

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-056

APPROVAL LETTER

SEP 18 2000

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
P.O. Box 247
Kulpsville, PA 19443

Dear Madam:

This is in reference to your abbreviated new drug application dated December 3, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Amoxicillin Tablets USP, 500 mg and 875 mg. 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.

Reference is also made to your amendments dated February 14, February 29, June 30, August 9, and August 30, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Amoxicillin Tablets USP, 500 mg and 875 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Amoxil[®] Tablets, 500 mg and 875 mg, respectively, of SmithKline Beecham Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506(A) of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,



Gary Buehler 9/18/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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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 Pharm.D.
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. A small amount of water, ginger ale, or cold drinks. These preparations should be consumed immediately. To be certain the child is receiving the required amount, 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 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 or combinations 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 100 mg/kg are not associated with significant clinical effects, including 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.

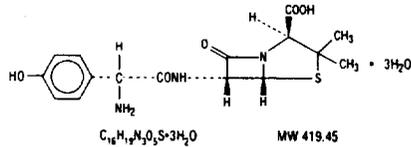
After reconstitution, the required amount of suspension should be placed directly on the child's tongue for swallowing. Alternate means of administration are to add the required amount of suspension to formula, milk, fruit juice, water, ginger ale, or cold drinks. These preparations should then be taken 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 HOI 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]acetamido]-3,3-dimethyl-7-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 $AUC_{0-\infty}$ of 35.4 ± 8.1 mcg·hr/mL and a C_{max} of 13.8 ± 4.1 mcg/mL. Dosing was at the start of a light meal following an overnight fast.

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).†

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.†
- 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 procedure† 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).†

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.†

- 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-rectal 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

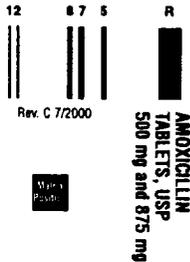
Amoxicillin, in combination with clarithromycin plus lansoprazole as triple therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce 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 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/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 [†]	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
			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.

[†] Dosing for infections caused by less susceptible organisms should follow the recommendations for severe infections.

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

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 [†]	Intent-to-Treat Analysis [‡]
Study 1	92 [†] [80-97.7] (n=48)	86 [‡] [73.3-93.5] (n=55)
Study 2	88 [†] [75.7-93.6] (n=66)	83 [‡] [72-90.8] (n=70)

[†] 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 ^{††}	Intent-to-Treat Analysis ^{‡‡}
Study 1	77 ^{††} [62.5-87.2] (n=51)	70 ^{‡‡} [56.8-81.2] (n=50)
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

- 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.
- 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.
- 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

TEVA PHARMACEUTICALS USA

Sellersville, PA 18960

PG Rev. A 6/00

LOT
EXP



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,
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
(as required).

**KEEP THIS AND ALL MEDICATIONS OUT OF
THE REACH OF CHILDREN.**

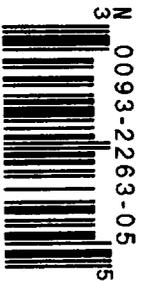
L52554

TEVA PHARMACEUTICALS USA

Sellersville, PA 18960

PG Rev. A 6/00

LOT
EXP



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

**AMOXICILLIN
Tablets, USP
875 mg**

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

Rx only



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 (as required).

**KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF
CHILDREN.**

L52555

PG Rev. A 6/00

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-2264-01



LOT
EXP

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
(as required).

**KEEP THIS AND ALL MEDICATIONS OUT OF
THE REACH OF CHILDREN.**

L52556

PG Rev. A 6/00

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-2264-05



LOT
EXP

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-056

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 65-056

3. NAME AND ADDRESS OF APPLICANT

TEVA Pharmaceuticals
1510 Delp Drive
Kulpsville, PA 19443

Phone: (215) 256-8400

Fax: (215) 256-8105

U.S. Agent

N/A

4. LEGAL BASIS FOR SUBMISSION

The application is based on Amoxil® Tablets manufactured by Smithkline Beecham (NDA# 50-754). The firm states that no effective patents or exclusivity periods are in force for the referenced product (pp. 11, 16).

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Amoxicillin Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

Original Submission: 12/3/99

Amendment, colorant formulation: 12/21/99

Amendment, Bio: 2/14/00

Amendment, Bio: 2/29/00

Amendment, Chemistry and Labeling: 6/30/00

Amendment, Chemistry: 8/30/00

FDA:

Acceptance for filing: 1/27/00
 Labeling, deficient: 3/3/00
 Bioequivalence, acceptable: 3/7/00
 Chemistry and Labeling, deficient: 6/5/00
 Labeling Deficient: 7/17/00
 Chemistry Telephone Amendment: 8/28/00, 8/29/00

10. PHARMACOLOGICAL CATEGORY
 Antibacterial

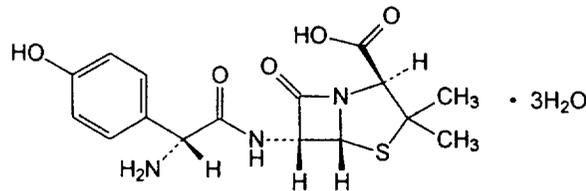
11. Rx or OTC
 Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
 Tablet

14. POTENCIES
 500 and 875 mg

15. CHEMICAL NAME AND STRUCTURE
 Amoxicillin. 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo, trihydrate [2S-[2 α ,5 α ,6 β (S*)]]-.
 $C_{16}H_{19}N_3O_5S \cdot 3H_2O$. 419.46. 61336-70-7. Antibacterial.



16. RECORDS AND REPORTS
 N/A

17. COMMENTS

Upon review, Dr. Vilayat Sayeed made the comments highlighted below. These concerns were communicated to the firm by telephone on August 28 and 29, 2000. The firm's August 30, 2000 telephone amendment response are provided below.

Comment: The stability data does not support the proposed water specification of The firm was requested to reduce the specification for water on stability to as for finished product release.

Response: The firm reduced the specification for water on stability to The firm provided the revised Finished Product Procedures Manual and Finished Product Stability Protocol which reflect the change.

Comment: TEVA has two sets of impurity specifications for the drug substance on pages 1841 and 1842. The firm was asked to clarify.

Response: The firm responded, "While the impurity specifications listed on page 1841 of our original application contained the drug substance manufacturer's stability limits of Largest Individual and Total we do not intend to accept material which does not comply with Teva USA's limits of Largest Individual and Total as listed in our laboratory procedure manual for the bulk drug."

