CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-205

Name: Amoxicillin and Clavulanate Potassium Tablets USP (Chewable), 200 mg/28.5 mg (base) and 400 mg/ 57 mg (base)

Sponsor: TEVA Pharmaceuticals USA

Approval Date: February 9, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-205

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APPLICATION NUMBER:

ANDA 65-205

APPROVAL LETTER

ANDA 65-205

FEB 9 2005

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

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 15, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Amoxicillin and Clavulanate Potassium Tablets USP, (Chewable), 200 mg/28.5 mg (base) and 400 mg/57 mg (base). 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 March 24, May 25, July 23 (2 amendments), September 7, October 22, November 4, November 10, November 19, December 1, and December 16, 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 Tablets USP, (Chewable), 200 mg/28.5 mg (base) and 400 mg/57 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Augmentin® Chewable Tablets, 200 mg/28.5 mg (base) and 400 mg/57 mg (base), respectively, 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.

Postmarketing 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 2/9/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-205
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff

HFD-643/S.Zuk/ Susan Zuk 2/7/05
HFD-643/S.Furness/ Yvonne Furness 2/7/05
HFD-617/R.Nguyen/ RN 2/3/05
HFD-613/J.Council/ } Acceptable per email attached. 2/3/05
HFD-613/L.Golson/ }

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F/T by: RTN/02/02/05

APPROVAL

Robert West 2/9/2005

Core sat's satisfactory.
Wayne Langwell 2/8/05.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-205

LABELING

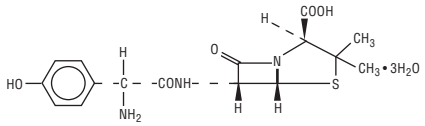
AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP, (CHEWABLE)

℞ only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of amoxicillin and clavulanate potassium chewable tablets and other antibacterial drugs, amoxicillin and clavulanate potassium chewable tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

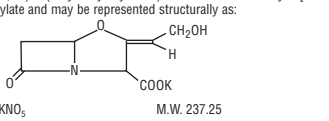
DESCRIPTION

Amoxicillin and clavulanate potassium tablets USP (chewable) are an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the ß-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 *(2S,5R,6R)-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 ß-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of ß-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated ß-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. Chemically, clavulanate potassium is potassium *(Z)-(2R,5R)*-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

Each chewable tablet contains 200 mg amoxicillin as the trihydrate and 28.5 mg clavulanic acid as the potassium salt or contains 400 mg amoxicillin as the trihydrate and 57 mg clavulanic acid as the potassium salt. Each amoxicillin and clavulanate potassium tablet USP, (chewable) 200 mg/28.5 mg contains 0.14 mEq potassium. Each amoxicillin and clavulanate potassium tablet USP, (chewable) 400 mg/57 mg contains 0.29 mEq potassium.

Inactive Ingredients: aspartame*, colloidal silicon dioxide, FD&C Red #40 aluminum lake, magnesium stearate, mannitol, microcrystalline cellulose, SA84 artificial ripe banana flavor, and S.D. artificial cherry flavor.

* See **PRECAUTIONS, Information for the Patient**.

CLINICAL PHARMACOLOGY

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of amoxicillin and clavulanate potassium. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin and clavulanate potassium can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In 1 study, the relative bioavailability of clavulanate was reduced when amoxicillin and clavulanate potassium was dosed at 30 and 150 minutes after the start of a high fat breakfast. The safety and efficacy of amoxicillin and clavulanate potassium have been established in clinical trials where amoxicillin and clavulanate potassium was taken without regard to meals.

Oral administration of single doses of amoxicillin and clavulanate potassium chewable tablets, 400 mg/57 mg and 400 mg/57 mg per 5 mL suspension to 28 adult volunteers yielded comparable pharmacokinetic data:

Dose*	$AUC_{0-\infty}$ (mcg.hr/mL)		C_{max} (mcg/mL)†	
(amoxicillin/clavulanate potassium)	amoxicillin (± S.D.)	clavulanate potassium (± S.D.)	amoxicillin (± S.D.)	clavulanate potassium (± S.D.)
400 mg/57 mg (5 mL of suspension)	17.29 ± 2.28	2.34 ± 0.94	6.94 ± 1.24	1.10 ± 0.42
400 mg/57 mg (1 chewable tablet)	17.24 ± 2.64	2.17 ± 0.73	6.67 ± 1.37	1.03 ± 0.33

* Administered at the start of a light meal.

