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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMOXIL® safely and effectively. See full prescribing information for AMOXIL®.

AMOXIL® (amoxicillin) tablets, for oral use
AMOXIL® (amoxicillin) for oral suspension
AMOXIL® (amoxicillin) chewable tablets, for oral use
Initial U.S. Approval: 1974

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

Warnings and Precautions,
Drug-Induced Enterocolitis Syndrome (DIES) (5.3) 5/2024

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

AMOXIL is a penicillin-class antibacterial indicated for treatment of infections due to susceptible strains of designated microorganisms. (1)

Adults and Pediatric Patients (1)

- Upper Respiratory Tract Infections of the Ear, Nose, and Throat
- Infections of the Genitourinary Tract
- Infections of the Skin and Skin Structure
- Infections of the Lower Respiratory Tract

Adult Patients only (1)

- *Helicobacter pylori* Infection and Duodenal Ulcer Disease

Usage

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 bacteria. (1)

----------DOSAGE AND ADMINISTRATION ----------

- In Adults, 750 to 1750 mg/day in divided doses every 8 to 12 hours.
- In Pediatric Patients over 3 Months of Age, 20 to 45 mg/kg/day in divided doses every 8 to 12 hours. Refer to full prescribing information for specific dosing regimens. (2.2, 2.3)
- The upper dose for neonates and infants aged 3 months or younger is 30 mg/kg/day divided every 12 hours. (2.3)
- Dosing for *H. pylori* Infection (in Adults): Triple therapy: 1 gram AMOXIL, 500 mg clarithromycin, and 30 mg lansoprazole, all given twice daily (every 12 hours) for 14 days. Dual therapy: 1 gram AMOXIL and 30 mg lansoprazole, each given three times daily (every 8 hours) for 14 days. (2.4)
- Reduce the dose in patients with severe renal impairment (GFR greater than 30 mL/min). (2.5)

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

- Tablets: 500 mg, 875 mg (3)
- For Oral Suspension: 200 mg/5 mL, 400 mg/5 mL (3)
- Chewable Tablets: 125 mg, 200 mg, 250 mg, 400 mg (3)

---------- CONTRAINDICATIONS ----------

- History of a serious hypersensitivity reaction (e.g., anaphylaxis or Stevens-Johnson syndrome) to AMOXIL or to other beta-lactams (e.g., penicillins or cephalosporins). (4)

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

- Anaphylactic reactions: Serious and occasionally fatal anaphylactic reactions have been reported in patients on penicillin therapy, including amoxicillin. Discontinue AMOXIL if a reaction occurs (5.1).
- Severe cutaneous adverse reactions (SCAR): Monitor closely. Discontinue if rash progresses. (5.2)
- Drug-induced enterocolitis syndrome (DIES) has been reported with amoxicillin use. If this occurs, discontinue AMOXIL and institute appropriate therapy. (5.3)
- *Clostridioides difficile*-associated diarrhea (CDAD) (ranging from mild diarrhea to fatal colitis): Evaluate if diarrhea occurs. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (greater than 1%) observed in clinical trials of AMOXIL tablets or for oral suspension were diarrhea, rash, vomiting, and nausea. (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----------

- Co-administration with probenicid is not recommended. (7.1)
- Concomitant use of AMOXIL and oral anticoagulants may increase the prolongation of prothrombin time. (7.2)
- Co-administration with allopurinol increases the risk of rash. (7.3)
- AMOXIL may reduce the efficacy of oral contraceptives. (7.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Adults and Pediatric Patients

- **Upper Respiratory Tract Infections of the Ear, Nose, and Throat:** AMOXIL is indicated in the treatment of infections due to susceptible (ONLY β-lactamase–negative) isolates of *Streptococcus* species. (α- and β-hemolytic isolates only), *Streptococcus pneumoniae*, *Staphylococcus* spp., or *Haemophilus influenzae*.

- **Infections of the Genitourinary Tract**: AMOXIL is indicated in the treatment of infections due to susceptible (ONLY β-lactamase–negative) isolates of *Escherichia coli, Proteus mirabilis*, or *Enterococcus faecalis*.

- **Infections of the Skin and Skin Structure:** AMOXIL is indicated in the treatment of infections due to susceptible (ONLY β-lactamase–negative) isolates of *Streptococcus* spp. (α- and β-hemolytic isolates only), *Staphylococcus* spp., or *E. coli*.

- **Infections of the Lower Respiratory Tract:** AMOXIL is indicated in the treatment of infections due to susceptible (ONLY β-lactamase–negative) isolates of *Streptococcus* spp. (α- and β-hemolytic isolates only), *S. pneumoniae, Staphylococcus* spp., or *H. influenzae*.

