

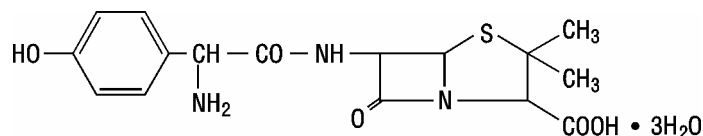
PRESCRIBING INFORMATION

AUGMENTIN ES-600[®]
(amoxicillin/clavulanate potassium)
Powder for Oral Suspension

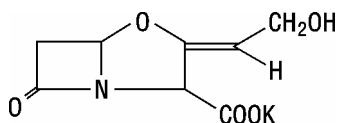
To reduce the development of drug-resistant bacteria and maintain the effectiveness of AUGMENTIN ES-600 (amoxicillin/clavulanate potassium) and other antibacterial drugs, AUGMENTIN ES-600 should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

AUGMENTIN ES-600 is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β -lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$, and the molecular weight is 419.46. Chemically, amoxicillin is (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:



Inactive Ingredients: Powder for Oral Suspension—Colloidal silicon dioxide, orange flavorings, xanthan gum, aspartame, hypromellose, and silicon dioxide.

• See PRECAUTIONS—Information for the Patient/Phenylketonurics.

36 Each 5 mL of reconstituted 600 mg/5 mL oral suspension of AUGMENTIN ES-600 contains
37 0.23 mEq potassium.

38 **CLINICAL PHARMACOLOGY**

39 The pharmacokinetics of amoxicillin and clavulanate were determined in a study of 19
40 pediatric patients, 8 months to 11 years, given AUGMENTIN ES-600 at an amoxicillin dose of
41 45 mg/kg q12h with a snack or meal. The mean plasma amoxicillin and clavulanate
42 pharmacokinetic parameter values are listed in the following table.

43
44 **Table 1. Mean (\pm SD) Plasma Amoxicillin and Clavulanate Pharmacokinetic**
45 **Parameter Values Following Administration of 45 mg/kg of AUGMENTIN ES-600**
46 **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} (hr)	2.0 (1.0 – 4.0)	1.1 (1.0 – 4.0)
AUC _{0-t} (mcg•hr/mL)	59.8 \pm 20.0	4.0 \pm 1.9
T _{1/2} (hr)	1.4 \pm 0.3	1.1 \pm 0.3
CL/F (L/hr/kg)	0.9 \pm 0.4	1.1 \pm 1.1

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

48
49 The effect of food on the oral absorption of AUGMENTIN ES-600 has not been studied.

50 Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the
51 clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of
52 10 mL of 250 mg/5 mL suspension of AUGMENTIN.

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

55 Neither component in AUGMENTIN ES-600 is highly protein-bound; clavulanic acid has
56 been found to be approximately 25% bound to human serum and amoxicillin approximately 18%
57 bound.

58 Oral administration of a single dose of AUGMENTIN ES-600 at 45 mg/kg (based on the
59 amoxicillin component) to pediatric patients, 9 months to 8 years, yielded the following
60 pharmacokinetic data for amoxicillin in plasma and middle ear fluid (MEF):

61

62 **Table 2. Amoxicillin Concentrations in Plasma and Middle Ear Fluid**
 63 **Following Administration of 45 mg/kg of AUGMENTIN ES-600 to Pediatric**
 64 **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 (n = 5)	0.2 – 5.5 (n = 4)
2 hour	mean	15.7	3.3
	median	13.0	2.4
	range	11.0 – 25.0 (n = 7)	1.9 – 6 (n = 5)
3 hour	mean	13.0	5.8
	median	12.0	6.5
	range	5.5 – 21.0 (n = 5)	3.9 – 7.4 (n = 5)

65 Dose administered immediately prior to eating.

66

67 Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain
 68 and spinal fluid. The results of experiments involving the administration of clavulanic acid to
 69 animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

70 **Microbiology:** Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal
 71 activity against many gram-positive and gram-negative microorganisms. Amoxicillin is,
 72 however, susceptible to degradation by β -lactamases, and therefore, the spectrum of activity does
 73 not include organisms which produce these enzymes. Clavulanic acid is a β -lactam, structurally
 74 related to the penicillins, which possesses the ability to inactivate a wide range of β -lactamase
 75 enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In
 76 particular, it has good activity against the clinically important plasmid-mediated β -lactamases
 77 frequently responsible for transferred drug resistance.

