**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use AUGMENTIN safely and effectively. See full prescribing information for AUGMENTIN.**

**AUGMENTIN® (amoxicillin and clavulanate potassium) tablets, for oral use**
**AUGMENTIN XR® (amoxicillin and clavulanate potassium) extended-release tablets, for oral use**
**AUGMENTIN® (amoxicillin and clavulanate potassium) chewable tablets, for oral use**
**AUGMENTIN® (amoxicillin and clavulanate potassium) for oral suspension**
**AUGMENTIN ES-600® (amoxicillin and clavulanate potassium) for oral suspension**
**Initial U.S. Approval: 1984**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage (1) | 7/2026 |
| Dosage and Administration (2) | 7/2026 |
| Contraindications, Renal Impairment (4.3) Removed | 7/2026 |

**----------INDICATIONS AND USAGE----------**

AUGMENTIN is a combination of amoxicillin, a penicillin-class antibacterial and clavulanate potassium, a beta-lactamase inhibitor, indicated for the treatment of infections caused by designated susceptible (confirmed or suspected) beta-lactamase-producing microorganisms (1):

Lower Respiratory Tract Infections (1.1)
- AUGMENTIN Tablets: adults and pediatric patients weighing 40 kg or more
- AUGMENTIN Chewable Tablets: pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- AUGMENTIN for Oral Suspension: pediatric patients weighing less than 40 kg, and in adult and pediatric patients who cannot swallow tablets

Community-Acquired Pneumonia (1.2)
- AUGMENTIN XR Extended-Release Tablets: adult and pediatric patients weighing 40 kg or more who are able to swallow tablets

Acute Bacterial Sinusitis (1.3)
- AUGMENTIN Tablets: adults and pediatric patients weighing 40 kg or more
- AUGMENTIN Chewable Tablets: pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- AUGMENTIN for Oral Suspension: pediatric patients weighing less than 40 kg, and in adult and pediatric patients who cannot swallow tablets
- AUGMENTIN XR Extended-Release Tablets: adult and pediatric patients weighing 40 kg or more who are able to swallow tablets
- AUGMENTIN ES-600 for Oral Suspension: pediatric patients 3 months to 12 years of age weighing 8kg to 40 kg

Acute Bacterial Otitis Media (1.4)
- AUGMENTIN Tablets: adults and pediatric patients weighing 40 kg or more
- AUGMENTIN Chewable Tablets: pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- AUGMENTIN for Oral Suspension: pediatric patients weighing less than 40 kg, and in adult and pediatric patients who cannot swallow tablets

Recurrent or Persistent Acute Otitis Media (1.5)
- AUGMENTIN ES-600 for Oral Suspension: pediatric patients 3 months to 12 years of age weighing 8 kg to 40 kg

Skin and Skin Structure Infections (1.6)
- AUGMENTIN Tablets: adults and pediatric patients weighing 40 kg or more
- AUGMENTIN Chewable Tablets: pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- AUGMENTIN for Oral Suspension: pediatric patients weighing less than 40 kg, and in adult and pediatric patients who cannot swallow tablets

Urinary Tract Infections (1.7)
- AUGMENTIN Tablets: adults and pediatric patients weighing 40 kg or more
- AUGMENTIN Chewable Tablets: pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- AUGMENTIN for Oral Suspension: pediatric patients weighing less than 40 kg, and in adult and pediatric patients who cannot swallow tablets

Limitations of Use (1.8)
- AUGMENTIN XR Extended-Release Tablets are not indicated for the treatment of community-acquired pneumonia and acute bacterial sinusitis due to *S. pneumoniae* with penicillin MICs greater than or equal to 4 mcg/mL. Data are limited with regard to infections due to *S. pneumoniae* with penicillin MICs greater than or equal to 4 mcg/mL.
- AUGMENTIN ES-600 for Oral Suspension is not indicated for the treatment of recurrent or persistent acute otitis media and acute bacterial sinusitis due to *S. pneumoniae* with penicillin MIC greater than or equal to 4 mcg/mL. Acute otitis media due to *S. pneumoniae* alone can be treated with amoxicillin.
- Therapy may be initiated before bacteriological results are available when beta-lactamase-producing pathogens are suspected. When results show susceptibility to amoxicillin alone, AUGMENTIN should not be used.

Usage to Reduce Development of Drug-Resistant Bacteria (1.9)
To reduce the development of drug-resistant bacteria and maintain the effectiveness of AUGMENTIN and other antibacterial drugs, AUGMENTIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

**----------DOSAGE AND ADMINISTRATION----------**
- Recommended dosage and administration for the various formulations of AUGMENTIN depends on the indication, patient age, weight, and ability to swallow tablets. Therefore, carefully follow the recommended dosage and administration instructions specified below.
- Adults and Pediatric Patients Weighing 40 kg or More (2.2)

| Infection Type | Frequency | Dose | Formulation Strength |
|---|---|---|---|
| **AUGMENTIN Tablets** | | | |
| Mild to Moderate Infections | Every 12 hours | One tablet | 500 mg/125 mg |
| | Every 8 hours | One tablet | 250 mg/125 mg |
| Severe Infections | Every 12 hours | One tablet | 875 mg/125 mg |
| | Every 8 hours | One tablet | 500 mg/125 mg |
| **AUGMENTIN XR Extended-Release Tablets** | | | |
| Community-acquired pneumonia Acute bacterial sinusitis | Every 12 hours | Two Tablets | 1,000 mg/62.5 mg |

- Pediatric Patients less than 3 Months of Age: 30 mg/kg/day divided into 2 doses every 12 hours using AUGMENTIN for Oral Suspension 125 mg/31.25 mg per 5 mL (2.3)
- Pediatric Patients 3 Months and Older and Weighing Less Than 40 kg (2.4)

| Infection Type | Frequency | Dose | Formulation Strength |
|---|---|---|---|
| **AUGMENTIN Chewable Tablets and AUGMENTIN for Oral Suspension** | | | |
| Mild to Moderate Infections | Every 12 hours | 25 mg/kg/day divided into 2 doses | 200 mg/28.5 mg or 400 mg/57 mg |
| | Every 8 hours | 20 mg/kg/day divided into 3 doses | 125 mg/31.25 mg or 250 mg/62.5 mg |
| Severe Infections | Every 12 hours | 45 mg/kg/day divided into 2 doses | 200 mg/28.5 mg or 400 mg/57 mg |
| | Every 8 hours | 40 mg/kg/day divided into 3 doses | 125 mg/31.25 mg or 250 mg/62.5 mg |

- Pediatric Patients 3 Months to 12 Years and Weighing 8 kg to 40 kg (2.5)

| Infection Type | Frequency | Dose | Formulation Strength |
|---|---|---|---|
| **AUGMENTIN ES-600 for Oral Suspension** | | | |
| Acute bacterial sinusitis Recurrent or persistent acute otitis media | Every 12 hours | 90 mg/kg/day divided into 2 doses | 600 mg/42.9 mg |

- Adjust dose for severe renal impairment (GFR less than 30 mL/min) and in patients on hemodialysis. (2.6, 8.6, 12.3)
- See full Prescribing Information for preparation of Oral Suspension. (2.7, 2.8)



Reference ID: 5836752

**----------DOSAGE FORMS AND STRENGTHS----------**

- AUGMENTIN Tablets: 250 mg/125 mg, 500 mg/125 mg, 875 mg/125 mg; 875 mg/125 mg tablets are scored. (3)
- AUGMENTIN XR Extended-Release Tablets: 1,000 mg/62.5 mg are scored. (3)
- AUGMENTIN Chewable Tablets: 125 mg/31.25 mg, 200 mg/28.5 mg, 250 mg/62.5 mg, 400 mg/57 mg. (3)
- AUGMENTIN for Oral Suspension: 125 mg/31.25 mg per 5 mL, 200 mg/28.5 mg per 5 mL, 250 mg/62.5 mg per 5 mL, 400 mg/57 mg per 5 mL. (3)
- AUGMENTIN ES-600 for Oral Suspension: 600 mg/42.9 mg per 5 mL. (3)

**----------CONTRAINDICATIONS----------**

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

**----------WARNINGS AND PRECAUTIONS----------**

- Serious (including fatal) hypersensitivity reactions: Discontinue AUGMENTIN if a reaction occurs and institute appropriate therapy. (5.1)
- Severe cutaneous adverse reactions (SCAR): Monitor closely. Discontinue if rash progresses. (5.2)
- Drug-induced enterocolitis syndrome (DIES): Discontinue if DIES occurs and institute appropriate therapy. (5.3)
- Hepatic dysfunction and cholestatic jaundice: Discontinue if signs/symptoms of hepatitis occur. Monitor liver function tests in patients with hepatic impairment. (5.4)
- *Clostridioides difficile*-associated diarrhea (CDAD): Evaluate patients if diarrhea occurs. (5.5)
- Patients with mononucleosis: Increased risk of skin rash. Avoid AUGMENTIN use in these patients. (5.6)

**----------ADVERSE REACTIONS----------**

- The most frequently reported adverse reactions with AUGMENTIN Tablets, AUGMENTIN Chewable Tablets, and AUGMENTIN for Oral Suspension were (incidence ≥3%) diarrhea/loose stools, nausea, skin rash, and urticaria. (6.1)
- The most frequently reported adverse reactions with AUGMENTIN XR Extended-Release Tablets were (incidence ≥2%) diarrhea, vaginal mycosis, nausea, and loose stools. (6.1)
- The most frequently reported adverse reactions with AUGMENTIN ES-600 for Oral Suspension were (incidence >4%) diarrhea, coughing, vomiting, contact dermatitis (i.e., diaper rash), fever, and upper respiratory tract infection. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact USAntibiotics, LLC at 1-844-454-5532 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

**----------DRUG INTERACTIONS----------**

- Concomitant use with probenecid is not recommended. (7.1)
- Concomitant use with oral anticoagulants may increase the prolongation of prothrombin time. (7.2)
- Concomitant use with allopurinol increases the risk of rash. (7.3)

**----------USE IN SPECIFIC POPULATIONS----------**

Renal Impairment: Dosage adjustment is recommended for severe renal impairment (GFR <30 mL/min). (2.6, 8.6)

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 7/2026**

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**FULL PRESCRIBING INFORMATION**

## 1 INDICATIONS AND USAGE

### 1.1 Lower Respiratory Tract Infections

AUGMENTIN is indicated for the treatment of lower respiratory tract infection due to confirmed or suspected beta-lactamase producing *Haemophilus influenzae* and *Moraxella catarrhalis* as follows *[see Clinical Pharmacology (12.4), Clinical Studies (14.1)]*:

- **AUGMENTIN Tablets:** adults and pediatric patients weighing greater than or equal to 40 kg
- **AUGMENTIN Chewable Tablets:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- **AUGMENTIN for Oral Suspension:** pediatric patients weighing less than 40 kg, and in adult and pediatric patients who cannot swallow tablets

### 1.2 Community-Acquired Pneumonia

**AUGMENTIN XR Extended-Release Tablets** are indicated in adult and pediatric patients weighing greater than or equal to 40 kg who are able to swallow tablets for the treatment of community-acquired pneumonia due to confirmed or suspected beta-lactamase-producing pathogens (i.e., *H. influenzae, M. catarrhalis, Haemophilus parainfluenzae, Klebsiella pneumoniae*, or methicillin-susceptible *Staphylococcus aureus*) and *Streptococcus pneumoniae* with reduced susceptibility to penicillin (i.e., penicillin MICs equal to 2 mcg/mL) *[see Clinical Pharmacology (12.4), Clinical Studies (14.3)]*.