First Generic
 DMF, acceptable: 5/22/00
 Labeling, acceptable: 8/18/00
 Bioequivalence, acceptable: 3/7/00
 EER, acceptable: 7/17/00

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend approval

19. REVIEWER:

Ruth Ganunis

DATE COMPLETED:

7/24/00

Page(s) 14

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

Chem Rev. 2

7/24/00

JUN 5 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 65-056

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Amoxicillin Tablets USP, 500 mg and 850 mg

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. Please describe the maximum holding time for the bulk finished product in the lined fiber drums prior to packaging in the market containers. Please note that up to a 30 day holding time is permitted without supporting data.
2. We note that the proposed PF monograph for Amoxicillin Tablets, USP eliminates the water specification of . Please include a specification for water in your finished and stability product testing procedures that is supported by your exhibit batch data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Since you are obtaining drug substance from TEVA Mexico, MO, you have proposed accepting material based on the COA and an identification test. This is acceptable provided that you have established the reliability of the supplier's analysis through appropriate validation. Please provide confirmation.
2. We note that you are using an alternative method for identification of the drug product. Please be advised that approval to use an alternate method that differs from that in the USP does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of dispute only the results obtained by the official methods and procedures in the USP will be considered conclusive.

3. If available, please provide updated room temperature stability data in your next amendment.

Sincerely yours,



Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-056

Bioequivalence Review(s)

A2.)

Amoxicillin Tablets
500 mg and 875 mg
ANDA #65-056
Reviewer: Kuldeep R. Dhariwal
File name: 65056SDW.D99

Teva Pharmaceuticals
1510 Delp Drive
Kulpsville
PA 19443
Submission Date:
December 3, 1999
February 14, 2000
February 29, 2000

Review of Fasting Study, Non-fasting Study, Dissolution Data, and Waiver Request

Introduction

First Generic: Yes

Type of Submission: Original ANDA, paper submission

Contents of submission:

Dissolution data and *in vivo* bioequivalence study under fasting and non-fasting conditions on 875 mg strength.

Dissolution data and waiver request for *in vivo* bioequivalence study requirements for 500 mg strength.

Indication: Treatment of infections due to susceptible strains of B-lactamase-negative microorganisms.

RLD: Amoxil[®] 875 mg as well as Amoxil[®] 500 mg (SmithKline Beecham) are listed as RLD in The Orange Book. As per Don Hare, the Orange Book will be corrected and only 875 mg strength will be listed as RLD.

Pharmacokinetics: Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. The half-life of amoxicillin is 61.3 minutes. 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 microgram/mL to 5 microgram/mL and 5.5 microgram/mL to 7.5 microgram/mL respectively.

Bioequivalence Study Under Fasting Conditions:

A. Study Information:

Protocol #:

IRB Approval: Yes

Consent Form Signed: Yes

Clinical Site: Phoenix International

Principal Investigator: Samuel Serfaty, M.D.

Analytical Facility: Phoenix International
Analytical Team Leader:
Study Dates: Period I August 1, 1999
Period II August 8, 1999
Washout Period: 7 days
Analysis Dates: August 26-September 17, 1999
Storage Period: 47 days
Study Design: Randomized, single dose, two-way
crossover.
Randomization Scheme: AB: 3,4,8,10,11,12,15,17,18,21,22,
24,25
BA: 1,2,5,6,7,9,13,14,16,19,20,23,26

Treatments:

A: Amoxicillin tablet, 1x875 mg; Teva Pharmaceuticals; Lot #1034-7; Batch size: ablets (theoretical), 129,505 tablets (actual); Manufacture Date: 5/19/1999; Assay: 98.3%

B: Amoxil[®] tablet, 1x875 mg; SmithKline Beecham; Lot #MB2223; Expiry Date: 05/2000; Assay: 98.1%

Formulation of Test Product:

Subjects:

Ingredients are listed in 110.
26 male, 19-44 years old subjects were enrolled according to inclusion/exclusion criteria specified in the protocol.

Housing:

From 12 hours pre-dose until 8 hours post-dose.

Dosing:

After 10 hour fast, with 240 mL of water.

Sample Collection:

Blood samples (5 mL) were collected in Vacutainers containing EDTA at predose (0 h) and at following times after dosing: 0.33,0.67,1,1.33,1.67, 2,2.5,3,4,5,6, and 8 hours.

B. Study Results:

1. Clinical:

Drop-outs: None
Adverse Events: One subject complained of dizziness on test drug.
Protocol Deviations: There were four sampling time deviations of 4 minutes or less. The actual times were used in pharmacokinetic calculations.

2. Analytical:

Within-Study:

Method: detection.
Internal Standard:
Linearity: Std. curve range:
0.10-19.047 mcg/mL.
Correlation coefficients were better than 0.9983.
Regression: 1/concentration, linear
QC Samples: 0.300, 8.001, 15.501 mcg/mL
Accuracy: Standards 94.9-105.1%
QC samples 96.7-103.9%
Precision: Standards 2.2-5.6%
QC samples 4.6-5.9%
Reassays: Some samples were reassayed due to anomalous values, above curve limit, and high/low standard missing.

Pre-Study Method Validation:

Specificity: Ten blank plasma samples did not show any interference near the retention times of amoxicillin or internal standard.

Linearity: Std. curve range: 0.10-19.047 mcg/mL. Correlation coefficients were better than 0.998.

QC samples: 0.300, 8.001, and 15.501 mcg/mL

Accuracy: Inter-day
Standards 95.5-106.6%
QC samples 96.5-99.2%
Intra-day

Precision:	QC samples	94.6-102.9%
	Inter-day	
	Standards	0.6-5.1%
	QC samples	5.8-6.5%
Recovery:	Intra-day	
	QC samples	1.1-2.2%
	0.300 mcg/mL	100.3% (9.1%CV)
	8.001 mcg/mL	90.2% (2.9%CV)
	15.501 mcg/mL	90.4% (0.9%CV)
	Internal std.	77.7% (4.7%CV)

Stability:

- Amoxicillin was stable at room temperature for at least 4.56 hours in unextracted samples.
- Amoxicillin was stable at 4⁰C for at least 96.5 hours in extracted samples.
- Freeze-thaw: stable over 2 cycles.
- Long-term: stability demonstrated for 77 days.

Comment: Method validation is acceptable.

3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations:	Table 2 and Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	LAUC _{0-t}	97.23-108.51%
	LAUC _{0-inf}	96.83-107.67%
	LC _{max}	96.26-114.57%
Test/Reference Ratios:	AUC _{0-t}	1.04 (0.70-1.52)
	AUC _{0-inf}	1.03 (0.70-1.40)
	C _{max}	1.09 (0.72-2.21)
AUC_{0-t}/AUC_{0-inf} Ratios:	Test	0.98 (0.96-0.99)
	Reference	0.98 (0.91-0.99)
Root MSE:	LAUC _{0-t}	0.11561
	LAUC _{0-inf}	0.11178
	LC _{max}	0.18346

Comments:

- The pharmacokinetic parameters and 90% confidence intervals were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.
- The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits. There was no statistically significant sequence, treatment or period effect for any of these parameters.
- The fasting study is acceptable.

