CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-162

Name: Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg (base) / 5 mL

Sponsor: TEVA Pharmaceuticals USA

Approval Date: March 12, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-162

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-162

APPROVAL LETTER

ANDA 65-162

MAR 12 2004

TEVA Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 27, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg (base)/5 mL. 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 November 6, and November 13, 2003; and January 9, and February 17, 2004.

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 and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg (base)/5 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Augmentin® ES-600 for Oral Suspension, 600 mg/42.9 mg (base)/ 5 mL, of GlaxoSmithKline). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A 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 final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 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 FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 3/12/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-162
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:

HFD-623/S.Zuk/3/04/04 S. Zuk 3/8/04
HFD-643/R.Adams/3/05/04 R.C. Adams 3/8/04
HFD-617/M.Anderson/3/05/04 M Anderson 3/9/04
HFD-613/J.Council/3/04/04 Park 3/5/04 for
HFD-613/L.Golson/3/05/04 3/8/04

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F/T by: mda/3/5/04

conc satisfactory
3/11/04

Robert L West
3/12/2004

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-162

APPROVED LABELING

ENLARGED TO 120%
BY FOIA STAFF

NDC 0093-8675-73

AMOXICILLIN AND CLAVULANATE POTASSIUM

65-162

For Oral Suspension, USP

***600 mg/42.9 mg per 5 mL**

*When reconstituted, each 5 mL contains:

AMOXICILLIN, as the trihydrate	600 mg
CLAVULANIC ACID, as clavulanate potassium	42.9 mg

Phenylketonurics: Contains phenylalanine 1.4 mg per 5 mL.

See package insert for full prescribing information.

℞ only

100 mL (when reconstituted)

TEVA

Usual Dosage: Administer every 12 hours.

Directions for mixing:

1. Tap bottle until all powder flows freely.
   ADD **85 mL** of WATER IN TWO PARTS.
2. Add approximately 2/3 of the water for reconstitution.
   Shake vigorously.
3. Add remaining water. Shake vigorously.

Keep tightly closed. Shake well before using. Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days.

Net contents: Equivalent to 12 g amoxicillin and 0.858 g clavulanic acid.

The potassium content per 5 mL is 0.23 mEq.

Use only if inner seal is intact.

Prior to reconstitution store dry powder at 20°-25°C (68°-77°F). [See USP Controlled Room Temperature].

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

Iss. 2/2004

Manufactured By:
Novopharm Limited
Toronto, Canada M1B 2K9

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

APPROVED

MAR 12 2004

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0093-8675-73

9

APPROVAL

65-162

AMOXICILLIN CLAVULANATE POTASSIUM

AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP, 600 mg/42.9 mg per 5 mL

℞ only

8675

ENLARGED TO 115% BY FOIA STAFF

PANELS 1 AND 2 OF 6

AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP, 600 mg/42.9 mg per 5 mL

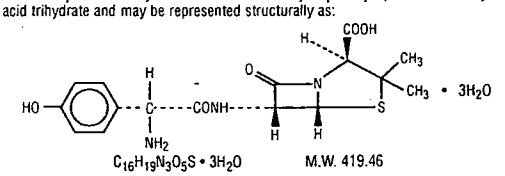
8675

℞ only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Amoxicillin and Clavulanate Potassium for Oral Suspension USP and other antibacterial drugs, Amoxicillin and Clavulanate Potassium for Oral Suspension USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Amoxicillin and Clavulanate Potassium for Oral Suspension USP is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. Chemically, amoxicillin is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate and may be represented structurally as:



$C_{16}H_{19}N_3O_5S \cdot 3H_2O$ M.W. 419.46

Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. Chemically clavulanate potassium is potassium (Z)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate and may be represented structurally as:

$C_8H_8KNO_5$ M.W. 237.25

MAR 12 2004

Each 5 mL of Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL contains 600 mg amoxicillin as the trihydrate and 42.9 mg clavulanic acid as the potassium salt (clavulanate potassium). The potassium content per 5 mL is 0.23 mEq.

Inactive Ingredients: Powder for Oral Suspension - aspartame*, 8K77 spray dried raspberry 954 flavor, citric acid, colloidal silicon dioxide, mannitol, hypromellose, PB82 spray dried orange 739 flavor, sodium citrate, sodium saccharin and xanthan gum.

*See **PRECAUTIONS**-Information for Patients/Phenylketonurics.

CLINICAL PHARMACOLOGY

The pharmacokinetics of amoxicillin and clavulanate were determined in a study of nineteen pediatric patients, aged 8 months to 11 years, given amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension at an amoxicillin dose of 45 mg/kg q12h with snack or meal. The mean plasma amoxicillin and clavulanate pharmacokinetic parameter values are listed in the following table.

Table 1. Mean (±SD) Plasma Amoxicillin and Clavulanate Pharmacokinetic Parameter Values Following Administration of 45 mg/kg of Amoxicillin and Clavulanate Potassium 600 mg/42.9 mg per 5 mL Suspension Every 12 Hours to Pediatric Patients

Parameter*	Amoxicillin	Clavulanate
C_{max} (mcg/mL)	15.7 ± 7.7	1.7 ± 0.9
T_{max} (h)	2.0 (1.0 – 4.0)	1.1 (1.0 – 4.0)
AUC_{0-t} (mcg • h/mL)	59.8 ± 20.0	4.0 ± 1.9
$T_{½}$ (h)	1.4 ± 0.3	1.1 ± 0.3
CL/F (L/h/kg)	0.9 ± 0.4	1.1 ± 1.1

*Arithmetic mean ± standard deviation, except T_{max} values which are medians (ranges).

The effect of food on the oral absorption of amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension has not been studied.

Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of 10 mL of amoxicillin and clavulanate potassium 250 mg/62.5 mg per 5 mL suspension.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Neither component in amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension is highly protein bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Oral administration of a single dose of amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension at 45 mg/kg (based on the amoxicillin component) to pediatric patients, aged 9 months to 8 years, yielded the following pharmacokinetic data for amoxicillin in plasma and middle ear fluid (MEF):

Table 2. Amoxicillin Concentrations in Plasma and Middle Ear Fluid Following Administration of 45 mg/kg of Amoxicillin and Clavulanate Potassium 600 mg/42.9 mg per 5 mL suspension to Pediatric Patients

Timepoint		Amoxicillin concentration in plasma (mcg/mL)	Amoxicillin concentration in MEF (mcg/mL)
1 hour	mean	7.7	3.2
	median	9.3	3.5
	range	1.5 – 14.0	0.2 – 5.5
		(n = 5)	(n = 4)
2 hour	mean	15.7	3.3
	median	13.0	2.4
	range	11.0 – 25.0	1.9 – 6
		(n = 7)	(n = 5)
3 hour	mean	13.0	5.8
	median	12.0	6.5
	range	5.5 – 21.0	3.9 – 7.4
		(n = 5)	(n = 5)

Dose administered immediately prior to eating.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

MICROBIOLOGY

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and, therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance.

The clavulanic acid component in amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics. Thus, amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension possesses the distinctive properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

Amoxicillin/clavulanic acid 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
Streptococcus pneumoniae (including isolates with penicillin MICs ≤ 2 mcg/mL)

Aerobic Gram-negative Microorganisms
Haemophilus influenzae (including β-lactamase-producing strains)
Moraxella catarrhalis (including β-lactamase-producing strains)

The following *in vitro* data are available, but their clinical significance is unknown.

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for amoxicillin/clavulanic acid. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive Microorganisms
Staphylococcus aureus (including β-lactamase-producing strains)
Streptococcus pyogenes

NOTE: Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

NOTE: *S. pyogenes* do not produce β-lactamase and, therefore, are susceptible to amoxicillin alone. Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to *S. pyogenes*.

Susceptibility Testing

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.[1,2] Standardized procedures are based on a dilution method (broth for *S. pneumoniae* and *H. influenzae*) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to the following criteria:

For testing *Streptococcus pneumoniae*[a]:

MIC (mcg/mL)	Interpretation
≤ 2/1	Susceptible (S)
4/2	Intermediate (I)
≥ 8/4	Resistant (R)

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

For testing *Haemophilus influenzae*[b]:

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

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Test Medium (HTM).[2]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration 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 that 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 amoxicillin/clavulanate potassium powder should provide the following MIC values:

Microorganism	MIC Range (mcg/mL)[c]
Escherichia coli ATCC 35218 (*H. influenzae* quality control)	4 to 16
Haemophilus influenzae[d] ATCC 49247	2 to 16
Streptococcus pneumoniae[e] ATCC 49619	0.03 to 0.12

[c] Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

[d] This quality control range is applicable to *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM[2].

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) disk should be interpreted according to the following criteria:

For *H. influenzae*[f]:

Zone Diameter (mm)	Interpretation
≥ 20	Susceptible (S)
≤ 19	Resistant (R)

[f] These zone diameter standards are applicable only to tests conducted with *Haemophilus* spp. using HTM.[2]

NOTE: Beta-lactamase-negative, ampicillin-resistant *H. influenzae* strains must be considered resistant to amoxicillin/clavulanic acid.

For *Streptococcus pneumoniae:*

Susceptibility of *S. pneumoniae* should be determined using a 1 mcg oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible to amoxicillin/clavulanic acid.[g] An amoxicillin/clavulanic acid MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤ 19 mm.

[g] These zone diameter standards for *S. pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.[2]

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for amoxicillin/clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 mcg amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 35218 (*H. influenzae* quality control)	18 to 22
Haemophilus influenzae[h] ATCC 49247	15 to 23

[h] This quality control limit applies only to tests conducted with *H. influenzae* ATCC 49247 using HTM.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Amoxicillin and Clavulanate Potassium for Oral Suspension, USP and other antibacterial drugs, Amoxicillin and Clavulanate Potassium for Oral Suspension, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL is indicated for the treatment of pediatric patients with recurrent or persistent acute otitis media due to *S. pneumoniae* (penicillin MICs ≤ 2 mcg/mL), *H. influenzae* (including β-lactamase-producing strains), or *M. catarrhalis* (including β-lactamase-producing strains) characterized by the following risk factors:

- antibiotic exposure for acute otitis media within the preceding 3 months, and either of the following:

- age ≤ 2 years

- daycare attendance

[See **CLINICAL PHARMACOLOGY, MICROBIOLOGY**.]

Note: Acute otitis media due to *S. pneumoniae* alone can be treated with amoxicillin. Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL is not indicated for the treatment of acute otitis media due to *S. pneumoniae* with penicillin MIC ≥ 4 mcg/mL.

Bacteriological studies to determine the causative organisms and their susceptibility to Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL should be performed, when indicated. Therapy may be instituted prior to obtaining the results from these studies when there is reason to believe the infection may involve both *S. pneumoniae* (penicillin MIC ≤ 2 mcg/mL) and the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted appropriately.

CONTRAINDICATIONS

Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of amoxicillin and clavulanate potassium-associated cholestatic jaundice/hepatic dysfunction.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. 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 AND CLAVULANATE POTASSIUM 600 MG/42.9 MG PER 5 ML, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN AND CLAVULANATE POTASSIUM 600 MG/42.9 MG PER 5 ML SHOULD BE DISCONTINUED AND THE 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/clavulanate potassium, and has ranged 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 one 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.

Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin/clavulanate potassium is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS**-*Liver*.)

PRECAUTIONS

General

Prescribing Amoxicillin and Clavulanate Potassium for Oral Suspension, USP in the absence of a proven infection or a prophylactic indication is unlikely to provide benefit to the patient and increase the risk of the development of drug-resistant bacteria.

While amoxicillin/clavulanate possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable if therapy is for longer than the drug is approved for administration.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Information for the Patients

Patients should be counseled that antibacterial drugs including Amoxicillin and Clavulanate Potassium for Oral Suspension, USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Amoxicillin and Clavulanate Potassium for Oral Suspension, USP is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of the therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Amoxicillin and Clavulanate Potassium for Oral Suspension, USP or other antibacterial drugs in the future.

Amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension should be taken every 12 hours with a meal or snack to reduce the possibility of gastrointestinal upset. If diarrhea develops and is severe or lasts more than 2 or 3 days, call your doctor.

PANEL 3 OF 6

PANELS 4 AND 5 OF 6

The entire prescribed course of treatment should be completed, even if your child begins to feel better after a few days. Keep suspension refrigerated. Shake well before using. When dosing a child with amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension (liquid), use a dosing spoon or medicine dropper. Be sure to rinse the spoon or dropper after each use. Bottles of amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension may contain more liquid than required. Follow your doctor's instructions about the amount to use and the days of treatment your child requires. Discard any unused medicine.

Phenylketonurics: Each 5 mL Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL contains 1.4 mg phenylalanine.

Drug Interactions
Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension and allopurinol administered concurrently.

In common with other broad-spectrum antibiotics, amoxicillin/clavulanate may reduce the efficacy of oral contraceptives.

Drug/Laboratory Test Interactions
Oral administration of amoxicillin and clavulanate potassium will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension, 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 and therefore amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate carcinogenic potential. The mutagenic potential of amoxicillin and clavulanate potassium was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations. Amoxicillin and clavulanate potassium at oral doses of up to 1,200 mg/kg/day (5.7 times the maximum adult human dose based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Teratogenic Effects
Pregnancy (Category B)
Reproduction studies performed in pregnant rats and mice given amoxicillin and clavulanate potassium at oral dosages up to 1,200 mg/kg/day (4.9 and 2.8 times the maximum adult human oral dose based on body surface area, respectively), revealed no evidence of harm to the fetus due to amoxicillin and clavulanate potassium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery
Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of amoxicillin and clavulanate potassium 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. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with amoxicillin and clavulanate potassium may be associated with an increased risk of necrotizing enterocolitis in neonates.

Nursing Mothers
Ampicillin-class antibiotics are excreted in human milk; therefore, caution should be exercised when amoxicillin and clavulanate potassium is administered to a nursing woman.

Pediatric Use
Safety and efficacy of amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension in infants younger than 3 months of age have not been established. Safety and efficacy of amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension have been demonstrated for treatment of acute otitis media in infants and children 3 months of age to 12 years of age (see **Description of Clinical Studies**).

ADVERSE REACTIONS
Amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension is generally well tolerated. The majority of side effects observed in pediatric clinical trials of acute otitis media were either mild or moderate, and transient in nature; 4.4% of patients discontinued therapy because of drug-related side effects. The most commonly reported side effects with probable or suspected relationship to amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension were contact dermatitis, i.e., diaper rash (3.5%), diarrhea (2.9%), vomiting (2.2%), moniliasis (1.4%), and rash (1.1%). The most common adverse experiences leading to withdrawal that were of probable or suspected relationship amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension were diarrhea (2.5%) and vomiting (1.4%).

The following adverse reactions have been reported for ampicillin-class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See **WARNINGS**.)

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized exanthematous pustulosis and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See **WARNINGS**.)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with amoxicillin and clavulanate potassium. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely.

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. A slight thrombocytosis was noted in less than 1% of the patients treated with amoxicillin and clavulanate potassium. There have been reports of increased prothrombin time in patients receiving amoxicillin and clavulanate potassium and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

Miscellaneous: Tooth discoloration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discoloration as it can usually be removed by brushing.

