

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-056

APPROVED DRAFT LABELING

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives ingredients differ from the RLD.	*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as the RLD.	*		
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. *Applicant does not propose the 400 mg dosage form. Therefore, text referencing this dosage form will be deleted. See FTR.	*		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling model

Amoxil® (amoxicillin) Tablets/50-754/S-002 by SmithKline Beecham Pharmaceuticals, approved 5/16/2000 and issued 7/99

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
[Vol. B1.3, 1829]

3. The firm's physical description/scoring of each tablet strength in the HOW SUPPLIED section is consistent with the firm's finished dosage form statements.
[Vol. B1.2, p. 2466 & 2482].

4. Manufacturing Facility

Teva Pharmaceuticals USA
New Jersey/Pennsylvania
[B1.3, 1968]

5. Patent and exclusivity –none pending

6. Package Sizes

RLD	-	500 mg	20s, 100s, 500s
	-	875 mg	20s, 100s, 500s
ANDA	-	500 mg	100s, 500s
	-	875 mg	100s, 500s

7. Container/Closure

500 mg – 100s & 500s:

- Bottle - High Density Polyethylene [natural colorant]
- Closure - nonchild-resistant cap

875 mg – 100s & 500s:

- Bottle - High Density Polyethylene [natural colorant]
- Closure - nonchild-resistant cap

[B1.2, 2237, 2257, 2275, 2453, 2454, 2322 & 2333]

8. Storage and/or Dispensing:

NDA - Store at or below 25°C (77°F). Dispense in a tight container.

ANDA - Store at controlled room temperature 15° to 30° C (59° to 86° F)
Dispense in a tight light-resistant container as defined in the USP, with a child-resistant closure (as required).

9. Tablet Scoring

NDA - 500 mg – none
- 875 mg – scored

ANDA - 500 mg – none
- 875 mg - scored

For more information on adverse reactions, 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. 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* (amoxicillin) is 0 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

HPD

Amoxil (amoxicillin) Chewable Tablets

- 10. Bioavailability/Bioequivalence - pending
- 11. Labeling Issue:

CLINICAL PHARMACOLOGY section:

Currently the applicant does not propose to market the 125 mg, 200 mg, 250 mg and 400 mg dosage form. Therefore, text referencing these strengths will be deleted from the CLINICAL PHARMACOLOGY section. This is consistent with a similar decision for ANDAs not mark the 400 mg and 875 mg dosage forms. In this case, ANDAs were requested to delete the text referencing both the 400 mg and the 875 mg dosage forms from the CLINICAL PHARMACOLOGY section.

- 12. The firm has decided not to include "Rx only" immediately beneath the title. [6/30/2000 submission].
- 13. CONTAINER: 500 mg and 875 mg – 100s and 500s
Satisfactory as of the 6/30/2000 submission.

Date of Review: 6/12/2000

Jacqueline Council
Primary Reviewer
Jacqueline Council, Pharm.D.
Steve [Signature]
Team Leader

7-17-2000
Date
7/17/00
Date

cc:

11

13

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.

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.

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 occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin. Amoxicillin may be removed from the body by hemodialysis.

ADMINISTRATION

Tablets and oral suspensions may be given with or without food. The oral suspension, 400-mg chewable tablet and the 200-mg tablet should be administered at the start of a light meal. The 200-mg tablet should not be administered with the 200-mg

Skin/skin structure Mild/Moderate

Severe

Genitourinary tract Mild/Moderate

Severe

8
12
50
8†

Gonorrhea
Acute, uncomplicated ano-genital and urethral infections in males and females 3 gr. sing. dose

¹ Dosing for infections caused by less susceptible organisms should follow the recommendations for severe infections.
² The children's dosage is intended for individuals weighing 40 kg or more should follow adult recommendations.
³ Each strength of Amoxicil suspension is available in 500 mg and 250 mg bottles by older children.

After reconstitution, the required amount of suspension should be administered directly on the child's tongue for swallowing. Additional instructions are to add the required amount of suspension to water, ginger ale, or cold drinks. These preparations should be consumed immediately. To be certain the child is receiving the full dose, the suspension should be consumed in entirety.

All patients with gonorrhea should be treated with amoxicillin.

(13)

is life-threatening and amenable only to amoxicillin

in AST (SGOT) and/or ALT (SGPT) has been noted, but no finding is unknown. Hepatic dysfunction including cholestasis and acute cytolytic hepatitis have

systems: Anemia, including hemolytic anemia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis during therapy with penicillins. These reactions are of continuation of therapy and are believed to be hyper-

Reversible hyperactivity, agitation, anxiety, insomnia, behavioral changes, and/or dizziness have been reported.

clarithromycin and lansoprazole
Combination therapy with amoxicillin plus clarithromycin plus lansoprazole, no adverse reactions were observed. Adverse reactions that were limited to those that had been previously reported with clarithromycin, or lansoprazole.

clarithromycin/lansoprazole
Adverse events for patients who received triple therapy (clarithromycin, amoxicillin, lansoprazole), headache (6%), and taste perversion (5%). No adverse events were observed at significantly higher rates than any dual therapy regimen.

lansoprazole
Adverse events for patients who received clarithromycin/lansoprazole dual therapy were diarrhea (8%) and emergent adverse events were observed at significantly higher rates with amoxicillin t.i.d. plus lansoprazole t.i.d. dual therapy alone.