Bioavailability Study Under Non-Fasting Conditions:

A. Study Information:

Protocol #:
IRB Approval: Yes
Consent Form Signed: Yes
Clinical Site: Phoenix International
Principal Investigator: Samuel Serfaty, M.D.
Analytical Facility: Phoenix International
Analytical Team Leader:
Study Dates: Period I August 2, 1999
Period II August 4, 1999
Period III August 6, 1999
Washout Period: 2 days
Analysis Dates: August 31-September 17, 1999
Storage Period: 46 days
Study Design: Randomized, single dose, three-way crossover.
Randomization Scheme: BAC: 1,7,18
CBA: 2,4,10
BCA: 3,5,17
ACB: 6,9,14
CAB: 8,11,12
ABC: 13,15,16

Treatments:

A: Amoxicillin tablet, 1x875 mg; Teva Pharmaceuticals; Lot #1034-7; administered after a 10 hour fast

B: Amoxicillin tablet, 1x875 mg; Teva Pharmaceuticals; Lot #1034-7; administered after a standard high-fat breakfast

C: Amoxil[®] tablet, 1x875 mg; SmithKline Beecham; Lot #MB2223; administered after a standard high-fat breakfast

Lot numbers of the drug products administered in this study are the same as those for the fasting study.

Subjects: 18 male, 20-39 years old subjects were enrolled according to inclusion/exclusion criteria specified in the protocol.

Housing: From 12 hours pre-dose until 8 hours post-dose.

Dosing:

Treatment A: Subjects were given a single oral dose of the assigned formulation with 240 mL of water after a 10.5 hour fast.

Treatments B and C: Subjects were given OGD approved standardized breakfast 30 minutes before dosing after a fast lasting at least 10 hours. All subjects completed their breakfast. The dose was given with 240 mL of water.

Sample Collection:

Blood samples (5 mL) were collected in Vacutainers containing EDTA at predose (0 h) and at following times after dosing: 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, and 8 hours.

B. Study Results:

1. Clinical:

Drop-outs:

Subject #15 was withdrawn prior to dosing in period II due to a positive drug screen for cannabinoids.

Adverse Events:

Two subjects reported that they feel tired.

Protocol Deviations:

There were four sampling time deviations. The actual times were used in pharmacokinetic calculations.

2. Analytical:

Within-Study:

Method:

Internal Standard:

Linearity:

Std. curve range:

0.10-19.047 mcg/mL.

Correlation coefficients were better than 0.9983.

Regression:

1/concentration, linear

QC Samples:

0.300, 8.001, 15.501 mcg/mL

Accuracy:

Standards 93.5-105.8%

QC samples 97.9-102.7%

Precision: Standards 1.4-4.7%
QC samples 2.7-5.5%
Reassays: Some samples were reassayed due to anomalous values and high/low standard missing.

3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations: Table 3, Figure 2
Pharmacokinetic Parameters: Table 4
AUC_{0-t}/AUC_{0-inf} Ratios: Test fasting: 0.97 (0.87-0.99)
Test non-fasting: 0.98 (0.95-0.99)
Ref non-fasting: 0.98 (0.96-0.99)

Comments:

1. The pharmacokinetic parameters and ratios of means were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer. The firm in its analysis of variance model included subject, period, treatment and first order carryover as factors. The reviewer did not use first order carryover in the model. The least squares means obtained by the reviewer therefore differ slightly from those reported by the firm. The ratios of means are within acceptable limits by either method.
2. The non-fasting study is acceptable.
3. The non-fasting study is not required for this drug product.

In Vitro Dissolution Testing:

The dissolution testing was conducted in 900 mL of water using apparatus II (paddle) at 75 rpm (USP method, Pharmacopeial Forum, volume 25, number 4). The test products dissolve more than in 90 minutes and meet USP specifications.

F₂ Test:

Test 875 mg vs. Test 500 mg	96.30
Ref 875 mg vs. Ref 500 mg	75.87
Test 875 mg vs. Ref 875 mg	82.32
Test 500 mg vs. Ref 500 mg	82.05

Waiver Request:

The firm is requesting a waiver of *in vivo* bioequivalence study requirements for 500 mg tablet. The 500 mg and 875 mg tablets are proportionally similar in their active and inactive

ingredients. The dissolution data are acceptable. The waiver can be granted.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Teva Pharmaceuticals on its Amoxicillin 875 mg tablet, lot #1034-7 comparing it to Amoxil[®] 875 mg tablet, lot #MB2223 manufactured by SmithKline Beecham is acceptable to the Division of Bioequivalence. The study demonstrates that Teva's Amoxicillin 875 mg tablet is bioequivalent to the reference product, Amoxil[®] 875 mg tablet manufactured by SmithKline Beecham.
2. The bioequivalence study conducted under non-fasting conditions by Teva Pharmaceuticals on its Amoxicillin 875 mg tablet, lot #1034-7 comparing it to Amoxil[®] 875 mg tablet, lot #MB2223 manufactured by SmithKline Beecham is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Teva's Amoxicillin 875 mg tablet is similar to that of the reference product, Amoxil[®] 875 mg tablet manufactured by SmithKline Beecham. However, the non-fasting study is not required.
3. The dissolution testing conducted by the firm on its 500 mg and 875 mg tablets is acceptable. The formulation for 500 mg test tablet is proportionally similar to the 875 mg strength of the test product which underwent bioequivalency testing. The waiver of the *in vivo* bioequivalence study requirements for 500 mg tablet of the test product is granted. The 500 mg test tablet is therefore deemed bioequivalent to Amoxil[®] 500 mg tablet manufactured by SmithKline Beecham.
4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water at 37°C using apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

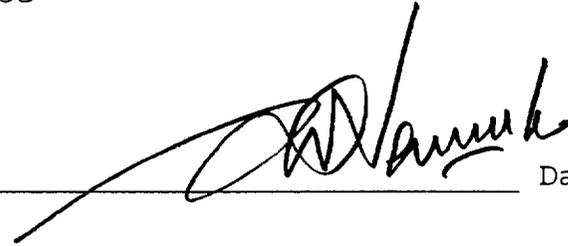
Not less than _____ of the labeled amount of amoxicillin in the dosage form is dissolved in 90 minutes.

5. From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

Moharival

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

 Date 3/6/00

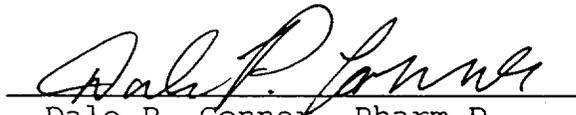
Concur:  Date 3/7/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table 1

Comparative Quantitative Composition of Amoxicillin Tablets

Ingredient	500 mg		875 mg	
	mg/tab	w/w %	mg/tab	w/w %
Amoxicillin Trihydrate				
Microcrystalline Cellulose				
Sodium Starch				
Crospovidone				
Colloidal Silicon				
Magnesium Stearate				
Coating:				
	-		-	
Total				

Test 500 mg tablet: Film-coated, capsule shaped, off-white tablet, debossed "93" on one side and "2263" on the other side.

