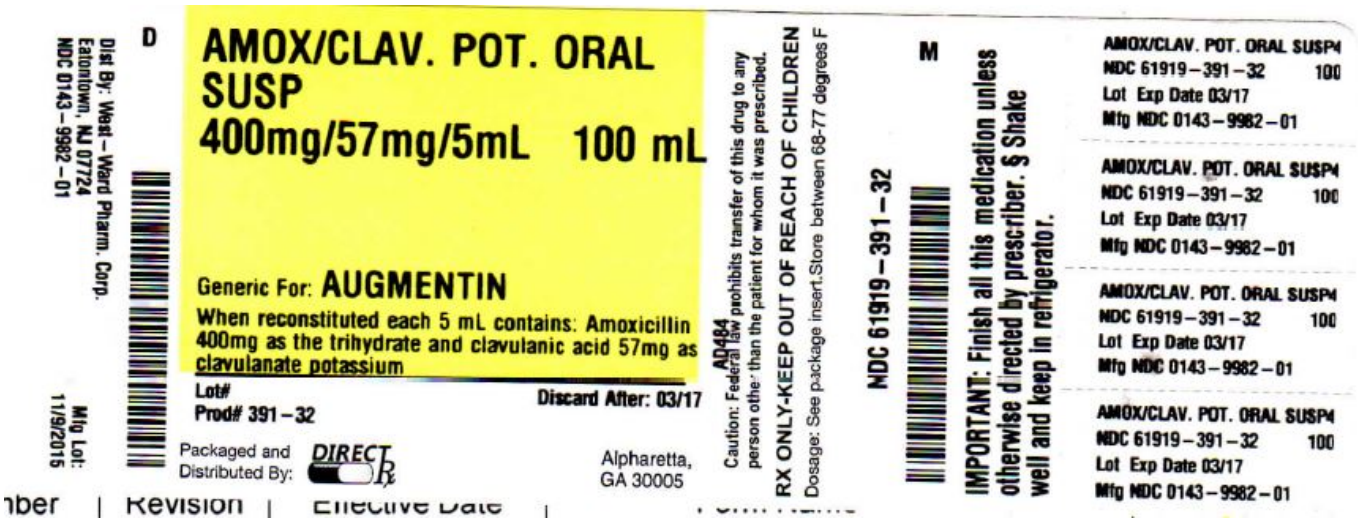
As noted before, though there was no significant difference in the percentage of adverse events in each group, there was a statistically significant difference in rates of severe diarrhea or withdrawals with diarrhea between the regimens.

14.2 Acute Bacterial Otitis Media and Diarrhea in Pediatric Patients
One US/Canadian clinical trial was conducted which compared 45/6.4 mg/kg/day (divided every 12 hours) of amoxicillin and clavulanate potassium for 10 days versus 40/10 mg/kg/day (divided every 8 hours) of amoxicillin and clavulanate potassium for 10 days in the treatment of acute otitis media. Only the suspension formulations were used in this trial. A total of 575 pediatric patients (aged 2 months to 12 years) were enrolled, with an even distribution among the 2 treatment groups and a comparable number of patients were evaluable (i.e., ≥ 84%) per treatment group. Otitis media-specific criteria were required for eligibility and a strong correlation was found at the end of therapy and follow-up between these criteria and physician assessment of clinical response. The clinical efficacy rates at the end of

therapy visit (defined as 2-4 days after the completion of therapy) and at the follow-up visit (defined as 22-28 days post-completion of therapy) were comparable for the 2 treatment groups, with the following cure rates obtained for the evaluable patients: At end of therapy, 87% (n = 265) and 82% (n = 260) for 45 mg/kg/day every 12 hours and 40 mg/kg/day every 8 hours, respectively. At follow-up, 67% (n = 249) and 69% (n = 243) for 45 mg/kg/day every 12 hours and 40 mg/kg/day every 8 hours, respectively.

Diarrhea was defined as either: (a) 3 or more watery or 4 or more loose/watery stools in 1 day; OR (b) 2 watery stools per day or 3 loose/watery stools per day for 2 consecutive days. The incidence of diarrhea was significantly lower in patients who received the every 12 hours regimen compared to patients who received the every 8 hours regimen (14% and 34%, respectively). In addition, the number of patients with either severe diarrhea or who were withdrawn with diarrhea was significantly lower in the every 12 hours treatment group (3% and 8% for the every 12 hours/10 day and every 8 hours/10 day, respectively). In the every 12 hours treatment group, 3 patients (1%) were withdrawn with an allergic reaction, while 1 patient in the every 8 hours group was withdrawn for this reason. The number of patients with a candidal infection of the diaper area was 4% and 6% for the every 12 hours and every 8 hours groups, respectively.

It is not known if the finding of a statistically significant reduction in diarrhea with the oral suspensions dosed every 12 hours, versus suspensions dosed every 8 hours, can be extrapolated to the chewable tablets. The presence of mannitol in the chewable tablets may contribute to a different diarrhea profile. The every 12 hour oral suspensions (200 mg/5 mL and 400 mg/5 mL) are sweetened with aspartame.



AUGMENTIN

amox/clav.pot.oral susp powder, for suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-391(NDC:0143-9982)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
AMOXICILLIN (UNII: 804826J2HU) (AMOXICILLIN ANHYDROUS - UNII:9EM05410Q9)	AMOXICILLIN ANHYDROUS	400 mg in 5 mL
CLAVULANIC ACID (UNII: 23521W1S24) (CLAVULANIC ACID - UNII:23521W1S24)	CLAVULANIC ACID	57 mg in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
ASPARTAME (UNII: Z0H242BBR1)	
SUCCINIC ACID (UNII: AB6MNQ6J6L)	
XANTHAN GUM (UNII: TTV12P4NEE)	

Product Characteristics			
Color		**Score**	
Shape		**Size**	
Flavor	FRUIT	**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:61919-391-32	5 mL in 1 BOTTLE; Type 0: Not a Combination Product	11/09/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065191	11/09/2015	

Labeler - Direct_Rx (079254320)

Registrant - Direct_Rx (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
Direct_Rx		079254320	repack(61919-391)

Revised: 7/2016 Direct_Rx