Adverse reactions with clarithromycin or lansoprazole. **ADVERSE REACTIONS**

Continue medication, treat symptomatically, and discontinue as required. If the overdose is very recent and emesis or other means of removal can be performed. A prospective study of 51 pediatric patients suggested that overdoses of less than 10 mg/kg are not associated with significant clinical effects, such as gastric emptying.³

In oliguric renal failure has been reported in a patient receiving amoxicillin. Renal impairment may occur with overdosage with amoxicillin. High blood levels of amoxicillin may be observed in patients with impaired renal function because amoxicillin is not removed from the body.

Oral suspensions may be given with or without food. The 400-mg chewable tablet and the 200-mg suspension should be administered at the start of a light meal. The 200-mg suspension should be administered with the 200-mg suspension.

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

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 non-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.

- ¹ Dosing for infections caused by less susceptible organisms should follow the recommendations for severe infections.
- ² 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.
- ³ Each strength of Amoxil suspension is available as a chewable tablet for use by older children.

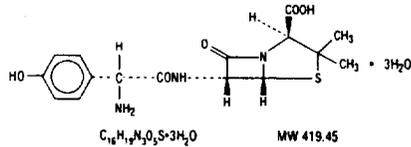
After reconstitution, the required amount of suspension should be placed directly on the child's tongue for swallowing. Alternate means of administration are to add the required amount of suspension to formula, milk, fruit juice, water, ginger ale, or cold drinks. These preparations should then be taken 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

NO BEF stit: but HOT Amc

DESCRIPTION: Amoxicillin is 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 (2S,5R,6R)-6-[(1R)-1-(2-amino-2-[p-hydroxyphenyl]acetylamido)-3,3-dimethyl-1-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. The structural formula is:



Each tablet, for oral administration, contains 500 mg or 875 mg amoxicillin as the trihydrate. Each tablet also contains colloidal silicon dioxide, croscopolone, D&C yellow #10 lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide and Inacotin.

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 Amoxicillin Tablets has been partially investigated. The 875 mg formulation has been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 500 mg formulation. 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 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 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 amoxicillin with 875 mg of Augmentin® (amoxicillin/clavulanate potassium) showed that the 875 mg tablet of amoxicillin produces an AUC_{0-12} 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.

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)
- Staphylococcus 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 (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:		<i>Staphylococcus</i> †	
MIC (mcg/mL)	Interpretation	MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)	≤ 0.25	Susceptible (S)
≥ 16	Resistant (R)	≥ 0.5	Resistant (R)

<i>Streptococcus</i> (except <i>S. pneumoniae</i>)		<i>S. pneumoniae</i> †	
MIC (mcg/mL)	Interpretation	MIC (mcg/mL)	Interpretation
≤ 0.25	Susceptible (S)	≤ 0.5	Susceptible (S)
0.5 to 4	Intermediate (I)	1	Intermediate (I)
≥ 8	Resistant (R)	≥ 2	Resistant (R)

For gram-negative aerobes:		<i>H. influenzae</i> †	
MIC (mcg/mL)	Interpretation	MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)	≤ 1	Susceptible (S)
16	Intermediate (I)	2	Intermediate (I)
≥ 32	Resistant (R)	≥ 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 (mcg/mL)
<i>E. coli</i> ATCC 25922	2 to 8
<i>E. faecalis</i> ATCC 29212	0.5 to 2
<i>H. influenzae</i> ATCC 49247†	2 to 8
<i>S. aureus</i> ATCC 29213	0.25 to 1

Using amoxicillin to determine susceptibility:

Microorganism	MIC Range (mcg/mL)
<i>S. pneumoniae</i> ATCC 49619†	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.

Dilution techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² 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:		<i>Staphylococcus</i> †	
Zone Diameter (mm)	Interpretation	Zone Diameter (mm)	Interpretation
≥ 17	Susceptible (S)	≥ 29	Susceptible (S)
≤ 16	Resistant (R)	≤ 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		<i>H. influenzae</i> †	
Zone Diameter (mm)	Interpretation	Zone Diameter (mm)	Interpretation
≥ 17	Susceptible (S)	≥ 22	Susceptible (S)
14 to 16	Intermediate (I)	19 to 21	Intermediate (I)
≤ 13	Resistant (R)	≤ 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)
<i>E. coli</i> ATCC 25922	16 to 22
<i>H. influenzae</i> ATCC 49247†	13 to 21
<i>S. aureus</i> ATCC 29213	27 to 35

Using 1-mcg oxacillin disk:

Microorganism	Zone Diameter (mm)
<i>S. pneumoniae</i> ATCC 49619†	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% CO₂.