Test 875 mg tablet: Film-coated, capsule shaped, off-white tablet, scored on one side, debossed "93" on one side of the score and "2264" on the other side of the score.

Reference tablets: 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.

Table 2

MEAN PLASMA AMOXICILLIN LEVELS (microgram/mL) FOR TEST (1) AND
 REFERENCE (2) PRODUCTS IN FASTING STUDY, n=26
 Dose= 1x875 mg

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	1.50	1.74	1.61	1.60	0.93
0.67	5.83	4.77	6.21	3.64	0.94
1	8.98	4.52	8.88	4.34	1.01
1.33	10.66	4.17	10.44	4.04	1.02
1.67	11.20	3.44	10.43	3.49	1.07
2	10.98	3.23	10.47	3.38	1.05
2.5	9.46	2.80	8.90	2.23	1.06
3	7.98	2.22	7.07	1.80	1.13
4	5.01	2.16	5.09	2.56	0.98
5	2.73	1.29	2.82	1.96	0.97
6	1.48	0.70	1.63	0.98	0.90
8	0.44	0.16	0.51	0.28	0.87

UNIT: PLASMA LEVEL=MICROGRAM/ML TIME=HRS
 ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	39.16	8.54	38.44	8.62	1.02
AUCT	38.42	8.41	37.49	8.46	1.02
CMAx	12.79	3.31	12.21	3.28	1.05
KE	0.61	0.08	0.58	0.09	1.05
LAUCI	38.28	0.22	37.49	0.23	1.02
LAUCT	37.55	0.22	36.56	0.23	1.03
LCMAx	12.38	0.26	11.79	0.27	1.05
THALF	1.16	0.15	1.23	0.21	0.95
TMAx	1.98	0.73	1.85	0.74	1.07

UNIT: AUC=MICROGRAM HR/ML CMAx=MICROGRAM/ML TMAx=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	39.16	38.44	1.02	96.93	106.81
AUCT	38.42	37.49	1.02	97.39	107.55
CMAx	12.79	12.21	1.05	96.53	113.01
LAUCI	38.28	37.49	1.02	96.83	107.67
LAUCT	37.55	36.56	1.03	97.23	108.51
LCMAx	12.38	11.79	1.05	96.26	114.57

Table 3

MEAN PLASMA AMOXICILLIN LEVELS (MICROGRAM/ML) FOR TEST AND REFERENCE
 PRODUCTS IN NON-FASTING STUDY, N=17
 Dose= 1x875 mg

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.33	1.03	1.04	0.36	0.48	0.09	0.23	2.84
0.67	4.78	2.52	3.42	2.58	1.30	1.19	1.40
1	8.14	3.83	7.35	4.50	3.83	2.89	1.11
1.33	9.46	3.66	9.73	4.43	6.79	3.95	0.97
1.67	9.78	3.39	10.65	3.21	9.11	3.73	0.92
2	9.69	2.64	10.34	2.24	10.07	2.85	0.94
2.5	7.92	2.27	8.74	1.83	9.60	1.93	0.91
3	6.08	1.83	6.95	1.89	8.28	2.18	0.87
4	3.87	1.41	4.05	1.45	4.71	1.64	0.96
5	2.19	1.06	2.14	0.72	2.55	0.88	1.03
6	1.25	0.75	1.21	0.45	1.39	0.51	1.03
8	0.46	0.40	0.42	0.13	0.46	0.15	1.09

(CONTINUED)

UNIT: PLASMA LEVEL=MICROGRAM/ML TIME=HRS
 MEAN PLASMA AMOXICILLIN LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.33	11.79	4.15
0.67	3.66	2.62
1	2.12	1.92
1.33	1.39	1.43
1.67	1.07	1.17
2	0.96	1.03
2.5	0.82	0.91
3	0.73	0.84
4	0.82	0.86
5	0.86	0.84
6	0.90	0.87
8	1.00	0.92

1= TEST FASTING
 2= TEST NON-FASTING
 3= REF NON-FASTING

Table 4

AMOXICILLIN PHARMACOKINETIC PARAMETERS IN NON-FASTING STUDY, N=17
Dose= 1x875 mg

UNIT: PLASMA LEVEL=MICROGRAM/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	32.96	7.48	33.61	4.81	32.83	4.33	0.98
AUCT	32.01	7.00	32.82	4.81	32.04	4.24	0.98
CMAx	11.02	3.20	12.23	2.88	11.62	2.64	0.90
KE	0.55	0.10	0.55	0.08	0.59	0.06	1.00
LAUCI	31.92	0.28	33.30	0.14	32.58	0.13	0.96
LAUCT	31.04	0.28	32.51	0.14	31.79	0.13	0.95
LCMAx	10.39	0.40	11.93	0.22	11.36	0.21	0.87
THALF	1.30	0.27	1.28	0.21	1.19	0.11	1.02
TMAx	1.81	0.45	1.78	0.41	2.20	0.51	1.02

(CONTINUED)

UNIT: AUC=MICROGRAM HR/ML CMAx=MICROGRAM/ML TMAx=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

PARAMETER	RMEAN13	RMEAN23
AUCI	1.00	1.02
AUCT	1.00	1.02
CMAx	0.95	1.05
KE	0.94	0.94
LAUCI	0.98	1.02
LAUCT	0.98	1.02
LCMAx	0.91	1.05
THALF	1.09	1.08
TMAx	0.83	0.81

UNIT: AUC=MICROGRAM HR/ML CMAx=MICROGRAM/ML TMAx=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND RATIOS

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	32.76	33.37	32.75	0.98	1.00	1.02
AUCT	31.81	32.58	31.95	0.98	1.00	1.02
CMAx	10.93	12.15	11.55	0.90	0.95	1.05
LAUCI	31.75	33.05	32.52	0.96	0.98	1.02
LAUCT	30.87	32.25	31.72	0.96	0.97	1.02
LCMAx	10.32	11.84	11.32	0.87	0.91	1.05

