

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AUGMENTIN ES-600 safely and effectively. See full prescribing information for AUGMENTIN ES-600.

AUGMENTIN ES-600® (amoxicillin and clavulanate potassium) Powder for Oral Suspension Initial U.S. Approval: 1984

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AUGMENTIN ES-600 and other antibacterial drugs, AUGMENTIN ES-600 should be used only to treat infections that are proven or strongly suspected to be caused by bacteria (1).

INDICATIONS AND USAGE

AUGMENTIN ES-600® is indicated for the treatment of pediatric patients with recurrent or persistent acute otitis media due to *S. pneumoniae* (penicillin MICs ≤ 2 mcg/mL), *H. influenzae* (including beta-lactamase-producing strains), or *M. catarrhalis* (including beta-lactamase-producing strains) characterized by the following risk factors (1):

- antibacterial drug exposure for acute otitis media within the preceding 3 months, and either of the following: 1) age 2 years or younger 2) daycare attendance

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

600 mg/42.9 mg per 5 mL. (3)

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction (e.g., anaphylaxis or Stevens-Johnson syndrome) to AUGMENTIN ES-600 or to other beta-lactams (e.g., penicillins or cephalosporins). (4.1)
- History of cholestatic jaundice/hepatic dysfunction associated with AUGMENTIN ES-600. (4.2)

WARNINGS AND PRECAUTIONS

- Serious (including fatal) hypersensitivity reactions: Discontinue AUGMENTIN ES-600 if a reaction occurs. (5.1)
- Hepatic dysfunction and cholestatic jaundice: Discontinue if signs/symptoms of hepatitis occur. Monitor liver function tests in patients with hepatic impairment. (5.2)
- Clostridium difficile*-associated diarrhea (CDAD): Evaluate patients if diarrhea occurs. (5.3)
- Patients with mononucleosis who receive AUGMENTIN ES-600 develop skin rash. Avoid AUGMENTIN ES-600 use in these patients. (5.4)

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 Dr. Reddy's Laboratories Inc., at 1-888-375-3784 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 AUGMENTIN ES-600 with oral anticoagulants may increase the prolongation of prothrombin time. (7.2)
- Co-administration with allopurinol increases the risk of rash. (7.3)
- AUGMENTIN ES-600 may reduce efficacy of oral contraceptives. (7.4)

USE IN SPECIFIC POPULATIONS

- Pediatric 3 months to 12 years old: Modify dose according to weight. (2.1, 8.4)
- Adults and pediatric patients weighing more than 40 kg: The safety and effectiveness of AUGMENTIN ES-600 Powder for Oral Suspension has not been established. (8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AUGMENTIN ES-600 and other antibacterial drugs, AUGMENTIN ES-600 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.

AUGMENTIN ES-600 is indicated for the treatment of pediatric patients with recurrent or persistent acute otitis media due to *S. pneumoniae* (penicillin MICs ≤ 2 mcg/mL), *H. influenzae* (including beta-lactamase – producing strains), or *M. catarrhalis* (including beta-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:
 - age 2 years or younger
 - daycare attendance

[see CLINICAL PHARMACOLOGY, Microbiology (12.4)]

NOTE: Acute otitis media due to *S. pneumoniae* alone can be treated with amoxicillin. AUGMENTIN ES-600 is not indicated for the treatment of acute otitis media due to *S. pneumoniae* with penicillin MIC ≥ 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 ≤ 2 mcg/mL) and the beta-lactamase-producing organisms listed above.

2 DOSAGE AND ADMINISTRATION

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

Dosage: Pediatric patients 3 months and older: Based on the amoxicillin component (600 mg/5 mL), the recommended dose of AUGMENTIN ES-600 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 AUGMENTIN ES-600 Powder for Oral Suspension providing 90 mg/kg/day
8	3.0 mL twice daily
12	4.5 mL twice daily
16	6.0 mL twice daily
20	7.5 mL twice daily
24	9.0 mL twice daily
28	10.5 mL twice daily
32	12.0 mL twice daily
36	13.5 mL twice daily

Pediatric patients weighing 40 kg and more: Experience with AUGMENTIN ES-600 in this group is not available.