78 The clavulanic acid component in AUGMENTIN ES-600 protects amoxicillin from
 79 degradation by β -lactamase enzymes and effectively extends the antibiotic spectrum of
 80 amoxicillin to include many bacteria normally resistant to amoxicillin and other β -lactam
 81 antibiotics. Thus, AUGMENTIN ES-600 possesses the distinctive properties of a broad-spectrum
 82 antibiotic and a β -lactamase inhibitor.

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

86 **Aerobic Gram-Positive Microorganisms:**
87 *Streptococcus pneumoniae* (including isolates with penicillin MICs ≤ 2 mcg/mL)

88 **Aerobic Gram-Negative Microorganisms:**
89 *Haemophilus influenzae* (including β -lactamase-producing strains)
90 *Moraxella catarrhalis* (including β -lactamase-producing strains)

91 The following in vitro data are available, but their clinical significance is unknown.

92 At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory
93 concentration (MIC) less than or equal to the susceptible breakpoint for amoxicillin/clavulanic
94 acid. However, with the exception of organisms shown to respond to amoxicillin alone, the
95 safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these
96 microorganisms have not been established in adequate and well-controlled clinical trials.

97 **Aerobic Gram-Positive Microorganisms:**
98 *Staphylococcus aureus* (including β -lactamase-producing strains)
99 *Streptococcus pyogenes*

100 **NOTE:** Staphylococci which are resistant to methicillin/oxacillin must be considered resistant
101 to amoxicillin/clavulanic acid.

102 **NOTE:** *S. pyogenes* do not produce β -lactamase, and therefore, are susceptible to amoxicillin
103 alone. Adequate and well-controlled clinical trials have established the effectiveness of
104 amoxicillin alone in treating certain clinical infections due to *S. pyogenes*.

105 **Susceptibility Testing: Dilution Techniques:** Quantitative methods are used to determine
106 antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the
107 susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a
108 standardized procedure.^{1,2} Standardized procedures are based on a dilution method (broth for
109 *S. pneumoniae* and *H. influenzae*) or equivalent with standardized inoculum concentrations and
110 standardized concentrations of amoxicillin/clavulanate potassium powder.

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

115 **For testing *Streptococcus pneumoniae*^a:**

<u>MIC (mcg/mL)</u>	<u>Interpretation</u>
$\leq 2/1$	Susceptible (S)
4/2	Intermediate (I)
$\geq 8/4$	Resistant (R)

116 ^a These interpretive standards are applicable only to broth microdilution susceptibility tests
117 using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.²

118 **For testing *Haemophilus influenzae*^b:**

<u>MIC (mcg/mL)</u>	<u>Interpretation</u>
$\leq 4/2$	Susceptible (S)
$\geq 8/4$	Resistant (R)

119 ^b These interpretive standards are applicable only to broth microdilution susceptibility tests with
120 *Haemophilus* spp. using *Haemophilus* Test Medium (HTM).²

121
122 A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the
123 antimicrobial compound in the blood reaches the concentration usually achievable. A report of
124 “Intermediate” indicates that the result should be considered equivocal, and, if the
125 microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be
126 repeated. This category implies possible clinical applicability in body sites where the drug is
127 physiologically concentrated or in situations where high dosage of drug can be used. This
128 category also provides a buffer zone that prevents small uncontrolled technical factors from
129 causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen
130 is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations
131 usually achievable; other therapy should be selected.

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

<u>Microorganism</u>	<u>MIC Range (mcg/mL)^c</u>
<i>Escherichia coli</i> ATCC 35218 (<i>H. influenzae</i> quality control)	4 to 16
<i>Haemophilus influenzae</i> ^d ATCC 49247	2 to 16
<i>Streptococcus pneumoniae</i> ^e ATCC 49619	0.03 to 0.12

135 ^c Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2
136 parts amoxicillin to 1 part clavulanic acid.

137 ^d This quality control range is applicable to *H. influenzae* ATCC 49247 tested by a broth
138 microdilution procedure using HTM²

139 ^e This quality control range is applicable to *S. pneumoniae* ATCC 49619 tested by a broth
140 microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse
141 blood.²

142
143 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters
144 also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds.
145 One such standardized procedure³ requires the use of standardized inoculum concentrations. This
146 procedure uses paper disks impregnated with 30 mcg of amoxicillin/clavulanate potassium
147 (20 mcg amoxicillin plus 10 mcg clavulanate potassium) to test the susceptibility of
148 microorganisms to amoxicillin/clavulanic acid.