1= TEST FASTING
2= TEST NON-FASTING
3= REF NON-FASTING

Table 5. In Vitro Dissolution Testing						
Drug (Generic Name): Amoxicillin Tablets Dose Strength: 500 mg and 875 mg ANDA No.: 65-056 Firm: Teva Submission Date: December 3, 1999 File Name: 65056SDW.D99						
I. Conditions for Dissolution Testing: USP method						
USP XXIII Basket: Paddle: x RPM: 75 No. Units Tested: 12 Medium: Water Volume: 900 mL Specifications: NLT 90 minutes Reference Drug: Amoxil [®] (SmithKline) Assay Methodology						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #1034-58 Strength(mg) 500			Reference Product Lot #KK1681 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
10	96.6	:	3.33	95.7	:	1.22
20	98.6	:	2.03	97.1	:	0.77
90	100.2	:	2.27	97.1	:	0.66
Sampling Times (Minutes)	Test Product Lot #1034-7 Strength(mg) 875			Reference Product Lot #MB2223 Strength(mg) 875		
	Mean %	Range	%CV	Mean %	Range	%CV
10	95.5	:	2.18	98.7	:	0.86
20	98.5	:	1.93	99.9	:	0.84
90	100.2	:	1.08	99.9	:	0.80

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-056

APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Amoxicillin Tablets, 500 mg and 875 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37°C using USP Apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than _____ of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

Please note that a food-effect study is not required for drug products (tablets, capsules, chewable tablets and suspensions) containing only amoxicillin.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FIG 1. PLASMA AMOXICILLIN LEVELS

AMOXICILLIN TABLETS, 875 MG, ANDA #65-056
UNDER FASTING CONDITIONS
DOSE=1 X 875 MG

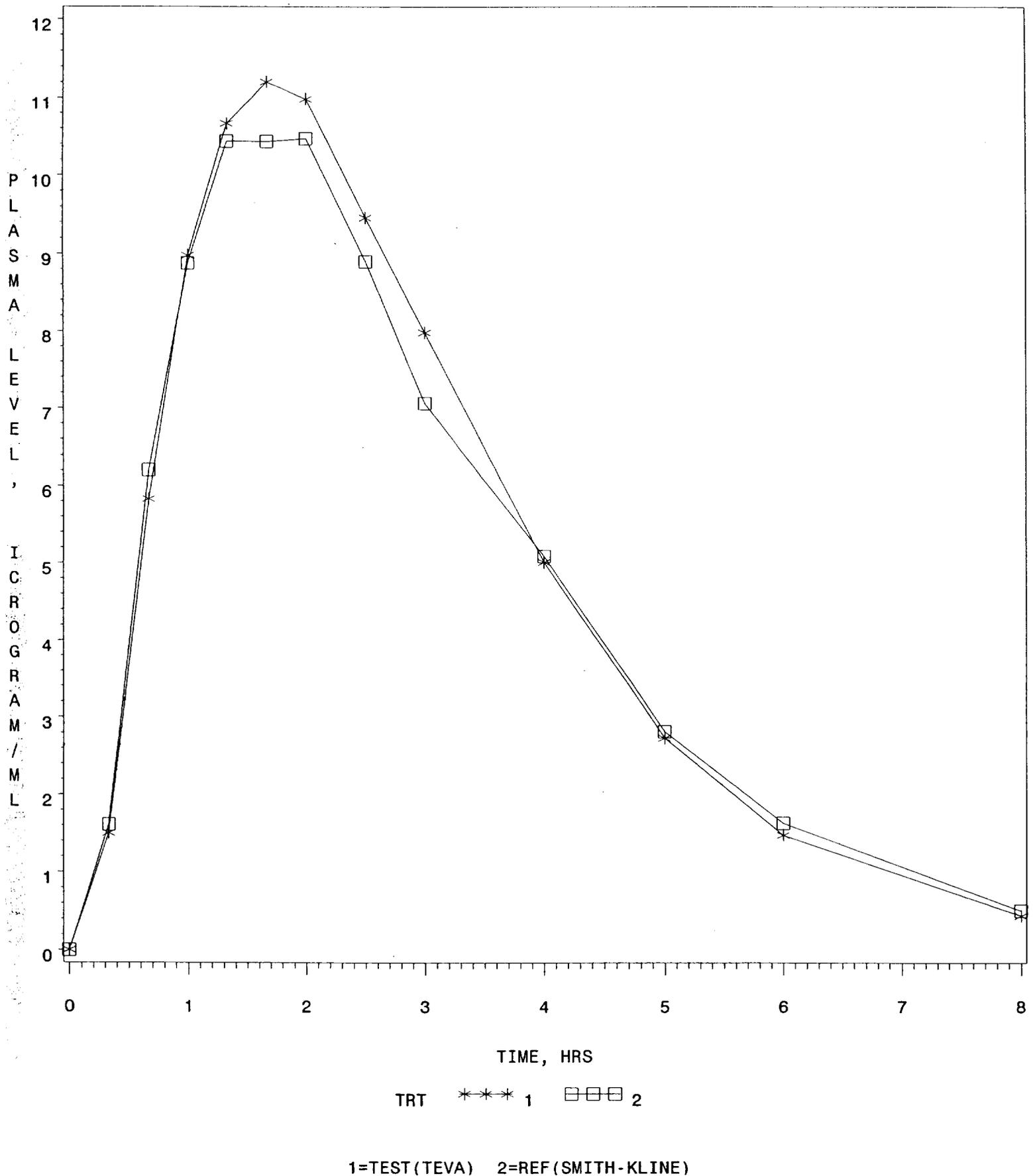
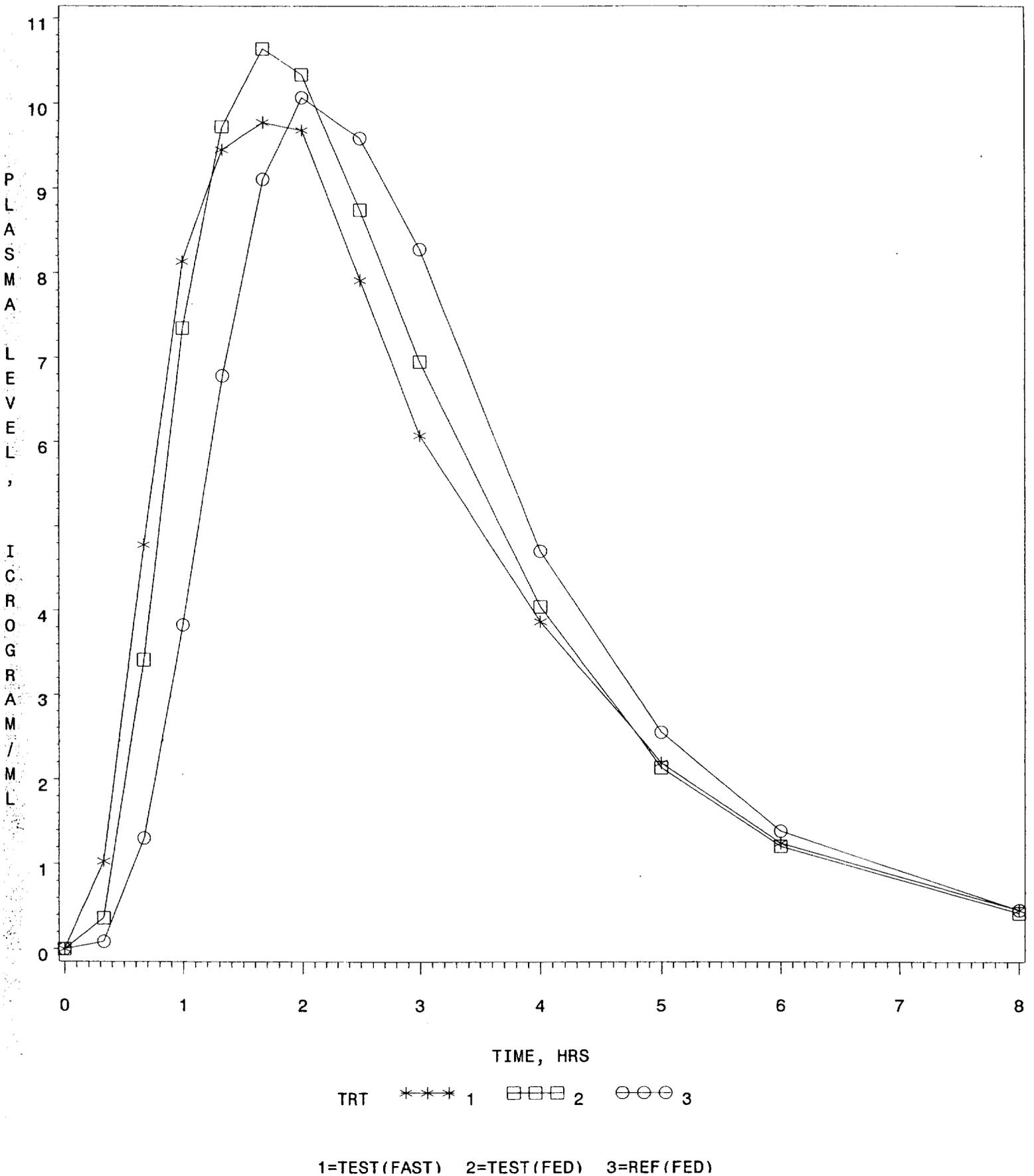


