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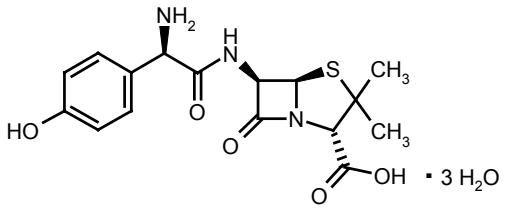
PRESCRIBING INFORMATION

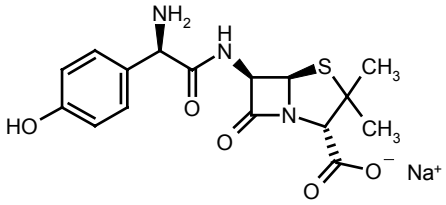
AUGMENTIN XR™
amoxicillin/clavulanate potassium
Extended Release Tablets

1 Description

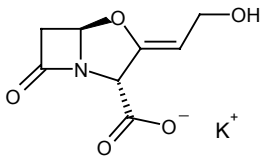
Augmentin XR is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin (present as amoxicillin trihydrate and amoxicillin sodium) and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin trihydrate molecular formula is $C_{16}H_{19}N_3O_5S•3H_2O$ and the molecular weight is 419.45. Chemically, amoxicillin trihydrate 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:



The amoxicillin sodium molecular formula is $C_{16}H_{18}N_3NaO_5S$ and the molecular weight is 387.39. Chemically, amoxicillin sodium is [2S-[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 β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$ and the molecular weight is 237.25. Chemically clavulanate potassium is potassium (*Z*)-(2*R*, 5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate, and may be represented structurally as:



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

Each *Augmentin XR* tablet contains 12.6 mg (0.32 mEq) of potassium and 29.3 mg (1.27 mEq) of sodium**.**

2 Clinical Pharmacology

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of *Augmentin XR*.

Augmentin XR is an extended-release formulation which provides sustained plasma concentrations of amoxicillin. Amoxicillin systemic exposure achieved with *Augmentin XR* 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* 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, 14.0 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* is optimally administered at the start of a standardized meal. Absorption of amoxicillin is decreased in the fasted state. *Augmentin XR* is not recommended to be taken with a high fat meal, because clavulanate absorption is decreased. The pharmacokinetics of the components of *Augmentin XR* following administration of two *Augmentin XR* tablets at the start of a standardized meal are presented below.

Mean (SD) Pharmacokinetic Parameters for Amoxicillin and Clavulanate Following Oral Administration of Two *Augmentin XR* Tablets (2000/125 mg) to Healthy Adult Volunteers [n=55] Fed a Standardized Meal

Parameter (units)	Amoxicillin	Clavulanate
AUC(0-inf) (µg.h/mL)	71.6 (16.5)	5.29 (1.55)
C_{max} (µg/mL)	17.0 (4.0)	2.05 (0.80)
T_{max} (hours)[†]	1.50 (1.00-6.00)	1.03 (0.75-3.00)
$T_{1/2}$ (hours)	1.27 (0.20)	1.03 (0.17)

[†]median (range)

The half-life of amoxicillin after the oral administration of *Augmentin XR* is approximately 1.3 hours, and that of clavulanate is approximately 1.0 hour.

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.

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

In a study of adults, the pharmacokinetics of amoxicillin and clavulanate were not affected by administration of an antacid (Maalox®), either simultaneously with or two hours after *Augmentin XR*.

Neither component in *Augmentin XR* is highly protein-bound; clavulanate has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

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

3 Microbiology

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

The clavulanic acid component in *Augmentin XR* protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics.

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

Aerobic Gram-positive Microorganisms
Streptococcus pneumoniae (including isolates with penicillin MICs ≤ 2 μg/mL)
Staphylococcus aureus (including β-lactamase producing strains)

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

Aerobic Gram-negative Microorganisms

Haemophilus influenzae (including β-lactamase producing strains)
Moraxella catarrhalis (including β-lactamase producing strains)
Haemophilus parainfluenzae (including β-lactamase producing strains)
Klebsiella pneumoniae (all known strains are β-lactamase producing)

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

Amoxicillin/clavulanic acid exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2.0 µg/mL or less against most (≥90%) strains of *Streptococcus pyogenes* and MICs of 4.0 µg/mL or less against most (≥90%) strains of the anaerobic bacteria listed below.

