PRESCRIBING INFORMATION

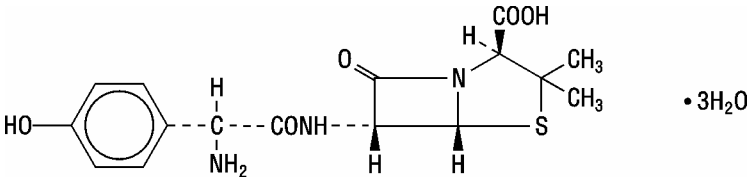
AMOXIL®

(amoxicillin capsules, tablets, chewable tablets, and powder for oral suspension)

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

DESCRIPTION

Formulations of AMOXIL contain amoxicillin, a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. 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. It may be represented structurally as:



The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S \bullet 3H_2O$, and the molecular weight is 419.45.

Capsules, tablets, and powder for oral suspension of AMOXIL are intended for oral administration.

Capsules: Each capsule of AMOXIL, with royal blue opaque cap and pink opaque body, contains 250 mg or 500 mg amoxicillin as the trihydrate. The cap and body of the 250-mg capsule are imprinted with the product name AMOXIL and 250; the cap and body of the 500-mg capsule are imprinted with AMOXIL and 500. Inactive ingredients: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, and titanium dioxide.

Tablets: Each tablet contains 500 mg or 875 mg amoxicillin as the trihydrate. Each film-coated, capsule-shaped, pink tablet is debossed with AMOXIL centered over 500 or 875, respectively. The 875-mg tablet is scored on the reverse side. Inactive ingredients: Colloidal silicon dioxide, crospovidone, FD&C Red No. 30 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

Chewable Tablets: Each cherry-banana-peppermint-flavored tablet contains 200 mg or 400 mg amoxicillin as the trihydrate.

Each 200-mg chewable tablet contains 0.0005 mEq (0.0107 mg) of sodium; the 400-mg chewable tablet contains 0.0009 mEq (0.0215 mg) of sodium. The 200-mg and 400-mg pale pink round tablets are imprinted with the product name AMOXIL and 200 or 400 along the edge of 1

side. Inactive ingredients: Aspartame*, crospovidone NF, FD&C Red No. 40 aluminum lake, flavorings, magnesium stearate, and mannitol.

*See PRECAUTIONS.

Powder for Oral Suspension: Each 5 mL of reconstituted suspension contains 125 mg, 200 mg, 250 mg, or 400 mg amoxicillin as the trihydrate. Each 5 mL of the 125-mg reconstituted suspension contains 0.11 mEq (2.51 mg) of sodium; each 5 mL of the 250-mg reconstituted suspension contains 0.15 mEq (3.36 mg) of sodium. Each 5 mL of the 200-mg reconstituted suspension contains 0.15 mEq (3.39 mg) of sodium; each 5 mL of the 400-mg reconstituted suspension contains 0.19 mEq (4.33 mg) of sodium.

Pediatric Drops for Oral Suspension: Each mL of reconstituted suspension contains 50 mg amoxicillin as the trihydrate and 0.03 mEq (0.69 mg) of sodium.

Amoxicillin trihydrate for oral suspension 125 mg/5 mL (reconstituted) is a strawberry-flavored pink suspension; the 200 mg/5 mL, 250 mg/5 mL (or 50 mg/mL), and 400 mg/5 mL are bubble-gum-flavored pink suspensions. Inactive ingredients: FD&C Red No. 3, flavorings, silica gel, sodium benzoate, sodium citrate, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. The effect of food on the absorption of amoxicillin from the tablets and suspension of AMOXIL has been partially investigated. The 400-mg and 875-mg formulations have been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 200-mg and 500-mg formulations. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. In blood serum, amoxicillin is approximately 20% protein-bound.

Orally administered doses of 250-mg and 500-mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 3.5 mcg/mL to 5.0 mcg/mL and 5.5 mcg/mL to 7.5 mcg/mL, respectively.

