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

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter(s)	
Approved Labeling	X
Labeling Review(s)	X
Medical Review(s)	
Bioequivalence Review(s)	X
Chemistry Review(s)	X
Statistical Review(s)	
Microbiology Review(s)	
Administrative Document(s)	X
Correspondence	X

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 Sue 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 Paul 3/5/04 for
HFD-613/L.Golson/3/05/04 3/5/04

V:\firmsnz\teva\ltrs&rev\65162apdltr.doc
F/T by: mda/3/5/04

Robert Lee West
3/12/2004

APPROVAL

comc satisfactory
Hayat Ayad 3/11/04

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

N
3

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

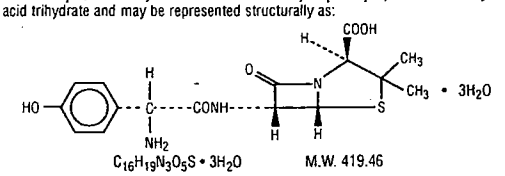
8675

℞ 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.

Manufactured By:
Novopharm Limited
Toronto, Canada M1B 2K9

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 2/2004

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