FIG 2. PLASMA AMOXICILLIN LEVELS

AMOXICILLIN TABLETS, 875 MG, ANDA #65-056
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 875 MG



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-056

APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Amoxicillin Tablets, 500 mg and 875 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37°C using USP Apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than _____ of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

Please note that a food-effect study is not required for drug products (tablets, capsules, chewable tablets and suspensions) containing only amoxicillin.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-056

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 65-056

DRUG PRODUCT: Amoxicillin Tablets, USP

FIRM: TEVA Pharmaceuticals

DOSAGE FORM: Tablets **STRENGTH:** 500 and 875 mg

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification provided on page 1973, Vol. 1.6. Acceptable EER dated 7/17/00.

BIO STUDY: The bio-study conducted on the applicant's product and Smithkline Beecham's Amoxil® capsules (875 mg) and the waiver for bio-study (500 mg) were found acceptable by the Division of Bioequivalence on 3/7/00.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and drug product are both USP. The applicant is using USP methods in testing the bulk drug and finished product. The firm is using in-house validated methods for identification and dissolution testing on the finished product.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Accelerated and room temperature stability data support the proposed 24 month expiration date. Containers used in the stability studies were identical to those described in the container section.

LABELING: See "Approval Summary".

STERILIZATION VALIDATION (IF APPLICABLE): Not-applicable to this drug product.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): Exhibit batch #1034-7 (875 mg) used for stability and bio-studies and exhibit batch #1034-58 (500 mg) used for stability studies were manufactured with bulk drug substance from TEVA Pharmaceuticals USA (API Division). Both exhibit batches were

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): See above

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch size is
The manufacturing process described in the master production record is the same as that described in the exhibit batch record.

CHEMIST: Ruth Ganunis
SUPERVISOR: Richard Adams

DATE: 8/22/00
DATE: 8/23/00

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 65-056

Date of Submission: December 3, 1999

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin Tablets USP, 500 mg and 875 mg

Labeling Deficiencies:

1. CONTAINER: 500 mg and 875 mg – 100s and 500s
 - a. We encourage you to differentiate your drug product strengths by using contrasting colors, boxing or some other means.
 - b. Revise the "Each tablet contains ..." statement to read, "Each tablet contains ___ mg amoxicillin as the trihydrate.
 - c. To be consistent with the innovator's labels, we encourage you to revise the "Usual Dosage ..." statement to read " Usual Dosage: 1 tablet every 12 hours. See package ...".
 - d. Following the storage temperature recommendations delete the word, "between", replace the hyphens with the word "to" add the text, "[See USP]".

2. INSERT
 - a. We encourage you to add the legend "Rx only" to follow the Title.
 - b. General Comments
 - i. We encourage you to use the abbreviation, "mcg" for micrograms instead of "µg".
 - ii. We encourage you to delete the terminal zero following a decimal point, i.e., "3" instead of "3.0", when expressing a range of doses.
 - c. DESCRIPTION

Add the following as the last sentence of the first paragraph:

The structural formula is:
 - d. CLINICAL PHARMACOLOGY

Revise the first five paragraphs of this section to be in accord with the attached labeling of the reference listed drug, Amoxil®, with the following exceptions:

 - First paragraph

... investigated. The 875 mg formulation ... However, food effect ... the 500 mg formulation.
 - Second paragraph

Orally administered doses of 500 mg ...

- Delete the paragraph, "Amoxicillin chewable ... respectively".
- Delete the paragraph, "Oral administration of single doses of 400 mg ... data" and the associated table.

e. PRECAUTIONS

i. Drug Interactions

Revise this subsection to be in accord with the attached labeling of the reference listed drug, Amoxil®.

ii. Drug/Laboratory Test Interactions

Delete the text "(e.g., Tes-Tape®)".

f. DOSAGE AND ADMINISTRATION

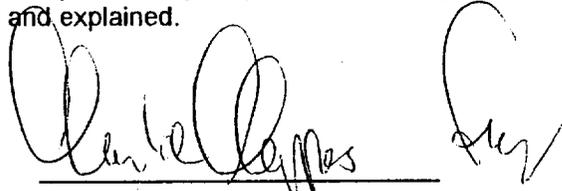
Revise this section to be in accord with the attached labeling of the reference listed drug, Amoxil®.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes, http://www.fda.gov/cder/ogd/rd/labeling_review_branch.html.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Robert L. West, M.S., R.Ph.
Director Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Portions of the Amoxil®'s package insert labeling.