Mean amoxicillin pharmacokinetic parameters from an open, two-part, single-dose crossover bioequivalence study in 27 adults comparing 875 mg of AMOXIL with 875 mg of AUGMENTIN® (amoxicillin/clavulanate potassium) showed that the 875-mg tablet of AMOXIL produces an $AUC_{0-\infty}$ of 35.4 ± 8.1 mcg•hr/mL and a C_{max} of 13.8 ± 4.1 mcg/mL. Dosing was at the start of a light meal following an overnight fast.

Orally administered doses of amoxicillin suspension, 125 mg/5 mL and 250 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 1.5 mcg/mL to 3.0 mcg/mL and 3.5 mcg/mL to 5.0 mcg/mL, respectively.

Oral administration of single doses of 400-mg chewable tablets and 400 mg/5 mL suspension of AMOXIL to 24 adult volunteers yielded comparable pharmacokinetic data:

Dose*	$AUC_{0-\infty}$ (mcg•hr/mL)	C_{max} (mcg/mL)†
Amoxicillin	amoxicillin (±S.D.)	amoxicillin (±S.D.)
400 mg (5 mL of suspension)	17.1 (3.1)	5.92 (1.62)
400 mg (1 chewable tablet)	17.9 (2.4)	5.18 (1.64)

*Administered at the start of a light meal.

†Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin. Following a 1-gram dose and utilizing a special skin window technique to determine levels of the antibiotic, it was noted that therapeutic levels were found in the interstitial fluid. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours.

Microbiology: Amoxicillin is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin 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:

Enterococcus faecalis

Staphylococcus spp.* (β-lactamase–negative strains only)

Streptococcus pneumoniae

Streptococcus spp. (α- and β-hemolytic strains only)

* Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

Aerobic Gram-Negative Microorganisms:

Escherichia coli (β-lactamase–negative strains only)

Haemophilus influenzae (β-lactamase–negative strains only)

Neisseria gonorrhoeae (β-lactamase–negative strains only)

Proteus mirabilis (β-lactamase–negative strains only)

Helicobacter:

Helicobacter pylori

Susceptibility Tests: ***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. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of **ampicillin** powder. Ampicillin is sometimes used to predict susceptibility of *S. pneumoniae* to amoxicillin; however, some intermediate strains have been shown to be susceptible to

amoxicillin. Therefore, *S. pneumoniae* susceptibility should be tested using amoxicillin powder. The MIC values should be interpreted according to the following criteria:

For Gram-Positive Aerobes:

Enterococcus

MIC (mcg/mL)	Interpretation
≤8	Susceptible (S)
≥16	Resistant (R)

Staphylococcus[a]

MIC (mcg/mL)	Interpretation
≤0.25	Susceptible (S)
≥0.5	Resistant (R)

Streptococcus (except *S. pneumoniae*)

MIC (mcg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5 to 4	Intermediate (I)
≥8	Resistant (R)

S. pneumoniae[b] from non-meningitis sources.

(**Amoxicillin** powder should be used to determine susceptibility.)

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

NOTE: These interpretive criteria are based on the recommended doses for respiratory tract infections.

For Gram-Negative Aerobes:

Enterobacteriaceae

MIC (mcg/mL)	Interpretation
≤8	Susceptible (S)
16	Intermediate

		(I)
	≥32	Resistant (R)

H. influenzae[c]

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

a. Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

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

c. These interpretive standards are applicable only to broth microdilution test with *H. influenzae* using *Haemophilus* Test Medium (HTM).[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations 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 **ampicillin** powder should provide the following MIC values:

Microorganism		MIC (mcg/mL)
E. coli	ATCC 25922	2 to 8
E. faecalis	ATCC 29212	0.5 to 2
H. influenzae	ATCC 49247[d]	2 to 8
S. aureus	ATCC 29213	0.25 to 1

Using **amoxicillin** to determine susceptibility:

Microorganism		MIC Range (mcg/mL)
S. pneumoniae	ATCC 49619[e]	0.03 to 0.12

d. This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.[1]

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

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[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 mcg ampicillin to test the susceptibility of microorganisms, except *S. pneumoniae*, to amoxicillin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for **ampicillin**.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-mcg ampicillin disk should be interpreted according to the following criteria:

For Gram-Positive Aerobes:

Enterococcus

Zone Diameter (mm)	Interpretation	
≥17	Susceptible	(S)
≤16	Resistant	(R)

Staphylococcus[f]

Zone Diameter (mm)	Interpretation	
≥29	Susceptible	(S)
≤28	Resistant	(R)

β-hemolytic streptococci

Zone Diameter (mm)	Interpretation	
≥26	Susceptible	(S)
19 to 25	Intermediate	(I)
≤18	Resistant	(R)

NOTE: For streptococci (other than β-hemolytic streptococci and *S. pneumoniae*), an ampicillin MIC should be determined.