OVERDOSAGE
Following overdosage, patients have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity, or drowsiness have also been observed in a small number of patients.

In the case of overdosage, discontinue amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension, 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.[4]

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 both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION
Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL does not contain the same amount of clavulanic acid (as the potassium salt) as any of the other amoxicillin and clavulanate potassium suspensions. Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL contains 42.9 mg of clavulanic acid per 5 mL whereas amoxicillin and clavulanate potassium, 200 mg/28.5 mg per 5 mL suspension contains 28.5 mg of clavulanic acid per 5 mL and the 400 mg/57 mg per 5 mL suspension contains 57 mg of clavulanic acid per 5 mL. Therefore, the amoxicillin and clavulanate potassium 200 mg/28.5 mg per 5 mL and 400 mg/57 mg per 5 mL suspensions should *not* be substituted for Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL, as they are not interchangeable.

Dosage
Pediatric patients 3 months and older: Based on the amoxicillin component (600 mg per 5 mL), the recommended dose of Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL is 90 mg/kg/day divided every 12 hours, administered for 10 days (see chart below).

Body Weight (kg)	Volume of Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL providing 90 mg/kg/day
8	3 mL twice daily
12	4.5 mL twice daily
16	6 mL twice daily
20	7.5 mL twice daily
24	9 mL twice daily
28	10.5 mL twice daily
32	12 mL twice daily
36	13.5 mL twice daily

Pediatric patients weighing 40 kg and more: Experience with Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL formulation in this group is not available.

Adults: Experience with Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL formulation in adults is not available and adults who have difficulty swallowing should not be given Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL in place of the amoxicillin and clavulanate potassium 500 mg or 875 mg tablet.

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See **WARNINGS**.)

DIRECTIONS FOR MIXING ORAL SUSPENSION
Prepare a suspension at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL

Bottle Size	Amount of Water Required for Suspension
100 mL	85 mL

Each teaspoonful (5 mL) will contain 600 mg amoxicillin as the trihydrate and 42.9 mg of clavulanic acid as the potassium salt.

Note: SHAKE ORAL SUSPENSION WELL BEFORE USING.

Administration
To minimize the potential for gastrointestinal intolerance, Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL should be taken at the start of a meal. Absorption of clavulanate potassium may be enhanced when amoxicillin and clavulanate potassium is administered at the start of a meal.

HOW SUPPLIED
The color of the dry powder for Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg per 5 mL is white to off-white powder.

Each 5 mL of reconstituted orange-raspberry-flavored suspension contains 600 mg amoxicillin and 42.9 mg clavulanic acid as the potassium salt.

NDC 0093-8675-73 ..... 100 mL Bottle

STORAGE
Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days. Prior to reconstitution store dry powder at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Dispense in original container.

Description of Clinical Studies
Two clinical studies were conducted in pediatric patients with acute otitis media.

A non-comparative, open-label study assessed the bacteriologic and clinical efficacy of amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension (90/6.4 mg/kg/day, divided every 12 hours) for 10 days in 521 pediatric patients (ages 3 to 50 months) with acute otitis media. The primary objective was to assess bacteriological response in children with acute otitis media due to *S. pneumoniae* with amoxicillin/clavulanic acid MICs of 4 mcg/mL. The study sought the enrollment

of patients with the following risk factors: failure of antibiotic therapy for acute otitis media in the previous 3 months, history of recurrent episodes of acute otitis media, ≤ 2 years of age, or daycare attendance. Prior to receiving amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension, all patients had tympanocentesis to obtain middle ear fluid for bacteriological evaluation. Patients from whom *S. pneumoniae* (alone or in combination with other bacteria) was isolated had a second tympanocentesis 4 to 6 days after the start of therapy. Clinical assessments were planned for all patients during treatment (4-6 days after starting therapy), as well as 2-4 days post-treatment and 15-18 days post-treatment. Bacteriological success was defined as the absence of the pretreatment pathogen from the on therapy tympanocentesis specimen. Clinical success was defined as improvement or resolution of signs and symptoms. Clinical failure was defined as lack of improvement or worsening of signs and/or symptoms at any time following at least 72 hours of amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension; patients who received an additional systemic antibacterial drug for otitis media after 3 days of therapy were considered clinical failures. Bacteriological eradication on therapy (day 4-6 visit) in the per protocol population is summarized in the following table:

Table 3. Bacteriologic eradication rates in the per protocol population

Pathogen	Bacteriologic eradication on therapy n/N	%	95% CI*
All *S. pneumoniae*	121/123	98.4	(94.3, 99.8)
S. pneumoniae with penicillin MIC = 2 mcg/mL	19/19	100	(82.4, 100.0)
S. pneumoniae with penicillin MIC = 4 mcg/mL	12/14	85.7	(57.2, 98.2)
H. influenzae	75/81	92.6	(84.6, 97.2)
M. catarrhalis	11/11	100	(71.5, 100.0)

*CI = confidence intervals; 95% CIs are not adjusted for multiple comparisons.

Clinical assessments were made in the per protocol population 2-4 days post-therapy and 15-18 days post-therapy. Patients who responded to therapy 2-4 days post-therapy were followed for 15-18 days post-therapy to assess them for acute otitis media. Nonresponders at 2-4 days post-therapy were considered failures at the latter timepoint.

Table 4. Clinical assessments in the per protocol population (includes *S. pneumoniae* patients with penicillin MICs = 2 or 4 mcg/mL*)

Pathogen	2-4 days post-therapy (primary endpoint) n/N	%	95% CI†
All *S. pneumoniae*	122/137	89.1	(82.6, 93.7)
S. pneumoniae with penicillin MIC = 2 mcg/mL	17/20	85.0	(62.1, 96.8)
S. pneumoniae with penicillin MIC = 4 mcg/mL	11/14	78.6	(49.2, 95.3)
H. influenzae	141/162	87.0	(80.9, 91.8)
M. catarrhalis	22/26	84.6	(65.1, 95.6)
	15-18 days post-therapy‡ (secondary endpoint)		
	n/N	**%**	**95% CI†**
All *S. pneumoniae*	95/136	69.9	(61.4, 77.4)
S. pneumoniae with penicillin MIC = 2 mcg/mL	11/20	55.0	(31.5, 76.9)
S. pneumoniae with penicillin MIC = 4 mcg/mL	5/14	35.7	(12.8, 64.9)
H. influenzae	106/156	67.9	(60.0, 75.2)
M. catarrhalis	14/25	56.0	(34.9, 75.6)

‡ Clinical assessments at 15-18 days post-therapy may have been confounded by viral infections and new episodes of acute otitis media with time elapsed post-treatment.

† CI = confidence intervals; 95% CIs are not adjusted for multiple comparisons.

* *S. pneumoniae* strains with penicillin MICs of 2 or 4 mcg/mL are considered resistant to penicillin.

In the intent-to-treat analysis, overall clinical outcomes at 2-4 days and 15-18 days post-treatment in patients with *S. pneumoniae* with penicillin MIC = 2 mcg/mL and 4 mcg/mL were 29/41 (71%) and 17/41 (41.5%), respectively.

In the intent-to-treat population of 521 patients, the most frequently reported adverse events were vomiting (6.9%), fever (6.1%), contact dermatitis (i.e., diaper rash) (6.1%), upper respiratory tract infection (4.0%), and diarrhea (3.8%). Protocol-defined diarrhea (i.e., three or more watery stools in one day or two watery stools per day for two consecutive days as recorded on diary cards) occurred in 12.9% of patients.

A double-blind, randomized, clinical study compared amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension (90/6.4 mg/kg/day, divided every 12 hours) to amoxicillin and clavulanate potassium (45/6.4 mg/kg/day, divided every 12 hours) for 10 days in 450 pediatric patients (ages 3 months to 12 years) with acute otitis media. The primary objective of the study was to compare the safety of amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension to amoxicillin and clavulanate potassium. There was no statistically significant difference between treatments in the proportion of patients with one or more adverse events. The most frequently reported adverse events for amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension and the amoxicillin and clavulanate potassium comparator were coughing (11.9% vs. 6.8%), vomiting (6.5% vs. 7.7%), contact dermatitis (i.e., diaper rash, 6.0% vs. 4.8%), fever (5.5% vs. 3.9%), and upper respiratory infection (3.0% vs. 9.2%), respectively. The frequencies of protocol-defined diarrhea with amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension (11.1%) and amoxicillin and clavulanate potassium (9.4%) were similar (95% confidence interval on difference: -4.2% to 7.7%). Only 2 patients in the amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL suspension group and 1 patient in the amoxicillin and clavulanate potassium group were withdrawn due to diarrhea.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2. NCCLS, Wayne, PA, Jan. 2000.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing -Eleventh Informational Supplement. Approved Standard NCCLS Document M100-S11, Vol. 21, No. 1. NCCLS, Wayne, PA, Jan. 2001.
3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1. NCCLS, Wayne, PA, Jan. 2000.
4. Swanson-Biearman B, Dean BS, Lopez G, Krenzelok EP. The effects of penicillin and cephalosporin ingestions in children less than 6 years of age. *Vet Hum Toxicol* 1988; 30:66-67.

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Toronto, Canada M1B 2K9

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

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PANEL 6 OF 6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-162

LABELING REVIEW(S)

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

ANDA Number: 65-162

Date of Submission: December 27, 2002

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
600 mg/42.9 mg*
*(clavulanate acid equivalent)

Labeling Deficiencies:

1. CONTAINER: 600 mg/42.9 mg per 5 mL – 100 mL

   a. Main Panel

      i. Revise " [redacted] " to read "*600 mg/42.9 mg per 5 mL".

      ii. Place an asterisk immediately prior to the "*When reconstituted, ..." statement.

      iii. Relocate the "Usual Dosage" statement to the side panel.

      iv. Correct the spelling of the word "shake".

   b. Side Panel

      i. Directions for mixing

      The recommended volume of water to be added for reconstitution differs from your "Directions for mixing" found in the DOSAGE AND ADMINISTRATION section of your insert labeling. Please revise and/or comment.

      ii. Include the potassium content of your drug product "per 5 mL".

      iii. In the sentence following the "Net contents" add the word "if" between the words "only" and "inner".

      iv. Revise the storage recommendations to read, "Prior to reconstitution store dry powder at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]".

2. INSERT

   a. General Comments

      i. Throughout the text delete the terminal zero, "1" instead of "1.0".

      ii. Use the abbreviation "mcg" for microorganisms instead of "—" throughout the text of the insert.

b. DESCRIPTION

i. First paragraph

A) In the first sentence print "and" instead of "And".

B) "Amoxicillin is an analog of ..." instead of "[redacted] amoxicillin is an analog of ...".

C) Delete the strength appearing in the first sentence.

ii. Place the following text immediately beneath the structure of clavulanate potassium:

Each 5 mL... contains 600 mg amoxicillin as the trihydrate and 49.5 mg clavulanic acid as the potassium salt (clavulanate potassium). The potassium content per 5 mL is 0.23 mEq.

iii. We note that you list " [redacted] instead of " [redacted] as an inactive ingredient. Please comment and/or revise. In addition, please note that the official title of " [redacted] ' is "hypromellose". We refer you to USP 26/NF21.

c. CLINICAL PHARMACOLOGY

i. Throughout this section, revise " [redacted] to read "600 mg/42.9 mg per 5 mL".

ii. In the second paragraph following Table 1, revise " [redacted] to read "200 mg/28.5 mg per 5 mL.

iii. Revise the fourth paragraph following Table 1 to read "... potassium 600 mg/42.9 mg per 5 mL is highly protein...".

iv. Table 2/Third column

Revise [redacted] to read ""7.7".

d. MICROBIOLOGY

i. Revise the first paragraph to read "potassium ... 600 mg/42.9 mg per 5 mL protects amoxicillin from ...".

ii. Start a new paragraph with the sentence, "The clavulanic acid ..." and revise to read, "...potassium 600 mg/42.9 mg per 5 mL possesses the distinctive ...".

iii. Aerobic Gram-positive Microorganisms/Susceptibility Testing/Dilution Techniques

A) For testing *Streptococcus pneumoniae*

Print "*Streptococcus pneumoniae*" in italic print.

B) For testing *Haemophilus influenzae*

Print "*Haemophilus influenzae*" and "*Haemophilus*" [two locations] in italic print.

e. Throughout the following sections revise "Amoxicillin and clavulanate potassium" to read "Amoxicillin and clavulanate potassium 600 mg/42.9 mg per 5 mL".

- INDICATIONS AND USAGE
- CONTRAINDICATIONS
- WARNINGS
- PRECAUTIONS
- ADVERSE REACTIONS
- OVERDOSAGE

f. PRECAUTIONS

i. To be consistent with your other subsection headings print "*General, Information for the Patients* and *Phenylketonurics"* in italic print.

ii. In paragraph three, print the subsection "*Information for the Patients"* as a separate subsection, starting on a separate line.

iii. *Drug Interactions*

Start a new paragraph with the sentence, "The concurrent administration...".

iv. *Drug/Laboratory Test Interactions*

Revise "~~————~~ to read "600 mg/42.9 mg per 5 mL".

v. Labor and Delivery

Add the following as the last sentence:

...will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with amoxicillin and clavulanate potassium may be associated with an increased risk of necrotizing enterocolitis in neonates.

g. ADVERSE REACTIONS/Gastrointestinal

Delete the extra spaces appearing in the text of the second paragraph.

h. DOSAGE AND ADMINISTRATION

i. First paragraph

Revise to read **"... potassium 600 mg/42.9 mg per 5 mL suspension ...potassium 600 mg/42.9 mg per 5 mL suspension...potassium 200 mg/28.5 mg per 5 mL suspension ...the 400 mg/57 mg per 5 mL suspension ...potassium 200 mg/28.5 mg per 5 mL and 400 mg/57 mg per 5 mL suspensions ...potassium 600 mg/42.9 mg suspensions...".**

ii. Revise "[redacted]" to read "600 mg/42.9 mg per 5 mL" in the following subsections.

Dosage
- Pediatric patients 3 months and older
- Pediatric patients weighing 40 kg and more

Adults
- Directions for Mixing Oral Suspension
- Administration

iii. Adults

A) Revise the first sentence to read, "...clavulanate potassium suspension...".

B) Start a new paragraph with the sentence, "Hepatically impaired...".

vi. Directions For Mixing Oral Suspension

A) We acknowledge that you are proposing to only market the 100 mL package size at this time. Therefore, delete the [redacted] from this subsection.

B) See comment 1(b)(i) under CONTAINER.

i. HOW SUPPLIED

i. Revise "[redacted]" to read "600 mg/42.9 mg per 5 mL".

ii. See comment 1(b)(iv) under CONTAINER.

iii. Include the color of the dry powder in your physical description of your drug product.

iv. See comment 1(b)(iv) under CONTAINER.

j. Description of Clinical Studies

Revise "[redacted]" to read "600 mg/42.9 mg per 5 mL".