### 1.3 Acute Bacterial Sinusitis

AUGMENTIN Tablets, Chewable Tablets, and for Oral Suspension are indicated for the treatment of acute bacterial sinusitis due to confirmed or suspected beta-lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis* as follows *[see Clinical Pharmacology (12.4), Clinical Studies (14.4)]:*

- **AUGMENTIN Tablets:** adults and pediatric patients weighing greater than or equal to 40 kg
- **AUGMENTIN Chewable Tablets:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- **AUGMENTIN for Oral Suspension:** pediatric patients weighing less than 40 kg, and in adult or pediatric patients who cannot swallow tablets

AUGMENTIN XR Extended-Release Tablets and ES-600 for Oral Suspension are indicated for the treatment of acute bacterial sinusitis due to confirmed or suspected beta-lactamase-producing *pathogens (*i.e., *H. influenzae and M. catarrhalis, H. parainfluenzae*, *K. pneumoniae*, or methicillin-susceptible *S. aureus*) and *S. pneumoniae* with reduced susceptibility to penicillin (i.e., penicillin MICs equal to 2 mcg/mL) as follows *[see Use in Specific Populations (8.4), Clinical Studies (14.4)]:*

- **AUGMENTIN XR Extended-Release Tablets:** adults and pediatric patients weighing greater than or equal to 40 kg who are able to swallow tablets

- **AUGMENTIN ES-600 for Oral Suspension**: pediatric patients 3 months to 12 years of age weighing 8 kg to 40 kg

### 1.4 Acute Bacterial Otitis Media

AUGMENTIN is indicated for the treatment of acute bacterial otitis media due to confirmed or suspected beta-lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis* as follows *[see Use in Specific Populations (8.4), Clinical Studies (14.5)]*:

- **AUGMENTIN Tablets:** adults and pediatric patients weighing greater than or equal to 40 kg
- **AUGMENTIN Chewable Tablets:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- **AUGMENTIN for Oral Suspension**: pediatric patients weighing less than 40 kg, and in adult and pediatric patients who cannot swallow tablets

### 1.5 Recurrent or Persistent Acute Otitis Media

**AUGMENTIN ES-600 for Oral Suspension** is indicated for the treatment of recurrent or persistent acute otitis media due to confirmed or suspected *S. pneumoniae* (MICs less than or equal to 2 mcg/mL), *H. influenzae* or *M. catarrhalis* (including beta-lactamase-producing strains) in pediatric patients 3 months to 2 years of age (or 2 to 12 years of age who attend daycare) weighing 8 kg to 40 kg and used an antibacterial drug for acute otitis media within the preceding 3 months *[see Use in Specific Populations (8.4), Clinical Studies (14.6)]*.

### 1.6 Skin and Skin Structure Infections

AUGMENTIN is indicated for the treatment of skin and skin structure infections due to confirmed or suspected beta-lactamase-producing *S. aureus*, *Escherichia coli*, and *Klebsiella* species as follows *[see Use in Specific Populations (8.4)]*:

- **AUGMENTIN Tablets:** adults and pediatric patients weighing greater than or equal to 40 kg
- **AUGMENTIN Chewable Tablets:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- **AUGMENTIN for Oral Suspension:** pediatric patients weighing less than 40 kg, and in adult and pediatric patients who cannot swallow tablets

### 1.7 Urinary Tract Infections

AUGMENTIN is indicated for the treatment of urinary tract infections due to confirmed or suspected beta-lactamase-producing *E. coli*, *Klebsiella* species, and *Enterobacter* species as follows *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]:*

- **AUGMENTIN Tablets:** adults and pediatric patients weighing greater than or equal to 40 kg
- **AUGMENTIN Chewable Tablets:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets
- **AUGMENTIN for Oral Suspension:** pediatric patients weighing less than 40 kg, and in adult and pediatric patients who cannot swallow tablets

### 1.8 Limitations of Use

- AUGMENTIN XR Extended-Release Tablets are not indicated for the treatment of community-acquired pneumonia and acute bacterial sinusitis due to *S. pneumoniae* with penicillin MICs greater than or equal to 4 mcg/mL. Data are limited with regard to infections due to *S. pneumoniae* with penicillin MICs greater than or equal to 4 mcg/mL *[see Clinical Studies (14)]*.
- AUGMENTIN ES-600 for Oral Suspension is not indicated for the treatment of recurrent or persistent acute otitis media and acute bacterial sinusitis due to *S. pneumoniae* with penicillin MIC greater than or equal to 4 mcg/mL. Acute otitis media due to *S. pneumoniae* alone can be treated with amoxicillin.
- Therapy may be initiated before bacteriological results are available when beta-lactamase-producing pathogens are suspected. When results show susceptibility to amoxicillin alone, AUGMENTIN should not be used.

### 1.9 Usage to Reduce Development of Drug-Resistant Bacteria

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Administration Instructions

- The recommended dosage and administration for the various formulations of AUGMENTIN (tablets, chewable tablets and for oral suspension), AUGMENTIN XR Extended-Release Tablets and AUGMENTIN ES-600 for Oral Suspension, depends on the indication, patient age, weight, and ability to swallow tablets. Therefore, carefully follow the recommended dosage and administration instructions specified below *[see Dosage and Administration (2.2 to 2.8)]*.
- AUGMENTIN Tablets and AUGMENTIN XR Extended-Release Tablets should only be used in adults and pediatric patients weighing 40 kg or more who can swallow tablets whole *[see Indications and Usage (1), Dosage and Administration (2.2), Use in Specific Populations (8.4)]*.
- Pediatric patients weighing 40 kg or more who can swallow tablets should receive the adult dose *[see Indications and Usage (1), Dosage and Administration (2.2), Use in Specific Populations (8.4)]*.
- AUGMENTIN ES-600 for Oral Suspension is not recommended for use in adults *[see Indications and Usage (1.3, 1.5), and Dosage and Administration (2.4)]*.
- Substitution among AUGMENTIN formulations should only occur when the amoxicillin-to-clavulanic acid ratio is matched; AUGMENTIN Chewable Tablets and Oral Suspension are substitutable on a mg-per-mg basis, and certain AUGMENTIN Tablet strengths are substitutable with specific AUGMENTIN for Oral Suspension or Chewable Tablet strengths. *[see Dosage and Administration (2.8)]*.

### 2.2 Recommended Dosage of AUGMENTIN Tablets and AUGMENTIN XR Extended-Release Tablets in Adults and Pediatric Patients Weighing 40 kg or More Who Are Able to Swallow Tablets

The recommended dosage for adults and pediatric patients weighing 40 kg or more who are able to swallow tablets are provided in Table 1.

AUGMENTIN Tablets

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

AUGMENTIN XR Extended-Release Tablets

AUGMENTIN XR Extended-Release Tablets should be taken at the start of a meal to enhance the absorption of amoxicillin and minimize the potential gastrointestinal intolerance. AUGMENTIN XR is not recommended to be taken with a high fat meal *[see Clinical Pharmacology (12.3)]*.

Take AUGMENTIN XR Extended-Release Tablets whole. AUGMENTIN XR Extended-Release Tablets can be split in half along the score line for patients with difficulty swallowing the AUGMENTIN XR tablets whole. Both halves of the tablet must be taken immediately.

**Table 1: Recommended Dosage for AUGMENTIN Tablets and AUGMENTIN XR Extended-Release Tablets in Adult and Pediatric Patients Weighing 40 kg or More**

| Infection Type | Frequency | Dose | Formulation strength |
|---|---|---|---|
| **AUGMENTIN Tablets** | | | |
| Mild to Moderate Infections | Every 12 hours | One tablet | 500 mg/125 mg |
| | Every 8 hours | One tablet | 250 mg/125 mg |
| Severe Infections | Every 12 hours | One tablet | 875 mg/125 mg |
| | Every 8 hours | One tablet | 500 mg/125 mg |
| **AUGMENTIN XR Extended-Release Tablets** | | | |
| Community-acquired pneumonia[a]<br>Acute bacterial sinusitis[b] | Every 12 hours | Two tablets | 1,000 mg/62.5 mg |

[a]Recommended duration of therapy is 7 to 10 days
[b]Recommended duration of therapy is 10 days

For patients who are unable to swallow tablets, see Table 6 for guidance on substitution across formulations *[see Dosage and Administration (2.8)]*.

AUGMENTIN ES-600 for Oral Suspension is not a substitute for AUGMENTIN Tablets in adults.

### 2.3 Recommended Dosage of AUGMENTIN for Oral Suspension in Pediatric Patients Less Than 3 Months of Age

AUGMENTIN 125 mg/31.25 mg per 5 mL for Oral Suspension is the recommended formulation for use in this pediatric age group *[see Use in Specific Populations (8.4)]*.

The recommended dosage for pediatric patients less than 3 months of age, based on the amoxicillin component, is 30 mg/kg/day orally divided into two doses every 12 hours.

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

### 2.4 Recommended Dosage of AUGMENTIN Chewable Tablets and AUGMENTIN for Oral Suspension in Pediatric Patients Aged 3 Months and Older and Weighing Less Than 40 kg

The recommended dosage of AUGMENTIN Chewable Tablets and AUGMENTIN for Oral Suspension for pediatric patients aged 3 months and older and weighing less than 40 kg are provided in Table 2.

AUGMENTIN Chewable Tablets and AUGMENTIN for Oral Suspension may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when AUGMENTIN Chewable Tablets and AUGMENTIN for Oral Suspension are administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, AUGMENTIN Chewable Tablets and AUGMENTIN for Oral Suspension should be taken at the start of a meal.

**Table 2: Recommended Dosage of AUGMENTIN Chewable Tablets and AUGMENTIN for Oral Suspension in Pediatric Patients Aged 3 Months and Older and Weighing Less Than 40 kg**

| Infection Type | Frequency[a] | Dose (Amoxicillin component) | Formulation Strength |
|---|---|---|---|
| **AUGMENTIN Chewable Tablets or AUGMENTIN for Oral Suspension[b]** | | | |
| Less Severe Infections | Every 12 hours | 25 mg/kg/day divided into 2 doses | 200 mg/28.5 mg or 400 mg/57 mg |
| | Every 8 hours | 20 mg/kg/day divided into 3 doses | 125 mg/31.25 mg or 250 mg/62.5 mg |
| Otitis media[c], sinusitis, lower respiratory tract infections, and more severe infections | Every 12 hours | 45 mg/kg/day divided into 2 doses | 200 mg/28.5 mg or 400 mg/57 mg |
| | Every 8 hours | 40 mg/kg/day divided into 3 doses | 125 mg/31.25 mg or 250 mg/62.5 mg |

[a]The every 12 hours regimen is recommended as it is associated with less diarrhea *[see Adverse Reactions (6.1)]*.
[b]Strength of amoxicillin/clavulanate potassium per 5 mL oral suspension or per chewable tablet
[c]The recommended duration of therapy for acute bacterial otitis media is 10 days

AUGMENTIN Tablets and AUGMENTIN XR Extended-Release Tablets should not be used in pediatric patients weighing less than 40 kg due to different amoxicillin-to-clavulanic acid ratios *[see Indications and Usage (1), Dosage and Administration (2.8), Use in Specific Populations (8.4)]*.

Pediatric Patients Weighing 40 kg or More: Pediatric patients weighing 40 kg or more should receive the adult dose *[see Indications and Usage (1), Dosage and Administration (2.2), Use in Specific Populations (8.4)]*.

### 2.5 Recommended Dosage of AUGMENTIN ES-600 for Oral Suspension in Pediatric Patients Aged 3 Months to 12 Years and Weighing 8 kg to 40 kg

The recommended dosage for pediatric patients aged 3 months to 12 years and weighing 8 kg to 40 kg are provided in Table 3.

For pediatric patients weighing greater than 40 kg, experience with AUGMENTIN ES-600 is not available.

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

**Table 3: Recommended Dosage of AUGMENTIN ES-600 in Pediatric Patients 3 Months to 12 Years and Weighing 8 kg to 40 kg**

| Infection Type | Frequency | Dose (Amoxicillin component) | Formulation Strength |
|---|---|---|---|
| **AUGMENTIN ES-600 for Oral Suspension** | | | |
| Acute bacterial sinusitis<br>Recurrent or persistent acute otitis media[a] | Every 12 hours | 90 mg/kg/day divided into 2 doses | 600 mg/42.9 mg[b] |

[a] The recommended duration of therapy for recurrent or persistent acute bacterial otitis media is 10 days

[b] Strength of amoxicillin/clavulanate potassium per 5 mL oral suspension

### 2.6 Recommended Dosage in Patients with Renal Impairment

AUGMENTIN

A reduced dosage is recommended in patients with severe renal impairment (see Table 4). No dosage adjustment is recommended in patients with mild to moderate renal impairment.