S. pneumoniae

S. pneumoniae should be tested using a 1-mcg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin. An amoxicillin MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

For Gram-Negative Aerobes:

Enterobacteriaceae

Zone Diameter (mm)	Interpretation	
≥17	Susceptible	(S)
14 to 16	Intermediate	(I)
≤13	Resistant	(R)

H. influenzae[g]

Zone Diameter (mm)	Interpretation	
≥22	Susceptible	(S)
19 to 21	Intermediate	(I)
≤18	Resistant	(R)

f. Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

g. These interpretive standards are applicable only to disk diffusion susceptibility tests with *H. influenzae* using *Haemophilus* Test Medium (HTM).[2]

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, disk diffusion susceptibility test procedures require the use of laboratory control microorganisms. The 10-mcg **ampicillin** disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
E. coli	ATCC 25922	16 to 22
H. influenzae	ATCC 49247[h]	13 to 21
S. aureus	ATCC 25923	27 to 35

Using 1-mcg **oxacillin** disk:

Microorganism		Zone Diameter (mm)
S. pneumoniae	ATCC 49619[i]	8 to 12

h. This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using HTM.[2]

i. This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Susceptibility testing for *Helicobacter pylori*: In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MICs) and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms.

Culture and susceptibility testing should be obtained in patients who fail triple therapy. If clarithromycin resistance is found, a non-clarithromycin-containing regimen should be used.

INDICATIONS AND USAGE

AMOXIL is indicated in the treatment of infections due to susceptible (ONLY β-lactamase–negative) strains of the designated microorganisms in the conditions listed below:

Infections of the ear, nose, and throat – due to *Streptococcus* spp. (α- and β-hemolytic strains only), *S. pneumoniae*, *Staphylococcus* spp., or *H. influenzae*.

Infections of the genitourinary tract – due to *E. coli, P. mirabilis*, or *E. faecalis*.

Infections of the skin and skin structure – due to *Streptococcus* spp. (α- and β-hemolytic strains only), *Staphylococcus* spp., or *E. coli*.

Infections of the lower respiratory tract – due to Streptococcus spp. (α- and β-hemolytic strains only), *S. pneumoniae, Staphylococcus* spp., or *H. influenzae*.

Gonorrhea, acute uncomplicated (ano-genital and urethral infections) – due to *N. gonorrhoeae* (males and females).

H. pylori eradication to reduce the risk of duodenal ulcer recurrence

Triple therapy: AMOXIL/clarithromycin/lansoprazole

AMOXIL, in combination with clarithromycin plus lansoprazole as triple therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

Dual therapy: AMOXIL/lansoprazole

AMOXIL, in combination with lansoprazole delayed-release capsules as dual therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected**. (See the clarithromycin package insert, MICROBIOLOGY.) Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

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

Indicated surgical procedures should be performed.

CONTRAINDICATIONS

A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. 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 AMOXIL, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXIL SHOULD BE DISCONTINUED AND 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, and may range 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 a 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 *C. difficile* colitis.

PRECAUTIONS

General: The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

Prescribing AMOXIL 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.

Phenylketonurics: Each 200-mg chewable tablet of AMOXIL contains 1.82 mg phenylalanine; each 400-mg chewable tablet contains 3.64 mg phenylalanine. The suspensions of AMOXIL do not contain phenylalanine and can be used by phenylketonurics.

Laboratory Tests: As with any potent drug, periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy.

All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with amoxicillin should have a follow-up serologic test for syphilis after 3 months.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.

Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin. This has been demonstrated in vitro; however, the clinical significance of this interaction is not well documented.

Drug/Laboratory Test Interactions: 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, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX®) 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted; however, the following information is available from tests on a 4:1 mixture of amoxicillin and potassium clavulanate (AUGMENTIN). AUGMENTIN was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. AUGMENTIN was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. AUGMENTIN was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays. In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 3 times the human dose in mg/m^2).

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. 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 poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions but moderately increased the height and duration of contractions. However, it is not known whether use of amoxicillin 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: Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

Pediatric Use: Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of AMOXIL should be modified in pediatric patients 12 weeks or younger (≤3 months). (See DOSAGE AND ADMINISTRATION—Neonates and infants.)

Information for Patients: AMOXIL may be taken every 8 hours or every 12 hours, depending on the strength of the product prescribed.

Patients should be counseled that antibacterial drugs, including AMOXIL, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When AMOXIL 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 AMOXIL or other antibacterial drugs in the future.

ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of penicillins:

Gastrointestinal: Nausea, vomiting, diarrhea, and hemorrhagic/pseudomembranous colitis.

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Serum sickness–like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria have been reported.

NOTE: These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to amoxicillin therapy.

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis have been reported.

Renal: Crystalluria has also been reported **(see OVERDOSAGE).**

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.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioral changes, and/or dizziness have been reported rarely.

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

Combination therapy with clarithromycin and lansoprazole: In clinical trials using combination therapy with amoxicillin plus clarithromycin and lansoprazole, and amoxicillin plus lansoprazole, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with amoxicillin, clarithromycin, or lansoprazole.

Triple therapy: *Amoxicillin/clarithromycin/lansoprazole:* The most frequently reported adverse events for patients who received triple therapy were diarrhea (7%), headache (6%), and taste perversion (5%). No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual therapy: *Amoxicillin/lansoprazole:* The most frequently reported adverse events for patients who received amoxicillin three times daily plus lansoprazole three times daily dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with amoxicillin three times daily plus lansoprazole three times daily dual therapy than with lansoprazole alone.

For more information on adverse reactions with clarithromycin or lansoprazole, refer to their package inserts, ADVERSE REACTIONS.

OVERDOSAGE

In case of overdosage, discontinue medication, 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.[3]

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 amoxicillin. Amoxicillin may be removed from circulation by hemodialysis.

DOSAGE AND ADMINISTRATION

Capsules, chewable tablets, and oral suspensions of AMOXIL may be given without regard to meals. The 400-mg suspension, 400-mg chewable tablet, and the 875-mg tablet have been

studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 200-mg and 500-mg formulations.

Neonates and infants aged ≤12 weeks (≤3 months): Due to incompletely developed renal function affecting elimination of amoxicillin in this age group, the recommended upper dose of AMOXIL is 30 mg/kg/day divided q12h.

Adults and pediatric patients >3 months:

Infection	Severity*	Usual Adult Dose	Usual Dose for Children >3 months†‡
Ear/Nose/Throat	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Lower Respiratory Tract	Mild/Moderate or Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Skin/Skin Structure	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours

Infection	Severity*	Usual Adult Dose	Usual Dose for Children >3 months†‡
Genitourinary Tract	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Gonorrhea Acute, uncomplicated ano-genital and urethral infections in males and females		3 grams as single oral dose	Prepubertal children: 50 mg/kg AMOXIL, combined with 25 mg/kg probenecid as a single dose. **NOTE: SINCE PROBENECID IS CONTRAINDICATED IN CHILDREN UNDER 2 YEARS, DO NOT USE THIS REGIMEN IN THESE CASES.**

*Dosing for infections caused by less susceptible organisms should follow the recommendations for severe infections.

†The children's dosage is intended for individuals whose weight is less than 40 kg. Children weighing 40 kg or more should be dosed according to the adult recommendations.

‡Each strength of the suspension of AMOXIL is available as a chewable tablet for use by older children.