Adults: Experience with AUGMENTIN ES-600 in adults is not available and adults who have difficulty swallowing should not be given AUGMENTIN ES-600 in place of the 500-mg or 875-mg tablet of AUGMENTIN.

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

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 below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

AUGMENTIN ES-600 Powder for Oral Suspension	
Bottle Size	Amount of Water Required for Reconstitution
75 mL	70 mL
125 mL	110 mL
200 mL	180 mL

Each teaspoonful (5 mL) will contain 600 mg amoxicillin as the trihydrate and 42.9 mg of clavulanic acid as the potassium salt.

NOTE: SHAKE ORAL SUSPENSION WELL BEFORE USING.

Information for the Pharmacist: For patients who wish to alter the taste of AUGMENTIN ES-600, immediately after reconstitution 1 drop of FLAVORx™ (apple, banana cream, bubble gum, cherry, or watermelon flavor) may be added for every 5 mL of AUGMENTIN ES-600. The resulting suspension is stable for 10 days under refrigeration. Stability of AUGMENTIN ES-600 when mixed with other flavors distributed by FLAVORx has not been evaluated for flavors other than the five flavors listed above.

Administration: To minimize the potential for gastrointestinal intolerance, AUGMENTIN ES-600 should be taken at the start of a meal. Absorption of clavulanate potassium may be enhanced when AUGMENTIN ES-600 is administered at the start of a meal.

3 DOSAGE FORMS AND STRENGTHS

Powder for Oral Suspension:

- **600 mg/42.9 mg per 5 mL:** Strawberry cream-flavored powder for oral suspension (each 5 mL of reconstituted suspension contains 600 mg amoxicillin and 42.9 mg of clavulanic acid as the potassium salt).

4 CONTRAINDICATIONS

4.1 Serious Hypersensitivity Reactions

AUGMENTIN ES-600 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

AUGMENTIN ES-600 is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with treatment with amoxicillin/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 AUGMENTIN ES-600. 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 AUGMENTIN ES-600, careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, discontinue AUGMENTIN ES-600 and institute appropriate therapy.

5.2 Hepatic Dysfunction

Use AUGMENTIN ES-600 with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin/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)*].

5.3 Clostridium difficile-Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AUGMENTIN ES-600, 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.

5.4 Skin Rash in Patients with Mononucleosis

A high percentage of patients with mononucleosis who receive amoxicillin develop an erythematous skin rash. Thus, AUGMENTIN ES-600 should not be administered to patients with mononucleosis.

5.5 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/or appropriate therapy instituted.

5.6 Phenylketonurics

AUGMENTIN ES-600 contains aspartame which contains phenylalanine. Each 5 mL of the 600 mg/42.9 mg per 5 mL suspension of AUGMENTIN ES-600 Powder for Oral Suspension contains 7 mg phenylalanine.

5.7 Development of Drug-Resistant Bacteria

Prescribing AUGMENTIN ES-600 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.

6 ADVERSE REACTIONS

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 AUGMENTIN ES-600 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 AUGMENTIN ES-600 (90/6.4 mg/kg/day, divided every 12 hours) to AUGMENTIN (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 AUGMENTIN ES-600 and the comparator of AUGMENTIN 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 AUGMENTIN ES-600 (11%) and AUGMENTIN (9%) were not statistically different. Two patients in the group treated with AUGMENTIN ES-600 and one patient in the group treated with AUGMENTIN 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 AUGMENTIN products, including AUGMENTIN ES-600. 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 AUGMENTIN.

Gastrointestinal: Nausea, indigestion, gastritis, stomatitis, glossitis, black “hairy” tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudo membranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial drug treatment.

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, hypersensitivity vasculitis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported [see *Warnings and Precautions (5.1)*].