Adult Patients only

- ***Helicobacter pylori* Infection and Duodenal Ulcer Disease:**

  Triple therapy for *Helicobacter pylori (H. pylori)* with clarithromycin and 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.

  Dual therapy for *H. pylori* with 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.

Usage
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 infections that are proven or strongly suspected to be caused by 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
To minimize the potential for gastrointestinal intolerance, AMOXIL should be taken at the start of a meal.

2.2 Dosage for Adults and Pediatric Patients Aged 3 Months (12 weeks) and Older

- 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.
- In some 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.

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Table 1. Dosage Recommendations for Adult and Pediatric Patients Aged 3 Months (12 weeks) and Older

Infection	Severity[a]	Recommended Dosage for Adults and Pediatric Patients Aged 3 Months and Older and Weight Greater than 40 kg	Recommended Dosage for Pediatric Patients Aged 3 Months and Older and Weight Less than 40 kg
Ear/Nose/Throat Skin/Skin Structure 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
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

[a] Dosage for infections caused by bacteria that are intermediate in their susceptibility to amoxicillin should follow the recommendations for severe infections.

2.3 Dosage in Pediatric Patients Aged Less than 12 Weeks (3 months)

- 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.
- 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 every 12 hours. There are currently no dosing recommendations for pediatric patients with impaired renal function.
- 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.

2.4 Dosage for *H. pylori* Infection in Adults

Triple therapy: The recommended adult oral dose is 1 gram AMOXIL, 500 mg clarithromycin, and 30 mg lansoprazole, all given twice daily (every 12 hours) for 14 days.

Dual therapy: The recommended adult oral dose is 1 gram AMOXIL and 30 mg lansoprazole, each given three times daily (every 8 hours) for 14 days.

Please refer to clarithromycin and lansoprazole full prescribing information.

2.5 Dosage in Renal Impairment for Adults and Pediatric Patients Aged 3 Months and Older and Weight Greater than 40 kg

- Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Renal impairment patients with a glomerular filtration rate of less than 30 mL/min should *NOT* receive the 875 mg dose. See dosage regimens in patients with severe renal impairment provided in Table 2.

Table 2. Dosing in Patients with Severe Renal Impairment

Patients with Renal Impairment	Dosage Regimen
GFR 10 to 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

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

2.6 Directions for Mixing Oral Suspension

Prepare a suspension at time of dispensing as follows: Tap bottle until all powder flows freely. Measure the total amount of water (see Table 3). Add approximately 1/3 of the water to powder. Replace cap and *shake vigorously* to wet powder. Add remaining water. Replace cap and *shake vigorously*.

Table 3. Amount of Water for Mixing For Oral Suspension

Strength	**Bottle Size**	**Total Amount of Water Required for Reconstitution**
For Oral Suspension 200 mg/5 mL	50 mL	39 mL
	75 mL	57 mL
	100 mL	76 mL
For Oral Suspension 400 mg/5 mL	50 mL	36 mL
	75 mL	54 mL
	100 mL	71 mL

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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.

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

3 DOSAGE FORMS AND STRENGTHS

AMOXIL:

- **Tablets**: 500 mg, 875 mg. 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.
- **For Oral Suspension:** 200 mg/5 mL, 400 mg/5 mL. Each 5 mL of reconstituted bubble-gum -flavored suspension contains 200 mg or 400 mg amoxicillin as the trihydrate.
- **Chewable Tablets:**
  125 mg – Each 125 mg cherry-banana-peppermint flavored tablet contains 125 mg of amoxicillin as the trihydrate. Each pale pink, oval tablet is imprinted with AMOXIL on one side and 125 on the other.
  200 mg – Each 200 mg cherry-banana-peppermint flavored tablet contains 200 mg of amoxicillin as the trihydrate. Each pale pink, round convex tablet is imprinted with AMOXIL and 200 along the edge of 1 side.
  250 mg – Each 250 mg cherry-banana-peppermint flavored tablet contains 250 mg of amoxicillin as the trihydrate. Each pale pink, oval tablet is imprinted with AMOXIL on one side and 250 on the other.
  400 mg – Each 400 mg cherry-banana-peppermint flavored tablet contains 400 mg of amoxicillin as the trihydrate. Each pale pink, round convex tablet is imprinted with AMOXIL and 400 along the edge of 1 side.