After reconstitution, the required amount of suspension should be placed directly on the child's tongue for swallowing. Alternate means of administration are to add the required amount of suspension to formula, milk, fruit juice, water, ginger ale, or cold drinks. These preparations should then be taken immediately. To be certain the child is receiving full dosage, such preparations should be consumed in entirety.

All patients with gonorrhea should be evaluated for syphilis. (See PRECAUTIONS—Laboratory Tests.)

Larger doses may be required for stubborn or severe infections.

General: It should be recognized that in the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those

recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy. Except for gonorrhea, treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by *Streptococcus pyogenes* to prevent the occurrence of acute rheumatic fever.

H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: *Triple therapy: AMOXIL/clarithromycin/lansoprazole

The recommended adult oral dose is 1 gram AMOXIL, 500 mg clarithromycin, and 30 mg lansoprazole, all given twice daily (q12h) for 14 days. (See INDICATIONS AND USAGE.)

Dual therapy: AMOXIL/lansoprazole

The recommended adult oral dose is 1 gram AMOXIL and 30 mg lansoprazole, each given three times daily (q8h) for 14 days. (See INDICATIONS AND USAGE.)

Please refer to clarithromycin and lansoprazole full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally impaired patients.

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

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

There are currently no dosing recommendations for pediatric patients with impaired renal function.

Directions for Mixing Oral Suspension: Prepare suspension at time of dispensing as follows: Tap bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (see table below) and shake vigorously to wet powder. Add remainder of the water and again shake vigorously.

125 mg/5 mL

Bottle Size	Amount of Water Required for Reconstitution
150 mL	116 mL

Each teaspoonful (5 mL) will contain 125 mg amoxicillin.

200 mg/5 mL

Bottle Size	Amount of Water Required for Reconstitution
50 mL	39 mL
75 mL	57 mL
100 mL	76 mL

Each teaspoonful (5 mL) will contain 200 mg amoxicillin.

250 mg/5 mL

Bottle Size	Amount of Water Required for Reconstitution
100 mL	74 mL
150 mL	111 mL

Each teaspoonful (5 mL) will contain 250 mg amoxicillin.

400 mg/5 mL

Bottle Size	Amount of Water Required for Reconstitution
50 mL	36 mL
75 mL	54 mL
100 mL	71 mL

Each teaspoonful (5 mL) will contain 400 mg amoxicillin.

Directions for Mixing Pediatric Drops: Prepare pediatric drops at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each mL of suspension will then contain amoxicillin trihydrate equivalent to 50 mg amoxicillin.

Bottle Size	Amount of Water Required for Reconstitution
15 mL	12 mL
30 mL	23 mL

NOTE: SHAKE BOTH ORAL SUSPENSION AND PEDIATRIC DROPS WELL BEFORE USING. Keep bottle tightly closed. Any unused portion of the reconstituted suspension must be discarded after 14 days. Refrigeration preferable, but not required.

HOW SUPPLIED

Capsules of AMOXIL: Each capsule contains 250 mg or 500 mg amoxicillin as the trihydrate.

250-mg Capsule

NDC 0029-6006-32 bottles of 500

500-mg Capsule

NDC 0029-6007-32	bottles of 500

Tablets of AMOXIL: Each tablet contains 500 mg or 875 mg amoxicillin as the trihydrate.

500-mg Tablet

NDC 0029-6046-12	bottles of 20
NDC 0029-6046-20	bottles of 100
NDC 0029-6046-25	bottles of 500

875-mg Tablet

NDC 0029-6047-12	bottles of 20
NDC 0029-6047-20	bottles of 100
NDC 0029-6047-25	bottles of 500

Chewable Tablets of AMOXIL: Each cherry-banana-peppermint-flavored tablet contains 200 mg or 400 mg amoxicillin as the trihydrate.

200-mg Tablet

NDC 0029-6044-12	bottles of 20
NDC 0029-6044-20	bottles of 100

400-mg Tablet

NDC 0029-6045-12	bottles of 20
NDC 0029-6045-20	bottles of 100

AMOXIL for Oral Suspension: Each 5 mL of reconstituted strawberry-flavored suspension contains 125 mg amoxicillin as the trihydrate. Each 5 mL of reconstituted bubble-gum-flavored suspension contains 200, 250, or 400 mg amoxicillin as the trihydrate.