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

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.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.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels:
Carton Labeling:
Unit Dose Blister Label:
Unit Dose Carton Label:
Professional Package Insert Labeling:
Patient Package Insert Labeling:
Auxiliary Labeling:
Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes No
What is the RLD on the 356(h) form:
NDA Number:
NDA Drug Name:
NDA Firm:
Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA? Yes No
Was this approval based upon an OGD labeling guidance? Yes No
If yes, give date of labeling guidance:
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:
Other Comments:

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 24	x		
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?			
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?			
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?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?*See comment under HOW SUPPLIED.	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 differ from the RLD.	X*		
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?			
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		X	

difference acceptable?			
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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 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?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
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.			

NOTES/QUESTIONS TO THE CHEMIST:

1. Directions for mixing

   The recommended volume of water to be added for reconstitution on the firm's container labels differs from the "Directions for mixing" found in the DOSAGE AND ADMINISTRATION section of the insert labeling. Which is accurate, 85 mL or — mL?

2. Has the firm provided data to support the final concentration after reconstitution, "Amoxicillin and Clavulanate Potassium 600 mg/42.9 mg per 5 mL"?

3. Has the firm provided stability data to support the recommended storage of 10 days in the refrigerator?

4. Is the statement "Contains phenylalanine 1.4 mg per 5 mL" accurate?

5. We plan to request the firm to revise the storage recommendations to read, "Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]".

   Is this consistent with the firm's stability data?

6. The firm indicates that clavulanic acid is produced by the fermentation of "*Steptomyces clavuligerus*". Is this accurate?

FOR THE RECORD:

1. Reference Listed drug: Augmentin-ES-600 (amoxicillin/clavulanate potassium) powder for oral suspension

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
[However, see comment under DESCRIPTION].
[B1.1, p. 8508]

3. Manufacturing Facility:

   Novopharm Limited
   Ontario, Canada
   [Vol. 1.2, p. 8589]

   Distributed by:

   Teva Pharmaceuticals
   North Wales, PA

4. Container/Closure:

   120 mL HDPE round bottle with a CRC.
   [Vol. 1.3, 8743]

5. Storage/Dispense:

   NDA/Insert – Store dry powder at or below 25°C (77°F). Dispense in tightly closed, moisture-proof containers.

6. Package Size:

   NDA – 50 mL, 75 mL , 100 mL and 150 mL bottles
   ANDA – 100 mL

7. Patent/Exclusivity: None

8. Storage/Dispense:

   NDA – Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days. Store at or below 25°C (77°F). Dispense in original container.

   ANDA – Same [See comment to firm.

9. This is the first ANDA for:
   Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
   600 mg/42.9 mg*
   *(clavulanate acid equivalent)

APPEARS THIS WAY
ON ORIGINAL

Date of Review:	8/20/03
Date of Submission:	12/27/03
Primary Reviewer: Jacqueline Council, Pharm.D.	Date: 9-16-03
Team Leader: Captain Lillie Golson	Date: 9/16/03

cc: ANDA: 65-162
DUP/DIVISION FILE
V:firmsnz/ltrs&rev/Teva/65162na1.l
Review

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

ANDA Number: 65-162

Date of Submission: November 13, 2003

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
600 mg/42.9 mg*
*(clavulanate acid equivalent)

Labeling Deficiencies:

1. CONTAINER: 600 mg/42.9 mg per 5 mL – 100 mL

   a. Relocate the "Phenylketonurics:..." statement to appear on the front panel.

   b. As previously requested, revise the storage recommendations to read, "Prior to reconstitution store dry powder at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]".

2. INSERT

   a. General Comments

      We acknowledge your comment regarding the "terminal zero".
      You may retain the terminal zero in the text, except in the DOSAGE AND ADMINISTRATION section.

   b. HOW SUPPLIED

      See comment under CONTAINER.

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

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.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.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels:
Carton Labeling:
Unit Dose Blister Label:
Unit Dose Carton Label:
Professional Package Insert Labeling:
Patient Package Insert Labeling:
Auxiliary Labeling:
Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes No
What is the RLD on the 356(h) form:
NDA Number:
NDA Drug Name:
NDA Firm:
Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA? Yes No
Was this approval based upon an OGD labeling guidance? Yes No
If yes, give date of labeling guidance:
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:
Other Comments:

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 26	x		
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		X	

labeling?			
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?			
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?			
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?		X	
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 differ from the RLD.	X*		
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?			
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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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		X	

container?			
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 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?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
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.			

NOTES/QUESTIONS TO THE CHEMIST:

1. Directions for mixing

   The recommended volume of water to be added for reconstitution on the firm's container labels differs from the "Directions for mixing" found in the DOSAGE AND ADMINISTRATION section of the insert labeling. Which is accurate, 85 mL or — mL?

2. Has the firm provided data to support the final concentration after reconstitution, "Amoxicillin and Clavulanate Potassium 600 mg/42.9 mg per 5 mL"?

3. Has the firm provided stability data to support the recommended storage of 10 days in the refrigerator?

4. Is the statement "Contains phenylalanine 1.4 mg per 5 mL" accurate?

5. We plan to request the firm to revise the storage recommendations to read, "Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]".

   Is this consistent with the firm's stability data?

6. The firm indicates that clavulanic acid is produced by the fermentation of "*Steptomyces clavuligerus*". Is this accurate?

Chemist response:
Here are the answers to your questions.

1. The product is constituted by adding 85 mL of water to 25 g powder. It looks like the insert is incorrect.
2. The firm performed a deliverable volume test to confirm that 100 mL is delivered. The average of 10 bottles was actually 101 mL.
3. The firm routinely tests the constituted product after 10 days of refrigerated storage as part of the stability study.
4. The phenylalanine is present due to aspartame. The 1.4 mg amount of phenylalanine is correct based on the amount of aspartame (2.5 mg).
5. Clavulanate comes from *Steptomyces clavuligerus.*
6. The stability studies were run at 25 +/- 2 degrees C. A storage statement of 20-25 degrees C would be OK.

-----Original Message-----

From: Anderson, Mark D
Sent: Monday, January 12, 2004 3:08 PM
To: Zuk, Susan
Cc: Council, Jacqueline
Subject: FW: 65162

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Reference Listed drug: Augmentin-ES-600/(600mg/42.9) (amoxicillin/clavulanate potassium) powder for oral suspension/ NDA 50755.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
[However, see comment under DESCRIPTION].
[B1.1, p. 8508]

3. Manufacturing Facility:

   Novopharm Limited
   Ontario, Canada
   [Vol. 1.2, p. 8589]

   Distributed by:

   Teva Pharmaceuticals
   North Wales, PA

4. Container/Closure:

   120 mL HDPE round bottle with a CRC.
   [Vol. 1.3, 8743]

5. Package Size:

   NDA – 50 mL, 75 mL , 100 mL and 150 mL bottles
   ANDA – 100 mL

6. Storage/Dispense:

   NDA/Insert – Store dry powder at or below 25°C (77°F). Dispense in tightly closed, moisture-proof containers.

7. Patent/Exclusivity: None

8. Storage/Dispense:

NDA – Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days. Store at or below 25°C (77°F). Dispense in original container.

ANDA – Same [See comment to firm.

9. This is the first ANDA for:
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
600 mg/42.9 mg*
*(clavulanate acid equivalent)

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 1/9/04

Date of Submission: 11/13/03

Primary Reviewer:
Jacqueline Council, Pharm.D.

2-2-04
Date:

Team Leader:
Captain Lillie Golsen

Date: 2/3/04

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cc: ANDA: 65-162
DUP/DIVISION FILE
V:firmsnz/ltrs&rev/Teva/65162na2.l
Review

APPROVAL SUMMARY

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

ANDA Number: 65-162

Date of Submission: February 17, 2004

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
600 mg/42.9 mg*
*(clavulanate acid equivalent)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes :

Container Labels: 100 mL

Satisfactory in final print as of the February 17, 2004 submission.

Professional Package Insert Labeling:

Satisfactory in final print as of the February 17, 2004 submission. [Insert code#8675,lss.2/2004]

Future revisions:
Container: Side panel – Usual Dosage
Revise to read, "Usual Dosage: ...hours. See accompanying prescribing information.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Augmentin-ES-600

NDA Number: 50755

NDA Drug Name: Amoxicillin/clavulanate potassium powder for oral suspension

NDA Firm: GlaxoSmithKline

Date of Approval of NDA Insert and supplement #:S-003 approved 5/12/03..

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: RLD
:

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 26	x		
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?			
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?			
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?		X	
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 differ from the RLD.	X*		
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?			
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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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 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?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
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.			

APPEARS THIS WAY
ON ORIGINAL

NOTES/QUESTIONS TO THE CHEMIST:

1. Directions for mixing

   The recommended volume of water to be added for reconstitution on the firm's container labels differs from the "Directions for mixing" found in the DOSAGE AND ADMINISTRATION section of the insert labeling. Which is accurate, 85 mL or — mL?

2. Has the firm provided data to support the final concentration after reconstitution, "Amoxicillin and Clavulanate Potassium 600 mg/42.9 mg per 5 mL"?

3. Has the firm provided stability data to support the recommended storage of 10 days in the refrigerator?

4. Is the statement "Contains phenylalanine 1.4 mg per 5 mL" accurate?

5. We plan to request the firm to revise the storage recommendations to read, "Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]".

   Is this consistent with the firm's stability data?

6. The firm indicates that clavulanic acid is produced by the fermentation of "*Steptomyces clavuligerus*". Is this accurate?

Chemist response:
Here are the answers to your questions.

1. The product is constituted by adding 85 mL of water to 25 g powder. It looks like the insert is incorrect.
2. The firm performed a deliverable volume test to confirm that 100 mL is delivered. The average of 10 bottles was actually 101 mL.
3. The firm routinely tests the constituted product after 10 days of refrigerated storage as part of the stability study.
4. The phenylalanine is present due to aspartame. The 1.4 mg amount of phenylalanine is correct based on the amount of aspartame (2.5 mg).
5. Clavulanate comes from *Steptomyces clavuligerus.*
6. The stability studies were run at 25 +/- 2 degrees C. A storage statement of 20-25 degrees C would be OK.

-----Original Message-----

From: Anderson, Mark D
Sent: Monday, January 12, 2004 3:08 PM
To: Zuk, Susan
Cc: Council, Jacqueline
Subject: FW: 65162

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Reference Listed drug: Augmentin-ES-600/(600mg/42.9) (amoxicillin/clavulanate potassium) powder for oral suspension/ NDA 50755/S-003 approved 5/12/03 by GlaxoSmithKlline.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
[B1.1, p. 8508]

3. Manufacturing Facility:

   Novopharm Limited
   Ontario, Canada
   [Vol. 1.2, p. 8589]

   Distributed by:

   Teva Pharmaceuticals
   North Wales, PA

4. Container/Closure:

   120 mL HDPE round bottle with a CRC.
   [Vol. 1.3, 8743]

5. Package Size:

   NDA – 50 mL, 75 mL , 100 mL and 150 mL bottles
   ANDA – 100 mL

6. Patent/Exclusivity: None

7. Storage/Dispense:

   NDA – Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days. Store at or below 25°C (77°F). Dispense in original container.

   ANDA – Prior to reconstitution store dry powder at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]". Dispense in original container.

8. This is the first ANDA for:
   Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
   600 mg/42.9 mg*
   *(clavulanate acid equivalent)

9. Bioequivalence:

Fasting Bioequivalence study: Amoxicillin and Clavulanate Potassium for Oral Suspension 600 mg/42.9 per 5 mL for oral suspension

- Amoxicillin

Parameter	ANDA	NDA	Insert [administrated at the start of a light meal (pediatric patients)]
ACUI (mcg.hr/mL ACUT (mcg.hr/mL)	27.9 27.4	27.1 26.6	59.8±20 [only value]
Cmax (mcg/mL)	10.9	10.8	15.7
T ½ (hr) Tmax	1.1 1.4	1.1 1.36	1.4 2

-Clavulanate potassium/ clavulanic acid

Parameter	ANDA	NDA	Insert [administrated at the start of a light meal (pediatric patients)]
ACUI (mcg.hr/mL ACUT (mcg.hr/mL)	2.3 2.2	2.2 2.1	4±1.9 [only value]
Cmax (mcg/mL)	1.1	1.1	1.7
T ½ (hr) Tmax (hr)	1 1	1 0.9	1.1 1.1

Non-Fasting Bioequivalence study: Amoxicillin and Clavulanate Potassium for Oral Suspension 600 mg/42.9 per 5 mL for oral suspension

- Amoxicillin

Parameter	ANDA	NDA	Insert [administrated with a snack or meal (pediatric patients)]
ACUI (mcg.hr/mL ACUT (mcg.hr/mL)	27.3 26.6	26.5 25.9	59.8±20 [only value]
Cmax (mcg/mL)	7.33	7.23	15.7
T ½ (hr) Tmax (hr)	1.2 2.4	1.2 2.1	1.4 2

-Clavulanate potassium/ clavulanic acid

Parameter	ANDA	NDA	Insert [administrated with a snack or meal (pediatric patients)]
ACUI (mcg.hr/mL ACUT (mcg.hr/mL)	1.33 1.24	1.28 1.19	4±1.9 [only value]
Cmax (mcg/mL)	.516	.607	1.7
T ½ (hr) Tmax (hr)	0.9 1.4	0.8 1.4	1.1 1.1

- The firm's pharmacokinetic parameters from the fasting and fed bioequivalence studies are comparable to the reference listed drug.
- The firm's pharmacokinetic parameters listed in the insert labeling are comparable to the bioequivalence study results, except the Cmax is slightly lower.
- The reported pharmacokinetic parameters from the fasting and fed bioequivalence studies were found to be within acceptable limits by the Division of Bioequivalence.
- The effect of food on the oral absorption of *Augmentin ES-600* has not been studied. However, it is recommended that this drug product should be taken at the start of a meal. Absorption may be enhanced when taken at the start of a meal.

APPEARS THIS WAY
ON ORIGINAL

Date of Review:	3/1/04
Date of Submission:	2/17/04
Primary Reviewer: Jacqueline Council, Pharm.D.	3-4-04 Date:
Team Leader: Captain Lillie Golson	Date: 3/4/04

cc: ANDA: 65-162
DUP/DIVISION FILE
V:firmsnz/ltrs&rev/Teva/65162ap.l
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-162

CHEMISTRY REVIEW(S)

ANDA 65-162

Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg (base) per 5 mL

Teva Pharmaceuticals USA

Susan Zuk
OGD, Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-162

2. REVIEW #: 1

3. REVIEW DATE: 6/25/03

4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original ANDA	12/27/02
New Correspondence	2/7/03

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative:	Vincent Andolina
Telephone:	(215) 591-8642
Facsimile:	(215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/ 42.9 mg per 5 mL

9. LEGAL BASIS FOR SUBMISSION: The RLD is Augmentin® ES 600, manufactured by Glaxo SmithKline, NDA # 50755. No patent claims or marketing exclusivities exist. This is the first generic application for this dosage strength.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: powder for oral suspension

12. STRENGTH/POTENCY: 600 mg/42.9 mg per 5 mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

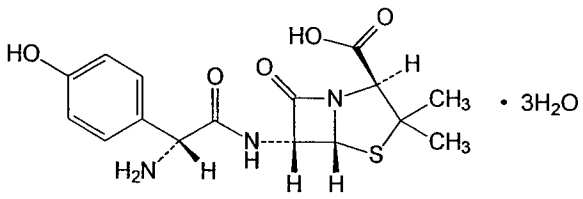
_____SPOTS product – Form Completed

___X___Not a SPOTS product

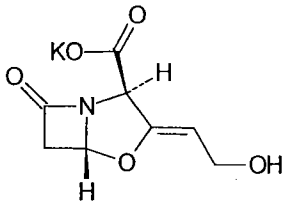
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Amoxicillin and Clavulanate Potassium

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



Clavulanate Potassium. 4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt. $C_8H_8KNO_5$. 237.25. 61177-45-5. Inhibitor (beta-lactamase).



