DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-754

SmithKline Beecham
Attention: Sharon Shapowal, R.Ph.
Assistant Director
U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929 (FP 1005)
Philadelphia, PA 19101-7929

JUL 10 1998

Dear Ms. Shapowal:

Please refer to your new drug application dated July 11, 1997, received July 14, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amoxil® (amoxicillin) Tablets, 500 mg and 875 mg in strength.

We note that this product is subject to the exception provisions of section 125 (d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

We acknowledge receipt of your submissions dated November 13, 1997; February 13, 1998, March 6, 1998, March 30, 1998, May 15, 1998 and June 4, 1998.

The User Fee goal date for this application is July 14, 1998.

This new drug application allows for a change in the dosing regimen of amoxicillin from thrice daily to twice daily in adults and to provide for the use of new swallow tablet formulations.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated July 9, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on July 9, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-754. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mr. Stephen T. Trostle, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely yours,

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

7/9/98

AM:L15A
PRESCRIBING INFORMATION
9416645

AMOXIL®
brand of
amoxicillin

capsules, tablets, chewable tablets, and powder for oral suspension

DESCRIPTION
Amoxil formulations contain amoxicilllin, 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:

(amoxicillin chemical structure)

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

Amoxil capsules, tablets, and powder for oral suspension are intended for oral administration.

Capsules: Each *Amoxil* capsule, 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, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

Chewable Tablets: Each oval, pink, cherry-banana-peppermint-flavored tablet contains 125 mg or 250 mg amoxicillin as the trihydrate. The tablets are imprinted with the product name AMOXIL on one side and 125 or 250 on the other side. Inactive ingredients: citric acid, corn starch, FD&C Red No. 40, flavorings, glycine, mannitol, magnesium stearate, saccharin sodium, silica gel, and sucrose. Each 125-mg chewable tablet contains 0.0019 mEq (0.044 mg) of sodium; the 250-mg chewable tablet contains 0.0037 mEq (0.085 mg) of sodium.

Powder for Oral Suspension: Each 5 mL of reconstituted suspension contains 125 mg or 250 mg amoxicillin as the trihydrate. Each 5 mL of the 125-mg reconstituted suspension contains 0.12 mEq (2.76 mg) of sodium; each 5 mL of the 250-mg reconstituted suspension contains 0.15 mEq (3.45 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 250 mg/5 mL or 50 mg/mL is a bubble-gum-flavored pink suspension. 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. It 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 µg/mL to 5.0 µg/mL and 5.5 µg/mL to 7.5 µg/mL, respectively.

Mean amoxicillin pharmacokinetic parameters from an open, two-part, single-dose crossover bioequivalence study in 27 adults comparing 875 mg of Amoxil (amoxicillin) 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 µg.hr/mL and a C_{max} of 13.8 ± 4.1 µg/mL. Dosing was at the start of a light meal following an overnight fast.

Amoxicillin chewable tablets, 125 mg and 250 mg, produced blood levels similar to those achieved with the corresponding doses of amoxicillin oral suspensions. 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 µg/mL to 3.0 µg/mL and 3.5 µg/mL to 5.0 µg/mL, respectively.

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 *Streptococcus pneumoniae* to amoxicillin; however, some intermediate strains have been shown to be susceptible to amoxicillin. Therefore, *Streptococcus 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 (µg/mL)	Interpretation
≤8	Susceptible (S)
≥16	Resistant (R)

Staphylococcus[a]

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

Streptococcus (except *S. pneumoniae*)

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

S. pneumoniae[b]

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

MIC (µg/mL)	Interpretation
≤0.5	Susceptible (S)
1	Intermediate (I)
≥2	Resistant (R)

For gram-negative aerobes:

Enterobacteriaceae

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

H. influenzae[c]

MIC (µg/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 *Haemophilus 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 (µg/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 (µg/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 µg 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-µg 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[1]

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-µg 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-µg **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-µg **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 (amoxicillin) 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), *Streptococcus 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), *Streptococcus pneumoniae*, *Staphylococcus* spp., or *H. influenzae*

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

Therapy may be instituted prior to obtaining results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to amoxicillin.

Indicated surgical procedures should be performed.

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 one-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 (amoxicillin),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 one-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**.)