125 mg/5 mL

NDC 0029-6008-22	150-mL bottle

200 mg/5 mL

NDC 0029-6048-54	50-mL bottle
NDC 0029-6048-55	75-mL bottle
NDC 0029-6048-59	100-mL bottle

250 mg/5 mL

NDC 0029-6009-23	100-mL bottle
NDC 0029-6009-22	150-mL bottle

400 mg/5 mL

NDC 0029-6049-54	50-mL bottle
NDC 0029-6049-55	75-mL bottle
NDC 0029-6049-59	100-mL bottle

Pediatric Drops of AMOXIL for Oral Suspension: Each mL of bubble-gum-flavored reconstituted suspension contains 50 mg amoxicillin as the trihydrate.

NDC 0029-6035-20	15-mL bottle
NDC 0029-6038-39	30-mL bottle

Store at or below 20°C (68°F)

- 250 mg and 500 mg capsules
- 125 mg and 250 mg unreconstituted powder

Store at or below 25°C (77°F)

- 200 mg and 400 mg unreconstituted powder
- 200-mg and 400-mg chewable tablets
- 500-mg and 875-mg tablets

Dispense in a tight container.

CLINICAL STUDIES

***H. pylori* eradication to reduce the risk of duodenal ulcer recurrence:** Randomized, double-blind clinical studies performed in the United States in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within 1 year) evaluated the efficacy of lansoprazole in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy, or in combination with amoxicillin capsules as dual 14-day therapy, for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of 2 different eradication regimens were established:

Triple therapy: Amoxicillin 1 gram twice daily/clarithromycin 500 mg twice daily/lansoprazole 30 mg twice daily.

Dual therapy: Amoxicillin 1 gram three times daily/lansoprazole 30 mg three times daily.

All treatments were for 14 days. *H. pylori* eradication was defined as 2 negative tests (culture and histology) at 4 to 6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

***H. pylori* Eradication Rates – Triple Therapy (amoxicillin/clarithromycin/lansoprazole)**

Percent of Patients Cured [95% Confidence Interval] (Number of Patients)

Study	Triple Therapy	Triple Therapy
	Evaluable Analysis[*]	Intent-to-Treat Analysis[†]
Study 1	92[‡] [80.0 - 97.7] (n = 48)	86[‡] [73.3 - 93.5] (n = 55)
Study 2	86[§] [75.7 - 93.6] (n = 66)	83[§] [72.0 - 90.8] (n = 70)

[*]This analysis was based on evaluable patients with confirmed duodenal ulcer (active or within 1 year) and *H. pylori* infection at baseline defined as at least 2 of 3 positive endoscopic tests from CLOtest®, (Delta West Ltd., Bentley, Australia), histology, and/or culture. Patients were included in the analysis if they completed the study.

Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

[†]Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within 1 year). All dropouts were included as failures of therapy.

[‡]($p<0.05$) versus lansoprazole/amoxicillin and lansoprazole/clarithromycin dual therapy.

[§]($p<0.05$) versus clarithromycin/amoxicillin dual therapy.

***H. pylori* Eradication Rates – Dual Therapy (amoxicillin/lansoprazole)**

Percent of Patients Cured [95% Confidence Interval] (Number of Patients)

Study	Dual Therapy	Dual Therapy
	Evaluable Analysis[*]	Intent-to-Treat Analysis[†]
Study 1	77[‡] [62.5 - 87.2] (n = 51)	70[‡] [56.8 - 81.2] (n = 60)
Study 2	66[§] [51.9 - 77.5] (n = 58)	61[§] [48.5 - 72.9] (n = 67)

[*]This analysis was based on evaluable patients with confirmed duodenal ulcer (active or within 1 year) and *H. pylori* infection at baseline defined as at least 2 of 3 positive endoscopic tests from CLOtest®, histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

[†]Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within 1 year). All dropouts were included as failures of therapy.

[‡]($p<0.05$) versus lansoprazole alone.

[§]($p<0.05$) versus lansoprazole alone or amoxicillin alone.

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3. 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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