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	A	5/20/02	R. Ganunis
	II			3	A	10/2/02	S. Zuk
	IV			3, 4	A	2/13/03	
	III			3, 4	A	4/29/02	
	III			3, 4	A	4/29/02	
	III			3, 4	A	5/27/03	
	III			3, 4	A	7/17/02	
	III			3, 4	A	5/23/03	
	III			3, 4	A	1/4/00	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	DP - Acceptable DS - Acceptable	3/5/03 2/24/03 and 4/21/03	
Methods Validation	N/A		
Labeling	Pending		Jackie Council
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____X Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-132

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is not approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product contains two active ingredients, amoxicillin and clavulanic acid. Amoxicillin functions as an antibacterial agent. Amoxicillin is present in the dry formulation as the trihydrate. It is a semi-synthetic derivative of 6-APA. Clavulanic acid functions as a β-lactamase inhibitor. Clavulanic acid is a direct fermentation product of *Streptomyces clavuligerus* and is structurally related to penicillins. It is active against plasmid mediated β-lactamases responsible for resistance to penicillins and cephalosporins. Clavulanic acid is present in the dry formula as the clavulanate potassium salt. This active ingredient is [redacted]. Clavulanate Potassium is a reactive compound which is extremely hygroscopic. Care must be taken in processing and storage of the product.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for a variety of bacteriological infections in pediatric populations. The recommended dosage is 90 mg/kg/day. A weight-dependent volume of prepared suspension is given every 12 hours over a 10-day period. The suspension is prepared by adding 85 mL water to the 120 mL bottle which contains 25 g of powder for oral suspension (20 doses).

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is deficient for the following reasons:

1. Composition statement contains inaccurate information
2. Justification for overage was not provided
3. Specifications and data for raw materials were incomplete
4. Methods were not validated
5. Function of outside labs was not provided
6. Data and specifications for in-process testing were incomplete

7. Specifications for stability were incomplete

III. Administrative

A. Reviewer's Signature

S. Zuk

B. Endorsement Block

S. Zuk/6/25/03 S. Zuk 6/27/03
R. Adams/6/26/03 R. C. Adams 6/27/03
M. Anderson/

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 17 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 65162
ANDA DUP 65162
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SZuk/6/25/03 S Zuk 6/27/03
HFD-643/RAdams/6/26/03 R.C. Adams 6/27/03
HFD-617/MAnderson/6/26/03 M Anderson 6/27/03

F/T by: EW 6/26/03

V:\FIRMSNZ\TEVA\LTRS&REV\65162NA.revR01.doc

TYPE OF LETTER: NOT APPROVABLE – MINOR

ANDA 65-162

Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg (base) per 5 mL

Teva Pharmaceuticals USA

Susan Zuk
OGD, Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-162

2. REVIEW #: 2

3. REVIEW DATE: 1/13/04

4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original ANDA	12/27/02
New Correspondence	2/7/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	11/6/03 *response to 6/27/03 deficiency letter*
Telephone Amendment	1/9/04 *response to Tecons 12/16/03 and 1/8/04*

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Address: 1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Representative: Vincent Andolina

Telephone: (215) 591-8642
Facsimile: (215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/ 42.9 mg per 5 mL

9. LEGAL BASIS FOR SUBMISSION: The RLD is Augmentin® ES 600, manufactured by Glaxo SmithKline, NDA # 50755. No patent claims or marketing exclusivities exist. This is the first generic application for this dosage strength.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: powder for oral suspension

12. STRENGTH/POTENCY: 600 mg/42.9 mg per 5 mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

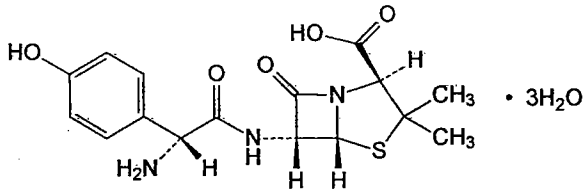
_____SPOTS product – Form Completed

___X___Not a SPOTS product

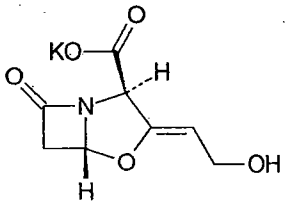
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Amoxicillin and Clavulanate Potassium

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



Clavulanate Potassium. 4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt. $C_8H_8KNO_5$. 237.25. 61177-45-5. Inhibitor (beta-lactamase).



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS 2	DATE REVIEW COMPLETED	COMMENTS
	II			3	A	11/3/03	Y. Pan
	II			3	A	6/27/03	Y. Pan
	IV			3, 4	A	2/13/03	
	III			3, 4	A	4/29/02	
	III			3, 4	A	4/29/02	
	III			3, 4	A	5/27/03	
	III			3, 4	A	7/17/02	
	III			3, 4	A	5/23/03	
	III			3, 4	A	1/4/00	

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	1/8/04	
Methods Validation	N/A		
Labeling	Acceptable	3/4/04	Jackie Council
Bioequivalence	Acceptable	9/5/03	Kuldeep Dhariwal
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____X Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-162

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product contains two active ingredients, amoxicillin and clavulanic acid. Amoxicillin functions as an antibacterial agent. Amoxicillin is present in the dry formulation as the trihydrate. It is a semi-synthetic derivative of 6-APA. Clavulanic acid functions as a β-lactamase inhibitor. Clavulanic acid is a direct fermentation product of *Streptomyces clavuligerus* and is structurally related to penicillins. It is active against plasmid mediated β-lactamases responsible for resistance to penicillins and cephalosporins. Clavulanic acid is present in the dry formula as the clavulanate potassium salt. This active ingredient is ——— ——— Clavulanate Potassium is a reactive compound which is extremely hygroscopic. Care must be taken in processing and storage of the product.

One exhibit batch was manufactured using Amoxicillin supplied by Teva Pharmaceuticals USA and Clavulanate Potassium from ——— .. This was a commercial-sized batch of ———. The batch was completely packaged and placed on stability study.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for a variety of bacteriological infections in pediatric populations. The recommended dosage is 90 mg/kg/day. A weight-dependent volume of prepared suspension is given every 12 hours over a 10-day period. The suspension is prepared by adding 85 mL water to the 120 mL bottle which contains 25 g of powder for oral suspension (20 doses).

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is recommended for approval once the labeling is found acceptable. The following support approval:

- Acceptable CMC review
- 18-months of acceptable long-term stability data
- Acceptable Bioequivalence review
- Acceptable EER
- Acceptable DMFs for Amoxicillin and Clavulanate Potassium

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

S. Zuk/1/13/04; 3/4/04 (as updated) Susan Zuk 3/8/04
R. Adams/1/13/04; 3/5/04 R. C. Adams 3/8/04
M. Anderson/3/5/04

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 17 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 65162
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SZuk/1/13/04; 3/4/04 (as updated) 3/8/04
HFD-643/RAdams/1/13/04; 3/5/04 3/8/04

F/T by:mda/3/5/04

V:\FIRMSNZ\TEVA\LTRS&REV\65162AP.R02.doc

TYPE OF LETTER: Approval Letter

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-162

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-162
Drug Product Name	Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
Strength	600 mg/42.9 mg(base)/5 mL
Applicant Name	Teva Pharmaceuticals
Address	1090 Horsham Road, PO Box 1090, North Wales, PA 19454
Submission Date(s)	December 27, 2002
Amendment Date(s)	N/A
Reviewer	Kuldeep R. Dhariwal, Ph.D.
First Generic	Yes
File Location	V:\firmsnz\Teva\ltrs&rev\65162N1202.doc

I. Executive Summary

This application references Augmentin ES-600® for oral suspension and includes one fasting and one fed BE study. The fasting study is a single-dose two-way crossover study using 18 male and 27 female normal healthy volunteers given a dose of 1x600/42.9 mg/5 mL. The results (point estimate, 90% CI) of the fasting BE study are: amoxicillin LAUCt of 103, 100.62-104.93%; amoxicillin LAUCi of 103, 100.69-104.94%; amoxicillin LCmax of 101, 95.82-106.26%; clavulanic acid LAUCt of 104, 95.85-112.97%; clavulanic acid LAUCi of 104, 96.35-112.58%; clavulanic acid LCmax of 100, 93.28-108.20%. The fed BE study is a single-dose two-way crossover study using 23 male and 24 female normal healthy volunteers given a dose of 1x600/42.9 mg/5 mL. The results of the fed BE study are: amoxicillin LAUCt of 103, 101.08-104.83%; amoxicillin LAUCi of 103, 101.25-104.88%, amoxicillin LCmax of 101, 97.71-105.33%; clavulanic acid LAUCt of 100, 91.95-109.13%; clavulanic acid LAUCi of 101, 94.73-108.71%; clavulanic acid LCmax of 100, 92.41-107.52%. These studies are acceptable. The dissolution (900 mL water, paddle at 75 rpm) testing is acceptable. This application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
Reference Product	Augmentin ES-600®
RLD Manufacturer	GlaxoSmithKline
NDA No.	50755
RLD Approval Date	June 22, 2001
Indication	For the treatment of pediatric patients with recurrent or persistent acute otitis media due to *S. pneumoniae* (penicillin MICs </= 2μg/mL), *H. influenzae* or *M. catarrhalis*.

B. PK/PD Information

Bioavailability	Well absorbed
Food Effect	The effect of food on the oral absorption of *Augmentin ES-600* has not been studied.
Excretion	Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of 10 mL of *Augmentin* 250 mg/5 mL suspension.
Relevant OGD or DBE History	The RLD for amoxicillin and clavulanate potassium for oral suspension 400 mg/57 mg (base)/5 mL is Augmentin® 400 by GlaxoSmithKline (NDA 50725). The innovator also markets 200 mg/28.5 mg (base)/5 mL under the same NDA. There are two approved generics on the market for this drug product. The DBE reviewed ANDA 65-132 from Ranbaxy and found it to be acceptable in December 2002. Fasting and fed studies are recommended on the higher strength and the lower strength is waived. The RLD for amoxicillin and clavulanate potassium for oral suspension 250 mg/62.5 mg (base)/5 mL is Augmentin® 250 by GlaxoSmithKline (NDA 50575). The innovator also markets 125 mg/31.25 mg (base)/5 mL under the same NDA. Fasting and fed studies are recommended on the higher strength and the lower strength is waived. The RLD for amoxicillin and clavulanate potassium for oral suspension 600 mg/42.9 mg (base)/5 mL is Augmentin ES-600® by GlaxoSmithKline (NDA 50755). This application is first generic application for this strength.
Agency Guidance	None
Drug Specific Issues (if any)	

Mean (+/-SD) Plasma Amoxicillin and Clavulanate Pharmacokinetic Parameter Values Following Administration of 45 mg/kg of *Augmentin ES-600* Every 12 Hours to Pediatric Patients

Parameter*	**Amoxicillin**	**Clavulanate**
C_{max} (µg/mL)	15.7 ± 7.7	1.7 ± 0.9
T_{max} (h)	2.0 (1.0-4.0)	1.1 (1.0-4.0)
AUC_{0-t} (µg•h/mL)	59.8 ± 20.0	4.0 ± 1.9
T1/2 (h)	1.4 ± 0.3	1.1 ± 0.3
CL/F (L/h/kg)	0.9 ± 0.4	1.1 ± 1.1

*Arithmetic mean ± standard deviation, except T_{max} values which are medians (ranges).

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	One
Single-dose fed	Yes	One
Steady-state	No	
In vitro dissolution	Yes	One
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

	Parent	Parent
Analyte name	Amoxicillin	Clavulanic acid
Internal Standard	Benzyl derivative of Amoxicillin	Methyl imidazole derivative of clavulanic acid
Method description	LC/MS/MS	LC/MS/MS
QC range, ng/mL	[redacted]	[redacted]
Standard curve range, ng/mL	199.94 to 24992.20	50.02 to 5002.16
Limit of quantitation, ng/mL	199.94	50.02
Average recovery of Drug (%)	45.77	115.28
Average Recovery of Int. Std (%)	44.90	84.43
Intraday precision range (%)	1.80 to 4.18	3.21 to 4.61
Intraday accuracy range (%)	98.75 to 104.03	99.04 to 102.23
Interday precision range (%)	1.58 to 3.85	1.78 to 3.05
Interday accuracy range (%)	100.58 to 101.49	101.40 to 102.91
Bench-top stability (hrs)	2 h at RT, 22 h at 4^0C	2 h at RT, 4 h at 4^0C
Stock stability (days)	440 days at -70^0C	440 days at -70^0C
Processed stability (hrs)	164 hrs at 5^0C	164 hrs at 5^0C
Freeze-thaw stability (cycles)	3	3
Long-term storage stability (days)	439 at -70^0C	439 at -70^0C
Dilution integrity	Yes	Yes
Specificity	Yes	Yes
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes
20% Chromatograms included (Y/N)	Y	Y
Random or Serial Selection of Chrom	Random	Random

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	02-543
Study Design	Two-way crossover
No. of subjects enrolled	48
No. of subjects completing	45
No. of subjects analyzed	Data from 45 subjects who completed the study were included in statistical analysis
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 18 Female: 27
Test product	Amoxicillin and Clavulanate Potassium for oral suspension
Reference product	Augmentin ES-600®
Strength tested	600/42.9 mg/5 mL
Dose	1x600/42.9 mg/5 mL

Amoxicillin

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC0-t	1.03	100.62-104.93
LAUCi	1.03	100.69-104.94
LCmax	1.01	95.82-106.26

Clavulanic acid

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC0-t	1.04	95.85-112.97
LAUCi	1.04	96.35-112.58
LCmax	1.00	93.28-108.20

Amoxicillin

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
PK anomaly	4	2	0.43	0.21	4	2	0.43	0.21
Other repeats	0	0	0	0	0	0	0	0
Total	4	2	0.43	0.21	4	2	0.43	0.21

Clavulanic acid

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
PK anomaly	3	4	0.32	0.43	3	4	0.32	0.43
Other repeats	0	0	0	0	0	0	0	0
Total	3	4	0.32	0.43	3	4	0.32	0.43

Did use of recalculated plasma concentration data change study outcome? No

2. Single-dose Fed Bioequivalence Study

Study No.	02-544
Study Design	Two-way crossover
No. of subjects enrolled	48
No. of subjects completing	47
No. of subjects analyzed	47
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 23 Female: 24
Test product	Amoxicillin and Clavulanate Potassium for oral suspension
Reference product	Augmentin ES-600®
Strength tested	600/42.9 mg/5 mL
Dose	1x600/42.9 mg/5 mL

Amoxicillin

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC0-t	1.03	101.08-104.83
LAUCi	1.03	101.25-104.88
LCmax	1.01	97.71-105.33

Clavulanic acid

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC0-t	1.00	91.95-109.13
LAUCi	1.01	94.73-108.71
LCmax	1.00	92.41-107.52

Amoxicillin

Reanalysis of Study Samples Additional information in Appendix, Table 16								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
PK anomaly	6	4	0.61	0.40	6	4	0.61	0.40
Poor chromatography	0	1	0	0.10	0	1	0	0.10
Low IS	4	0	0.40	0	4	0	0.40	0
Above range	1	0	0.10	0	1	0	0.10	0
Amount below second std. after rejecting first	3	2	0.30	0.20	3	2	0.30	0.20
Total	14	7	1.41	0.70	14	7	1.41	0.70

All samples of subjects 9, 26, 31, 32, 33, 34 and 35 were repeated due to run failure.