**Table 4: Recommended Dosage of AUGMENTIN in Patients with Severe Renal Impairment**

| Patients with Severe Renal Impairment | Dosage |
|---|---|
| GFR 10 mL/min to less than 30 mL/min | 500 mg or 250 mg every 12 hours, depending on the severity of the infection |
| GFR less than 10 mL/min | 500 mg or 250 mg every 24 hours, depending on severity of the infection |
| Hemodialysis | 500 mg or 250 mg every 24 hours, depending on severity of the infection<br><br>Administer an additional dose both during and at the end of dialysis |

Patients with a GFR of less than 30 mL/min should not receive the 875 mg/125 mg dose of AUGMENTIN

AUGMENTIN XR Extended-Release Tablets and AUGMENTIN ES-600 for Oral Suspension
Patients with severe renal impairment or those on intermittent hemodialysis should not receive AUGMENTIN XR Extended-Release Tablets or AUGMENTIN ES-600 for Oral Suspension *[see Use in Specific Populations (8.6)]*.

### 2.7 Preparation and Storage (after reconstitution) of AUGMENTIN for Oral Suspension and AUGMENTIN ES-600 for Oral Suspension

Prepare the oral suspension at time of dispensing as follows:

- Shake the bottle to loosen powder.
- Measure the total amount of water (see Table 5) to be added in two parts.
- Add 2/3 of the total required water, close the bottle, and shake vigorously.
- Add the remaining water, close, and shake again.
- Shake well before each use.
- Administer the reconstituted AUGMENTIN for oral suspension, use a dosing spoon or medicine dropper to a pediatric patient.
- Rinse the dosing spoon or dropper after each use.

Flavoring Information:

For patients who wish to alter the taste of AUGMENTIN ES-600 for Oral Suspension, 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 for Oral Suspension. The resulting suspension is stable for 10 days under refrigeration. Stability of AUGMENTIN ES-600 for Oral Suspension when mixed with flavors other than the 5 flavors listed above has not been evaluated.

Storage

Store reconstituted AUGMENTIN suspension under refrigeration; discard after 10 days. A slight color change during storage is normal.

**Table 5: Amount of Water for Mixing AUGMENTIN for Oral Suspension & AUGMENTIN ES-600 for Oral Suspension**

| Strength of Oral Suspension (amoxicillin/clavulanic acid) | Bottle Size | Amount of Water for Reconstitution |
|---|---|---|
| 125 mg/31.25 mg per 5 mL | 75 mL<br>100 mL<br>150 mL | 67 mL<br>90 mL<br>134 mL |
| 200 mg/28.5 mg per 5 mL | 50 mL<br>75 mL<br>100 mL | 50 mL<br>75 mL<br>95 mL |
| 250 mg/62.5 mg per 5 mL | 75 mL<br>100 mL<br>150 mL | 65 mL<br>87 mL<br>130 mL |
| 400 mg/57 mg per 5 mL | 50 mL<br>75 mL<br>100 mL | 50 mL<br>70 mL<br>90 mL |
| 600 mg/42.9 mg per 5 mL | 75 mL<br>125 mL<br>200 mL | 70 mL<br>110 mL<br>180 mL |

### 2.8 Switching Between Dosage Forms and Strengths

AUGMENTIN Tablets, Chewable Tablets, and for Oral Suspension

- Substitution among AUGMENTIN formulations should only occur when the amoxicillin-to-clavulanic acid ratio is matched; AUGMENTIN Chewable Tablets and AUGMENTIN for Oral Suspension are substitutable on a mg-per-mg basis, and certain AUGMENTIN Tablet strengths are substitutable with specific AUGMENTIN for Oral Suspension or AUGMENTIN Chewable Tablet strengths.
- AUGMENTIN Chewable Tablets and AUGMENTIN for Oral Suspension formulations are for pediatric patients weighing less than 40 kg and in pediatric patients who cannot swallow tablets and may be substituted for each other where appropriate.
- AUGMENTIN Tablets should not be used in pediatric patients weighing less than 40 kg *[see Indications and Usage (1), Dosage and Administration (2.4), Use in Specific Populations (8.4)]*.

AUGMENTIN ES-600 for Oral Suspension

- AUGMENTIN ES-600 for Oral Suspension should only be used in pediatric patients weighing 8 kg to 40 kg. AUGMENTIN ES-600 for Oral Suspension is not substitutable with other AUGMENTIN and AUGMENTIN XR Extended-Release Tablet formulations *[see Indications and Usage (1.3, 1.5), Dosage and Administration (2.4), Use in Specific Populations (8.4)]*.
- Experience with AUGMENTIN ES-600 for Oral Suspension in adults or pediatric patients weighing more than 40 kg is not available. AUGMENTIN ES-600 for Oral Suspension should not be used as a substitute for AUGMENTIN 500 mg/125 mg or 875 mg/125 mg Tablets.

AUGMENTIN XR Extended-Release Tablets

- AUGMENTIN XR Extended-Release Tablets provide extended amoxicillin exposure compared with immediate-release tablets; therefore, two AUGMENTIN 500 mg tablets are not equivalent to one AUGMENTIN XR 1,000 mg tablet *[see Clinical Pharmacology (12.3)]*.
- AUGMENTIN XR Extended-Release Tablets should not be used in pediatric patients weighing less than 40 kg *[see Indications and Usage (1), Dosage and Administration (2.4), Use in Specific Populations (8.4)]*.

Table 6 provides guidance on selecting the appropriate strength when switching between AUGMENTIN Tablets and AUGMENTIN for Oral Suspension or Chewable Tablets to ensure the appropriate amoxicillin-to-clavulanic acid ratio.

**Table 6: Selecting Appropriate Strengths of AUGMENTIN When Switching Between Tablets, Oral Suspension, or Chewable Tablets**

| AUGMENTIN Tablet Strength | Substitutable Strength of AUGMENTIN for Oral Suspension or Chewable Tablets[a] |
|---|---|
| 250 mg/125 mg[b] | No equivalent available |
| 500 mg/125 mg[c] | 125 mg/31.25 mg<br>or<br>250 mg/62.5 mg |
| 875 mg/125 mg | 200 mg/28.5 mg<br>or<br>400 mg/57 mg |
| 1,000 mg/62.5 mg | Not substitutable with immediate-release formulations |

[a]One Chewable Tablet has the same amount of amoxicillin and clavulanic acid as 5 mL of the corresponding strength of Oral Suspension. Chewable tablets may only be used as a substitute in pediatric patients weighing less than 40 kg.
[b]AUGMENTIN 250 mg/125 mg tablet is NOT substitutable with AUGMENTIN 250 mg/62.5 mg chewable tablet.
[c]Two AUGMENTIN 250 mg/125 mg Tablets are not substitutable with one AUGMENTIN 500 mg/125 mg Tablet.

## 3 DOSAGE FORMS AND STRENGTHS

**AUGMENTIN Tablets**

- 250 mg/125 mg Tablets: Each white oval film-coated tablet, debossed with AUGMENTIN on one side and 250/125 on the other side, contains 250 mg of amoxicillin (as amoxicillin trihydrate) and 125 mg of clavulanic acid as the potassium salt.
- 500 mg/125 mg Tablets: Each white oval film-coated tablet, debossed with AUGMENTIN on one side and 500/125 on the other side, contains 500 mg of amoxicillin (as amoxicillin trihydrate) and 125 mg of clavulanic acid as the potassium salt.
- 875 mg/125 mg Tablets: Each scored white capsule-shaped tablet, debossed with AUGMENTIN 875 on one side and scored on the other side, contains 875 mg of amoxicillin (as amoxicillin trihydrate) and 125 mg of clavulanic acid as the potassium salt.

**AUGMENTIN XR Extended-Release Tablets**
Each white, oval film-coated bilayer scored tablet, debossed with AUGMENTIN XR, contains 1,000 mg of amoxicillin (as amoxicillin sodium and amoxicillin trihydrate) and 62.5 mg clavulanic acid as the potassium salt.

**AUGMENTIN Chewable Tablets**
- 125 mg/31.25 mg Chewable Tablets: Each mottled yellow, round, lemon-lime-flavored tablet, debossed with BMP, 189 contains 125 mg of amoxicillin (as amoxicillin trihydrate) and 31.25 mg of clavulanic acid as the potassium salt.
- 200 mg/28.5 mg Chewable Tablets: Each mottled pink, round, biconvex cherry-banana-flavored tablet, debossed with AUGMENTIN 200, contains 200 mg of amoxicillin (as amoxicillin trihydrate) and 28.5 mg of clavulanic acid as the potassium salt.
- 250 mg/62.5 mg Chewable Tablets: Each mottled yellow, round, lemon-lime-flavored tablet, debossed with BMP 190, contains 250 mg of amoxicillin (as amoxicillin trihydrate) and 62.5 mg of clavulanic acid as the potassium salt.
- 400 mg/57 mg Chewable Tablets: Each mottled pink, round, biconvex cherry-banana-flavored tablet, debossed with AUGMENTIN 400, contains 400 mg of amoxicillin (as amoxicillin trihydrate) and 57 mg of clavulanic acid as the potassium salt.

**AUGMENTIN for Oral Suspension**
- 125 mg/31.25 mg per 5 mL: Banana-flavored powder for oral suspension. Each 5 mL of reconstituted suspension contains 125 mg of amoxicillin (as amoxicillin trihydrate) and 31.25 mg of clavulanic acid as the potassium salt.
- 200 mg/28.5 mg per 5 mL: Orange-flavored powder for oral suspension. Each 5 mL of reconstituted suspension contains 200 mg of amoxicillin (as amoxicillin trihydrate) and 28.5 mg of clavulanic acid as the potassium salt.
- 250 mg/62.5 mg per 5 mL: Orange-flavored powder for oral suspension. Each 5 mL of reconstituted suspension contains 250 mg of amoxicillin (as amoxicillin trihydrate) and 62.5 mg of clavulanic acid as the potassium salt.
- 400 mg/57 mg per 5 mL: Orange-flavored powder for oral suspension. Each 5 mL of reconstituted suspension contains 400 mg of amoxicillin (as amoxicillin trihydrate) and 57 mg of clavulanic acid as the potassium salt.

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

## 4 CONTRAINDICATIONS

### 4.1 Serious Hypersensitivity Reactions
AUGMENTIN 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 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 beta-lactam antibacterials. 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, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. AUGMENTIN is contraindicated in patients with a history of serious hypersensitivity reactions to amoxicillin, clavulanate, or to other beta-lactam antibacterial drugs *[see Contraindications (4.1)]*. If an allergic reaction occurs, discontinue AUGMENTIN and institute appropriate therapy.

### 5.2 Severe Cutaneous Adverse Reactions

AUGMENTIN may cause severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). If patients develop a skin rash, they should be monitored closely, and AUGMENTIN discontinued if lesions progress.

### 5.3 Drug-Induced Enterocolitis Syndrome

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

### 5.4 Hepatic Dysfunction

Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of AUGMENTIN. Hepatotoxicity is usually reversible; however, deaths have been reported. These cases have generally been associated with serious underlying diseases or concomitant medications. AUGMENTIN is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with treatment with amoxicillin and clavulanate potassium *[see Contraindications (4.2), Use in Specific Populations (8.7), Adverse Reactions (6.2)]*.

### 5.5 *Clostridioides difficile*-Associated Diarrhea (CDAD)

*Clostridioides difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AUGMENTIN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

### 5.6 Skin Rash in Patients with Mononucleosis

A high percentage of patients with mononucleosis who receive amoxicillin develop an erythematous skin rash. Avoid AUGMENTIN use in patients with mononucleosis *[see Adverse Reactions (6.2)]*.

### 5.7 Potential for Microbial Overgrowth

The possibility of superinfections with mycotic or bacterial pathogens should be considered during therapy. If superinfections occur (commonly involving *Pseudomonas* spp. or *Candida* spp.), discontinue AUGMENTIN and institute appropriate therapy.

### 5.8 Risks in Patients with Phenylketonuria

Phenylalanine can be harmful to patients with phenylketonuria (PKU). Certain formulations of AUGMENTIN contain aspartame, which is a source of phenylalanine: 200 mg Chewable Tablets (2.1 mg phenylalanine per tablet); 400 mg Chewable Tablets (4.2 mg phenylalanine per tablet); 200 mg/5 mL and 400 mg/5 mL AUGMENTIN for Oral Suspension and AUGMENTIN ES-600 for Oral Suspension (7 mg phenylalanine per 5 mL). Before prescribing these AUGMENTIN formulations to patients with PKU, consider the combined daily amount of phenylalanine from all sources, including AUGMENTIN.