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

152 **For *H. influenzae*^f:**

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥20	Susceptible (S)
≤19	Resistant (R)

153 ^f These zone diameter standards are applicable only to tests conducted with *Haemophilus* spp.
154 using HTM.²

155 **NOTE:** Beta-lactamase–negative, ampicillin-resistant *H. influenzae* strains must be
156 considered resistant to amoxicillin/clavulanic acid.

157 **For *Streptococcus pneumoniae*:**

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

162 ^g These zone diameter standards for *S. pneumoniae* apply only to tests performed using
163 Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.³

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

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

<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i> ATCC 35218 (<i>H. influenzae</i> quality control)	18 to 22
<i>Haemophilus influenzae</i> ^h ATCC 49247	15 to 23

172 ^h This quality control limit applies only to tests conducted with *H. influenzae* ATCC 49247
173 using HTM.

174 **INDICATIONS AND USAGE**

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

- 179 • antibiotic exposure for acute otitis media within the preceding 3 months, and either of the
180 following:
181 – age ≤2 years
182 – daycare attendance

183 [See CLINICAL PHARMACOLOGY, Microbiology.]

184 **NOTE:** Acute otitis media due to *S. pneumoniae* alone can be treated with amoxicillin.
185 AUGMENTIN ES-600 is not indicated for the treatment of acute otitis media due to
186 *S. pneumoniae* with penicillin MIC ≥ 4 mcg /mL.

187 Therapy may be instituted prior to obtaining the results from bacteriological studies when
188 there is reason to believe the infection may involve both *S. pneumoniae* (penicillin MIC
189 ≤ 2 mcg/mL) and the β -lactamase-producing organisms listed above.

190 To reduce the development of drug-resistant bacteria and maintain the effectiveness of
191 AUGMENTIN ES-600 and other antibacterial drugs, AUGMENTIN ES-600 should be used only
192 to treat or prevent infections that are proven or strongly suspected to be caused by susceptible
193 bacteria. When culture and susceptibility information are available, they should be considered in
194 selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and
195 susceptibility patterns may contribute to the empiric selection of therapy.

196 **CONTRAINDICATIONS**

197 AUGMENTIN ES-600 is contraindicated in patients with a history of allergic reactions to any
198 penicillin. It is also contraindicated in patients with a previous history of cholestatic
199 jaundice/hepatic dysfunction associated with AUGMENTIN.

200 **WARNINGS**

201 **SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC)**
202 **REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY.**
203 **THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A**
204 **HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY**
205 **TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A**
206 **HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE**
207 **REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING**
208 **THERAPY WITH AUGMENTIN ES-600, CAREFUL INQUIRY SHOULD BE MADE**
209 **CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS,**
210 **CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS,**
211 **AUGMENTIN ES-600 SHOULD BE DISCONTINUED AND THE APPROPRIATE**
212 **THERAPY INSTITUTED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE**
213 **IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN,**
214 **INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING**
215 **INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

216 **Pseudomembranous colitis has been reported with nearly all antibacterial agents,**
217 **including amoxicillin/clavulanate potassium, and has ranged in severity from mild to**
218 **life-threatening. Therefore, it is important to consider this diagnosis in patients who**
219 **present with diarrhea subsequent to the administration of antibacterial agents.**

220 Treatment with antibacterial agents alters the normal flora of the colon and may permit
221 overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one
222 primary cause of “antibiotic-associated colitis.”

223 After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic
224 measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug
225 discontinuation alone. In moderate to severe cases, consideration should be given to management
226 with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug
227 clinically effective against *C. difficile* colitis.

228 AUGMENTIN ES-600 should be used with caution in patients with evidence of hepatic
229 dysfunction. Hepatic toxicity associated with the use of amoxicillin/clavulanate potassium is
230 usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per
231 estimated 4 million prescriptions worldwide). These have generally been cases associated with
232 serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and
233 ADVERSE REACTIONS—Liver.)