1, 1

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 65-056

Date of Submission: December 3, 1999

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin Tablets USP, 500 mg and 875 mg

Labeling Deficiencies:

1. CONTAINER: 500 mg and 875 mg – 100s and 500s
 - a. We encourage you to differentiate your drug product strengths by using contrasting colors, boxing or some other means.
 - b. Revise the "Each tablet contains ..." statement to read, "Each tablet contains ___ mg amoxicillin as the trihydrate.
 - c. To be consistent with the innovator's labels, we encourage you to revise the "Usual Dosage ..." statement to read " Usual Dosage: 1 tablet every 12 hours. See package ...".
 - d. Following the storage temperature recommendations delete the word, "between", replace the hyphens with the word "to" add the text, "[See USP]".

2. INSERT
 - a. We encourage you to add the legend "Rx only" to follow the Title.
 - b. General Comments
 - i. We encourage you to use the abbreviation, "mcg" for micrograms instead of "µg".
 - ii. We encourage you to delete the terminal zero following a decimal point, i.e., "3" instead of "3.0", when expressing a range of doses.
 - c. DESCRIPTION

Add the following as the last sentence of the first paragraph:

The structural formula is:
 - d. CLINICAL PHARMACOLOGY

Revise the first five paragraphs of this section to be in accord with the attached labeling of the reference listed drug, Amoxil®, with the following exceptions:

 - First paragraph

... investigated. The 875 mg formulation ... However, food effect ... the 500 mg formulation.
 - Second paragraph

Orally administered doses of 500 mg ...

- Delete the paragraph, "Amoxicillin chewable ... respectively".
- Delete the paragraph, "Oral administration of single doses of 400 mg ... data" and the associated table.

e. PRECAUTIONS

i. Drug Interactions

Revise this subsection to be in accord with the attached labeling of the reference listed drug, Amoxil®.

ii. Drug/Laboratory Test Interactions

Delete the text "(e.g., Tes-Tape®)".

f. DOSAGE AND ADMINISTRATION

Revise this section to be in accord with the attached labeling of the reference listed drug, Amoxil®.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes, http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Portions of the Amoxil®'s package insert labeling.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23			
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

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, by SmithKline Beecham Pharmaceuticals, approved 5/11/99 and issued 4/99

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

10. Bioavailability/Bioequivalence - pending

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 65-056
Date of Submission: June 30, 2000
Applicant's Name: Teva Pharmaceuticals USA
Established Name: Amoxicillin Tablets USP, 500 mg and 875 mg
Labeling Deficiencies:

1. INSERT

a. General Comment

Portion of your insert labeling require further revisions due to the approval of the reference listed drug, "Amoxil®" insert labeling on May 16, 2000.

b. CLINICAL PHARMACOLOGY (Microbiology)

To be consistent with the reference listed drug and to improve the promptness of locating a microorganism, we encourage you to list the microorganisms in a column instead of side-by-side.

c. ADVERSE REACTIONS

i. Liver

Revise this subsection to be consistent with the attached insert labeling of the reference listed drug, Amoxil®.

ii. Hemic and Lymphatic Systems

Revise this subsection to be consistent with the attached insert labeling of the reference listed drug, Amoxil®.

d. DOSAGE AND ADMINISTRATION (Adults and pediatric patients >3 months

Revise this subsection to be consistent with the attached insert labeling of the reference listed drug, Amoxil®.

Please revise your insert labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

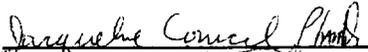
Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes, http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.

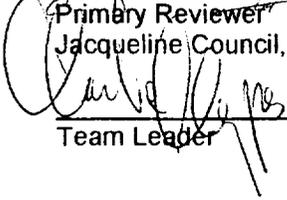
11. Labeling Issue:

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 marketing 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.

Date of Review: 2/14/2000



Primary Reviewer
Jacqueline Council, Pharm.D.


Team Leader

2-29-2000

Date

7/3/00

Date

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Richman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Portions of the Amoxil®'s package insert labeling.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23			
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-056

CORRESPONDENCE



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road
PO BOX 904
Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive
PO BOX 247
Kulpsville, PA 19443

Phone: (215) 256-8400
FAX: (215) 721-9669

Phone: (215) 256-8400
FAX: (215) 256-7855

August 30, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT

N/A F

ANDA #65-056
AMOXICILLIN TABLETS USP, 500 mg and 875 mg
TELEPHONE AMENDMENT - RESPONSE TO AUGUST 28, 2000 AND AUGUST 29, 2000
TELEPHONE CONVERSATIONS

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA in response to comments set forth in an August 28, 2000 telephone conversation with Mark Anderson and the Review Chemist and on August 29, 2000 with Richard Adams and the Review Chemist.

Based on these discussions, Teva has reduced the stability water specification to be the same as the release specification. Please find the revised Finished Product Procedures Manual (Version 2.2) and Finished Product Stability Protocol for your review (Attachments 1 & 2, respectively). While the impurity specifications listed on page 1841 of our original application contained the drug substance manufacturer's stability limits of *Total* we do not intend to accept material which does not comply with Teva USA's limits of *Total* as listed in our laboratory procedure manual for the bulk drug.

It is Teva Pharmaceutical USA's opinion that the information provided herein represents a complete response to all of the Agency's comments presented in the August 28, 2000 and August 29, 2000 telephone conversations. This information is submitted for your continued review and approval. If there are any further questions, please do not hesitate to contact me at (215) 591-3142 or facsimile at (215) 591-8812.

Sincerely,

Deborah A. Jaskot
Executive Director, Regulatory Affairs
DAJ/brb
Enclosures





Noted:
① To Jackie Council
② To Ruth Gonupis
M Anderson
7/7/00

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
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Phone: (215) 256-8400
FAX: (215) 721-9669

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

June 30, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

FACSIMILE AMENDMENT

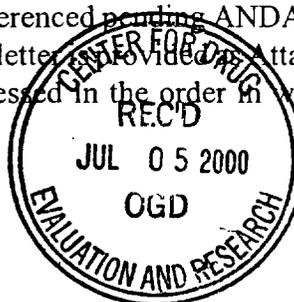
NDA ORIG AMENDMENT

N/FA

ANDA #65-056
AMOXICILLIN TABLETS USP, 500 mg and 875 mg
FACSIMILE AMENDMENT - RESPONSE TO REVIEW LETTER DATED JUNE 5, 2000

Dear Mr. Buehler:

We submit herewith a Facsimile Amendment to the above referenced pending ANDA in response to your letter of June 5, 2000. A copy of the June 5, 2000 review letter is provided as Attachment 1. The deficiencies presented in the aforementioned letter are addressed in the order in which they were presented.



I. Chemistry

A. Deficiencies

1.

2.

1
1
1

B.