4 CONTRAINDICATIONS

AMOXIL is contraindicated in patients who have experienced a serious hypersensitivity reaction (e.g., anaphylaxis or Stevens-Johnson syndrome) to AMOXIL or to other β-lactam antibacterial drugs (e.g., penicillins and cephalosporins).

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylactic Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy including amoxicillin. 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 regarding previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, AMOXIL should be discontinued, and appropriate therapy instituted.

5.2 Severe Cutaneous Adverse Reactions

AMOXIL 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 skin rash they should be monitored closely, and AMOXIL discontinued if lesions progress.

5.3 Drug-Induced Enterocolitis Syndrome (DIES)

Drug-induced enterocolitis syndrome (DIES) has been reported with amoxicillin use *[see Adverse Reactions (6.2)],* with most cases occurring in pediatric patients ≤ 18 years of age. 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 AMOXIL and institute appropriate therapy.

5.4 *Clostridioides difficile*-Associated Diarrhea (CDAD)

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AMOXIL, 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

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may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial 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.

5.5 Development of Drug-Resistant Bacteria

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

5.6 Skin Rash in Patients with Mononucleosis

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

5.7 Phenylketonurics

AMOXIL chewable tablets contain aspartame which contains phenylalanine. Each 200 mg chewable tablet contains 1.82 mg phenylalanine; each 400 mg chewable tablet contains 3.64 mg phenylalanine. The oral suspension formulations of AMOXIL do not contain phenylalanine and can be used by phenylketonurics.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Anaphylactic reactions *[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)]*
- *Clostridioides difficile*-Associated Diarrhea (CDAD) *[see Warnings and Precautions (5.4)]*

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.

The most common adverse reactions (greater than 1%) observed in clinical trials of AMOXIL tablets or oral suspension were diarrhea, rash, vomiting, and nausea.

Triple therapy*:* The most frequently reported adverse events for patients who received triple therapy (amoxicillin/clarithromycin/ lansoprazole) were diarrhea (7%), headache (6%), and taste perversion (5%).

Dual therapy*:* The most frequently reported adverse events for patients who received double therapy amoxicillin/lansoprazole were diarrhea (8%) and headache (7%). For more information on adverse reactions with clarithromycin or lansoprazole, refer to the Adverse Reactions section of their package inserts.

6.2 Postmarketing Experience

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In addition to adverse events reported from clinical trials, the following events have been identified during postmarketing use of penicillins. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to AMOXIL.

- **Infections and Infestations:** Mucocutaneous candidiasis.

- **Gastrointestinal:** Drug-induced enterocolitis syndrome (DIES), black hairy tongue, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment *[see Warnings and Precautions (5.4)]*.

- **Immune**: Hypersensitivity reactions, anaphylactic/anaphylactoid 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.

- **Liver:** A moderate rise in AST and/or ALT 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 been reported *[see Overdosage (10)]*.

- **Hemic and Lymphatic Systems:** Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. 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, aseptic meningitis, and/or dizziness 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 of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.

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 the incidence of rashes in patients receiving both drugs as compared to patients receiving amoxicillin alone. It is not known whether this potentiation of rashes is due to allopurinol or the hyperuricemia present in these patients.

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7.4 Oral Contraceptives

AMOXIL may affect the intestinal flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

7.5 Other Antibacterials

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.

7.6 Effects on Laboratory Tests

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 AMOXIL, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX®) be used.

Following administration of ampicillin or amoxicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 2000 mg/kg (3 and 6 times the 3 g human dose, based on body surface area). There was no evidence of 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, amoxicillin should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

Oral ampicillin is poorly absorbed during labor. 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 of the necessity for an obstetrical intervention.

8.3 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.

8.4 Pediatric Use

The safety and effectiveness of AMOXIL for the treatment of upper respiratory tract infections, and infections of the genitourinary tract, skin and skin structure and lower respiratory tract have been established in pediatric patients.

The safety and effectiveness of AMOXIL for the treatment of *H.Pylori* infection have not been established in pediatric patients.

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 or younger) *[see Dosage and Administration (2.3)]*.

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8.5 Geriatric Use

An analysis of clinical studies of AMOXIL was conducted to determine whether subjects aged 65 and over respond differently from younger subjects. These analyses have not identified 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 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, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Dosing in Renal Impairment

Amoxicillin is primarily eliminated by the kidney and dosage adjustment is usually required in patients with severe renal impairment (GFR less than 30 mL/min). See *Dosing in Renal Impairment (2.5)* for specific recommendations in patients with renal impairment.

10 OVERDOSAGE

In case of overdosage, discontinue AMOXIL, 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.