Other formulations, including the 125 mg/31.25 mg and 250 mg/62.5 mg Chewable Tablets and the corresponding for Oral Suspension (125 mg/31.25 mg per 5 mL and 250 mg/62.5 mg per 5 mL), do not contain aspartame.

### 5.9 Development of Drug-Resistant Bacteria

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

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Allergic Reactions, including Anaphylaxis *[see Warnings and Precautions (5.1)]*
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (5.2)]*
- Drug-Induced Enterocolitis Syndrome (DIES) *[see Warnings and Precautions (5.3)]*
- Hepatic Dysfunction *[see Warnings and Precautions (5.4)]*
- *Clostridioides difficile*-associated diarrhea (CDAD) *[see Warnings and Precautions (5.5)]*
- Skin Rash in Patients with Mononucleosis *[see Warnings and Precautions (5.6)]*

### 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.

AUGMENTIN Tablets, AUGMENTIN Chewable Tablets, and AUGMENTIN for Oral Suspension

The most frequently reported adverse reactions in clinical trials were diarrhea/loose stools (9%), nausea (3%), skin rash and urticaria (3%), vomiting (1%) and vaginitis (1%). Less than 3% of patients discontinued therapy due to adverse reactions. The overall incidence of adverse reactions, particularly diarrhea, increased with higher recommended doses. Other less frequently reported adverse reactions (<1%) included abdominal discomfort, flatulence, and headache.

In two pivotal trials in adults with lower respiratory tract or urinary tract infections, the overall incidence of adverse reactions was similar between AUGMENTIN 875 mg/125 mg Tablets every 12 hours and AUGMENTIN 500 mg/125 mg Tablets every 8 hours *[see Clinical Studies (14.1, 14.2)]*. The most common adverse reaction was diarrhea, reported in 15% of patients receiving AUGMENTIN 875 mg/125 mg every 12 hours and 14% of patients receiving AUGMENTIN 500 mg/125 mg every 8 hours. The rate of severe diarrhea or discontinuation due to diarrhea was 1% versus 2%, respectively.

In a controlled clinical trial of pediatric patients aged 2 months to 12 years with acute otitis media *[see Clinical Studies (14.5)],* diarrhea was defined in the protocol as ≥3 watery stools or ≥4 loose/watery stools in 1 day, or ≥2 watery stools or ≥3 loose/watery stools per day for 2 consecutive days, as recorded on diary cards. The incidence of diarrhea was significantly lower in patients treated with AUGMENTIN for Oral Suspension 45 mg/kg/day divided every 12 hours (14%) compared to patients treated with AUGMENTIN for Oral Suspension 40 mg/kg/day divided every 8 hours (34%). It is not known whether the statistically significant reduction in diarrhea with the oral suspension dosed every 12 hours, versus suspensions dosed every 8 hours, can be extrapolated to the chewable tablets, all of which contain mannitol *[see Description (11)]*. The presence of mannitol in the chewable tablets may contribute to a different diarrhea profile. Severe diarrhea or discontinuation due to diarrhea occurred in 3% and 8% of patients, respectively. Allergic reactions leading to discontinuation occurred in 1% and <1% of patients, and candidal infection of the diaper area was reported in 4% and 6% of patients, respectively.

AUGMENTIN XR Extended-Release Tablets

In clinical trials, 5,643 patients have been treated with AUGMENTIN XR Extended-Release Tablets. The most frequently reported adverse reactions were diarrhea (15%), vaginal mycosis (3%), nausea (2%), and loose stools (2%). AUGMENTIN XR Extended-Release Tablets were associated with a higher rate of diarrhea requiring corrective therapy (4% versus 3% for AUGMENTIN XR Extended-Release Tablets and all comparators, respectively). Two percent of patients discontinued therapy due to adverse reactions.

AUGMENTIN ES-600 for Oral Suspension

Two clinical trials evaluated the safety of a 10-day treatment course of AUGMENTIN ES-600 for Oral Suspension 90/6.4 mg/kg/day, divided every 12 hours, in pediatric patients with recurrent or persistent acute otitis media *[see Clinical Studies (14.6)]*. The first trial involved 521 pediatric patients (aged 3 months to 50 months), and the second trial involved 450 pediatric patients (aged 3 months to 12 years).

In the first trial, the most frequently reported adverse reactions were vomiting (7%), fever (6%), contact dermatitis (i.e., diaper rash) (6%), upper respiratory tract infection (4%), and diarrhea (4%). Diarrhea, defined in the protocol as ≥3 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 for Oral Suspension at 90/6.4 mg/kg/day, divided every 12 hours to AUGMENTIN for Oral Suspension at 45/6.4 mg/kg/day, divided every 12 hours for ten days. Adverse reactions were similar between treatment groups. The most frequently reported adverse reactions for AUGMENTIN ES-600 for Oral Suspension and the comparator 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. Protocol-defined diarrhea occurred in 11% of patients receiving AUGMENTIN ES-600 for Oral Suspension and 9% of patients receiving the comparator; the difference was not statistically different. Two patients in the AUGMENTIN ES-600 for Oral Suspension group and one patient in the comparator group discontinued treatment due to diarrhea.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of AUGMENTIN products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Gastrointestinal:* Drug-induced enterocolitis syndrome (DIES), diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment *[see Warnings and Precautions (5.3, 5.5)]*.

*Immune:* Hypersensitivity reactions, anaphylactic reactions (including shock), angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and

frequently fever), hypersensitivity vasculitis *[see Warnings and Precautions (5.1)]*.

*Skin and Appendages:* Rashes, pruritus, urticaria, erythema multiforme, SJS, TEN, DRESS, AGEP, exfoliative dermatitis, and linear IgA bullous dermatosis *[see Warnings and Precautions (5.1, 5.2, 5.6)]*.

*Liver:* A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibacterials. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been reported with AUGMENTIN. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. Deaths have been reported *[see Contraindications (4.2), Warnings and Precautions (5.4)]*.

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

*Hemic and Lymphatic Systems:* Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. There have been reports of increased prothrombin time in patients receiving AUGMENTIN and anticoagulant therapy concomitantly *[see Drug Interactions (7.2)]*.

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

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

## 7 DRUG INTERACTIONS

### 7.1 Probenecid

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

### 7.2 Oral Anticoagulants

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

### 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. Discontinue allopurinol at the first appearance of skin rash when used concomitantly with AUGMENTIN.

### 7.4 Interference of AUGMENTIN with Glucose 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. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Available data from published epidemiologic studies and pharmacovigilance case reports over several decades of use with amoxicillin and clavulanate during pregnancy have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal outcomes. A study in women with preterm prelabor rupture of membranes (PPROM) reported that prophylactic treatment with amoxicillin and clavulanate may be associated with an increased risk of necrotizing enterocolitis in neonates *(see Data)*. Reproduction studies conducted in pregnant rats, given doses greater than or equal to 4 and 10 times the Maximum Recommended Human Dose (MRHD) of amoxicillin trihydrate and clavulanate respectively in AUGMENTIN based on body surface area, revealed no evidence of fetal harm *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

*Human Data*

One randomized, controlled trial included 4,826 pregnant women with premature rupture of fetal membranes who were randomly assigned to 250 mg erythromycin (n=1,197), 250 mg amoxicillin and 125 mg clavulanate (n=1,212), amoxicillin and clavulanate plus erythromycin (n=1,192), or placebo (n=1,225) four times daily for 10 days or until delivery. Amoxicillin and clavulanate was associated with a significantly increased rate of proven neonatal necrotizing enterocolitis: 1.9% (n=24) in the amoxicillin and clavulanate only group versus 0.5% (n=6) in the placebo group (p=0.001), and 1.8% (n=44) in the any amoxicillin and clavulanate group versus 0.7% (n=17) in the no amoxicillin and clavulanate group (p=0.0005).

*Animal Data*

In an embryofetal developmental study in pregnant rats, amoxicillin and clavulanate (2:1 ratio formulation of amoxicillin:clavulanate) were administered at oral doses up to 1,200 mg/kg/day during the period of organogenesis (gestation days (GD) 6-15). No evidence of fetal harm was observed. Based on body surface area comparisons, the dose corresponds to approximately 4 times the MRHD for amoxicillin trihydrate and 10 times the MRHD for clavulanate potassium.

In a pre-and postnatal developmental study in pregnant rats, amoxicillin and clavulanate (2:1 ratio formulation of amoxicillin:clavulanate) were administered at oral doses up to 1,200 mg/kg/day beginning from GD 15 through Day 21 of lactation. No effects on maternal reproductive function or on developmental and reproductive parameters of the offspring were observed up to the highest dose, corresponding to approximately 4 times the MRHD for amoxicillin trihydrate and 10 times the MRHD for clavulanate potassium, based on body surface area comparisons.

### 8.2 Lactation

Risk Summary

Data from a published clinical lactation study report that amoxicillin is present in human milk. There are reports of diarrhea, irritability, and rash in infants exposed to amoxicillin and clavulanate through breast milk; therefore, infants exposed to AUGMENTIN should be monitored for these symptoms. There are no data on the effects of amoxicillin and clavulanate on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AUGMENTIN and any potential adverse effects on the breastfed child from AUGMENTIN or from the underlying maternal condition.

### 8.4 Pediatric Use

The five AUGMENTIN dosage forms (tablets, chewable tablets, oral suspension, XR tablets, and ES-600 for oral suspension) are different products. They are approved for different pediatric indications, age groups, and weights; have different dosing regimens; and have different preparation and administration instructions. Therefore, select the recommended dosage form based on the pediatric indication, age group, and weight *[see Dosage and Administration (2)]*.

Lower Respiratory Tract Infections

The safety and effectiveness of AUGMENTIN have been established for the treatment of lower respiratory tract infections due to confirmed or suspected beta-lactamase producing isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* as follows *[see Indications and Usage (1.1), Clinical Pharmacology (12.3), Clinical Studies (14.1*)]:

- **AUGMENTIN Tablets:** pediatric patients weighing greater than or equal to 40 kg. Effectiveness is supported by adequate and well-controlled studies in adults, with pediatric pharmacokinetic data demonstrating comparable amoxicillin and clavulanate exposures, and under the assumption that disease course and response are sufficiently similar in these pediatric patients to adults.
- **AUGMENTIN Chewable Tablets and for Oral Suspension:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets. Effectiveness is supported by adequate and well-controlled studies in adults, with pediatric pharmacokinetic data bridging to the less than 40 kg population.

Community-Acquired Pneumonia

The safety and effectiveness of **AUGMENTIN XR Extended-Release Tablets** have been established for the treatment of community-acquired pneumonia due to confirmed or suspected beta-lactamase-producing pathogens (i.e., *H. influenzae, M. catarrhalis, Haemophilus parainfluenzae, Klebsiella pneumoniae*, or methicillin-susceptible *Staphylococcus aureus*) and *Streptococcus pneumoniae* with reduced susceptibility to penicillin (i.e., penicillin MICs = 2 mcg/mL) in pediatric patients weighing greater than or equal to 40 kg who are able to swallow tablets. Effectiveness is supported by adequate and well-controlled studies in adults and a pediatric pharmacokinetic study demonstrating comparable exposures. The adverse event profile in 44 pediatric patients (7 to 15 years of age weighing greater than or equal to 40 kg) was consistent with that observed in adults *[see Indications and Usage (1.2), Clinical Pharmacology (12.3), Clinical Studies (14.3)]*.

Acute Bacterial Sinusitis

The safety and effectiveness of AUGMENTIN (tablets, chewable tablets and for oral suspension) have been established for the treatment of acute bacterial sinusitis due to confirmed or suspected beta-lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis* as follows *[see Indications and Usage (1.3), Clinical Pharmacology (12.3), Clinical Studies (14.4)]*:

- **AUGMENTIN Tablets:** pediatric patients weighing greater than or equal to 40 kg. Effectiveness is supported by adequate and well-controlled studies in adults, with pediatric pharmacokinetic data demonstrating comparable amoxicillin and clavulanate exposures, and under the assumption that disease course and response are sufficiently similar in these pediatric patients to adults.
- **AUGMENTIN Chewable Tablets and for Oral Suspension:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets. Effectiveness is supported by adequate and well-controlled studies in adults, with pediatric pharmacokinetic data bridging to the less than 40 kg pediatric population.