A
C

2. [unclear] an alternative method for identification of

II. Labeling

Final printed labels, insert, and a side-by-side comparison which incorporate revisions from deficiency comments are enclosed as Attachment 4. With regard to comment 1.a., please note that different colors are used on the container labels for the different strengths in order to easily differentiate them. Regarding comment 1.b., we have made your requested change, however, we have modified the wording slightly based on TEVA Pharmaceuticals USA format. Regarding comment 2.a., based on TEVA Pharmaceuticals USA format and recently approved labeling for other products, "Rx only" has not been included in our insert.

III. Bioequivalency

We have previously incorporated the comments presented by the Division of Bioequivalence into our testing. We note that a food-effect study is not required for drug products containing

ANDA #65-056

AMOXICILLIN TABLETS USP, 500 mg and 875 mg

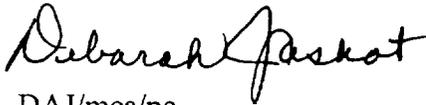
FACSIMILE AMENDMENT - RESPONSE TO REVIEW LETTER DATED JUNE 5, 2000

PAGE 3 of 3

only amoxicillin. Additionally we note that the bioequivalency comments provided are preliminary and are subject to revision after review of the entire application.

The information provided herein represents, in our opinion, a complete response to your letter of June 5, 2000 and is submitted towards the continued review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or by facsimile at (215) 256-8105.

Sincerely,



DAJ/mea/pe

Enclosures

29-03
-1-00
21
TEVA
Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

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Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

NDA ORIG AMENDMENT

N/AB

February 29, 2000

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Hetro Park North II
500 Standish Place, Room 150
Rockville, MD 20855-2773

**BIOEQUIVALENCE
TELEPHONE AMENDMENT**

ANDA #65-056
MOXICILLIN TABLETS USP, 500 mg and 875 mg
BIOEQUIVALENCE TELEPHONE AMENDMENT - RESPONSE TO TELEPHONE
CONVERSATION ON FEBRUARY 22, 2000

Dear Mr. Sporn:

We submit herewith a Bioequivalence Telephone Amendment to the above-referenced pending ANDA in accordance with a telephone conversation with Ms. Jennifer Fan from the Division of Bioequivalence on February 22, 2000. Specifically, per that conversation, we are providing individual patient plasma concentration plots for the Fed Study.

This information is submitted for your review and approval of ANDA 65-056. If you have any questions, do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8405.

Sincerely,

Deborah Jaskot

J/mea
Enclosures



29-80
-100
2/



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

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Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

NDA ORIG AMENDMENT

N/AB

February 29, 2000

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Hetro Park North II
500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE
TELEPHONE AMENDMENT

NDA #65-056
MOXICILLIN TABLETS USP, 500 mg and 875 mg
BIOEQUIVALENCE TELEPHONE AMENDMENT - RESPONSE TO TELEPHONE
CONVERSATION ON FEBRUARY 22, 2000

Dear Mr. Sporn:

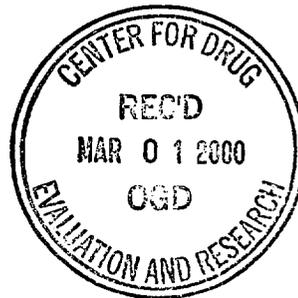
We submit herewith a Bioequivalence Telephone Amendment to the above-referenced pending ANDA in accordance with a telephone conversation with Ms. Jennifer Fan from the Division of Bioequivalence on February 22, 2000. Specifically, per that conversation, we are providing individual patient linear plasma concentration plots for the Fed Study.

This information is submitted for your review and approval of ANDA 65-056. If you have any questions, do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8405.

Sincerely,

Deborah Jaskot

J/mea
Enclosures





Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
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TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

BIOEQUIVALENCE

February 14, 2000

NDA ORIG AMENDMENT

N/A B

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**BIOEQUIVALENCE
TELEPHONE AMENDMENT**

ANDA #65-056
AMOXICILLIN TABLETS USP, 500 mg and 875 mg
BIOEQUIVALENCE TELEPHONE AMENDMENT - RESPONSE TO TELEPHONE
CONVERSATION ON FEBRUARY 7, 2000

Dear Mr. Sporn:

We submit herewith a Bioequivalence Telephone Amendment to the above-referenced pending ANDA in accord with a telephone conversation with Ms. Jennifer Fan from the Division of Bioequivalence on February 7, 2000. Specifically, per that conversation, we are providing individual patient linear plasma concentration plots for the Fasted Study.

This information is submitted for your review and approval of ANDA 65-056. If you have further questions, do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

DAJ/mea
Enclosures



ANDA 65-056

Teva Pharmaceutical USA
Attention: Deborah Jaskot
1510 Delp Drive
Kulpsville, PA 19443
|||||

JAN 27 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated December 21, 1999 and your correspondence dated December 21, 1999.

NAME OF DRUG: Amoxicillin Tablets USP, 500 mg and 875 mg

DATE OF APPLICATION: December 3, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 6, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,



Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program
Support
Office of Generic Drugs
Center for Drug Evaluation and
Research

ANDA
CC:

FILED IN 100-100000-1

..... of RSR  _date 1/25/00
_date 1/24/00
_date



65-056

Corporate Headquarters:

TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Phone: (215) 256 8400
FAX: (215) 721 9669

Corresponding Address:

TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
FAX: (215) 256 7855

December 3, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
AMOXICILLIN TABLETS USP, 500 mg and 875 mg

Dear Mr. Sporn:

We submit herewith an abbreviated new drug application for the drug product Amoxicillin Tablets USP, 500 mg and 875 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 15 volumes; 7 for the archival copy and 8 for the review copy.

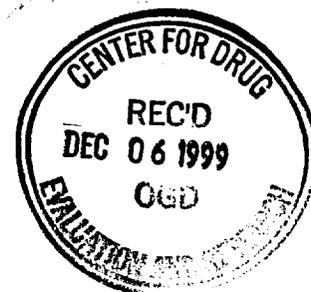
The application contains a full report of 2 *in vivo* bioequivalence studies. These studies compared Amoxicillin Tablets USP, 875 mg manufactured by TEVA Pharmaceuticals USA to the reference listed drug, Amoxil[®] Tablets, 875 mg, under both fasting and post-prandial conditions.

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 256-8400, ext. 5249, or by facsimile at (215) 256-8105.

Sincerely,



DAJ/mea
Enclosures





Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:

TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

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Toll Free: (888) TEVA USA
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December 21, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC

ANDA # 65-056
AMOXICILLIN TABLETS USP, 500 mg and 875 mg
NEW CORRESPONDENCE

Dear Mr. Sporn:

We submit herewith an amendment to the above-referenced pending ANDA in accord with a telephone communication from Emily Thomas of your office and Philip Erickson on December 21, 1999. Specifically, at her request, we are providing the quantitative formulation of the
: from

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 256-8400, ext. 5249, or by facsimile at (215) 256-8105

Sincerely,

Deborah Jaskot

DAJ/mea
Enclosures