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibacterial drugs. 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 AUGMENTIN or AUGMENTIN ES-600. 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 (5.2)*].

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 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 AUGMENTIN and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, headache, 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 AUGMENTIN ES-600 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 [INRI]) 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.

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 AUGMENTIN ES-600 and allopurinol administered concurrently.

7.4 Oral Contraceptives

AUGMENTIN ES-600 may affect intestinal flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

7.5 Effects on Laboratory Test

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 AUGMENTIN ES-600, 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 of AUGMENTIN in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Reproduction studies performed in pregnant rats and mice given AUGMENTIN (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 AUGMENTIN. 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 AUGMENTIN ES-600 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 AUGMENTIN ES-600.

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 AUGMENTIN 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 AUGMENTIN 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 AUGMENTIN is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy of AUGMENTIN ES-600 in infants younger than 3 months have not been established. Safety and efficacy of AUGMENTIN ES-600 have been demonstrated for treatment of acute otitis media in infants and children 3 months to 12 years [*see Description of Clinical Studies (14)*].

The safety and effectiveness of AUGMENTIN ES-600 Powder 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 AUGMENTIN XR™ Extended Release Tablets in adults with acute bacterial sinusitis, studies of AUGMENTIN ES-600 Powder for Oral Suspension in pediatric patients with acute otitis media, and by similar pharmacokinetics of amoxicillin and clavulanate in pediatric patients taking AUGMENTIN ES-600 Powder for Oral Suspension [*see CLINICAL PHARMACOLOGY (12)*] and adults taking AUGMENTIN XR.

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 the case of overdosage, discontinue AUGMENTIN ES-600, 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 overdosage of less than 250 mg/kg of amoxicillin is not associated with significant clinical symptoms and does not require gastric emptying.⁴

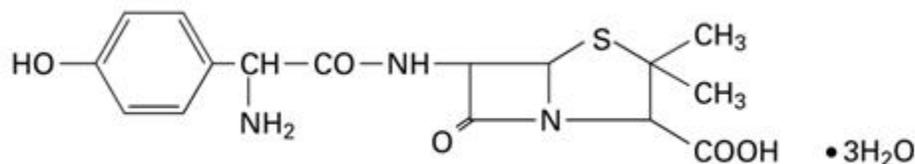
Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

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.

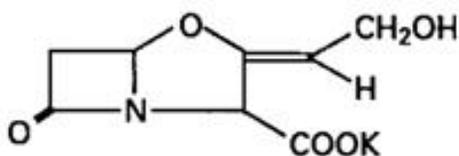
Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation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

11 DESCRIPTION

AUGMENTIN ES-600 is an oral antibacterial combination consisting of the semisynthetic antibacterial 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 (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 beta-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of beta-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated beta-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KN_2O_5$ 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:



Inactive Ingredients: - Aspartame*, colloidal silicon dioxide, silicon dioxide, sodium carboxymethylcellulose, strawberry cream flavor and xanthan gum [see *Warnings and Precautions* (5.6)]. Each 5 mL of reconstituted 600 mg/42.9 mg per 5 mL oral suspension of AUGMENTIN ES-600 contains 0.23 mEq potassium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

AUGMENTIN ES-600 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 AUGMENTIN ES-600 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 (\pm SD) Plasma Amoxicillin and Clavulanate Pharmacokinetic Parameter Values Following Administration of 45 mg/kg of AUGMENTIN ES-600 Every 12 Hours to Pediatric Patients

PARAMETER	AMOXICILLIN	CLAVULANATE
C _{max} (mcg/mL)	15.7 \pm 7.7	1.7 \pm 0.9
T _{max} (hourr)	2.0 (1.0 – 4.0)	1.1 (1.0 – 4.0)
AUC _{0-T} (mcg*hour/mL)	59.8 \pm 20.0	4.0 \pm 1.9
T _{1/2} (hour)	1.4 \pm 0.3	1.1 \pm 0.3
CL/F (L/hour/kg)	0.9 \pm 0.4	1.1 \pm 1.1

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

The effect of food on the oral absorption of AUGMENTIN ES-600 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 250 mg/5 mL suspension of AUGMENTIN.