Aerobic Gram-positive Microorganisms

Streptococcus pyogenes

Anaerobic Microorganisms

Bacteroides fragilis (including β-lactamase producing strains)
Fusobacterium nucleatum (including β-lactamase producing strains)
Peptostreptococcus magnus
Peptostreptococcus micros

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

Susceptibility Testing

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure[1,2]. Standardized procedures are based on a dilution method (broth or agar; broth for *S. pneumoniae* and *Haemophilus* species) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

The MIC values should be interpreted according to the following criteria:

For testing *Klebsiella pneumoniae*:

MIC (µg/mL)	Interpretation
≤ 8/4	Susceptible (S)
16/8	Intermediate (I)
≥ 32/16	Resistant (R)

For testing *Streptococcus pneumoniae*[a]:

MIC (µg/mL)	Interpretation
≤ 2/1	Susceptible (S)
4/2	Intermediate (I)
≥ 8/4	Resistant (R)

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

For testing *Staphylococcus* species and *Haemophilus* species[b] *:*

MIC (µg/mL)	Interpretation
≤ 4/2	Susceptible (S)
≥ 8/4	Resistant (R)

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

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

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

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

Microorganism	MIC Range (µg/mL)[c]
Escherichia coli ATCC 35218	4 to 16
Escherichia coli ATCC 25922	2 to 8
Haemophilus influenzae[d] ATCC 49247	2 to 16
Staphylococcus aureus ATCC 29213	0.12 to 0.5
Streptococcus pneumoniae[e] ATCC 49619	0.03 to 0.12

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

[d] This quality control range is applicable to *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.[2]

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg of amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

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

For testing *Klebsiella pneumoniae*:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
14 – 17	Intermediate (I)
≤ 13	Resistant (R)

For testing *Staphylococcus* and *Haemophilus*[f] species:

Zone Diameter (mm)	Interpretation
≥ 20	Susceptible (S)
≤ 19	Resistant (R)

[f] These zone diameter standards are applicable only to tests conducted with *Haemophilus* spp. using HTM.[2]

NOTE: Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.
NOTE: Beta-lactamase negative, ampicillin-resistant *H. influenzae* strains must be considered resistant to amoxicillin/clavulanic acid.

For testing *Streptococcus pneumoniae:*
Susceptibility of *S. pneumoniae* should be determined using a 1 µg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin/clavulanic acid. [g] An amoxicillin/clavulanic acid MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

[g] These zone diameter standards for *S. pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.[2]

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

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

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 35218	17 to 22
Escherichia coli ATCC 25922	18 to 24
Staphylococcus aureus ATCC 25923	28 to 36
Haemophilus influenzae[h] ATCC 49247	15 to 23

[h] This quality control limit applies only to tests conducted with *H. influenzae* ATCC 49247 using HTM. [2]

4 Indications and Usage

Augmentin XR Extended Release Tablets are indicated for the treatment of patients with community-acquired pneumonia or acute bacterial sinusitis due to confirmed, or suspected β-lactamase-producing pathogens (i.e., *H. influenzae*, *M. catarrhalis*, *H. parainfluenzae*, *K. pneumoniae*, or methicillin-susceptible *S. aureus*) and *S. pneumoniae* with reduced susceptibility to penicillin (i.e., penicillin MICs = 2 µg/mL). *Augmentin XR* is not indicated for the treatment of infections due to *S. pneumoniae* with penicillin MIC ≥4 µg/mL. Data are limited with regard to infections due to *S. pneumoniae* with penicillin MICs ≥4 µg/ml (See CLINICAL STUDIES Section).