234 **PRECAUTIONS**

235 **General:** While amoxicillin/clavulanate possesses the characteristic low toxicity of the
236 penicillin group of antibiotics, periodic assessment of organ system functions, including renal,
237 hepatic, and hematopoietic function, is advisable if therapy is for longer than the drug is
238 approved for administration.

239 A high percentage of patients with mononucleosis who receive ampicillin develop an
240 erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients
241 with mononucleosis.

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

245 Prescribing AUGMENTIN ES-600 in the absence of a proven or strongly suspected bacterial
246 infection or a prophylactic indication is unlikely to provide benefit to the patient and increases
247 the risk of the development of drug-resistant bacteria.

248 **Information for the Patient:** AUGMENTIN ES-600 should be taken every 12 hours with a
249 meal or snack to reduce the possibility of gastrointestinal upset. If diarrhea develops and is
250 severe or lasts more than 2 or 3 days, call your doctor.

251 Keep suspension refrigerated. Shake well before using. When dosing a child with the
252 suspension (liquid) of AUGMENTIN ES-600, use a dosing spoon or medicine dropper. Be sure
253 to rinse the spoon or dropper after each use. Bottles of suspension of AUGMENTIN ES-600 may
254 contain more liquid than required. Follow your doctor's instructions about the amount to use and
255 the days of treatment your child requires. Discard any unused medicine.

256 Patients should be counseled that antibacterial drugs including AUGMENTIN ES-600, should
257 only be used to treat bacterial infections. They do not treat viral infections (e.g., the common
258 cold). When AUGMENTIN ES-600 is prescribed to treat a bacterial infection, patients should be
259 told that although it is common to feel better early in the course of therapy, the medication
260 should be taken exactly as directed. Skipping doses or not completing the full course of therapy
261 may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood

262 that bacteria will develop resistance and will not be treatable by AUGMENTIN ES-600 or other
263 antibacterial drugs in the future.

264 **Phenylketonurics:** Each 5 mL of the 600 mg/5 mL suspension of AUGMENTIN ES-600
265 contains 7 mg phenylalanine.

266 **Drug Interactions:** Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent
267 use with AUGMENTIN ES-600 may result in increased and prolonged blood levels of
268 amoxicillin. Co-administration of probenecid cannot be recommended.

269 The concurrent administration of allopurinol and ampicillin increases substantially the
270 incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin
271 alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the
272 hyperuricemia present in these patients. There are no data with AUGMENTIN ES-600 and
273 allopurinol administered concurrently.

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

276 **Drug/Laboratory Test Interactions:** Oral administration of AUGMENTIN will result in
277 high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in
278 false-positive reactions when testing for the presence of glucose in urine using CLINITEST[®],
279 Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin and
280 therefore AUGMENTIN ES-600, it is recommended that glucose tests based on enzymatic
281 glucose oxidase reactions (such as CLINISTIX[®]) be used.

282 Following administration of ampicillin to pregnant women, a transient decrease in plasma
283 concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol
284 has been noted. This effect may also occur with amoxicillin and therefore
285 AUGMENTIN ES-600.

286 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals
287 have not been performed to evaluate carcinogenic potential. The mutagenic potential of
288 AUGMENTIN was investigated in vitro with an Ames test, a human lymphocyte cytogenetic
289 assay, a yeast test, and a mouse lymphoma forward mutation assay, and in vivo with mouse
290 micronucleus tests and a dominant lethal test. All were negative apart from the in vitro mouse
291 lymphoma assay where weak activity was found at very high, cytotoxic concentrations.
292 AUGMENTIN at oral doses of up to 1,200 mg/kg/day (5.7 times the maximum adult human
293 dose based on body surface area) was found to have no effect on fertility and reproductive
294 performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

295 **Teratogenic Effects:** Pregnancy (Category B). Reproduction studies performed in pregnant
296 rats and mice given AUGMENTIN at oral dosages up to 1,200 mg/kg/day (4.9 and 2.8 times the
297 maximum adult human oral dose based on body surface area, respectively), revealed no evidence
298 of harm to the fetus due to AUGMENTIN. There are, however, no adequate and well-controlled
299 studies in pregnant women. Because animal reproduction studies are not always predictive of
300 human response, this drug should be used during pregnancy only if clearly needed.