Clavulanic acid

Reanalysis of Study Samples Additional information in Appendix, Table 16								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
PK anomaly	6	3	0.61	0.30	6	3	0.61	0.30
Poor chromatography	0	3	0	0.30	0	3	0	0.30
Low IS	2	1	0.20	0.10	2	1	0.20	0.10
Amount below second std. after rejecting first	11	11	1.11	1.11	11	11	1.11	1.11
Total	19	18	1.92	1.81	19	18	1.92	1.81

All samples of subjects 9,26,28,31,32,33,34 and 35 were repeated due to run failure.

Did use of recalculated plasma concentration data change study outcome? No

F. Formulation

Location in appendix	Section B, Page 27
Inactive ingredients within IIG Limits (yes or no)	Yes
If No, list ingredients outside of limits	
If a tablet, is the product scored? (yes or no)	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	Water
Volume (mL)	900
USP Apparatus type	2 (paddle)
Rotation (rpm)	75
Firm's proposed specifications	NLT – % (Q) in 20 minutes
FDA-recommended specifications	NLT – % (Q) in 15 minutes
F2 metric calculated (yes or no)	No
If no, reason why F2 not calculated	Rapidly dissolving oral suspension
Method is acceptable (yes or no)	Yes

F2 metric, lower strengths compared to highest strength: N/A			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A			
add rows as needed			

F2 metric, test compared to reference: N/A	
Strength	F2 metric
add rows as needed	

H. Waiver Request(s):

No

Strengths for which waivers requested
Regulation cited
Proportional to strength tested in vivo (yes or no)
Dissolution is acceptable (yes or no)
Waiver granted (yes or no)

I. Deficiency Comments:

None

J. Recommendations

1. The fasting bioequivalence study conducted by Teva Pharmaceuticals comparing its amoxicillin and clavulanate potassium for oral suspension 600 mg/42.9 mg (base)/5 mL, lot # 10995P1 with the reference listed drug Augmentin ES-600® for oral suspension, lot #TC2009 is acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Teva's amoxicillin and clavulanate potassium for oral suspension 600 mg/42.9 mg (base)/5 mL is bioequivalent to the reference product, Augmentin ES-600® for oral suspension manufactured by GlaxoSmithKline.
2. The single-dose bioequivalence study conducted under non-fasting conditions by Teva Pharmaceuticals comparing its amoxicillin and clavulanate potassium for oral suspension 600 mg/42.9 mg (base)/5 mL, lot # 10995P1 with the reference listed drug Augmentin ES-600® for oral suspension, lot #TC2009 is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, Teva's amoxicillin and clavulanate potassium for oral suspension 600 mg/42.9 mg (base)/5 mL is bioequivalent to the reference product, Augmentin ES-600® for oral suspension manufactured by GlaxoSmithKline.
3. The in vitro dissolution testing conducted by the firm on its test product is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water using USP apparatus 2 (paddle) at 75 rpm. The test product should meet the following specifications:

   Not less than —% (Q) of the labeled amount of amoxicillin in the dosage form is dissolved in 15 minutes.
   Not less than —% (Q) of the labeled amount of clavulanic acid in the dosage form is dissolved in 15 minutes.

Dhariwal 9/5/03

Kuldeep R. Dhariwal, Ph. D., Branch II

9/5/2003

S. Nerurkar, Ph. D., Branch II

9/5/03

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	02-543
Study Title	An Open-label, single-dose, two-way crossover bioequivalence study of two oral suspension formulations of amoxicillin/clavulanate potassium, 600/42.9 mg/5 mL in healthy subjects, under fasting conditions
Clinical Site	[redacted]
Principal Investigator	[redacted] M.D., Ph.D.
Study/Dosing Dates	Period 1 August 24, 2002 Period 2 August 31, 2002
Analytical Site	Novopharm Limited, 1290 Ellesmere Road, Toronto, Ontario, M1P 2Y1, Canada
Analytical Director	Kayode Awaiye, B.Sc., M.B.A.
Analysis Dates	October 15 to November 5, 2002
Storage Period (no. of days from first sample to final analysis)	73 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Amoxicillin and Clavulanic Potassium for Oral Suspension	Augmentin ES-600®
Manufacturer	Novopharm for Teva	GlaxoSmithKline
Batch/Lot No.	10995P1	TC2009
Manufacture Date	6/12/2002	N/A
Expiration Date	N/A	1/03
Strength	600/42.9 mg/5 mL	600/42.9 mg/5 mL
Dosage Form	Oral Suspension	Oral Suspension
Batch Size	[redacted]	N/A
Production Batch Size	[redacted]	N/A
Potency	Amoxicillin: 107.2% Clavulanic acid: 110.2%	Amoxicillin: 110.1% Clavulanic acid: 105.3%
Content Uniformity	Not given	Not given
Formulation	See Appendix Section B	N/A
Dose Administered	1x600/42.9 mg/5 mL	1x600/42.9 mg/5 mL
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	N/A
Washout Period	7 days
Randomization Scheme	AB: 2,3,6,7,9,10,13,16,18,19,22,24,25,26,29,31,33, 35, 38,40,41,44,46,48 BA: 1,4,5,8,11,12,14,15,17,20,21,23,27,28,30,32, 34,36,37,39,42,43,45,47
Blood Sampling Times	0,0.33,0.67,1,1.25,1.5,1.75,2,2.33,2.67,3,3.5,4,5,6, 7,8,10,12 and 14 hours
Blood Volume Collected/Sample	7 mL in potassium EDTA tubes
Blood Sample Processing/Storage	Samples were centrifuged at 3000 rpm for 10 minutes at 4^0C within 10 minutes of collection. The plasma was separated and stored at -70^0C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 h
Length of Confinement	10 h prior to until 14 h after dosing
Safety Monitoring	Post-clinical laboratory tests for hematology, serum chemistry and urinalysis were conducted at the end of the study. Vital signs and ECG measurements were not carried out unless deemed necessary.

Table 1. Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	57.8
Mean	32	Mean	68.6	18-40	75.55	Male	40	Afr. Amer.	35.5
SD	10	SD	12.2	41-64	24.44	Female	60	Hispanic	
Range	19-52	Range	50.3-96.7	65-75				Asian	6.6
				>75				Others	

Study Results

Table 2. Dropout Information

Subject No	48	26
Reason	Allergic reaction to drug product	Rash
Period	Prior to period 2 dosing	Period 1
Replacement	N	N

Subject No	46
Reason	Positive methadone test results
Period	Prior to period 2 dosing
Replacement	N

Table 3. Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Elevated Urea	1	3
Elevated Creatinine	2	4
Headache	2	1
Rash	2	0
Vomiting	1*	0
Dizziness	1	1
Sweating	1	0
Itchiness	1	0
Weakness	1	0
Diarrhea	0	1
Total:	**12**	**10**

* 9 h 18 minutes after dosing

Table 4. Protocol Deviations

Type	Subject #s (Test)	Subject #s (Reference)
9 h and 40 min fasting instead of 10 h prior to dosing	1 (#5)	0
Use of Witch Hazel Astringent one day prior to dosing in period 2	1 (#43)	0

There were some sampling time deviations. Actual times were used in the pharmacokinetic calculations.

Comments: Adverse events and protocol deviations did not compromise the integrity of study.

Table 5. Assay Validation – Within Study (Vol. C1.7, pages 2236-2274)

	Amoxicillin			Clavulanic acid		
QC Conc. (ng/mL)	540.60	9010.04	18020.1	108.64	1810.59	3621.18
Inter day Precision (%CV)	6.41	4.09	4.01	6.15	4.80	5.07
Inter day Accuracy (%)	100.74	97.99	97.90	98.97	96.19	95.53

Cal. Standards Conc. (ng/mL)	199.94, 399.87, 1249.61,2499.22, 4998.43, 9996.86, 14995.3, 24992.2	50.02, 100.04, 250.11, 500.22,1250.54, 2000.86, 3001.30, 4001.73, 5002.16
Inter day Precision (%CV)	1.63-5.10	2.07-5.16
Inter day Accuracy (%)	96.28-101.70	94.56-102.63
Linearity Range (range of R^2 values)	0.9958-0.9999	0.9940-0.9998

Chromatograms: Any interfering peaks? No

Table 6. SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
19.2.5	6/13/1997	Repeat analysis of biostudy samples and reported data

Comments on repeat assays:

The firm reassayed seven samples of amoxicillin and seven samples of clavulanic acid for pharmacokinetic reasons and used reassayed values. The reviewer recalculated pharmacokinetic parameters using original assay values and repeated statistical analyses using recalculated PK parameters. The study remains acceptable.

Comments on Within-Study Validation: Acceptable.

Conclusion: Analytical method is acceptable.

Table 7. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 10 and Figures 1 and 2.

Amoxicillin (1=Test, 2=Reference)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	27965.571	5011.892	27147.077	4862.256	1.030
AUCT	27464.268	4977.060	26666.897	4809.885	1.030
CMAX	10970.755	3084.934	10867.322	3136.616	1.010
KE	0.601	0.106	0.597	0.089	1.006
LAUCI	27563.171	0.169	26759.806	0.169	1.030
LAUCT	27060.580	0.171	26280.974	0.170	1.030
LCMAX	10593.927	0.262	10483.213	0.265	1.011
THALF	1.192	0.224	1.186	0.181	1.004
TMAX	1.405	0.436	1.363	0.364	1.031

Clavulanic acid (1=Test, 2=Reference)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	2396.580	753.323	2260.404	731.238	1.060
AUCT	2293.692	747.250	2157.072	719.085	1.063
CMAX	1127.588	338.926	1106.836	353.380	1.019
KE	0.683	0.094	0.707	0.128	0.967
LAUCI	2257.995	0.376	2141.178	0.342	1.055
LAUCT	2147.173	0.401	2036.774	0.352	1.054
LCMAX	1068.921	0.353	1053.419	0.320	1.015
THALF	1.033	0.144	1.013	0.188	1.020
TMAX	1.001	0.213	0.948	0.223	1.057

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 8. LSMEANS AND 90% CONFIDENCE INTERVALS

Amoxicillin (1=Test, 2=Reference)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	27926.88	27162.16	1.03	100.78	104.85
AUCT	27424.18	26681.46	1.03	100.72	104.85
CMAX	10925.02	10839.69	1.01	95.88	105.69
LAUCI	27535.38	26787.01	1.03	100.69	104.94
LAUCT	27031.52	26307.34	1.03	100.62	104.93
LCMAX	10554.42	10459.64	1.01	95.82	106.26

Clavulanic acid (1=Test, 2=Reference)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	2380.54	2269.66	1.05	98.66	111.11
AUCT	2277.62	2165.95	1.05	98.73	111.58
CMAX	1119.81	1109.38	1.01	94.54	107.34
LAUCI	2240.46	2151.18	1.04	96.35	112.58
LAUCT	2129.34	2046.31	1.04	95.85	112.97
LCMAX	1060.85	1055.92	1.00	93.28	108.20

Table 9. Additional Study Information

Amoxicillin

Root mean square error, AUCT	0.05894
Root mean square error, AUCI	0.05823
Root mean square error, Cmax	0.14560
Mean ratio AUC0-t/AUC∞	Test 0.98 (0.96-0.99) Reference 0.98 (0.97-0.99)

Clavulanic acid

Root mean square error, AUCT	0.23127
Root mean square error, AUCI	0.21911
Root mean square error, Cmax	0.20888
Mean ratio AUC0-t/AUC∞	Test 0.95 (0.82-0.97) Reference 0.95 (0.92-0.97)

Comments: (on pharmacokinetic analysis)

1. Ke and AUCi were determined for all subjects.
2. Indicate the number of subjects with the following:
   a. measurable drug concentrations at 0 hr: none
   b. first scheduled post-dose sampling time as Tmax: none for amoxicillin, 1 for clavulanic acid
   c. first measurable drug concentration as Cmax: none
3. The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
4. Amoxicillin: There was statistically significant period effect for LAUCt and LAUCi. Clavulanic acid: There was statistically significant period effect for LAUCt and LAUCi and LCmax.
5. The 90% confidence intervals for AUCt, AUCi, and Cmax are within the acceptable limits of 80-125%.

Conclusion: The single-dose fasting bioequivalence study is acceptable.