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

Neither component in AUGMENTIN ES-600 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 AUGMENTIN ES-600 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 AUGMENTIN ES-600 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 – 14.0	0.2 – 5.5
		(n = 5)	(n = 4)
2 hour	mean	15.7	3.3
	median	13.0	2.4
	range	11.0 – 25.0	1.9 – 6
		(n = 7)	(n = 5)
3 hour	mean	13.0	5.8
	median	12.0	6.5
	range	5.5 – 21.0	3.9 – 7.4
		(n = 5)	(n = 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

Mechanism of Action

Amoxicillin binds to penicillin-binding proteins within the bacterial cell wall and inhibits bacterial cell wall synthesis. Clavulanic acid is a beta-lactam, structurally related to penicillin, that may inactivate certain beta-lactamase enzymes.

Mechanism of Resistance

Resistance to penicillins may be mediated by destruction of the beta-lactam ring by a beta-lactamase, altered affinity of penicillin for target, or decreased penetration of the antimicrobial drug to reach the target site. Amoxicillin alone is susceptible to degradation by beta-lactamases, and therefore its spectrum of activity does not include bacteria that produce these enzymes.

Amoxicillin/clavulanic acid has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section (1).

Gram-positive bacteria:

Streptococcus pneumoniae (including isolates with penicillin MICs ≤ 2 mcg/mL)

Gram-negative bacteria:

Haemophilus influenzae (including beta-lactamase-producing isolates)

Moraxella catarrhalis (including beta-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 beta-lactamase-producing isolates)

Streptococcus pyogenes

Susceptibility Test Methods: When available, the clinical microbiology laboratory should provide cumulative results of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas 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 the most effective antimicrobial.

Dilution Technique: 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 standard test method^{1,2} (broth for *S. pneumoniae* and *H. influenzae*). The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion Technique: Quantitative methods that require measurement of zone diameters also provides reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method^{2,3}. This procedure uses paper disks impregnated with 30 mcg amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg

clavulanate potassium) to test susceptibility of microorganisms to amoxicillin/clavulanate potassium. Disk diffusion zone sizes should be interpreted according to criteria provided in Table 3.

Table 3. Susceptibility Test Result Interpretive Criteria for Amoxicillin/Clavulanate Potassium

Pathogen	Minimum Inhibitory Concentration (mcg/mL)			Disk Diffusion (Zone Diameter in mm)		
	S	I	R	S	I	R
<i>Streptococcus pneumoniae</i> (non-meningitis isolates)	≤ 2/1	4/2	≥ 8/4	Not Applicable (NA)		
<i>Haemophilus influenzae</i>	≤ 4/2	NA	≥ 8/4	≥ 20	NA	≤ 19

S=Susceptible, I=Intermediate, R=Resistant

NOTE: Susceptibility of *S. pneumoniae* should be determined using a 1-mcg oxacillin disk.

NOTE: For nonmeningitis isolates, a penicillin MIC of ≤0.06 mcg/mL (or oxacillin zone ≥ 20 mm) can predict susceptibility to amoxicillin/clavulanic acid².

NOTE: Beta-lactamase-negative, ampicillin-resistant (BLNAR) *H. influenzae* isolates should be considered resistant to amoxicillin/clavulanic acid despite apparent in vitro susceptibility of some BLNAR isolates to these agents.

A report of “Susceptible” (S) indicates that the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of “Intermediate” (I) indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible antimicrobials, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high doses of antimicrobial can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” (R) indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

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 test.¹⁻³ Standard amoxicillin/clavulanate potassium powder should provide the following range of MIC noted in Table 4. For the disk diffusion technique using the 30 mcg amoxicillin/clavulanate potassium disk, the criteria in Table 4 should be achieved.