301 **Labor and Delivery:** Oral ampicillin-class antibiotics are generally poorly absorbed during
302 labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased
303 the uterine tone, frequency of contractions, height of contractions, and duration of contractions.
304 However, it is not known whether the use of AUGMENTIN in humans during labor or delivery
305 has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or
306 increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of
307 the newborn will be necessary. In a single study in women with premature rupture of fetal
308 membranes, it was reported that prophylactic treatment with AUGMENTIN may be associated
309 with an increased risk of necrotizing enterocolitis in neonates.

310 **Nursing Mothers:** Ampicillin-class antibiotics are excreted in human milk; therefore, caution
311 should be exercised when AUGMENTIN is administered to a nursing woman.

312 **Pediatric Use:** Safety and efficacy of AUGMENTIN ES-600 in infants younger than 3 months
313 have not been established. Safety and efficacy of AUGMENTIN ES-600 have been
314 demonstrated for treatment of acute otitis media in infants and children 3 months to 12 years (see
315 Description of Clinical Studies).

316 **ADVERSE REACTIONS**

317 AUGMENTIN ES-600 is generally well tolerated. The majority of side effects observed in
318 pediatric clinical trials of acute otitis media were either mild or moderate, and transient in nature;
319 4.4% of patients discontinued therapy because of drug-related side effects. The most commonly
320 reported side effects with probable or suspected relationship to AUGMENTIN ES-600 were
321 contact dermatitis, i.e., diaper rash (3.5%), diarrhea (2.9%), vomiting (2.2%), moniliasis (1.4%),
322 and rash (1.1%). The most common adverse experiences leading to withdrawal that were of
323 probable or suspected relationship to AUGMENTIN ES-600 were diarrhea (2.5%) and vomiting
324 (1.4%).

325 The following adverse reactions have been reported for ampicillin-class antibiotics:

326 **Gastrointestinal:** Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black
327 “hairy” tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous
328 colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic
329 treatment. (See WARNINGS.)

330 **Hypersensitivity Reactions:** Skin rashes, pruritus, urticaria, angioedema, serum sickness–
331 like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently
332 fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized
333 exanthematous pustulosis, and an occasional case of exfoliative dermatitis (including toxic
334 epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines
335 and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be
336 discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal
337 hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.)

338 **Liver:** A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated
339 with ampicillin-class antibiotics, but the significance of these findings is unknown. Hepatic

340 dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin,
341 and/or alkaline phosphatase, has been infrequently reported with AUGMENTIN. It has been
342 reported more commonly in the elderly, in males, or in patients on prolonged treatment. The
343 histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular,
344 or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction
345 may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction,
346 which may be severe, is usually reversible. On rare occasions, deaths have been reported (less
347 than 1 death reported per estimated 4 million prescriptions worldwide). These have generally
348 been cases associated with serious underlying diseases or concomitant medications.

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

351 **Hemic and Lymphatic Systems:** Anemia, including hemolytic anemia, thrombocytopenia,
352 thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported
353 during therapy with penicillins. These reactions are usually reversible on discontinuation of
354 therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in
355 less than 1% of the patients treated with AUGMENTIN. There have been reports of increased
356 prothrombin time in patients receiving AUGMENTIN and anticoagulant therapy concomitantly.

357 **Central Nervous System:** Agitation, anxiety, behavioral changes, confusion, convulsions,
358 dizziness, insomnia, and reversible hyperactivity have been reported rarely.

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

362 **OVERDOSAGE**

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

366 In the case of overdose, discontinue AUGMENTIN ES-600, treat symptomatically, and
367 institute supportive measures as required. If the overdose is very recent and there is no
368 contraindication, an attempt at emesis or other means of removal of drug from the stomach may
369 be performed. A prospective study of 51 pediatric patients at a poison control center suggested
370 that overdoses of less than 250 mg/kg of amoxicillin are not associated with significant clinical
371 symptoms and do not require gastric emptying.⁴

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

374 Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin
375 overdose in adult and pediatric patients. In case of overdose, adequate fluid intake and
376 diuresis should be maintained to reduce the risk of amoxicillin crystalluria.

377 Renal impairment appears to be reversible with cessation of drug administration. High blood
378 levels may occur more readily in patients with impaired renal function because of decreased

379 renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are
380 removed from the circulation by hemodialysis.