The safety and effectiveness of AUGMENTIN (XR tablets and ES-600 for oral suspension) have been established for the treatment of acute bacterial sinusitis due to confirmed or suspected beta-lactamase-producing *pathogens (*i.e., *H. influenzae and M. catarrhalis, H. parainfluenzae*, *K.*

*pneumoniae*, or methicillin-susceptible *S. aureus*) and *S. pneumoniae* with reduced susceptibility to penicillin (i.e., penicillin MICs = 2 mcg/mL) as follows *[see Indications and Usage (1.3), Clinical Pharmacology (12.3), Clinical Studies (14.4)]:*

- **AUGMENTIN XR Extended-Release Tablets:** adults and pediatric patients weighing greater than or equal to 40 kg who are able to swallow tablets. Effectiveness is supported by adequate and well-controlled studies in adults and a pediatric pharmacokinetic study demonstrating comparable exposures. The adverse event profile in 44 pediatric patients (7 to 15 years of age weighing greater than or equal to 40 kg) was consistent with that observed in adults.
- **AUGMENTIN ES-600 for Oral Suspension**: pediatric patients 3 months to 12 years of age who weigh 8 kg to 40 kg. Effectiveness is supported by adequate and well-controlled studies in adults, with pediatric pharmacokinetic data demonstrating comparable exposures in pediatric patients less than 40 kg.

Acute Bacterial Otitis Media

The safety and effectiveness of AUGMENTIN have been established for the treatment of acute bacterial otitis media due to confirmed or suspected beta-lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis* as follows *[see Indications and Usage (1.4), Clinical Pharmacology (12.3), Clinical Studies (14.5)]*:

- **AUGMENTIN Tablets:** pediatric patients weighing greater than or equal to 40 kg. Effectiveness is supported by adequate and well-controlled studies in adults, with pediatric pharmacokinetic data demonstrating comparable amoxicillin and clavulanate exposures, and under the assumption that disease course and response are sufficiently similar in these pediatric patients to adults.
- **AUGMENTIN Chewable Tablets and for Oral Suspension:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets. Effectiveness is supported by adequate and well-controlled studies conducted in adults, with additional data from a study conducted in pediatric patients with acute bacterial otitis media aged 2 months to 12 years.

Recurrent or Persistent Acute Otitis Media

The safety and effectiveness of **AUGMENTIN ES-600 for Oral Suspension** is established for the treatment of recurrent or persistent acute otitis media due to confirmed or suspected *S. pneumoniae* (MICs less than or equal to 2 mcg/mL), *H. influenzae* or *M. catarrhalis* (including beta-lactamase-producing strains) in pediatric patients 3 months to 2 years of age (or 2 to 12 years of age who attend daycare) weighing 8 kg to 40 kg and used an antibacterial drug for acute otitis media within the preceding 3 months. Effectiveness is supported by adequate and well-controlled studies conducted in pediatric patients *[see Indications and Usage (1.5), Clinical Pharmacology (12.3), Clinical Studies (14.6)]*.

Skin and Skin Structure Infections

The safety and effectiveness of AUGMENTIN have been established for the treatment of skin and skin structure infections due to confirmed or suspected beta-lactamase-producing *S. aureus*, *Escherichia coli*, and *Klebsiella* species as follows *[see Indications and Usage (1.6), Clinical Pharmacology (12.3)]:*

- **AUGMENTIN Tablets:** pediatric patients weighing greater than or equal to 40 kg. Effectiveness is supported by adequate and well-controlled studies in adults, with pediatric pharmacokinetic data demonstrating comparable amoxicillin and clavulanate exposures, and under the assumption that disease course and response are sufficiently similar in these pediatric patients to adults.
- **AUGMENTIN Chewable Tablets and for Oral Suspension:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets. Effectiveness is supported by adequate and well-controlled studies conducted in pediatric patients.

Urinary Tract Infections

The safety and effectiveness of AUGMENTIN have been established for the treatment of urinary tract infections due to confirmed or suspected beta-lactamase-producing *E. coli*, *Klebsiella* species, and *Enterobacter* species as follows *[see Indications and Usage (1.7), Clinical Pharmacology (12.3), Clinical Studies (14.2)]:*

- **AUGMENTIN Tablets:** pediatric patients weighing greater than or equal to 40 kg. Effectiveness is supported by adequate and well-controlled studies in adults, with pediatric pharmacokinetic data demonstrating comparable amoxicillin and clavulanate exposures, and under the assumption that disease course and response are sufficiently similar in these pediatric patients to adults.
- **AUGMENTIN Chewable Tablets and for Oral Suspension:** pediatric patients weighing less than 40 kg, and in pediatric patients who cannot swallow tablets. Effectiveness is supported by adequate and well-controlled studies conducted in pediatric patients.

Use Not Established in Certain Pediatric Populations

The safety and effectiveness of AUGMENTIN have not been established in the following pediatric populations:

- AUGMENTIN ES-600 for Oral Suspension in pediatric patients less than 3 months of age, or pediatric patients 3 months to 12 years of age weighing more than 40 kg
- AUGMENTIN Tablets and AUGMENTIN XR Extended-Release Tablets in pediatric patients weighing less than 40 kg, due to different amoxicillin-to-clavulanate ratios from the Chewable Tablets and for Oral Suspension formulations *[see Dosage and Administration (2.4)]*.

Data are insufficient to support extrapolation in these age groups due to developmental differences in renal function. Elimination of amoxicillin may be delayed, while clavulanate elimination is not altered. Dosage should be modified in pediatric patients less than 12 weeks (3 months) *[see Dosage and Administration (2.3)]*.

### 8.5 Geriatric Use

Of the 3,119 patients included in clinical studies of AUGMENTIN Tablets, 32% were 65 years of age and older and 14% were 75 years of age and older. In clinical studies of AUGMENTIN XR Extended-Release Tablets, 18% of patients were 65 years of age and older and 7% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other clinical experience has not identified differences in responses between elderly and younger patients.

AUGMENTIN is substantially excreted by the kidney, and the risk of adverse reactions to AUGMENTIN may be greater in patients with renal impairment than in patients with normal renal function. Because geriatric patients are more likely to have renal impairment, monitor for adverse reactions. Dosage adjustment is recommended in patients with severe renal impairment *[see Dosage and Administration (2.6), Use in Specific Populations (8.6)]*.

### 8.6 Renal Impairment

Amoxicillin is primarily eliminated by the kidney. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis.

AUGMENTIN

No dosage adjustment is recommended in patients with mild to moderate renal impairment. A reduced dosage is recommended in patients with severe renal impairment (GFR less than 30 mL/min). Patients with a GFR of less than 30 mL/min should not receive the 875 mg/125 mg dose of AUGMENTIN *[see Dosage and Administration (2.6)]*.

AUGMENTIN XR Extended-Release Tablets and AUGMENTIN ES-600 for Oral Suspension

The pharmacokinetics of AUGMENTIN XR Extended-Release Tablets and AUGMENTIN ES-600 for Oral Suspension have not been studied in patients with renal impairment. Patients with severe renal impairment (GFR less than 30 mL/min) and patients on intermittent hemodialysis should not receive AUGMENTIN XR Extended-Release Tablets or AUGMENTIN ES-600 for Oral Suspension *[see Dosage and Administration (2.6)]*.

### 8.7 Hepatic Impairment

Monitor hepatic function as appropriate during therapy with AUGMENTIN *[see Contraindications (4.2), Warnings and Precautions (5.4)]*.

## 10 OVERDOSAGE

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

In the case of overdosage, discontinue AUGMENTIN, treat symptomatically, and institute supportive measures as required. A prospective study of 51 pediatric patients at a poison control center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.[1] Consider contacting the

Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

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.

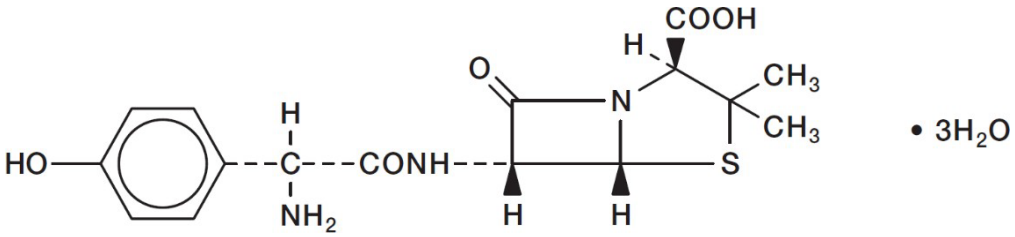
## 11 DESCRIPTION

AUGMENTIN® (amoxicillin and clavulanate potassium) is an oral antibacterial combination consisting of the semisynthetic antibacterial amoxicillin and the beta-lactamase inhibitor clavulanate potassium (the potassium salt of clavulanic acid).

- In AUGMENTIN Tablets, Chewable Tablets, For Oral Suspension, and AUGMENTIN ES-600 for Oral Suspension, amoxicillin is present as amoxicillin trihydrate.
- In AUGMENTIN XR Extended-Release Tablets, amoxicillin is present as a mixture of amoxicillin trihydrate and amoxicillin sodium.

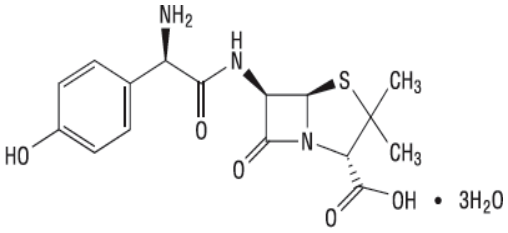
Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid.

Amoxicillin trihydrate has a molecular formula of $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ and a molecular weight of 419.46. Chemically, it 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:



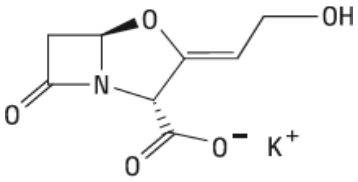

Amoxicillin sodium has a molecular formula of $C_{16}H_{18}N_3NaO_5S$ and a molecular weight of

387.39. Chemically, it is [2 -[2α,5α,6β(S*)]]-6-[[Amino (4- hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2- carboxylic acid monosodium salt 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.

Clavulanate potassium has a molecular formula of $C_8H_8KNO_5$ and a molecular weight of 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:




**AUGMENTIN Tablets**

- 250 mg/125 mg: Each tablet contains 250 mg of amoxicillin (equivalent to 287 mg of amoxicillin trihydrate) and 125 mg of clavulanic acid (equivalent to 149 mg of clavulanate potassium).
- 500 mg/125 mg: Each tablet contains 500 mg of amoxicillin (equivalent to 574 mg of amoxicillin trihydrate) and 125 mg of clavulanic acid (equivalent to 149 mg of clavulanate potassium).
- 875 mg/125 mg: Each tablet contains 875 mg of amoxicillin (equivalent to 1004 mg of amoxicillin trihydrate)and 125 mg of clavulanic acid (equivalent to 149 mg of clavulanate potassium).

Each AUGMENTIN tablet contains 25 mg of potassium.

Inactive Ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

**AUGMENTIN XR Extended-Release Tablets**
Each AUGMENTIN XR Extended-Release Tablet contains 1,000 mg of amoxicillin (437.5 mg of amoxicillin equivalent to 463.8 mg of amoxicillin sodium and 562.5 mg of amoxicillin in the form of amoxicillin trihydrate) and 62.5 mg of clavulanic acid (equivalent to 74.5 mg of clavulanate potassium).

Each tablet of AUGMENTIN XR contains approximately 12 mg of potassium and 28 mg of sodium.

Inactive Ingredients: Citric acid, colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, titanium dioxide, and xanthan gum.

**AUGMENTIN Chewable Tablets**

- **125 mg/31.25 mg:** Each chewable tablet contains 125 mg of amoxicillin (equivalent to 143 mg of amoxicillin trihydrate) and 31.25 mg of clavulanic acid (equivalent to 37.23 mg of clavulanate potassium).