Table 10 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Amoxicillin: ng/mL, n=45 (1=Test, 2=Reference)

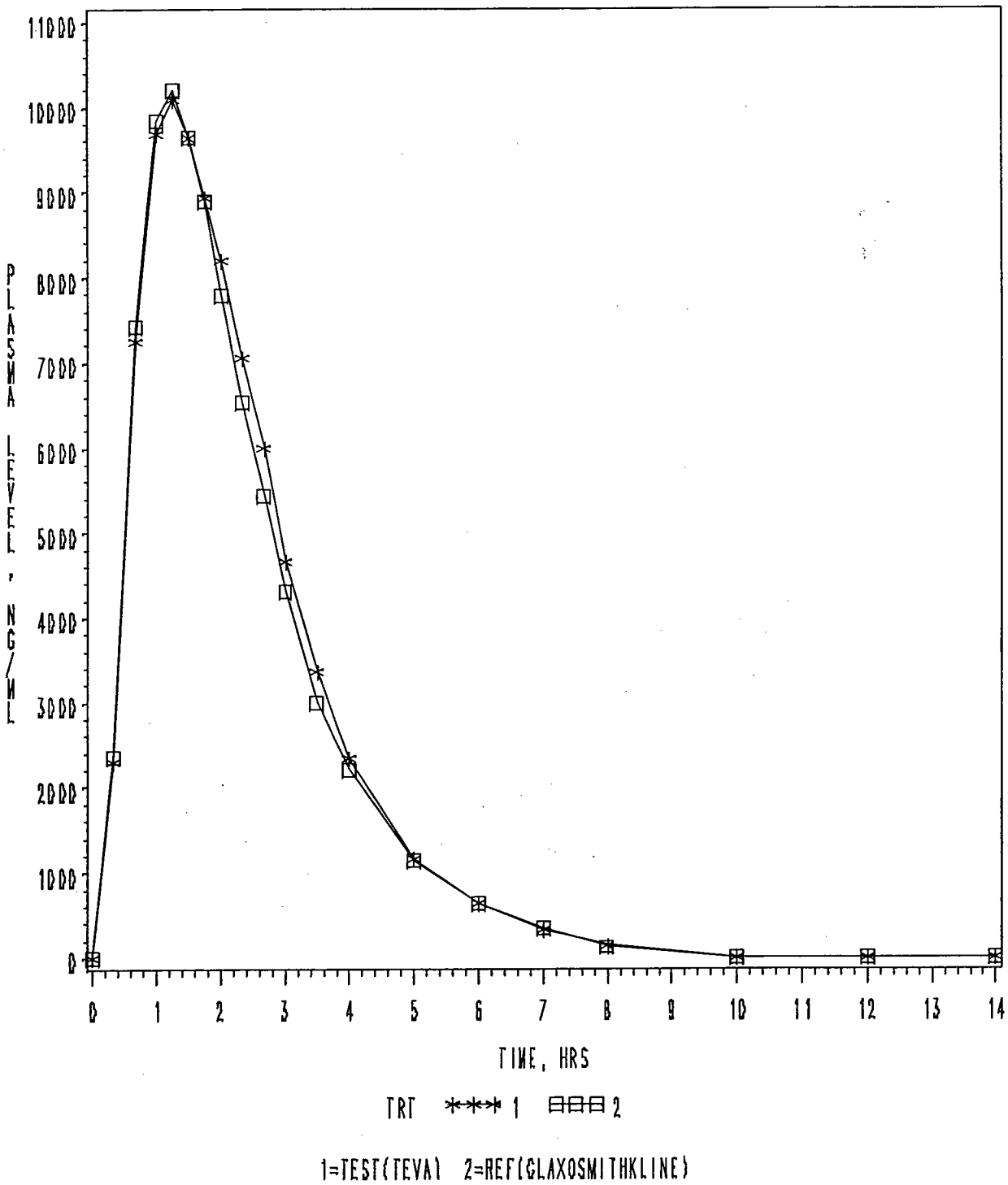
	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	2303.74	1315.56	2365.16	1388.79	0.97
0.67	7255.00	3068.08	7427.12	3065.50	0.98
1	9684.87	3406.16	9842.32	3560.12	0.98
1.25	10088.29	2882.70	10206.18	2873.72	0.99
1.5	9638.77	2663.50	9641.50	2324.07	1.00
1.75	8931.69	2121.57	8894.73	1989.63	1.00
2	8202.02	2040.46	7801.07	1701.96	1.05
2.33	7054.23	1845.96	6537.34	1330.74	1.08
2.67	5996.68	1665.36	5438.50	1232.29	1.10
3	4659.13	1461.97	4310.69	1192.61	1.08
3.5	3370.27	1238.89	2994.80	942.47	1.13
4	2346.95	926.60	2215.54	882.25	1.06
5	1156.81	480.29	1137.38	505.35	1.02
6	644.42	264.47	635.87	271.01	1.01
7	328.48	197.05	345.22	173.20	0.95
8	144.57	154.54	130.01	146.33	1.11
10	5.90	39.59	0.00	0.00	.
12	0.00	0.00	0.00	0.00	.
14	0.00	0.00	0.00	0.00	.

Clavulanic acid: ng/mL, n=45 (1=Test, 2=Reference)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	340.78	235.04	366.61	284.10	0.93
0.67	978.07	387.06	995.62	399.94	0.98
1	1082.52	330.70	1060.82	330.58	1.02
1.25	1006.29	297.64	962.48	269.40	1.05
1.5	869.22	248.85	803.38	221.48	1.08
1.75	735.91	217.27	685.30	197.97	1.07
2	613.30	198.12	560.12	173.60	1.09
2.33	487.76	170.86	440.27	138.93	1.11
2.67	391.07	138.14	347.80	118.45	1.12
3	298.99	113.30	273.25	100.26	1.09
3.5	215.01	87.07	189.82	70.18	1.13
4	153.94	65.89	135.36	59.56	1.14
5	71.23	48.49	58.69	48.25	1.21
6	25.34	34.06	17.24	31.22	1.47
7	2.29	10.74	2.37	11.14	0.97
8	0.00	0.00	0.00	0.00	.
10	0.00	0.00	0.00	0.00	.
12	0.00	0.00	0.00	0.00	.
14	0.00	0.00	0.00	0.00	.

FIG 1. PLASMA AMOXICILLIN LEVELS

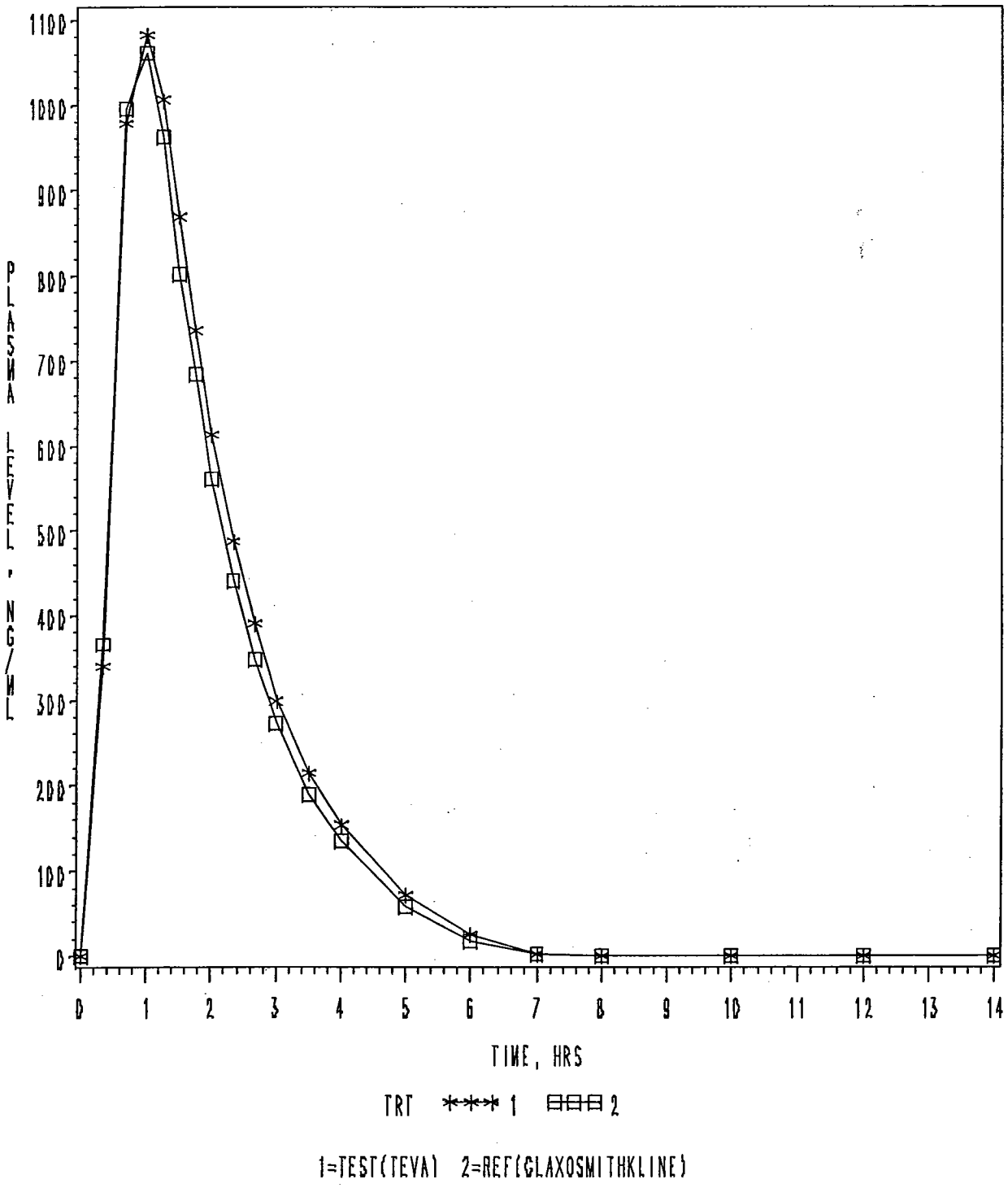
AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION, 600 MG/42.9 MG, ANDA #65-162
UNDER FASTING CONDITIONS
DOSE=1 X 600 MG/42.9 MG



1=TEST(TEVA) 2=REF(GLAXOSMITHKLINE)

FIG 2. PLASMA CLAVULANIC ACID LEVELS

AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION, 600 MG/42.9 MG, ANDA #65-162
UNDER FASTING CONDITIONS
DOSE=1 X 600 MG/42.9 MG



1=TEST(TEVA) 2=REF(GLAXOSMITHKLINE)

2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	02-544
Study Title	An Open-label, single-dose, two-way crossover bioequivalence study of two oral suspension formulations of amoxicillin/clavulanate potassium, 600/42.9 mg/5 mL in healthy subjects, under fed conditions
Clinical Site	[redacted]
Principal Investigator	[redacted] M.D., Ph.D.
Study/Dosing Dates	Period 1 August 12, 2002 Period 2 August 19, 2002
Analytical Site	Novopharm Limited, 1290 Ellesmere Road, Toronto, Ontario, M1P 2Y1, Canada
Analytical Director	Kayode Awaiye, B.Sc., M.B.A.
Analysis Dates	September 9 to October 25, 2002
Storage Period (no. of days from first sample to final analysis)	74 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Amoxicillin and Clavulanate Potassium for Oral Suspension	Augmentin ES-600®
Manufacturer	Novopharm for Teva	GlaxoSmithKline
Batch/Lot No.	10995P1	TC2009
Manufacture Date	6/12/2002	N/A
Expiration Date	N/A	1/03
Strength	600/42.9 mg/5 mL	600/42.9 mg/5 mL
Dosage Form	Oral Suspension	Oral Suspension
Batch Size	[redacted]	N/A
Production Batch Size	[redacted]	N/A
Potency	Amoxicillin: 107.2% Clavulanic acid: 110.2%	Amoxicillin: 110.1% Clavulanic acid: 105.3%
Content Uniformity	Not given	Not given
Formulation	See Appendix Section B	N/A
Dose Administered	1x600/42.9 mg/5 mL	1x600/42.9 mg/5 mL
Route of Administration	Oral	
Standard Breakfast	Yes	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	N/A
Washout Period	7 days
Randomization Scheme	AB: 2,3,5,8,10,12,14,16,17,19,21,24,26,27,30,31,33, 34,37,39,42,43,45,47 BA: 1,4,6,7,9,11,13,15,18,20,22,23,25,28,29,32,35, 36,38,40,41,44,46,48
Blood Sampling Times	0,0.33,0.67,1,1.25,1.50,1.75,2.0,2.33,2.67,3,3.5,4, 5,6,7,8,10,12 and 14 hours
Blood Volume Collected/Sample	7 mL in potassium EDTA tubes
Blood Sample Processing/Storage	Samples were centrifuged at 3000 rpm for 10 minutes at 4^0C within 10 minutes of collection. The plasma was separated and stored at -70^0C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 11
Length of Fasting	10 h
Length of Confinement	10 h prior to until 14 h after dosing
Safety Monitoring	Post-clinical laboratory tests for hematology, serum chemistry and urinalysis were conducted at the end of the study. Vital signs and ECG measurements were not carried out unless deemed necessary.

Table 11 Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	78.72
Mean	31	Mean	67.4	18-40	91.48	Male	48.93	Afr. Amer.	14.89
SD	7	SD	10.8	41-64	8.5	Female	51.06	Hispanic	
Range	19-51	Range	46-98.8	65-75				Asian	6.38
				>75				Others	

Study Results

Table 12 Dropout Information

Subject No	11
Reason	Itchiness, body rash (allergic reaction)
Period	End of period 1
Replacement	N

Table 13 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Nausea	1	0
Diarrhea	1	0
Elevated AST	1	0
Body rash (subject #11)	0	1
Total:	**3**	**1**

Table 14 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Reference)
Subject took Advil® 5 days prior to dosing	#45	

The test product was not shaken before each individual dose was dispensed.
There were some sampling time deviations. Actual times were used in the pharmacokinetic calculations.

Comments: Adverse events, protocol deviations did not compromise the integrity of study.

Table 15 Assay Validation – Within Study

	Amoxicillin			Clavulanic acid		
QC Conc. (ng/mL)	540.60	9010.04	18020.1	108.64	1810.59	3621.18
Inter day Precision (%CV)	6.53	5.12	4.64	5.58	5.18	5.51
Inter day Accuracy (%)	99.94	98.70	97.65	99.84	97.36	95.84
Cal. Standards Conc. (ng/mL)	199.94, 399.87, 1249.61,2499.22, 4998.43, 9996.86, 14995.3, 24992.2			50.02, 100.04, 250.11, 500.22,1250.54, 2000.86, 3001.30, 4001.73, 5002.16		
Inter day Precision (%CV)	1.79-7.23			2.77-7.20		
Inter day Accuracy (%)	98.11-100.99			96.82-102.20		
Linearity Range (range of R^2 values)	0.9876-0.9999			0.9817-0.9999		

Chromatograms: Any interfering peaks? No

Table 16 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
19.2.5	6/13/97	Repeat analysis of biostudy samples and reported data

Comments on repeat assays.

The firm reassayed ten samples of amoxicillin and nine samples of clavulanic acid for pharmacokinetic reasons and used reassayed values. The reviewer recalculated pharmacokinetic parameters using original assay values and repeated statistical analyses using recalculated PK parameters. The study remains acceptable.

Comments on Within-Study Validation: Acceptable.

Conclusion: Analytical method is acceptable.