381 **DOSAGE AND ADMINISTRATION**

382 **AUGMENTIN ES-600, 600 mg/5 mL, does not contain the same amount of clavulanic acid**
383 **(as the potassium salt) as any of the other suspensions of AUGMENTIN.**

384 **AUGMENTIN ES-600 contains 42.9 mg of clavulanic acid per 5 mL, whereas the**
385 **200 mg/5 mL suspension of AUGMENTIN contains 28.5 mg of clavulanic acid per 5 mL**
386 **and the 400 mg/5 mL suspension contains 57 mg of clavulanic acid per 5 mL. Therefore,**
387 **the 200 mg/5 mL and 400 mg/5 mL suspensions of AUGMENTIN should *not* be substituted**
388 **for AUGMENTIN ES-600, as they are not interchangeable.**

389 **Dosage: Pediatric patients 3 months and older:** Based on the amoxicillin component
390 (600 mg/5 mL), the recommended dose of AUGMENTIN ES-600 is 90 mg/kg/day divided every
391 12 hours, administered for 10 days (see chart below).

Body Weight (kg)	Volume of AUGMENTIN ES-600 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

392 **Pediatric patients weighing 40 kg and more:** Experience with AUGMENTIN ES-600
393 (600 mg/5 mL formulation) in this group is not available.

394 **Adults:** Experience with AUGMENTIN ES-600 (600 mg/5 mL formulation) in adults is not
395 available and adults who have difficulty swallowing should not be given AUGMENTIN ES-600
396 (600 mg/5 mL) in place of the 500-mg or 875-mg tablet of AUGMENTIN.

397 Hepatically impaired patients should be dosed with caution and hepatic function monitored at
398 regular intervals. (See WARNINGS.)

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

AUGMENTIN ES-600 (600 mg/5 mL Suspension)

Bottle Size	Amount of Water Required for Reconstitution
75 mL	65 mL
125 mL	110 mL
200 mL	175 mL

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

405 **Note:** SHAKE ORAL SUSPENSION WELL BEFORE USING.

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

409 HOW SUPPLIED

410 **AUGMENTIN ES-600, 600 mg/5 mL, for Oral Suspension:** Each 5 mL of reconstituted
411 orange-flavored suspension contains 600 mg amoxicillin and 42.9 mg clavulanic acid as the
412 potassium salt.

NDC 0029-6094-3975 mL bottle

NDC 0029-6094-24200 mL bottle

NDC 0029-6094-45125 mL bottle

413 STORAGE

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

416 Description of Clinical Studies

417 Two clinical studies were conducted in pediatric patients with acute otitis media.

418 A non-comparative, open-label study assessed the bacteriologic and clinical efficacy of
419 AUGMENTIN ES-600 (90/6.4 mg/kg/day, divided every 12 hours) for 10 days in 521 pediatric
420 patients (3 to 50 months) with acute otitis media. The primary objective was to assess
421 bacteriological response in children with acute otitis media due to *S. pneumoniae* with
422 amoxicillin/clavulanic acid MICs of 4 mcg/mL. The study sought the enrollment of patients with
423 the following risk factors: Failure of antibiotic therapy for acute otitis media in the previous
424 3 months, history of recurrent episodes of acute otitis media, ≤ 2 years, or daycare attendance.
425 Prior to receiving AUGMENTIN ES-600, all patients had tympanocentesis to obtain middle ear
426 fluid for bacteriological evaluation. Patients from whom *S. pneumoniae* (alone or in combination
427 with other bacteria) was isolated had a second tympanocentesis 4 to 6 days after the start of
428 therapy. Clinical assessments were planned for all patients during treatment (4-6 days after
429 starting therapy), as well as 2-4 days post-treatment and 15-18 days post-treatment.
430 Bacteriological success was defined as the absence of the pretreatment pathogen from the
431 on-therapy tympanocentesis specimen. Clinical success was defined as improvement or
432 resolution of signs and symptoms. Clinical failure was defined as lack of improvement or
433 worsening of signs and/or symptoms at any time following at least 72 hours of

434 AUGMENTIN ES-600; patients who received an additional systemic antibacterial drug for otitis
 435 media after 3 days of therapy were considered clinical failures. Bacteriological eradication on
 436 therapy (day 4-6 visit) in the per protocol population is summarized in the following table:
 437