  Each 125 mg/31.25 mg chewable tablet of AUGMENTIN contains 6 mg potassium.

  Inactive ingredients: colloidal silicon dioxide, D&C Yellow No.10, flavorings, glycine, magnesium stearate, mannitol, and sodium saccharin.

- **200 mg/28.5 mg:** Each chewable tablet contains 200 mg of amoxicillin (equivalent to 230 mg of amoxicillin trihydrate) and 28.5 mg of clavulanic acid (equivalent to 34 mg of clavulanate potassium).

  Each 200 mg/28.5 mg chewable tablet of AUGMENTIN contains 6 mg potassium.

  Inactive ingredients: aspartame, colloidal silicon dioxide, FD&C Red No. 40, flavorings, magnesium stearate, and mannitol *[see Warnings and Precautions (5.8)]*.
- **250 mg/62.5 mg:** Each chewable tablet contains 250 mg of amoxicillin (equivalent to 287 mg of amoxicillin trihydrate) and 62.5 mg of clavulanic acid (equivalent to 74.5 mg of clavulanate potassium).

  Each 250 mg/62.5 mg chewable tablet of AUGMENTIN contains 13 mg potassium.

  Inactive ingredients: colloidal silicon dioxide, D&C Yellow No.10, flavorings, glycine, magnesium stearate, mannitol, and sodium saccharin.
- **400 mg/57 mg:** Each chewable tablet contains 400 mg of amoxicillin (equivalent to 460 mg of amoxicillin trihydrate), 57 mg of clavulanic acid (equivalent to 68 mg of clavulanate potassium), and 12 mg of potassium.

  Each 400 mg/57 mg chewable tablet of AUGMENTIN contains 12 mg potassium.

Inactive ingredients: aspartame, colloidal silicon dioxide, FD&C Red No. 40, flavorings, magnesium stearate, and mannitol *[see Warnings and Precautions (5.8)]*.

**AUGMENTIN for Oral Suspension**

- **125 mg/31.25 mg:** Following constitution, each 5 mL of oral suspension contains 125 mg of amoxicillin (equivalent to 143 mg of amoxicillin trihydrate) and 31.25 mg of clavulanic acid (equivalent to 37.23 mg of clavulanate potassium).

  Each 5 mL of reconstituted 125 mg/31.25 mg oral suspension of AUGMENTIN contains 7 mg potassium.

  Inactive ingredients: colloidal silicon dioxide, flavorings, mannitol, silica gel, sodium saccharin, succinic acid, and xanthan gum.
- **200 mg/28.5 mg:** Following constitution, each 5 mL of oral suspension contains 200 mg of amoxicillin (equivalent to 230 mg of amoxicillin trihydrate) and 28.5 mg of clavulanic acid (equivalent to 34 mg of clavulanate potassium).

  Each 5 mL of reconstituted 200 mg/28.5 mg oral suspension of AUGMENTIN contains 6 mg potassium.

  Inactive ingredients: aspartame, colloidal silicon dioxide, flavorings, hypromellose, silica gel, and xanthan gum *[see Warnings and Precautions (5.8)]*.

- **250 mg/62.5 mg:** Following constitution, each 5 mL of oral suspension contains 250 mg of amoxicillin (equivalent to 287 mg of amoxicillin trihydrate) and 62.5 mg of clavulanic acid (equivalent to 74.5 mg of clavulanate potassium).

  Each 5 mL of reconstituted 250 mg/62.5 mg oral suspension of AUGMENTIN contains 14 mg potassium.

  Inactive ingredients: colloidal silicon dioxide, flavorings, mannitol, silica gel, sodium saccharin, succinic acid, and xanthan gum.

- **400 mg/57 mg:** Following constitution, each 5 mL of oral suspension contains 400 mg of amoxicillin (equivalent to 460 mg of amoxicillin trihydrate) and 57 mg of clavulanic acid (equivalent to 68 mg of clavulanate potassium).

  Each 5 mL of reconstituted 400 mg/57 mg oral suspension of AUGMENTIN contains 12 mg potassium.

  Inactive ingredients: aspartame, colloidal silicon dioxide, flavorings, hypromellose, silica gel, and xanthan gum *[see Warnings and Precautions (5.8)]*.

**AUGMENTIN ES-600 for Oral Suspension**
Following reconstitution, each 5 mL of oral suspension contains 600 mg of amoxicillin (as amoxicillin trihydrate) and 42.9 mg of clavulanic acid (equivalent to 51.1 mg of clavulanate potassium).

Each 5 mL of reconstituted AUGMENTIN ES-600 for Oral Suspension contains approximately 9 mg of potassium and 4 mg of sodium.

Inactive Ingredients: Aspartame, colloidal silicon dioxide, silicon dioxide, sodium carboxymethylcellulose, strawberry cream flavor, and xanthan gum *[see Warnings and Precautions (5.8)]*.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action
AUGMENTIN is an antibacterial drug *[see Clinical Pharmacology (12.4)]*.

### 12.2 Pharmacodynamics
The antibacterial activity of amoxicillin/clavulanate is primarily driven by the percentage of the dosing interval during which unbound (free) amoxicillin plasma concentrations exceed the minimum inhibitory concentration (%*f*T>MIC) of the target bacterial organism. Clavulanate inhibits β-lactamase enzymes and thereby restores activity of amoxicillin against certain β-lactamase–producing bacteria.

### 12.3 Pharmacokinetics
Absorption
*AUGMENTIN (Tablets, Chewable Tables, and Oral Suspension)*
Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While AUGMENTIN 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 AUGMENTIN was dosed at 30 and 150 minutes after the start of a high-fat breakfast.

*AUGMENTIN Tablets*
Mean amoxicillin and clavulanate potassium pharmacokinetic parameters in healthy adult subjects following administration of AUGMENTIN Tablets are shown in Table 7.

**Table 7: Mean (±S.D.) Amoxicillin and Clavulanate Potassium Pharmacokinetic Parameters[a,b] with AUGMENTIN Tablets**

| Dosing Regimen | $C_{max}$ (mcg/mL) | | $AUC_{0-24}$ (mcg*h/mL) | |
|---|---|---|---|---|
| | Amoxicillin | Clavulanate potassium | Amoxicillin | Clavulanate potassium |
| 250 mg/125 mg every 8 hours | 3.3 ± 1.12 | 1.5 ± 0.70 | 26.7 ± 4.56 | 12.6 ± 3.25 |
| 500 mg/125 mg every 12 hours | 6.5 ± 1.41 | 1.8 ± 0.61 | 33.4 ± 6.76 | 8.6 ± 1.95 |
| 500 mg/125 mg every 8 hours | 7.2 ± 2.26 | 2.4 ± 0.83 | 53.4 ± 8.87 | 15.7 ± 3.86 |
| 875 mg/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 healthy adult subjects (n= 15 for clavulanate in the low-dose regimens). Peak concentrations occurred ~1.5 hours after the dose.
[b]Administered at the start of a light meal.

*AUGMENTIN for Oral Suspension and Chewable Tablets*
Mean pharmacokinetic parameters in healthy adult subjects following administration of AUGMENTIN for Oral Suspension and Chewable Tablets are shown in Table 8.

**Table 8: Mean (±S.D.) Amoxicillin and Clavulanate Potassium Pharmacokinetic Parameters[a,b] with AUGMENTIN for Oral Suspension and Chewable Tablets**

| Dose of AUGMENTIN | $C_{max}$ (mcg/mL) | | $AUC_{0-24}$ (mcg*h/mL) | |
|---|---|---|---|---|
| Amoxicillin and Clavulanate potassium | Amoxicillin | Clavulanate potassium | Amoxicillin | Clavulanate potassium |
| 400 mg/57 mg (5 mL of suspension) | 6.94 ± 1.24 | 1.10 ± 0.42 | 17.29 ± 2.28 | 2.34 ± 0.94 |
| 400 mg/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 healthy adult subjects. Peak concentrations occurred ~1 hour post-dose.
[b]Administered at the start of a light meal.

Administration of 5 mL of AUGMENTIN Oral Suspension 250 mg/62.5 mg or the equivalent dose of 10 mL of AUGMENTIN Oral Suspension 125 mg/31.25 mg results in:

- Mean $C_{max}$ (mcg/mL): amoxicillin 6.9; clavulanate 1.6 (mean peak ~1 hour post-dose)
- AUC during first 4 hours (mcg•h/mL): amoxicillin 12.6; clavulanate 2.9

One 250 mg/62.5 mg AUGMENTIN Chewable Tablet (or two 125 mg/31.25 mg AUGMENTIN Chewable Tablets) provides an equivalent dose to 5 mL of the AUGMENTIN Oral Suspension 250 mg/62.5 mg, yielding similar serum concentrations of amoxicillin and clavulanic acid.

*AUGMENTIN XR Extended-Release Tablets*
AUGMENTIN XR is an extended-release formulation which provides sustained plasma concentrations of amoxicillin. Amoxicillin systemic exposure achieved with AUGMENTIN XR Extended-Release Tablets is similar to that produced by the oral administration of equivalent doses of amoxicillin alone.

In a study of healthy adult volunteers, the pharmacokinetics of AUGMENTIN XR Extended-Release Tablets were compared when administered in a fasted state, at the start of a standardized meal (612 kcal, 89.3 g carb, 24.9 g fat, and 14 g protein), or 30 minutes after a high-fat meal.

When the systemic exposure to both amoxicillin and clavulanate is taken into consideration, AUGMENTIN XR Extended-Release Tablets is optimally administered at the start of a standardized meal. Absorption of amoxicillin is decreased in the fasted state. AUGMENTIN XR Extended-Release Tablets is not recommended to be taken with a high-fat meal, because clavulanate absorption is decreased.

The pharmacokinetics of the components of AUGMENTIN XR Extended-Release Tablets following administration of two AUGMENTIN XR Extended-Release Tablets at the start of a standardized meal are presented in Table 9

**Table 9: Mean (SD) Pharmacokinetic Parameters Following Oral Administration of Two AUGMENTIN XR Extended-Release Tablets (2,000 mg/125 mg) to Healthy Adult Volunteers (n=55) Fed a Standardized Meal**

| Parameter (units) | Amoxicillin | Clavulanate |
|---|---|---|
| $AUC_{(0\text{-}inf)}$(mcg•hr/mL) | 71.6 (16.5) | 5.29 (1.55) |
| $C_{max}$ (mcg/mL) | 17.0 (4.0) | 2.05 (0.80) |
| $T_{max}$ (hours)[a] | 1.50 (1.00 to 6.00) | 1.03 (0.75 to 3.00) |
| $T_{1/2}$ (hours) | 1.27 (0.20) | 1.03 (0.17) |

[a]Median (range)

*AUGMENTIN ES-600 for Oral Suspension*
The effect of food on AUGMENTIN ES-600 for Oral Suspension has not been formally evaluated. The mean plasma amoxicillin and clavulanate pharmacokinetic parameter values are listed in Table 10.

Distribution
The protein binding of amoxicillin and clavulanic acid to human serum is approximately 18% and 25%, respectively. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of the brain and spinal fluid.

Metabolism and Excretion
The half-life of amoxicillin after the oral administration of AUGMENTIN is approximately 1.3 hours and that of clavulanic acid is approximately 1 hour.

*AUGMENTIN and AUGMENTIN ES-600 for Oral Suspension*
Following administration of a single 250 mg/125 mg or 500 mg/125 mg tablet, approximately 50–70% of amoxicillin and approximately 25–40% of clavulanic acid are excreted unchanged in urine during the first 6 hours.

*AUGMENTIN XR Extended-Release Tablets*
Clearance of amoxicillin is predominantly renal, with approximately 60% to 80% of the dose being excreted unchanged in urine, whereas clearance of clavulanate has both a renal (30% to 50%) and a non-renal component.

Specific Populations:
*Pediatric Patients:*
*AUGMENTIN for Oral Suspension*
Two hours after administration of a single 35 mg/kg oral dose of AUGMENTIN suspension to fasting pediatrics, mean concentrations of 3 mcg/mL of amoxicillin and 0.5 mcg/mL of clavulanic acid were detected in middle ear effusions.