Of the common epidemiological risk factors for patients with resistant pneumococcal infections, only age >65 years was studied. Patients with other common risk factors for resistant pneumococcal infections (e.g., alcoholism, immune-suppressive illness, and presence of multiple co-morbid conditions) were not studied.

In patients with community-acquired pneumonia in whom penicillin-resistant *S. pneumoniae* is suspected, bacteriological studies should be performed to determine the causative organisms and their susceptibility when *Augmentin XR* is prescribed. Once the results are known, therapy should be adjusted appropriately.

Acute bacterial sinusitis or community-acquired pneumonia due to a penicillin-susceptible strain of *S. pneumoniae* plus a beta-lactamase-producing pathogen can be treated with another *Augmentin* product containing lower daily doses of amoxicillin (i.e., 500 mg q8h or 875 mg q12h). Acute bacterial sinusitis or community-acquired pneumonia due to *S. pneumoniae* alone can be treated with amoxicillin.

5 Contraindications

Augmentin XR is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with treatment with amoxicillin/clavulanate.

Augmentin XR is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/minute) and in hemodialysis patients.

6 Warnings

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN

TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN XR*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN XR* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

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

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

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

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

7 Precaution

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

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

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

Information for Patients: *Augmentin XR* should be taken every 12 hours with a meal or snack to reduce the possibility of gastrointestinal upset. If diarrhea develops and is severe or lasts more than 2 or 3

days, call your doctor. The entire prescribed course of treatment should be completed, even if you begin to feel better after a few days. Discard any unused medicine.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin XR* may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. In *Augmentin XR* controlled clinical trials, 22 patients received concomitant allopurinol and *Augmentin XR*. No rashes were reported in these patients. However, this sample size is too small to allow for any conclusions to be drawn regarding the risk of rashes with concomitant *Augmentin XR* and allopurinol use.

In common with other broad-spectrum antibiotics, *Augmentin XR* may reduce the efficacy of oral contraceptives.

Drug/Laboratory Test Interactions: Oral administration of *Augmentin XR* will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore *Augmentin XR*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore *Augmentin XR*.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations. *Augmentin* at oral doses of up to 1200 mg/kg/day (1.9 times the maximum human dose of amoxicillin and 15 times the maximum human dose of clavulanate based on body surface area) was found to have no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Teratogenic effects. Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral doses up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to *Augmentin*. In terms of body surface area, the doses in rats were 1.6 times the maximum human oral dose of amoxicillin and 13 times the maximum human dose for clavulanate. For mice, these doses were 0.9 and 7.4 times the maximum human oral dose of amoxicillin and clavulanate, respectively. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin XR* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin XR* is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

Geriatric Use: Of the total number of subjects in clinical studies of *Augmentin XR*, 19.2% were 65 and over and 7.9% were 75 and older. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other clinical experience has not reported differences in responses between the elderly and younger patients, but a greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of dose-dependent toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Each *Augmentin XR* tablet contains 29.3 mg (1.27 mEq) of sodium**.**

8 Adverse Reactions

In clinical trials, 4144 patients have been treated with *Augmentin XR*. The majority of side effects observed in clinical trials were of a mild and transient nature; 2% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects which were suspected or probably drug-related were diarrhea (15.6%), nausea (2.2%), genital moniliasis (2.1%) and abdominal pain (1.6%). *Augmentin XR* had a higher rate of diarrhea which required corrective therapy (4.0% vs. 2.4% for *Augmentin XR* and all comparators, respectively).

The following adverse reactions have been reported for ampicillin class antibiotics:
Gastrointestinal: 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 antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), acute generalized exanthematous pustulosis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin* or *Augmentin XR*. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely.

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. Mild to moderate thrombocytosis was noted in <1% of patients treated with *Augmentin* and 3.6% of patients treated with *Augmentin XR*. There have been reports of increased prothrombin time in patients receiving *Augmentin* and anticoagulant therapy concomitantly.

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

9 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 XR*, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison control center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.[4]

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis. (See DOSAGE AND ADMINISTRATION).