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-dianthromycin-containing regimen should be used.

INDICATIONS AND USAGE: 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 parodontal 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.

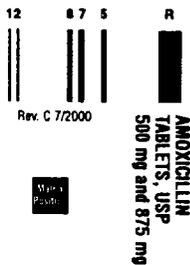
***H. pylori* eradication to reduce the risk of duodenal ulcer recurrence**

Triple therapy: amoxicillin/clarithromycin/ lansoprazole
Amoxicillin, 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 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: amoxicillin/lansoprazole
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.

152573



Rev. C 7/2000

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 AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN 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 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 Clinistix[®], 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 estradiol, estradiol-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/m²).

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, the 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 amoxicillin should be modified in pediatric patients 12 weeks or younger (≤ 3 months). (See **DOSE 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 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, 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.

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.

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

DOSEAGE AND ADMINISTRATION
The 875 mg tablet has been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 500 mg formulation.

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 amoxicillin is 30 mg/kg/day divided q12h.

Adults and pediatric patients >3 months:

Infection	Severity ¹	Usual Adult Dose	Usual Dose for Children >3 months ²
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
			25 mg/kg/day in divided doses every 12 hours or 20 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
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	Prophylactic children: 50 mg/kg amoxicillin, combined with 25mg/kg probenecid as a single dose.

NOTE: SINCE PROBENECID IS CONTRAINDICATED IN CHILDREN UNDER 2 YEARS, DO NOT USE THIS REGIMEN IN THESE CASES.

¹ Dosing for infections caused by less susceptible organisms should follow the recommendations for severe infections.

² 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.

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

Dual therapy: amoxicillin/lansoprazole
The recommended adult oral dose is 1 gram 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.

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 <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.

HOW SUPPLIED:
Amoxicillin Tablets USP, 500 mg, are available as film-coated, capsule-shaped, off-white tablets, debossed "93" on one side and "2263" on the other side. They are available in bottles of 100.

Amoxicillin Tablets USP, 875 mg, are available as film-coated, capsule-shaped, off-white tablets, scored on one side, debossed "93" on one side of the score and "2264" on the other side of the score. They are available in bottles of 100.

Store at controlled room temperature between 15° and 30°C (59° and 86°F).

Dispense in a light-resistant container as defined in the USP, with a child-resistant closure (as required).

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 l.i.d./lansoprazole 30 mg l.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 ¹	Intent-to-Treat Analysis ²
Study 1	92 ¹ [80-97.7] (n=48)	86 ² [73.3-93.5] (n=55)
Study 2	88 ¹ [75.7-93.6] (n=66)	83 ² [72-90.8] (n=70)

¹ 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.

² 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 ¹	Intent-to-Treat Analysis ²
Study 1	77 ¹ [62.5-87.2] (n=51)	70 ² [56.8-81.2] (n=50)
Study 2	66 ¹ [51.9-77.5] (n=58)	61 ² [48.5-72.9] (n=67)

¹ 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.

² 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

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

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Printed in USA
Rev. C 7/2000
15273

NDC 0093-2263-01

AMOXICILLIN Tablets, USP 500 mg

Each tablet contains:
Amoxicillin Trihydrate equivalent
to 500 mg Amoxicillin.

R only



TEVA

USUAL DOSAGE: 1 tablet every 12 hours.

See package insert for full prescribing information.

Store at controlled room temperature,

15° to 30°C (59° to 86°F) (see USP

Dispense in a light, light-resistant container as defined in the

USP, with a child-resistant closure (if required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF

CHILDREN

L52553

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PG Rev. A 6/00

NDC 0093-2263-05

AMOXICILLIN Tablets, USP 500 mg

Each tablet contains:
Amoxicillin Trihydrate equivalent
to 500 mg Amoxicillin.

R only



TEVA

USUAL DOSAGE: 1 tablet every 12 hours.

See package insert for full prescribing information.

Store at controlled room temperature,

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Dispense in a light, light-resistant container as

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(as required).

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NDC 0093-2264-01

**AMOXICILLIN
Tablets, USP
875 mg**

Each tablet contains:
Amoxicillin Trihydrate equivalent
to 875 mg Amoxicillin.

Rx only

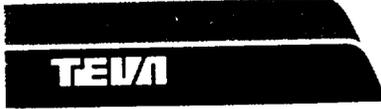


NDC 0093-2264-05

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Tablets, USP
875 mg**

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Rx only



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Store at controlled room temperature,
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N 0093-2264-01



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