*AUGMENTIN ES-600 for Oral Suspension*
The pharmacokinetics of AUGMENTIN ES-600 for Oral Suspension were evaluated in 19 pediatric patients (8 months to 11 years) receiving AUGMENTIN ES-600 for Oral Suspension at 45 mg/kg every 12 hours with a snack or meal. Mean pharmacokinetic parameters are listed in Table 10.

**Table 10: Mean (±SD) Pharmacokinetic Parameters Following Administration of AUGMENTIN ES-600 for Oral Suspension (45 mg/kg) Every 12 Hours in Pediatric Patients***

| Parameter | Amoxicillin | Clavulanate |
|---|---|---|
| $C_{max}$ (mcg/mL) | 15.7 ± 7.7 | 1.7 ± 0.9 |
| $T_{max}$ (hr) | 2.0 (1.0 to 4.0) | 1.1 (1.0 to 4.0) |
| $AUC_{0-T}$ (mcg*hr/mL) | 59.8 ± 20.0 | 4.0 ± 1.9 |
| $T_{½}$ (hr) | 1.4 ± 0.3 | 1.1 ± 0.3 |
| CL/F (L/hr/kg) | 0.9 ± 0.4 | 1.1 ± 1.1 |

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

Oral administration of a single dose of AUGMENTIN ES-600 for Oral Suspension at 45 mg/kg (based on the amoxicillin component) to pediatric patients (9 months to 8 years), yielded the following pharmacokinetic data for amoxicillin in plasma and middle ear fluid (MEF) (Table 11).

**Table 11: Amoxicillin Concentrations in Plasma and Middle Ear Fluid Following AUGMENTIN ES-600 for Oral Suspension (45 mg/kg) in Pediatric Patients***

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

*Dose administered immediately prior to eating.

*AUGMENTIN XR Extended-Release Tablets*

In a study of pediatric patients with acute bacterial sinusitis, 7 to 15 years of age, and weighing at least 40 kg, the pharmacokinetics of amoxicillin and clavulanate were assessed following administration of AUGMENTIN XR Extended-Release Tablets 2,000 mg/125 mg (as two 1,000 mg/62.5 mg tablets) every 12 hours with food (Table 12).

**Table 12 Mean (SD) Pharmacokinetic Parameters for Amoxicillin and Clavulanate Following Oral Administration of Two AUGMENTIN XR Tablets (2,000 mg/125 mg) Every 12 Hours with Food to Pediatric Patients (7 to 15 Years of Age and Weighing 40 kg or greater) With Acute Bacterial Sinusitis**

| Parameter (units) | Amoxicillin (n=24) | Clavulanate (n=23) |
|---|---|---|
| AUC(0-τ) (mcg•hr/mL) | 57.8 (15.6) | 3.18 (1.37) |
| Cmax (mcg/mL) | 11.0 (3.34) | 1.17 (0.67) |
| Tmax (hours)[a] | 2.0 (1.0 to 5.0) | 2.0 (1.0 to 4.0) |
| $T_{1/2}$(hours) | 3.32 (2.21)[b] | 0.94 (0.13)[c] |

[a] Median (range)
[b] n = 18
[c] n = 17

Drug Interaction Studies

*Clinical Studies*

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid *[see Drug Interactions (7.1)]*.

## 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.

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 antibacterial 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.

Antimicrobial Activity

Amoxicillin and clavulanic acid has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

**Lower Respiratory Tract Infections**

Gram-negative bacteria:
- *Haemophilus influenzae*
- *Moraxella catarrhalis*

**Community-Acquired Pneumonia**

Gram-positive bacteria:
- *Staphylococcus aureus* (methicillin-susceptible)
- *Streptococcus pneumoniae*

Gram-negative bacteria:
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Klebsiella pneumoniae*
- *Moraxella catarrhalis*

**Acute Bacterial Sinusitis**

Gram-positive bacteria:
- *Staphylococcus aureus* (methicillin-susceptible)
- *Streptococcus pneumoniae*

Gram-negative bacteria:
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Klebsiella pneumoniae*
- *Moraxella catarrhalis*

**Acute Bacterial Otitis Media, including Recurrent or Persistent Acute Otitis Media**

Gram-positive bacteria:

*Streptococcus pneumoniae*

Gram-negative bacteria:
- *Haemophilus influenzae*
- *Moraxella catarrhalis*

**Skin and Skin Structure Infections**

Gram-positive bacteria:

*Staphylococcus aureus* (methicillin-susceptible)

Gram-negative bacteria:

*Escherichia coli*

*Klebsiella* spp.

**Urinary Tract Infections**

Gram-negative bacteria (including beta-lactamase-producing strains):

*Escherichia coli*

*Klebsiella* spp.

*Enterobacter* spp.

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for amoxicillin and clavulanic acid against isolates of similar genus or organism group. However, the efficacy of amoxicillin and clavulanic acid in treating clinical infections caused by these bacteria have not been established in adequate and well-controlled trials.

Gram-positive bacteria:

*Enterococcus faecalis*

*Staphylococcus epidermidis*

*Staphylococcus saprophyticus*

*Streptococcus pyogenes*

*Viridans group Streptococcus*

Gram-negative Bacteria

*Eikenella corrodens*

*Proteus mirabilis*

*Anaerobic Bacteria*

*Bacteroides species including Bacteroides fragilis*

*Fusobacterium species*

*Peptostreptococcus species*

Susceptibility Testing:

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis
Amoxicillin and clavulanate (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 was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at concentrations that were also associated with decreased cell survival. Amoxicillin and clavulanate was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Clavulanate potassium alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test and was negative in each of these assays.

Impairment of Fertility
Amoxicillin and clavulanate (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 comparisons, these doses correspond to approximately 4 times the MRHD for adults for amoxicillin trihydrate and 10 times the MRHD for clavulanate potassium.

## 14 CLINICAL STUDIES

### 14.1 Lower Respiratory Tract Infections in Adults Treated with AUGMENTIN Tablets
A randomized, controlled trial was conducted in 562 adults with lower respiratory tract infections, comparing AUGMENTIN 875 mg/125 mg every 12 hours with AUGMENTIN 500 mg/125 mg every 8 hours. Comparable efficacy was demonstrated between the two regimens.

### 14.2 Complicated Urinary Tract Infections in Adults Treated with AUGMENTIN Tablets
A randomized, controlled trial was conducted in adults with pyelonephritis (n=361) or complicated urinary tract infection (n=268), defined as urinary tract abnormalities that predispose to relapse after bacteriuria eradication. Patients were randomized 1:1 to receive AUGMENTIN 875 mg/125 mg every 12 hours (n=308) or AUGMENTIN 500 mg/125 mg every 8 hours (n=321). Among bacteriologically evaluable patients, bacteriologic success rates were comparable between the two dosing regimens when assessed immediately after therapy and at follow-up visits.

**Table 13: Bacteriologic Efficacy Rates in Complicated Urinary Tract Infections in Adults**

| 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) |

### 14.3 Community-Acquired Pneumonia in Adult and Pediatric Patients Weighing ≥40 kg Treated with AUGMENTIN XR Extended-Release Tablets

Four randomized, controlled, double-blind clinical studies and one non-comparative study were conducted in adults with community-acquired pneumonia (CAP). In comparative studies, 904 patients received AUGMENTIN XR Extended-Release Tablets at a dose of 2,000 mg/125 mg orally every 12 hours for 7 or 10 days. In the non-comparative study to assess both clinical and bacteriological efficacy, 1,122 patients received AUGMENTIN XR Extended-Release Tablets 2,000 mg/125 mg orally every 12 hours for 7 days. In the 4 comparative studies, the combined clinical success rate at test of cure ranged from 86% to 95% in clinically evaluable patients who received AUGMENTIN XR Extended-Release Tablets.

Data on the efficacy of AUGMENTIN XR Extended-Release Tablets in the treatment of community-acquired pneumonia due to *S. pneumoniae* with reduced susceptibility to penicillin were accrued from the 4 controlled clinical studies and the 1 non-comparative study. The majority of these cases were accrued from the non-comparative study. Results are shown in Table 14.

**Table 14: Clinical Outcome for CAP due to *S. pneumoniae***

| Penicillin MICs of *S. pneumoniae* Isolates | Intent-To-Treat | | | Clinically Evaluable | | |
|---|---|---|---|---|---|---|
| | n/N[a] | % | 95% CI[b] | n/N[a] | % | 95% CI[b] |
| All *S. pneumoniae* | 318/367 | 87 | — | 275/297 | 93 | — |
| MIC greater than or equal to 2.0 mcg/mL[c] | 30/35 | 86 | 69.7, 95.2 | 24/25 | 96 | 79.6, 99.9 |
| MIC equal to 2.0 mcg/mL | 22/24 | 92 | 73.0, 99.0 | 18/18 | 100 | 81.5, 100 |
| MIC greater than or equal to 4.0 mcg/mL[d] | 8/11 | 73 | 39.0, 94.0 | 6/7 | 86 | 42.1, 99.6 |

[a]n/N equals patients with pathogen eradicated or presumed eradicated/total number of patients.
[b]Confidence limits calculated using exact probabilities.
[c]*S. pneumoniae* strains with penicillin MICs of greater than or equal to 2 mcg/mL are considered resistant to penicillin.
[d]Includes one patient each with *S. pneumoniae* penicillin MICs of 8 and 16 mcg/mL in the Intent-To-Treat group only.

### 14.4 Acute Bacterial Sinusitis in Adult and Pediatric Patients Weighing ≥40 kg Treated with AUGMENTIN XR Extended-Release Tablets

Adults with a diagnosis of acute bacterial sinusitis (ABS) were evaluated in 3 clinical studies. In one study, 363 patients were randomized to receive either AUGMENTIN XR Extended-Release Tablets 2,000 mg/125 mg orally every 12 hours or levofloxacin 500 mg orally daily for 10 days in a double-blind, multicenter, prospective trial. These patients were clinically and radiologically

evaluated at the test of cure (day 17 to 28) visit. The combined clinical and radiological responses were 84% for AUGMENTIN XR Extended-Release Tablets and 84% for levofloxacin at the test of cure visit in clinically evaluable patients (95% CI for the treatment difference equals -9.4, 8.3). The clinical response rates at the test of cure were 87% and 89%, respectively.

The other 2 trials were non-comparative, multicenter studies designed to assess the bacteriological and clinical efficacy of AUGMENTIN XR Extended-Release Tablets (2,000 mg/125 mg orally every 12 hours for 10 days) in the treatment of 2,288 patients with ABS. Evaluation timepoints were the same as in the prior study. Patients underwent maxillary sinus puncture for culture prior to receiving study medication. Patients with acute bacterial sinusitis due to *S. pneumoniae* with reduced susceptibility to penicillin were accrued through enrollment in these 2 open-label non-comparative clinical trials. Clinical success rates for key pathogens in these studies are shown in Table 15.

**Table 15: Clinical Success Rates in Patients with Acute Bacterial Sinusitis**

| **Penicillin MICs of *S. pneumoniae* Isolates** | **Intent-To-Treat** | | | **Clinically Evaluable** | | |
|---|---|---|---|---|---|---|
| | **n/N[a]** | **%** | **95% CI[b]** | **n/N[a]** | **%** | **95% CI[b]** |
| All *S. pneumoniae* | 344/370 | 93 | — | 318/326 | 98 | — |
| MIC greater than or equal to 2.0 mcg/mL[c] | 35/36 | 97 | 85.5, 99.9 | 30/31 | 96 | 83.3, 99.9 |
| MIC equal to 2.0 mcg/mL | 23/24 | 96 | 78.9, 99.9 | 19/20 | 95 | 75.1, 99.9 |
| MIC greater than or equal to 4.0 mcg/mL[d] | 12/12 | 100 | 73.5, 100 | 11/11 | 100 | 71.5, 100 |
| *H. influenzae* | 265/305 | 87 | — | 242/259 | 93 | — |
| *M. catarrhalis* | 94/105 | 90 | — | 86/90 | 96 | — |

[a]n/N equals patients with pathogen eradicated or presumed eradicated/total number of patients.
[b]Confidence limits calculated using exact probabilities.
[c]*S. pneumoniae* strains with penicillin MICs of greater than or equal to 2 mcg/mL are considered resistant to penicillin.
[d]Includes one patient each with *S. pneumoniae* penicillin MICs of 8 and 16 mcg/mL.