Table 17 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 20 and Figures 3 and 4

Amoxicillin (1=Test, 2=Reference)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	27318.535	4774.491	26515.594	4691.180	1.030
AUCT	26662.171	4754.007	25906.236	4662.028	1.029
CMAX	7331.455	1414.939	7235.763	1434.420	1.013
KE	0.571	0.088	0.577	0.101	0.989
LAUCI	26896.159	0.181	26109.771	0.178	1.030
LAUCT	26233.121	0.184	25495.187	0.181	1.029
LCMAX	7200.656	0.192	7103.218	0.193	1.014
THALF	1.244	0.197	1.240	0.230	1.004
TMAX	2.437	0.717	2.183	0.714	1.116

Clavulanic acid (1=Test, 2=Reference)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1335.728	628.126	1283.731	508.173	1.041
AUCT	1241.095	627.497	1195.820	503.914	1.038
CMAX	516.423	197.442	507.376	162.090	1.018
KE	0.758	0.110	0.792	0.108	0.957
LAUCI	1197.634	0.489	1180.530	0.433	1.014
LAUCT	1085.111	0.562	1083.305	0.480	1.002
LCMAX	477.401	0.419	478.979	0.363	0.997
THALF	0.934	0.146	0.892	0.127	1.047
TMAX	1.464	0.453	1.486	0.363	0.986

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 18 LS Means and 90% Confidence Intervals

Amoxicillin (1=Test, 2=Reference)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	27329.71	26517.20	1.03	101.29	104.84
AUCT	26672.71	25906.83	1.03	101.13	104.78
CMAX	7330.52	7229.13	1.01	97.44	105.37

LAUCI	26909.45	26112.80	1.03	101.25	104.88
LAUCT	26245.90	25497.12	1.03	101.08	104.83
LCMAX	7200.53	7097.60	1.01	97.71	105.33

Clavulanic acid (1=Test, 2=Reference)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1337.10	1284.13	1.04	97.73	110.52
AUCT	1242.40	1196.20	1.04	97.06	110.67
CMAX	516.55	507.35	1.02	95.02	108.61
LAUCI	1198.44	1180.98	1.01	94.73	108.71
LAUCT	1085.70	1083.83	1.00	91.95	109.13
LCMAX	477.38	478.92	1.00	92.41	107.52

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 19 Additional Study Information

Amoxicillin

Root mean square error, AUCt	0.05265
Root mean square error, AUCi	0.05090
Root mean square error, Cmax	0.10839
AUC0-t/AUCi ratios	Test 0.98 (0.95-0.99) Reference 0.98 (0.95-0.99)

Clavulanic acid

Root mean square error, AUCt	0.24725
Root mean square error, AUCi	0.19854
Root mean square error, Cmax	0.21856
AUC0-t/AUCi ratios	Test 0.91 (0.54-0.98) Reference 0.92 (0.65-0.97)

Comments: (on pharmacokinetic analysis)

1. Ke and AUCi were determined for all subjects.
2. Indicate the number of subjects with the following:
   a. measurable drug concentrations at 0 hr: none
   b. first scheduled post-dose sampling time as Tmax: none
   c. first measurable drug concentration as Cmax: none
3. The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
4. There were no statistically significant period or sequence effects.
5. The 90% confidence intervals for LAUCt, LAUCi, and LCmax are within the acceptable limits of 80-125%.

Conclusion: The single-dose fed bioequivalence study is acceptable.

Table 20 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Amoxicillin: ng/mL, n=47 (1=Test, 2=Reference)

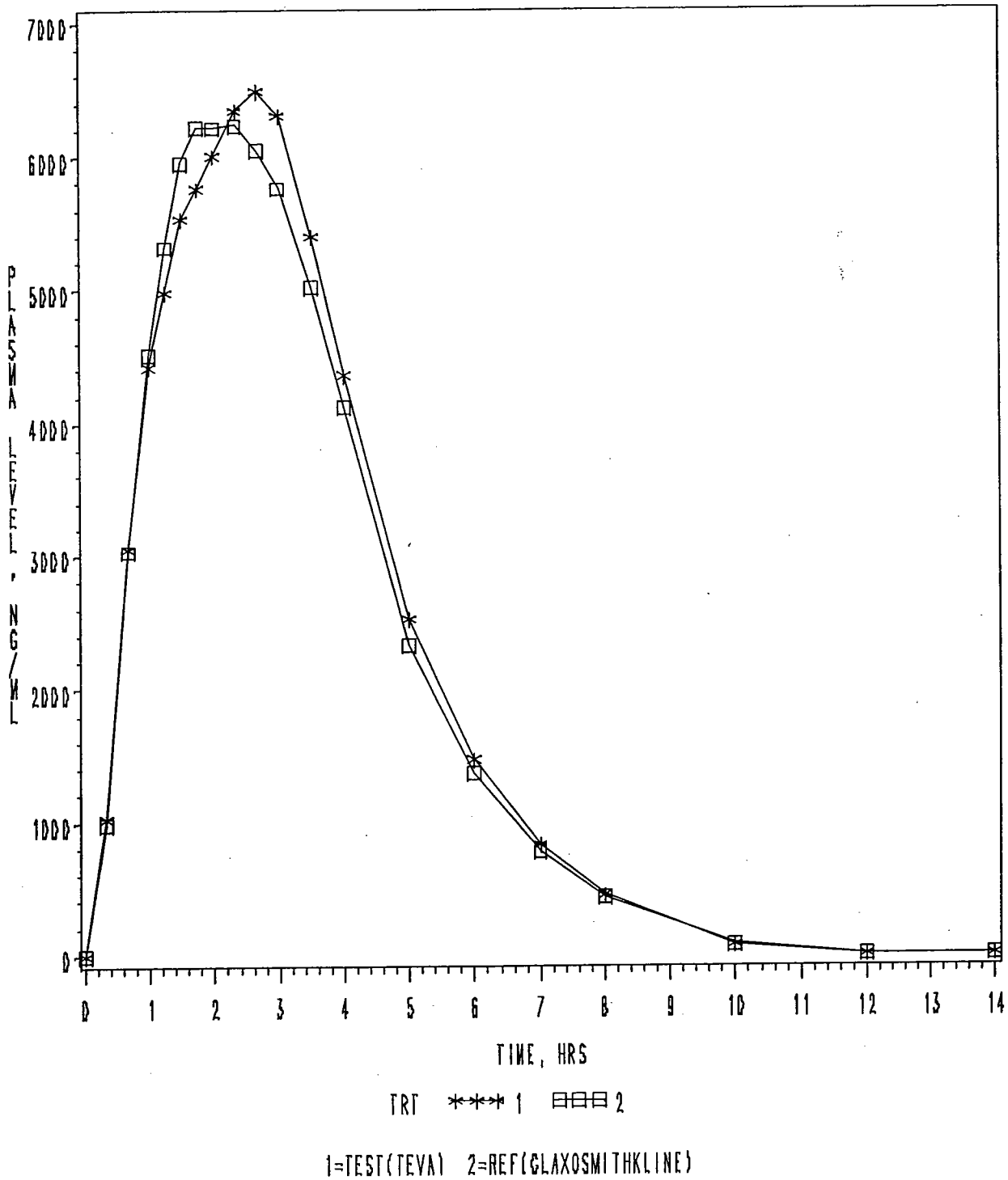
	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	1030.38	758.54	984.15	773.61	1.05
0.67	3052.32	1911.56	3034.88	1693.20	1.01
1	4424.68	2012.82	4515.55	1856.35	0.98
1.25	4988.14	1975.59	5321.98	1956.72	0.94
1.5	5540.10	2001.72	5959.70	1982.16	0.93
1.75	5765.68	1863.46	6222.02	1769.57	0.93
2	6011.00	1562.92	6220.69	1438.72	0.97
2.33	6353.06	1329.77	6243.38	1254.20	1.02
2.67	6492.17	1304.27	6056.65	1083.61	1.07
3	6309.19	1430.73	5764.98	1095.34	1.09
3.5	5401.31	1397.65	5023.92	1165.50	1.08
4	4362.09	1303.58	4121.67	1254.90	1.06
5	2519.38	862.83	2328.46	845.65	1.08
6	1471.41	587.36	1366.09	604.82	1.08
7	829.12	365.81	773.13	460.51	1.07
8	451.16	276.19	430.60	335.83	1.05
10	77.15	129.71	79.76	151.22	0.97
12	0.00	0.00	0.00	0.00	.
14	0.00	0.00	0.00	0.00	.

Clavulanic acid: ng/mL, n=47 (1=Test, 2=Reference)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	85.01	85.59	88.75	89.68	0.96
0.67	294.27	203.42	295.82	189.19	0.99
1	419.76	197.55	409.39	176.65	1.03
1.25	456.13	189.92	448.24	170.85	1.02
1.5	462.98	173.08	460.33	142.09	1.01
1.75	451.16	182.09	443.86	132.58	1.02
2	408.72	167.52	406.00	133.82	1.01
2.33	363.53	166.46	359.86	141.99	1.01
2.67	308.22	168.57	295.28	135.92	1.04
3	251.97	167.18	235.11	125.93	1.07
3.5	175.72	131.42	160.57	92.44	1.09
4	119.87	102.25	106.76	79.00	1.12
5	42.42	60.93	36.07	46.26	1.18
6	12.44	31.63	8.98	24.40	1.39
7	2.59	12.45	1.09	7.44	2.39
8	0.00	0.00	0.00	0.00	.
10	0.00	0.00	0.00	0.00	.
12	0.00	0.00	0.00	0.00	.
14	0.00	0.00	0.00	0.00	.

FIG 3. PLASMA AMOXICILLIN LEVELS

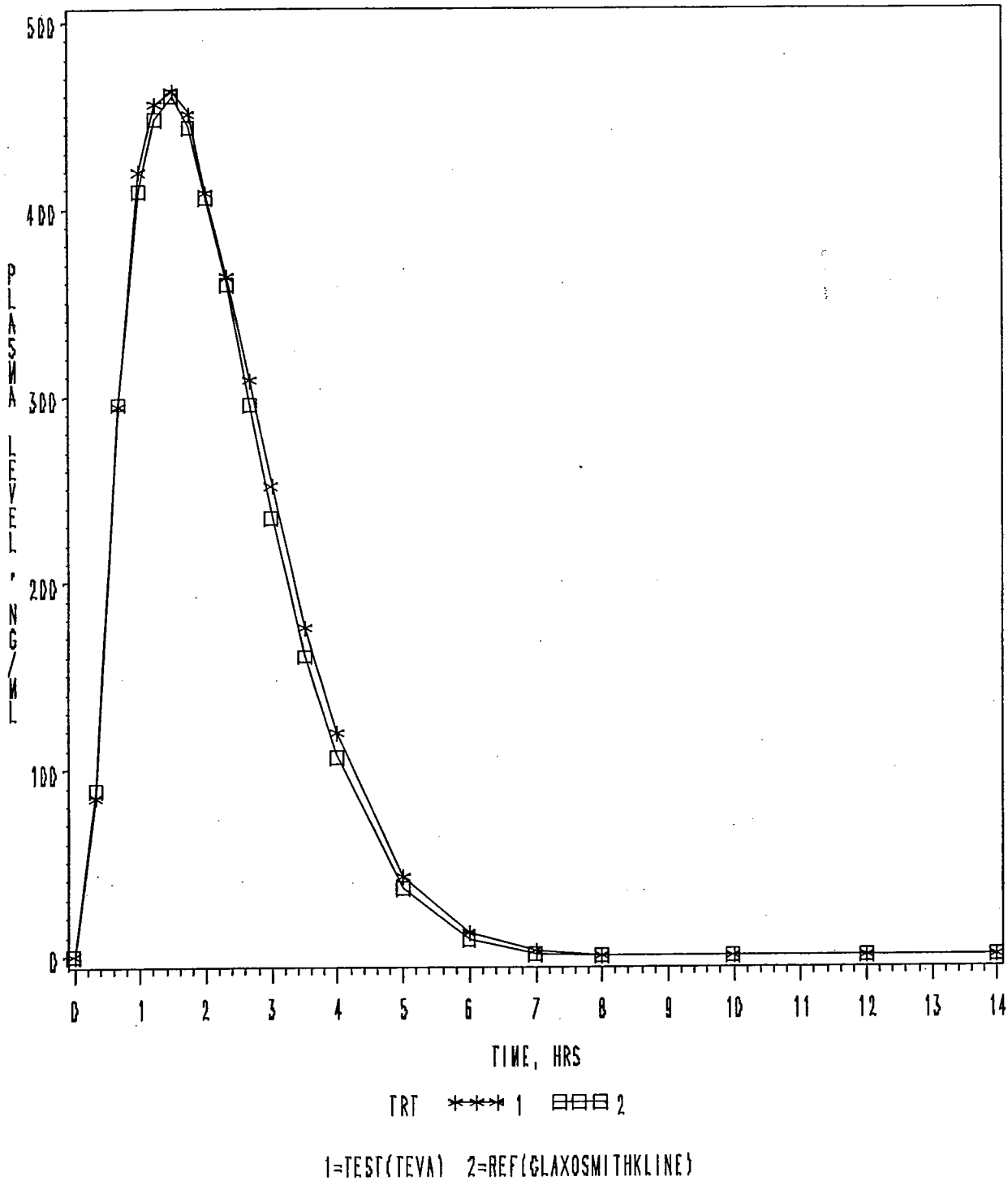
AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION, 600 MG/42.9 MG, ANDA #65-162
UNDER FED CONDITIONS
DOSE=1 X 600 MG/42.9 MG



1=TEST(TEVA) 2=REF(GLAXOSMITHKLINE)

FIG 4. PLASMA CLAVULANIC ACID LEVELS

AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION, 600 MG/42.9 MG, ANDA #65-162
UNDER FED CONDITIONS
DOSE=1 X 600 MG/42.9 MG



1=TEST(TEVA) 2=REF(GLAXOSMITHKLINE)

B. Formulation Data

Ingredients	Amount per tablet	%w/w^
Amoxicillin Trihydrate USP*		
Clavulanate Potassium [redacted] **		
Colloidal Silicon Dioxide, NF		
Mannitol, USP		
Sodium Saccharin, USP		
Citric Acid [redacted] USP		
Sodium Citrate ([redacted], USP		
Xanthan Gum, NF		
Aspartame, NF		
[redacted] USP)		
[redacted](spray dried) Orange Flavor #739 [redacted] (PB82)		
[redacted] (spray dried) Raspberry [redacted] #954 [redacted] (BK77)		
Total Weight		

*1.148 mg of Amoxicillin Trihydrate = 1 mg Amoxicillin anhydrous

** [redacted]

^ Percentage is calculated on weight/weight basis of powder constituents only.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

C. Dissolution Data

Table 1

Amoxicillin

Sampling Time (min)	Test Product, 600 mg/42.9 mg/5 mL Lot No. 10995P1			Reference Product, 600 mg/42.9 mg/5 mL Lot No. TC2009		
	Mean	%CV	Range	Mean	%CV	Range
5	77.8	26.22		102.1	1.11	
10	99.1	10.04		104.7	0.59	
15	105.0	2.39		105.2	0.54	
20	105.5	1.16		105.5	0.48	
25	105.9	0.67		105.2	0.45	

Clavulanic acid

Sampling Time (min)	Test Product, 600 mg/42.9 mg/5 mL Lot No. 10995P1			Reference Product, 600 mg/42.9 mg/5 mL Lot No. TC2009		
	Mean	%CV	Range	Mean	%CV	Range
5	94.7	15.53		104.5	0.93	
10	108.2	5.21		104.9	0.48	
15	111.1	1.12		104.5	0.51	
20	110.8	1.27		104.2	0.59	
25	110.8	0.68		103.6	0.56	

APPEARS THIS WAY
ON ORIGINAL

D. Consult Reviews

None

E. SAS outputs

	Fasting study	Fed study
Amoxicillin data and output	651621.doc	651625.doc
Clavulanic acid data and output	651623.doc	651627.doc

F. Additional Attachments

None

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-162 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
600 mg/42.9 mg (base)/5 mL

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 2 (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than——%(Q) of the labeled amount of amoxicillin in the dosage form is dissolved in 15 minutes.