10 Dosage and Administration

Augmentin XR should be taken at the start of a meal to enhance the absorption of amoxicillin and to minimize the potential for gastrointestinal intolerance. Absorption of the amoxicillin component is decreased when *Augmentin XR* is taken on an empty stomach (See CLINICAL PHARMACOLOGY).

The recommended dose of *Augmentin XR* is 4000 mg/250 mg daily according to the following table:

Indication	Dose	Duration
Acute Bacterial Sinusitis	2 tablets q12h	10 days
Community Acquired Pneumonia	2 tablets q12h	7-10 days

***Augmentin* Tablets (250 mg or 500 mg) CANNOT be used to provide the same dosages as *Augmentin XR* Extended Release Tablets. This is because *Augmentin* XR contains 62.5 mg of clavulanic acid, while the *Augmentin* 250 mg and 500 mg tablets each contain 125 mg of clavulanic acid. In addition, the Extended Release Tablet provides an extended time course of plasma amoxicillin concentrations compared to immediate release Tablets. Thus, two *Augmentin* 500 mg tablets are not equivalent to one *Augmentin XR* tablet.**

Renally impaired patients: The pharmacokinetics of *Augmentin XR* have not been studied in patients with renal impairment. *Augmentin XR* is contraindicated in severely impaired patients with a creatinine clearance of <30 mL/minute and in hemodialysis patients (See CONTRAINDICATIONS).

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

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 16 have not been established.

Geriatric Use: No dosage adjustment is required for the elderly (See PRECAUTIONS).

11 How Supplied

***AUGMENTIN XR* (amoxicillin/clavulanate potassium) EXTENDED RELEASE TABLETS:** Each white, oval filmcoated bilayer tablet, debossed with AC 1000/62.5, contains amoxicillin trihydrate and amoxicillin sodium equivalent to a total of 1000 mg of amoxicillin and clavulanate potassium equivalent to 62.5 mg of clavulanic acid.

NDC 0029-6096-28 Bottles of 28 (7 day XR pack)
NDC 0029-6096-40 Bottles of 40 (10 day XR pack)

12 Storage

Store tablets at or below 25°C (77°F). Dispense in original container.

13 Clinical Studies

Community-Acquired Pneumonia

Three randomized, controlled, double-blind clinical studies and one noncomparative study were conducted in adults with community-acquired pneumonia (CAP). In comparative studies, 582 patients received *Augmentin XR* at a dose of 2000/125 mg orally every 12 hours for 7 or 10 days. In the noncomparative study to assess both clinical and bacteriological efficacy, 1,122 patients received *Augmentin XR* 2000/125mg orally every 12 hours for 7 days. In the three comparative studies, the combined clinical success rate at test of cure ranged from 86.3 to 94.7% in clinically evaluable patients in the *Augmentin XR* group; in the noncomparative study, the clinical success rate was 85.6%.

Data on the efficacy of *Augmentin XR* in the treatment of community acquired pneumonia due to *Streptococcus pneumoniae* with reduced susceptibility to penicillin was accrued from the three controlled clinical studies and the one non-comparative study. The majority of these cases were accrued from the non-comparative study.

Clinical Outcome for CAP due to *S. pneumoniae*						
Penicillin MIC of *S. pneumoniae* Isolates	**Intent To Treat**			**Clinically Evaluable**		
	n*/N	**%**	**95% CI ‡**	***n*/N***	**%**	**95% CI ‡**
All *S. pneumoniae*	184/214	86.0	--	157/172	91.3	--
MIC ≥2.0 µg/ml**	17/20	85.0	62.1, 96.8	14/15	93.3	68.1, 99.8
MIC = 2.0 µg/ml	13/14	92.9	66.1, 99.8	10/10	100	69.2, 100
MIC = 4.0 µg/ml	4/6	66.7	22.3, 95.7	4/5	80.0	28.4, 99.5

* *n*/N= patients with pathogen eradicated or presumed eradicated/ total number of patients

‡ Confidence limits calculated using exact probabilities

** *S. pneumoniae* strains with penicillin MICs of ≥2 µg/mL are considered resistant to penicillin.

Acute Bacterial Sinusitis

Adults with a diagnosis of Acute Bacterial Sinusitis (ABS) were evaluated in three clinical studies. In one study, 363 patients were randomized to receive either *Augmentin XR* 2000/125 mg orally q12h 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 17-28) visit. The combined clinical and radiological responses were 83.7% for *Augmentin XR* and 84.3% for levofloxacin at the test of cure visit in clinically evaluable patients (95% CI for the treatment difference = -9.4, 8.3). The clinical response rates at the test of cure were 87.0% and 88.6%, respectively.