Table 4. Acceptable Quality Control Ranges for Amoxicillin/Clavulanate Potassium

Quality Control Organism	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion (Zone Diameter in mm)
<i>Enterococcus faecalis</i> ATCC® ^a 29212	0.25/0.12-1.0/0.5	NA
<i>Escherichia coli</i> ATCC® 25922	2/1-8/4	18-24
<i>Escherichia coli</i> ATCC® 35218 ^{b,c}	4/2 to 16/8	17 to 22
<i>Haemophilus influenzae</i> ATCC 49247	2/1 to 16/8	15 to 23
<i>Staphylococcus aureus</i>	NA	28-36

ATCC® 25923		
<i>Staphylococcus aureus</i> ATCC® 29213	0.12/0.06-0.5/0.25	NA
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03/0.015 to 0.12/0.06	NA

^a ATCC = American Type Culture Collection

^b QC strain recommended when testing beta-lactam/beta-lactamase inhibitors².

^c This strain may lose its plasmid and develop susceptibility to beta-lactam antimicrobial agents after repeated transfers onto culture media. Minimize by removing new culture from storage at least monthly or whenever the strain begins to show decreased MICs to ampicillin, piperacillin, or ticarcillin².

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. AUGMENTIN (4:1 ratio formulation of amoxicillin:clavulanate) was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. AUGMENTIN 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. AUGMENTIN 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.

AUGMENTIN (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 AUGMENTIN 600-ES 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 AUGMENTIN ES-600 (90/6.4 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 AUGMENTIN ES-600, 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 AUGMENTIN ES-600; 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 5. Bacteriologic Eradication Rates in the Per Protocol Population

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

* CI = 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. Nonresponders at 2 to 4 days post-therapy were considered failures at the latter timepoint.

Table 6. Clinical Assessments in the Per Protocol Population (Includes *S. pneumoniae* Patients With Penicillin MICs = 2 mcg/mL or 4 mcg/mL*)

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

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

* *S. pneumoniae* strains with penicillin MICs of 2 mcg/mL or 4 mcg/mL are considered resistant to penicillin.

† CI = confidence intervals; 95% CIs are not adjusted for multiple comparisons.

‡ 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 = 2 mcg/mL and 4 mcg/mL were 29/41 (71%) and 17/41 (42%), respectively.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Ninth Edition*. CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fourth Informational Supplement*, CLSI document M100-S24, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2014.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition*. CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
4. 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

AUGMENTIN ES-600 Powder for Oral Suspension:

Each 5 mL of reconstituted strawberry cream-flavored suspension contains 600 mg amoxicillin trihydrate and 42.9 mg clavulanic acid as the potassium salt.

NDC 43598-003-51	75 mL bottle
NDC 43598-003-69	125 mL bottle
NDC 43598-003-54	200 mL bottle

Storage

Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days. Store dry powder for oral suspension at or below 25°C (77°F). Dispense in original container.

17 PATIENT COUNSELING INFORMATION

Take AUGMENTIN ES-600 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.

Counsel patients that antibacterial drugs, including AUGMENTIN ES-600, should only be used to treat bacterial infections. Antibacterial drugs do not treat viral infections (e.g., the common cold). When AUGMENTIN ES-600 is prescribed to treat a bacterial infection, tell patients 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 AUGMENTIN ES-600 or other antibacterial drugs in the future.

Counsel patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patient 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.

Keep suspension refrigerated. Shake well before using. When dosing a child with the suspension (liquid) of AUGMENTIN ES-600, use a dosing spoon or medicine dropper. Be sure to rinse the spoon or dropper after each use. Bottles of suspension of AUGMENTIN ES-600 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.

Counsel patients that AUGMENTIN ES-600 contains a penicillin class drug product that can cause allergic reactions in some individuals.

Counsel patients with phenylketonuria: Each 5 mL of the 600 mg/42.9 mg per 5 mL suspension of AUGMENTIN ES-600 contains 7 mg phenylalanine.

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