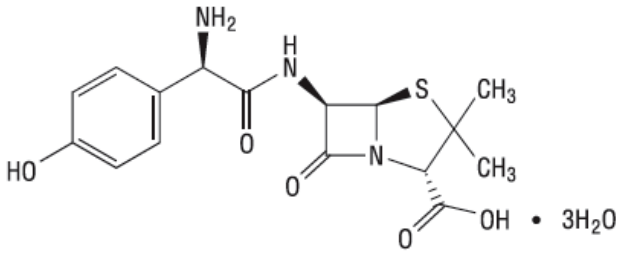
Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin[1].

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.

11 DESCRIPTION

AMOXIL is a semisynthetic antibacterial (amoxicillin), 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.

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Tablets: Each tablet contains 500 mg or 875 mg of 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 in each 500 mg or 875 mg tablet: Colloidal silicon dioxide, crospovidone, D&C Red No. 30 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

For Oral Suspension: Each 5 mL of reconstituted suspension contains 200 mg or 400 mg of amoxicillin as the trihydrate. 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. Inactive ingredients: FD&C Red No. 3, flavorings, silica gel, sodium benzoate, sodium citrate, sucrose, and xanthan gum.

Chewable Tablets: Each tablet contains 125 mg or 200 mg or 250 mg or 400 mg of amoxicillin as the trihydrate. Inactive ingredients in each 125 mg or 250 mg chewable tablet: Mannitol, FD&C Red No. 40 aluminum lake, glycine, magnesium stearate, silica gel, flavorings, citric acid, saccharin sodium, and confectioner's sugar. Inactive ingredients in each 200 mg and 400 mg chewable tablet: Mannitol, crospovidone, FD&C Red No. 40 aluminum lake, flavorings, magnesium stearate, and aspartame *[see Warnings and Precautions (5.7)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

AMOXIL is an antibacterial drug *[see Microbiology (12.4)]*.

12.2 Pharmacokinetics

Absorption: AMOXIL 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; 400 mg and 875 mg formulations have been studied only when administered at the start of a light meal.

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.

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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:

Table 4: Mean Pharmacokinetic Parameters of AMOXIL (400 mg chewable tablets and 400 mg/5 mL suspension) in Healthy Adults

Dose[*] Amoxicillin	**$AUC_{0-\infty}$ (mcg•hr/mL)** Amoxicillin (±S.D.)	**C_{max} (mcg/mL)**[†] 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.

Distribution: AMOXIL diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. In blood serum, amoxicillin is approximately 20% protein-bound. 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.

Metabolism and Excretion: The half-life of amoxicillin is 61.3 minutes. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours. Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin. Since most of the amoxicillin is excreted unchanged in the urine, its excretion can be delayed by concurrent administration of probenecid *[see Drug Interactions (7.1)]*.

12.3 Microbiology

Mechanism of Action
AMOXIL is similar to penicillin in its bactericidal action against susceptible bacteria during the stage of active multiplication. It acts through the inhibition of cell wall biosynthesis that leads to the death of the bacteria.

Resistance
Resistance to AMOXIL is mediated primarily through enzymes called beta-lactamases that cleave the beta-lactam ring of amoxicillin, rendering it inactive.

Antimicrobial Activity
AMOXIL 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)]*.

Gram-Positive Bacteria
Enterococcus faecalis
Staphylococcus spp.
Streptococcus pneumoniae
Streptococcus spp. (alpha and beta-hemolytic)

Gram-Negative Bacteria
Escherichia coli
Haemophilus influenzae
Helicobacter pylori
Proteus mirabilis

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.

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13 NONCLINICAL TOXICOLOGY

13.1 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 2 times the 3 g human dose based on body surface area).

14 CLINICAL STUDIES

14.1 *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 (see Table 5). **Dual therapy:** Amoxicillin 1 gram three times daily/lansoprazole 30 mg three times daily (see Table 6). 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.

Table 5. *H. pylori* Eradication Rates When AMOXIL is Administered as Part of a Triple Therapy Regimen

Study	Triple Therapy	Triple Therapy
	Evaluable Analysis[a] **[95% Confidence Interval]** **(number of patients)**	**Intent-to-Treat Analysis[b]** **[95% Confidence Interval]** **(number of patients)**
Study 1	92 [80.0 to 97.7] (n equals 48)	86 [73.3 to 93.5] (n equals 55)
Study 2	86 [75.7 to 93.6] (n equals 66)	83 [72.0 to 90.8] (n equals 70)

[a] 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.

[b] 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.