438 **Table 3. Bacteriologic Eradication Rates in the Per Protocol Population**

Pathogen	Bacteriologic Eradication on Therapy		
	n/N	%	95% CI*
All <i>S. pneumoniae</i>	121/123	98.4	(94.3, 99.8)
<i>S. pneumoniae</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	85.7	(57.2, 98.2)
<i>H. influenzae</i>	75/81	92.6	(84.6, 97.2)
<i>M. catarrhalis</i>	11/11	100	(71.5, 100.0)

439 *CI = confidence intervals; 95% CIs are not adjusted for multiple comparisons.
 440

441 Clinical assessments were made in the per protocol population 2-4 days post-therapy and
 442 15-18 days post-therapy. Patients who responded to therapy 2-4 days post-therapy were followed
 443 for 15-18 days post-therapy to assess them for acute otitis media. Nonresponders at 2-4 days
 444 post-therapy were considered failures at the latter timepoint.
 445

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

Pathogen	2-4 Days Post-Therapy (Primary Endpoint)		
	n/N	%	95% CI [†]
All <i>S. pneumoniae</i>	122/137	89.1	(82.6, 93.7)
<i>S. pneumoniae</i> with penicillin MIC = 2 mcg/mL	17/20	85.0	(62.1, 96.8)
<i>S. pneumoniae</i> with penicillin MIC = 4 mcg/mL	11/14	78.6	(49.2, 95.3)
<i>H. influenzae</i>	141/162	87.0	(80.9, 91.8)
<i>M. catarrhalis</i>	22/26	84.6	(65.1, 95.6)
	15-18 Days Post-Therapy [‡] (Secondary Endpoint)		
	n/N	%	95% CI [†]
All <i>S. pneumoniae</i>	95/136	69.9	(61.4, 77.4)
<i>S. pneumoniae</i> with penicillin MIC = 2 mcg/mL	11/20	55.0	(31.5, 76.9)
<i>S. pneumoniae</i> with penicillin MIC = 4 mcg/mL	5/14	35.7	(12.8, 64.9)
<i>H. influenzae</i>	106/156	67.9	(60.0, 75.2)
<i>M. catarrhalis</i>	14/25	56.0	(34.9, 75.6)

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

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

451 [‡]Clinical assessments at 15-18 days post-therapy may have been confounded by viral
 452 infections and new episodes of acute otitis media with time elapsed post-treatment.

453

454 In the intent-to-treat analysis, overall clinical outcomes at 2-4 days and 15-18 days
 455 post-treatment in patients with *S. pneumoniae* with penicillin MIC = 2 mcg/mL and 4 mcg/mL
 456 were 29/41 (71%) and 17/41 (41.5%), respectively.

457 In the intent-to-treat population of 521 patients, the most frequently reported adverse events
 458 were vomiting (6.9%), fever (6.1%), contact dermatitis (i.e., diaper rash) (6.1%), upper
 459 respiratory tract infection (4.0%), and diarrhea (3.8%). Protocol-defined diarrhea (i.e., 3 or more
 460 watery stools in one day or 2 watery stools per day for 2 consecutive days as recorded on diary
 461 cards) occurred in 12.9% of patients.

462 A double-blind, randomized, clinical study compared AUGMENTIN ES-600
 463 (90/6.4 mg/kg/day, divided every 12 hours) to AUGMENTIN (45/6.4 mg/kg/day, divided every
 464 12 hours) for 10 days in 450 pediatric patients (3 months to 12 years) with acute otitis media.
 465 The primary objective of the study was to compare the safety of AUGMENTIN ES-600 to
 466 AUGMENTIN. There was no statistically significant difference between treatments in the
 467 proportion of patients with 1 or more adverse events. The most frequently reported adverse

468 events for AUGMENTIN ES-600 and the comparator of AUGMENTIN were coughing (11.9%
469 versus 6.8%), vomiting (6.5% versus 7.7%), contact dermatitis (i.e., diaper rash, 6.0% versus
470 4.8%), fever (5.5% versus 3.9%), and upper respiratory infection (3.0% versus 9.2%),
471 respectively. The frequencies of protocol-defined diarrhea with AUGMENTIN ES-600 (11.1%)
472 and AUGMENTIN (9.4%) were similar (95% confidence interval on difference: -4.2% to
473 7.7%). Only 2 patients in the group treated with AUGMENTIN ES-600 and 1 patient in the
474 group treated with AUGMENTIN were withdrawn due to diarrhea.

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491
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