Not less than —%(Q) of the labeled amount of clavulanic acid in the dosage form is dissolved in 15 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments a re 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 f or 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

CC: ANDA 65-162
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

9/5/03

Printed in final on 9/5/03

Endorsements: (Final with Dates)
HFD-655/ Dhariwal 9/5/03
HFD-655/ Nerurkar
HFD-650/ D. Conner 9/5/03

BIOEQUIVALENCY - ACCEPTABLE Submission date: 12/27/2002

1. **FASTING STUDY** (STF) Strengths: 600/42.9 mg/5 mL
Clinical: [redacted] **Outcome: AC**

Analytical: Novopharm Limited
1290 Ellesmere Road, Toronto
Ontario, Canada

2. **FOOD STUDY** (STP) Strengths: 600/42.9 mg/5 mL
Clinical: [redacted] **Outcome: AC**

Analytical: Novopharm Limited
1290 Ellesmere Road, Toronto
Ontario, Canada

Outcome Decisions: **AC** - Acceptable

WinBio Comments: Fasting and fed studies acceptable.
Dissolution testing acceptable.

1/1

DIVISION OF BIOEQUIVALENCE

ANDA #: 65-162 SPONSOR : Teva

DRUG AND DOSAGE FORM : Amoxicillin and Clavulanate Potassium for Oral Suspension, USP

STRENGTH(S) : 600 mg/42.9 mg (base)/5 mL

TYPES OF STUDIES : Fasting and Fed

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : Novopharm Limited, Ontario, Canada

STUDY SUMMARY : The fasting and fed studies are acceptable.

DISSOLUTION : The dissolution testing was conducted by the FDA method. The results are acceptable.

DSI INSPECTION STATUS

Inspection needed: ~~Yes, if the sites have not been inspected recently~~. NO	Inspection status:	Inspection results:
First Generic Yes New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Kuldeep R. Dhariwal, Ph.D. BRANCH: II

INITIAL : KRD DATE : 9/5/03

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH: II

INITIAL : SNerurkar DATE : 9/5/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 9/5/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-162

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : February 14, 2003

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 14-FEB-2003

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Amoxicillin and Clavulanate Potassium For Oral Suspension USP, 600 mg/42.9 mg (base) to determine if the application is substantially complete for filing.

TEVA Pharmaceuticals USA, has submitted ANDA 65-162 for Amoxicillin and Clavulanate Potassium For Oral Suspension USP, 600 mg/42.9 mg (base). The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by TEVA on December 27, 2002 for its Amoxicillin and Clavulanate Potassium product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS
First Generic ANDA

ANDA# 65-162 FIRM NAME TEVA Pharmaceuticals USA

DRUG NAME Amoxicilline and Clavulanate Potassium for Oral Suspension USP

DOSAGE FORM Oral Suspension, 600 mg/42.9 mg/5 mL

Requested by: _____
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence

[X] **Study meets statutory requirements**

[ ] **Study does NOT meet statutory requirements**
Reason:

[ ] **Waiver meets statutory requirements** N/A

[ ] **Waiver does NOT meet statutory requirements**
Reason:

RECOMMENDATION: X COMPLETE ___INCOMPLETE

Reviewed by: Michele M. Mallory 2/19/03
Reviewer Date:

Team Leader Date: 2-19-03

Director, Division of Bioequivalence Date: 2/19/03

Item Verified:	Yes	No	Required Amount	Amount Sent	Comments
Protocol	✓				
Assay Methodology	✓				
Procedure SOP	✓				
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	✓				
Pre-screening of Patients	✓				
Chromatograms	✓				
Consent Forms	✓				
Composition	✓				
Summary of Study	✓				
Individual Data & Graphs, Linear & Ln	✓				
PK/PD Data Disk (or Elec Subm)	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				
Clinical Site	✓				
Analytical Site	✓				
Study Investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				

BIO Batch Size	✓				
Assay of Active Content Drug	✓				
Content Uniformity	N/A				
Date of Manufacture	✓				
Exp. Date of RLD	✓				
BioStudy Lot Numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data	N/A				

Additional Comments regarding the ANDA:

APPEARS THIS WAY
ON ORIGINAL

Created PDF Form:BIO CHKLST.PDF 05/15/02

RECORD OF TELEPHONE CONVERSATION

ANDA #: 65-162

DATE: February 5, 2003

TIME: 10:15 am

DRUG: Amoxicillin/Clavulanate Potassium for Oral Suspension USP,600 mg/42.9 mg per 5 mL

FIRM: Mr. Philip Erickson for TEVA Pharmaceuticals USA

FDA PARTICIPANTS: Emily Thomas

PHONE NUMBER: 215-591-3141

TOPIC: Revision needed

I asked Phil to revise p. 67 that had a typo. ✓ I asked him to send me the qualitative and quantitative breakdown for the two flavors used. I also asked him to provide a small rationale to support their stability data that did not contain the typical 3 month accelerated data points. ✓

↓

Did provide rationale
; actual data on 3 mo. accelerated (filed) 40°C/75% RH

asked for further breakdown than what was provide 2/7/03 for Raspberry flavor
~~Sandra~~ Vincent said he would contact
; get the info ASAP.

EThomas
2/7/03
4pm

RECORD OF TELEPHONE CONVERSATION

Susan Zuk and I called Vincent Andolina about TEVA's pending application for Amoxicillin and Clavulanate Potassium for Oral Suspension, 600 mg/42.9 mg/5 mL.

We explained that we had completed our review of the 11/6/03 amendment but before a recommendation for approval could be made, the firm would need to submit an amendment agreeing to a — month expiration date for the product. The firm is proposing 15 month data based on 15 month room temperature stability data. We said because the product failed accelerated stability as well as intermediate temperature data (at 3 months station) that we could not grant 15 months dating.

Mr. Andolina said he would discuss the issue with his associates and if the firm is in agreement with — month dating he would submit an amendment stating this.

This concluded the conversation.

V:\firmsnz\teva\telecons\65162.001

DATE:

12/16/03

ANDA NUMBER:

65-162

PRODUCT NAME:

Amox/Clavulanate Potassium for OS 600 mg/42.9 mg/5 mL

FIRM NAME:

TEVA

FIRM REPRESENTATIVE:

Vincent Andolina

PHONE NUMBER:

215-591-8642

FDA REPRESENTATIVES:

Susan Zuk
Mark Anderson

SIGNATURES:

Mark Anderson

Mark Anderson

RECORD OF TELEPHONE CONVERSATION

Richard Adams, Susan Zuk, and I called Vincent Andolina about TEVA's pending application for Amoxicillin and Clavulanate Potassium for Oral Suspension, 600 mg/42.9 mg/5 mL.

We had previously told the firm that their proposed product would be eligible only for — months expiration dating due to failing results on accelerated and intermediate stability conditions. The firm had provided 15 months satisfactory room temperature data and was requesting a 15 month expiration dating.

Mr. Andolina called back as a result of our first call and said the firm disagreed with the need for — month dating. Today's call was to address his concerns.

Mr. Andolina said the firm now has 18 months of acceptable room temperature data which he feels supports a 15 month dating for the product.

Mr. Adams said he had discussed the issue of expiration dating in the face of failing accelerated/intermediate data with Division management. He said that we would be able to approve the product for 15 months upon receipt of acceptable 18 month data. However he said due to continuing concerns about the effect of temperature excursions on the product, the firm would need to commit to placing the first 3 production batches on accelerated stability as well as room temperature and recall any batches that fail at the first month test station.

Mr. Andolina said he would be submitting an amendment with the 18 month data and the requested commitment.

V:\firmsnz\teva\telecons\65162.002

DATE:

1/8/04

ANDA NUMBER:

65-162

PRODUCT NAME:

Amox/Clavulanate Potassium for OS 600 mg/42.9 mg/5 mL

FIRM NAME:

TEVA

FIRM REPRESENTATIVE:

Vincent Andolina

PHONE NUMBER:

215-591-8642

FDA REPRESENTATIVES:

Richard Adams
Susan Zuk
Mark Anderson

SIGNATURES:

Mark Anderson
Mark Anderson

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-162

CORRESPONDENCE

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Phone: (215) 591 8642
FAX: (215) 591 8812

December 27, 2002

Gary Buehler, 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 AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP, 600 mg/ 42.9 mg per 5 mL

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Amoxicillin and Clavulanate Potassium For Oral Suspension USP, 600 mg/ 42.9 mg per 5 mL

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 **43** volumes; **21** for the archival copy and **22** for the review copy.

The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Amoxicillin and Clavulanate Potassium For Oral Suspension USP, 600 mg/42.9 mg per 5 mL manufactured by TEVA Pharmaceutical Industries, Ltd. to the reference listed drug, Augmentin® ES 600 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) 591-8642 or by facsimile at (215) 591-8812.

Sincerely,

Vincent Andolina

VA/st
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 8642
FAX: (215) 591 8812

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

L NEW CORRESP

NC

February 7, 2003

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

NEW CORRESPONDENCE

ANDA# 65-162
AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP, 600 mg/ 42.9 mg per 5 mL
NEW CORRESPONDENCE

Dear Mr. Buehler:

We submit herewith a new correspondence to the above-referenced original abbreviated new drug application in response to a February 5, 2003 telephone request from Ms. Emily Thomas of the Office of Generic Drugs. Specifically, Ms. Thomas requested the following information:

1. A revised copy of a Comparative Dissolution Study originally provided within the ANDA. Specifically, page 67 contains a typographical error.

2. Quantitative and Qualitative composition of the following ——— Flavors:
   a) ——— Orange Flavor # 739 (PB82)
   b) ——— Raspberry Powder # 954 —(BK77)

3. Rationale for the inclusion of the 6-month intermediate ICH stability data was submitted in the original ANDA.

The comments are addressed in the order in which they are presented above.

RECEIVED
FEB 10 2003
OGD / CDER

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

2/7/2003 TEVA LETTER

The information presented herein represents, in our opinion, a complete response to the request presented in the February 5, 2003 telephone conversation. This information is submitted for your continued review and acceptance of ANDA # 65-162. If there are any further questions, please do not hesitate to contact me at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,

Vincent Ambolino

VA/st
Enclosures

ANDA 65-162

FEB 20 2003

TEVA Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

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 conversations dated February 5, 2003 and February 7, 2003 and the correspondences dated February 7, 2003 and February 11, 2003.

NAME OF DRUG: Amoxicillin and Clavulanate Potassium for Oral Suspension, 600 mg/42.9 mg(base) per 5 mL

DATE OF APPLICATION: December 27, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 30, 2002

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,

Gregory D. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 65-162
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB GDavis 20-FEB-2003 date
HFD-615/EThomas, CSO Emily Thomas 2/12/03 date
Word File V:\Firmsnz\teva\ltrs&rev\65162.ack
F/T EST02/12/03
ANDA Acknowledgment Letter!

MINOR AMENDMENT

ANDA 65-162

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 27 2003

APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-8642

ATTN: Vincent Andolina FAX: 215-591-8812

FROM: Mark Anderson PROJECT MANAGER: 301-827-5789

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 27, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 600 mg/42.9 mg (base) per 5 mL.

Reference is also made to your amendment(s) dated: February 7, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments are provided.

MA

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

6/27/2003 FDA FAX

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Phone: (215) 591 8642
FAX: (215) 591 8812

November 6, 2003

ORIG AMENDMENT

N/AM

MINOR AMENDMENT

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

ANDA# 65-162
AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP,
600 mg/ 42.9 mg per 5 mL
MINOR AMENDMENT – RESPONSE TO JUNE 27, 2003 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a Minor Amendment to the above-referenced pending ANDA in response to your June 27, 2003 review letter. For ease of review, a copy of the letter is provided in **Attachment 1**. Comments are addressed in the order in which they were presented.

A. Deficiencies:

1. [redacted]

2. [redacted]

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information from

11/6/2003 TEVA LETTER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Phone: (215) 591 8642
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November 13, 2003

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

MINOR AMENDMENT

ORIG AMENDMENT
N/A MAF

ANDA# 65-162
AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP,
600 mg/ 42.9 mg per 5 mL
LABELING AMENDMENT – RESPONSE TO SEPTEMBER 17, 2003 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a Labeling Amendment to the above-referenced pending ANDA in response to your September 17, 2003 review letter from the Division of Labeling and Program Support. For ease of review, a copy of the letter is provided in **Attachment 1**. Comments are addressed in the order in which they were presented.

Labeling Deficiencies:

1. CONTAINER: 600 mg/42.9 mg per 5 mL – 100mL

   a. Main Panel

      i. Our container labeling has been revised for the strength of our drug product to read, " 600 mg/42.9 mg per 5 mL".

      ii. As requested by the Agency, we have added an asterisk next to "When reconstituted" on our container labeling.

      iii. We have relocated our Usual Dosage statement from the main panel to the side panel of our container labeling.

      iv. We have revised the spelling of the word shake on our container labeling

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Please find four copies of draft packaging insert and a comparison to our previous revision in **Attachment 3**.

Please note as we acknowledge the Agency request to submit final print labeling at this time, we intend to wait until the Agency has made their final comments before submitting the final print container labeling and package insert.

The information presented herein represents, in our opinion, a complete response to the September 17, 2003 review letter. We look forward to your continued review and approval of ANDA # 65-162. Should you have any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,

Vincent Andolina

VA/st
Enclosures

Administrative Offices:
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Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

January 9, 2004

ORIG AMENDMENT
N/Am
TELEPHONE AMENDMENT

Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
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ANDA# 65-162
AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP,
600 mg/ 42.9 mg per 5 mL
TELEPHONE AMENDMENT – RESPONSE TO DECEMBER 16, 2003 & JANUARY 8, 2004
TELEPHONE CONTACTS

Dear Mr. Buehler:

We submit herewith a Telephone Amendment to the above-referenced pending ANDA in response to a telephone deficiency communicated on December 16, 2003 by Mark Anderson, R.Ph., Project Manager, as well as a second contact on January 8, 2004 with Mr. Anderson, Richard Adams, Chemistry Team Leader; Susan Zuk, Ph.D., review chemist: and Yanping Pan, Ph.D., review chemist. Specifically, in the December 16, 2003 conversation Mr. Anderson requested a commitment from Teva to propose —month expiration dating for this product. During the second contact on January 8, 2003, Mr. Adams stated the Office of Generic Drugs would grant tentative 15-month expiration dating subject to Teva's commitment to place the first three production batches on accelerated and room temperature stability, and recall any batch which fails the first month test station for accelerated and/or any room temperature test conditions.

We have provided in **Attachment 1,** room temperature stability data at 18-months for the exhibit lot # 10995P1. It is Teva's opinion that the acceptable 18-month room temperature data provided herein easily supports an 18-month expiration date. However, given the Agency's historically conservative approach to Amoxicillin/Clavulanate products and in accord with the above referenced discussion, we propose 15-months expiration dating. To further support our proposal for 15-month expiration dating, we have provided in **Attachment 2** a table which summarizes the Assay and Related Substances stability data for Lot # 10995P1 at room temperature at 9-month through 18-months. According to the provided table, all results are well within the specifications.

In accord with our discussion, Teva will accept a tentative 15-month expiration date for this product, and commits to place the first three production batches on room temperature and accelerated stability, and recall any batch which fails the first month test station for accelerated and/or any room temperature conditions.

The information presented herein represents, in our opinion, a complete response to the December 16, 2003 and January 8, 2004 telephone contacts. We look forward to your approval of ANDA # 65-162. Should you have any questions regarding the information contained herein, please contact me at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,

Vincent Andolina

VA/st
Enclosures