### 14.5 Acute Bacterial Otitis Media in Pediatric Patients Treated with AUGMENTIN for Oral Suspension

One randomized, controlled US/Canadian clinical trial evaluated two dosing regimens for AUGMENTIN for Oral Suspension in pediatric patients (aged 2 months to 12 years) with acute otitis media. Patients received either 45 mg/6.4 mg/kg/day divided every 12 hours or 40 mg/10 mg/kg/day divided every 8 hours for 10 days. A total of 575 patients were enrolled, with ≥84% evaluable in each group.

Clinical cure rates obtained in the evaluable patients at the end of therapy and follow-up visits are presented in Table 16.

**Table 16: Clinical Cure Rates at End of Therapy and Follow-Up Visits**

| | AUGMENTIN 45 mg/kg/day, divided every 12 hours | AUGMENTIN 40 mg/kg/day, divided every 8 hours |
|---|---|---|
| Clinical Cure at End of Therapy Visit[a] | 87% (n=265) | 82% (n=260) |
| Clinical Cure at Follow-Up Visit | 67% (n= 249) | 69% (n=243) |

[a]Clinical cure at end of therapy visit was defined as 2 to 4 days after the completion of therapy.
[b]Clinical cure at follow-up visit was defined as 22 to 28 days post-completion of therapy.

### 14.6 Recurrent or Persistent Acute Otitis Media in Pediatric Patients 3 Months to 12 Years Weighing 8 kg to 40 kg Treated with AUGMENTIN ES-600 For Oral Suspension

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 for Oral Suspension (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 pediatric patients 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 day care attendance. Prior to receiving AUGMENTIN ES-600 for Oral Suspension, all patients had tympanocentesis to obtain middle ear fluid for bacteriological evaluation. Patients from whom *S. pneumoniae* (alone or in combination with other bacteria) was isolated had a second tympanocentesis 4 to 6 days after the start of therapy. Clinical assessments were planned for all patients during treatment (4 to 6 days after starting therapy), as well as 2 to 4 days post-treatment and 15 to 18 days post-treatment. Bacteriological success was defined as the absence of the pretreatment pathogen from the on-therapy tympanocentesis specimen. Clinical success was defined as improvement or resolution of signs and symptoms. Clinical failure was defined as lack of improvement or worsening of signs and/or symptoms at any time following at least 72 hours of AUGMENTIN ES-600 for Oral Suspension; patients who received an additional systemic antibacterial drug for otitis media after 3 days of therapy were considered clinical failures. Bacteriological eradication on therapy (day 4 to 6 visit) in the per protocol population is summarized in Table 17.

**Table 17: Bacteriologic Eradication Rates in the Per Protocol Population**

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

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

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

**Table 18: Clinical Assessments in the Per Protocol Population (Includes S. pneumoniae Patients with Penicillin MICs equal to 2 or 4 mcg/mL*)**

| **2 to 4 Days Post-Therapy (Primary Endpoint)** | | | |
|---|---|---|---|
| **Pathogen** | **n/N** | **%** | **95% CI†** |
| All *S. pneumoniae* | 122/137 | 89 | (82.6, 93.7) |
| *S. pneumoniae* with penicillin MIC equal to 2 mcg/mL | 17/20 | 85 | (62.1, 96.8) |
| *S. pneumoniae* with penicillin MIC equal to 4 mcg/mL | 11/14 | 79 | (49.2, 95.3) |
| *H. influenzae* | 141/162 | 87 | (80.9, 91.8) |
| *M. catarrhalis* | 22/26 | 85 | (65.1, 95.6) |
| **15 to 18 Days Post-Therapy‡ (Secondary Endpoint)** | | | |
| **Pathogen** | **n/N** | **%** | **95% CI†** |
| All *S. pneumoniae* | 95/136 | 70 | (61.4, 77.4) |
| *S. pneumoniae* with penicillin MIC equal to 2 mcg/mL | 11/20 | 55 | (31.5, 76.9) |
| *S. pneumoniae* with penicillin MIC equal to 4 mcg/mL | 5/14 | 36 | (12.8, 64.9) |
| *H. influenzae* | 106/156 | 68 | (60.0, 75.2) |
| *M. catarrhalis* | 14/25 | 56 | (34.9, 75.6) |

**S. pneumoniae* strains with penicillin MICs of 2 or 4 mcg/mL are considered resistant to penicillin.
†CI equals 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 equal to 2 mcg/mL and 4 mcg/mL were 29/41 (71%) and 17/41 (42%), respectively.

## 15 REFERENCES

1. Swanson-Biearman B, Dean BS, Lopez G, Krenzelok EP. The effects of penicillin and cephalosporin ingestions in children less than six years of age. Vet Hum Toxicol. 1988; 30:66-67.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

AUGMENTIN (amoxicillin and clavulanate potassium) is supplied as film-coated tablets, film–coated extended-release tablets, chewable tablets, and powder for oral suspension in multiple strengths and flavors. Table 19 describes the available AUGMENTIN formulations, strengths, appearance, and package configurations.

**Table 19: AUGMENTIN Formulations, Strengths, Description, NDC Numbers and How Supplied**

| Formulation | Strength (amoxicillin/ clavulanic acid) | Description | NDC | Package |
|---|---|---|---|---|
| AUGMENTIN Tablets | 250 mg/ 125 mg | White oval, film-coated, debossed AUGMENTIN one side, 250/125 the other side | NDC 81964-018-30<br><br>NDC 81964-018-78 | Bottle of 30<br><br>Unit dose (10x10) 100 tablets |
| AUGMENTIN Tablets | 500 mg/ 125 mg | White oval, film-coated, debossed AUGMENTIN one side, 500/125 the other side | NDC 81964-006-14<br><br>NDC 81964-006-78 | Bottle of 20<br><br>Unit dose (10x10) 100 tablets |
| AUGMENTIN Tablets | 875 mg/ 125 mg | White capsule-shaped, debossed AUGMENTIN 875 one side, scored on the other side | NDC 81964-021-14<br><br>NDC 81964-021-78<br><br>NDC 81964-021-01 | Bottle of 20<br><br>Unit dose (10x10) 100 tablets<br><br>Bottle of 100 |
| AUGMENTIN XR Extended-release tablets | 1,000 mg/ 62.5 mg | White oval, film-coated bilayer scored tablets, debossed AUGMENTIN XR | NDC 81964-020-28<br><br>NDC 81964-020-40 | Bottles of 28 (7-day XR pack)<br><br>Bottles of 40 (10-day XR pack) |
| AUGMENTIN Chewable Tablets | 125 mg/ 31.25 mg | Mottled yellow, round, lemon-lime flavor, debossed BMP 189 | NDC 81964-014-31 | Unit dose (5x6) 30 tablets |
| AUGMENTIN Chewable Tablets | 200 mg/ 28.5 mg | Mottled pink, round, cherry-banana flavor, debossed AUGMENTIN 200. | NDC 81964-015-14 | Unit dose (4x5) 20 tablets |

| Formulation | Strength (amoxicillin/ clavulanic acid) | Description | NDC | Package |
|---|---|---|---|---|
| AUGMENTIN Chewable Tablets | 250 mg/ 62.5 mg | Mottled yellow, round, lemon-lime flavor, debossed BMP 190 | NDC 81964-016-31 | Unit dose (5x6) 30 tablets |
| AUGMENTIN Chewable Tablets | 400 mg/ 57 mg | Mottled pink, round, cherry-banana flavor, debossed AUGMENTIN 400 | NDC 81964-017-14 | Unit dose (4x5) 20 tablets |
| AUGMENTIN for Oral Suspension | 125 mg/ 31.25 mg per 5 mL | Banana flavor powder for oral suspension | NDC 81964-012-01<br>NDC 81964-012-03<br>NDC 81964-012-05 | 75 mL bottle<br>100 mL bottle<br>150 mL bottle |
| AUGMENTIN for Oral Suspension | 200 mg/ 28.5 mg per 5 mL | Orange flavor powder for oral suspension | NDC 81964-013-50<br>NDC 81964-013-51<br>NDC 81964-013-52 | 50 mL bottle<br>75 mL bottle<br>100 mL bottle |
| AUGMENTIN for Oral Suspension | 250 mg/ 62.5 mg per 5 mL | Orange flavor powder for oral suspension | NDC 81964-004-07<br>NDC 81964-004-10<br>NDC 81964-004-15 | 75 mL bottle<br>100 mL bottle<br>150 mL bottle |
| AUGMENTIN for Oral Suspension | 400 mg/ 57 mg per 5 mL | Orange flavor powder for oral suspension | NDC 81964-008-50<br>NDC 81964-008-51<br>NDC 81964-008-52 | 50 mL bottle<br>75 mL bottle<br>100 mL bottle |
| AUGMENTIN ES-600 for Oral Suspension | 600 mg/ 42.9 mg per 5 mL | Strawberry cream flavored powder for oral suspension | NDC 81964-003-51<br>NDC 81964-003-69<br>NDC 81964-003-54 | 75 mL bottle<br>125 mL bottle<br>200 mL bottle |

Storage

**Tablets and Chewable Tablets**

Store AUGMENTIN Tablets, Chewable Tablets, and AUGMENTIN XR Extended-Release Tablets at or below 25°C (77°F).

**Powder for Oral Suspension**

Store AUGMENTIN for Oral Suspension and AUGMENTIN ES-600 for Oral Suspension at or below 25°C (77°F).

**Reconstituted Oral Suspension**
Store reconstituted AUGMENTIN for Oral Suspension and AUGMENTIN ES-600 for Oral Suspension in the original container under refrigeration. Discard unused reconstituted suspension after 10 days. A slight color change during storage is normal. *[see Dosage and Administration (2.7)]*.

## 17 PATIENT COUNSELING INFORMATION

Administration Instructions
Advise patients or caregivers that when dosing a child with AUGMENTIN for oral suspension, they should use a dosing spoon or medicine dropper. Be sure to rinse the spoon or dropper after each use *[see Dosage and Administration (2.7)]*.

Allergic Reactions
Counsel patients that AUGMENTIN contains a penicillin class drug product that can cause allergic reactions in some individuals *[see Warnings and Precautions (5.1, 5.3)]*.

Severe Cutaneous Adverse Reactions (SCAR)
Advise patients about the signs and symptoms of serious skin manifestations. Instruct patients to stop taking AUGMENTIN immediately and promptly report the first signs or symptoms of skin rash, mucosal lesions, or any other sign of hypersensitivity *[see Warnings and Precautions (5.2)]*.

Diarrhea
Counsel patients that diarrhea is a common problem caused by antibacterial drugs, including AUGMENTIN, which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible. If diarrhea develops and is severe or lasts more than 2 or 3 days, advise the patients to call their doctor *[see Warnings and Precautions (5.5)]*.

Risks in Patients with Phenylketonuria
Counsel patients with phenylketonuria that certain AUGMENTIN formulations contain aspartame, a source of phenylalanine *[see Warnings and Precautions (5.8)]:*

- Each 5 mL of AUGMENTIN ES-600 for Oral Suspension contains 7 mg phenylalanine.
- AUGMENTIN 200 mg/28.5 mg and 400 mg/57 mg for Oral Suspension and Chewable Tablets contain aspartame. Each 200 mg chewable tablet contains 2.1 mg phenylalanine; each 400 mg chewable tablet contains 4.2 mg phenylalanine; and each 5 mL of the 200 mg/5 mL or 400 mg/5 mL oral suspension contains 7 mg phenylalanine.

Antibacterial Resistance
Patients should be counseled that antibacterial drugs, including AUGMENTIN, should only be used to treat bacterial infections. Antibacterial drugs do not treat viral infections (e.g., the common cold). When AUGMENTIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken

exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by AUGMENTIN or other antibacterial drugs in the future *[see Warnings and Precautions (5.9)]*.

Storage Instructions

Advise patients to keep AUGMENTIN for oral suspension refrigerated and to shake well before using. Bottles of AUGMENTIN for oral suspension may contain more liquid than required. Advise patients to follow their doctor's instructions about the amount to use and the days of treatment required. Discard any unused medicine *[see Dosage and Administration (2.3, 2.4, 2.7), How Supplied/Storage and Handling (16)]*.

Manufactured by:
USAntibiotics, LLC
Bristol, TN 37620 (USA)

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