Table 6. *H. pylori* Eradication Rates When Amoxicillin is Administered as Part of a Dual Therapy Regimen

Study	Dual Therapy	Dual Therapy
	Evaluable Analysis[a] **[95% Confidence Interval]** **(number of patients)**	**Intent-to-Treat Analysis[b]** **[95% Confidence Interval]** **(number of patients)**

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Study 1	77 [62.5 to 87.2] (n equals 51)	70 [56.8 to 81.2] (n equals 60)
Study 2	66 [51.9 to 77.5] (n equals 58)	61 [48.5 to 72.9] (n equals 67)

[a] 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.

[b] 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.

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

AMOXIL ®
amoxicillin tablets, USP: 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 on one side, respectively. The 875-mg tablet is scored on the reverse side.

500 mg Tablet
NDC 81964-024-01 Bottles of 100
NDC 81964-024-05 Bottles of 500
NDC 81964-024-14 Bottles of 20

875 mg Tablet
NDC 81964-019-01 Bottles of 100
NDC 81964-019-14 Bottles of 20

AMOXIL ®
amoxicillin for oral suspension, USP: Each 5 mL of reconstituted bubble-gum-flavored suspension contains 200 mg or 400 mg amoxicillin as the trihydrate. The powder for each strength is light pink in color and pink when the product is reconstituted.

200 mg/5 mL
NDC 81964-023-50 50-mL bottle
NDC 81964-023-51 75-mL bottle
NDC 81964-023-52 100-mL bottle

400 mg/5 mL
NDC 81964-007-50 50-mL bottle
NDC 81964-007-51 75-mL bottle
NDC 81964-007-52 100-mL bottle

AMOXIL ®
amoxicillin chewable tablets, USP:

125 mg – Each 125 mg cherry-banana-peppermint flavored tablet contains 125 mg of amoxicillin as the trihydrate. Each pale pink, oval tablet is imprinted with AMOXIL on one side and 125 on the other.

200 mg – Each 200 mg cherry-banana-peppermint flavored tablet contains 200 mg of amoxicillin as the trihydrate. Each pale pink, round convex tablet is imprinted with AMOXIL and 200 along the edge of 1 side.

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250 mg – Each 250 mg cherry-banana-peppermint flavored tablet contains 250 mg of amoxicillin as the trihydrate. Each pale pink, oval tablet is imprinted with AMOXIL on one side and 250 on the other.

400 mg – Each 400 mg cherry-banana-peppermint flavored tablet contains 400 mg of amoxicillin as the trihydrate. Each pale pink, round convex tablet is imprinted with AMOXIL and 400 along the edge of 1 side.

125 mg chewable tablets
NDC 81964-026-60 Bottles of 60
NDC 81964-026-01 Bottles of 100

200 mg chewable tablets
NDC 81964-028-14 Unit dose (4 x 5) 20 chewable tablets

250 mg chewable tablets
NDC 81964-027-30 Bottles of 30
NDC 81964-027-01 Bottles of 100

400 mg chewable tablets
NDC 81964-029-14 Unit dose (4 x 5) 20 chewable tablets
NDC 81964-029-01 Bottles of 100

Store at or below 25° C (77° F).

Dispense in a tight container.

17 PATIENT COUNSELING INFORMATION

Administration Instructions
Advise patients that AMOXIL may be taken every 8 hours or every 12 hours, depending on the dose prescribed.

Allergic Reactions
Counsel patients that AMOXIL contains a penicillin class drug product that can cause allergic reactions in some individuals.

Severe Cutaneous Adverse Reactions (SCAR)
Advise patients about the signs and symptoms of serious skin manifestations. Instruct patients to stop taking AMOXIL 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 which usually ends when the antibacterial drug 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 their last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

Antibacterial Resistance
Patients should be counseled that antibacterial drugs, including AMOXIL, should only be used to treat or prevent bacterial infections. Antibacterial drugs 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.

Storage and Special Handling Instructions

It is preferable to refrigerate AMOXIL suspensions, but not required. Shake oral suspensions well before each use. Keep bottle tightly closed. When dosing a child with the suspension (liquid), use a calibrated oral syringe. Be sure to rinse the calibrated oral syringe after each use. Bottles of suspension of AMOXIL may contain more liquid than required. Follow your doctor's instructions about the amount to use and the days of treatment your child requires. Discard any unused portion of the suspension after 14 days.

Phenylketonuria

Counsel patients with phenylketonuria: Each 200 mg chewable tablet contains 1.82 mg phenylalanine; each 400 mg chewable tablet contains 3.64 mg phenylalanine.

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

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