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 *Clostridium 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.

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 with amoxicillin may result in increased and prolonged blood levels.

Chloramphenicol, erythromycins, 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® 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.

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 ten (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 (amoxicillin) should be modified in pediatric patients 12 weeks or younger (≤3 months). (See **DOSAGE AND ADMINISTRATION**--Neonates and infants.)

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

Hypersensitivity Reactions: Erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, 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) has been noted, but the significance of this finding is unknown.

Hemic and Lymphatic Systems: 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, behavioral changes, and/or dizziness have been reported rarely.

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 t.i.d. plus lansoprazole t.i.d. dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with amoxicillin t.i.d. plus lansoprazole t.i.d. 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. 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

Amoxil capsules, chewable tablets and oral suspensions may be given without regard to meals. However, the 875-mg tablet has been studied only when administered at the start of a light meal.

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 (amoxicillin) 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	20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	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	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	20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	40 mg/kg/day in divided doses every 8 hours
Genitourinary tract	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	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.

§ Children weighing 40 kg or more should be dosed according to the adult recommendations.

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/minute should not receive the 875-mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute 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.

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

Larger doses may be required for stubborn or severe infections.

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 (amoxicillin) 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.

General: The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults.

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.

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.

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.

Bottle Size	Amount of Water Required for Reconstitution
125 mg/5 mL	
80 mL	62 mL
100 mL	78 mL
150 mL	116 mL

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

125 mg unit dose	5 mL

250 mg/5 mL	
80 mL	59 mL
100 mL	74 mL
150 mL	111 mL

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

250 mg unit dose	5 mL

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

Amoxil (amoxicillin) Capsules. Each capsule contains 250 mg or 500 mg amoxicillin as the trihydrate.

250-mg Capsule

NDC 0029-6006-30 bottles of 100
NDC 0029-6006-32 bottles of 500

500-mg Capsule

NDC 0029-6007-30 bottles of 100
NDC 0029-6007-32 bottles of 500

Amoxil (amoxicillin) Tablets. 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

Amoxil (amoxicillin) Chewable Tablets. Each cherry-banana-peppermint-flavored tablet contains 125 mg or 250 mg amoxicillin as the trihydrate.

125-mg Tablet

NDC 0029-6004-39 bottles of 60

250-mg Tablet

NDC 0029-6005-13 bottles of 30
NDC 0029-6005-30 bottles of 100

Amoxil (amoxicillin) 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 250 mg amoxicillin as the trihydrate.

125 mg/5 mL

NDC 0029-6008-21 80-mL bottle
NDC 0029-6008-23 100-mL bottle
NDC 0029-6008-22 150-mL bottle

250 mg/5 mL

NDC 0029-6009-21 80-mL bottle
NDC 0029-6009-23 100-mL bottle
NDC 0029-6009-22 150-mL bottle
NDC 0029-6008-18 125-mg unit dose bottle
NDC 0029-6009-18 250-mg unit dose bottle

Amoxil (amoxicillin) Pediatric Drops 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 capsules, unreconstituted powder, and chewable tablets at or below 20°C (68°F). Store 500-mg and 875-mg tablets at or below 25°C (77°F). 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 U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one 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 two different eradication regimens were established:

Triple therapy: amoxicillin 1 gram b.i.d./clarithromycin 500 mg b.i.d./lansoprazole 30 mg b.i.d.

Dual therapy: amoxicillin 1 gram t.i.d./lansoprazole 30 mg t.i.d.
All treatments were for 14 days. *H. pylori* eradication was defined as two 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 Evaluable Analysis[π]	Triple Therapy 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)

π This analysis was based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three 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 one 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 Evaluable Analysis[#]	Dual Therapy 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 one year) and *H. pylori* infection at baseline defined as at least two of three 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 one year). All dropouts were included as failures of therapy.
¶¶ ($p<0.05$) versus lansoprazole alone.
¶ ($p<0.05$) versus lansoprazole alone or amoxicillin alone.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fourth Edition; Approved Standard. NCCLS Document M7-A4, Vol. 17, No. 2. NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition; Approved Standard. NCCLS Document M2-A6, Vol. 17, No. 1. NCCLS, Wayne, PA, January 1997.
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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