The other two trials were non-comparative, multicenter studies designed to assess the bacteriological and clinical efficacy of *Augmentin XR* (2000/125 mg orally q12h for 10 days) in the treatment of 1554 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. At test of cure, the clinical success rates were 87.5% and 87.1% (intention-to-treat) and 92.5% and 94.0% (per protocol populations).

Patients with acute bacterial sinusitis due to *S. pneumoniae* with reduced susceptibility to penicillin were accrued through enrollment in these two open-label non-comparative clinical trials. Microbiologic eradication rates for key pathogens in these studies are shown in the following table:

Clinical Outcome for ABS						
Penicillin MIC of *S. pneumoniae* Isolates	**Intent To Treat**			**Clinically Evaluable**		
	n*/N	**%**	**95% CI ‡**	***n*/N***	**%**	**95% CI ‡**
All *S. pneumoniae*	222/240	92.5	--	210/215	97.7	--
MIC ≥2.0 µg/ml**	25/26	96.2	80.4, 99.9	22/23	95.7	78.1, 99.9
MIC = 2.0 µg/ml	16/17	94.1	71.3, 99.9	13/14	92.9	66.1, 99.8
MIC ≥4.0 µg/ml***	9/9	100	66.4, 100	9/9	100	66.4, 100
H. influenzae	177/203	87.2	--	160/170	94.1	--
M. catarrhalis	67/74	90.5	--	61/62	98.4	--

* *n*/N= patients with pathogen eradicated or presumed eradicated/ total number of patients

‡ Confidence limits calculated using exact probabilities

** *S. pneumoniae* strains with penicillin MICs of ≥2 µg/mL are considered resistant to penicillin.

*** Includes one patient each with *S. pneumoniae* penicillin MICs of 8 and 16 µg/mL

Safety

In a randomized, double-blind, multicenter study, *Augmentin XR* (2000 /125 mg orally q12h, n = 255) was compared to *Augmentin* (875 /125 mg orally q12h, n = 259), administered for 7 days for the treatment of community-acquired pneumonia. Adverse events, regardless of relationship to test drug, were reported by 49.4% of patients in the *Augmentin XR* group (vs. 51.4% in comparator group). Treatment-related adverse events were reported in 25.1% of patients in the *Augmentin XR* group (vs. 24.7% in comparator group); most were mild and transient in nature. Adverse events which led to withdrawal were reported by 2.4% of patients in the *Augmentin XR* group (vs. 5.4% in comparator group). In each group, the most frequently reported adverse events were diarrhea (18.0% vs. 14.3%, p=0.28), nausea (4.3% vs. 5.4%), and headache (4.3% vs. 5.0%). Only one patient (0.4%) in the *Augmentin XR* group and two patients (0.8%) in the comparator group withdrew due to diarrhea. Serious adverse events considered suspected or probably related to test drug were reported in 0.8% of patients (vs. 0.4% in comparator)

14 References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2. NCCLS, Wayne, PA, Jan. 2000.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing – Twelfth Informational Standard. M100-S12, Vol. 22, No. 1. NCCLS, Wayne, PA, Jan. 2002.

3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1. NCCLS, Wayne, PA, Jan. 2000.
4. Swanson-Biearman B, Dean BS, Lopez G, Krenzelok EP. The effects of penicillin and cephalosporin ingestions in children less than six years of age. *Vet Hum Toxicol* 1988;30:66-67.

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GlaxoSmithKline

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