† Mean values of 28 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

Oral administration of 5 mL of amoxicillin and clavulanate potassium oral suspension, 250 mg/62.5 mg per 5 mL or the equivalent dose of 10 mL amoxicillin and clavulanate potassium oral suspension, 125 mg/31.25 mg per 5 mL provides average peak serum concentrations approximately 1 hour after dosing of 6.9 mcg/mL for amoxicillin and 1.6 mcg/mL for clavulanic acid. The areas under the serum concentration curves obtained during the first 4 hours after dosing were 12.6 mcg.hr/mL for amoxicillin and 2.9 mcg.hr/mL for clavulanic acid when 5 mL of amoxicillin and clavulanate potassium oral suspension, 250 mg/62.5 mg per 5 mL or equivalent dose of 10 mL of amoxicillin and clavulanate potassium oral suspension, 125 mg/31.25 mg per 5 mL was administered to adult volunteers. One amoxicillin and clavulanate potassium chewable tablet, 250 mg/62.5 mg or 2 amoxicillin and clavulanate potassium chewable tablets, 125 mg/31.25 mg are equivalent to 5 mL of amoxicillin and clavulanate potassium oral suspension, 250 mg/62.5 mg per 5 mL and provide similar serum levels of amoxicillin and clavulanic acid.

Amoxicillin serum concentrations achieved with amoxicillin and clavulanate potassium are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half-life of amoxicillin after the oral administration of amoxicillin and clavulanate potassium is 1.3 hours and that of clavulanic acid is 1.0 hour. Time above the minimum inhibitory concentration of 1.0 mcg/mL for amoxicillin has been shown to be similar after corresponding q12h and q8h dosing regimens of amoxicillin and clavulanate potassium in adults and children.

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 oral suspension, 250 mg/62.5 mg per 5 mL.

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

Neither component in amoxicillin and clavulanate potassium is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

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.

Two hours after oral administration of a single 35 mg/kg dose of amoxicillin and clavulanate potassium oral suspension to fasting children, average concentrations of 3.0 mcg/mL of amoxicillin and 0.5 mcg/mL of clavulanic acid were detected in middle ear effusions.

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 ß-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a ß-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of ß-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated ß-lactamases frequently responsible for transferred drug resistance.

The formulation of amoxicillin and clavulanic acid in amoxicillin and clavulanate potassium protects amoxicillin from degradation by ß-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other ß-lactam antibiotics. Thus, amoxicillin and clavulanate potassium possesses the distinctive properties of a broad-spectrum antibiotic and a ß-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**.

Gram-Positive Aerobes

Staphylococcus aureus (ß-lactamase and non-ß-lactamase-producing)§

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

Gram-Negative Aerobes

Enterobacter species (Although most strains of *Enterobacter* species are resistant *in vitro*, clinical efficacy has been demonstrated with amoxicillin and clavulanate potassium in urinary tract infections caused by these organisms.)
Escherichia coli (ß-lactamase and non-ß-lactamase-producing)
Haemophilus influenzae (ß-lactamase and non-ß-lactamase-producing)
Klebsiella species (All known strains are ß-lactamase-producing)
Moraxella catarrhalis (ß-lactamase and non-ß-lactamase-producing)

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

Amoxicillin/clavulanic acid exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 mcg/mL or less against most (≥ 90%) strains of *Streptococcus pneumoniae*‡; MICs of 0.06 mcg/mL or less against most (≥ 90%) strains of *Neisseria gonorrhoeae*; MICs of 4 mcg/mL or less against most (≥ 90%) strains of staphylococci and anaerobic bacteria; and MICs of 8 mcg/mL or less against most (≥ 90%) strains of other listed organisms. 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.

‡ Because amoxicillin has greater *in vitro* activity against *S. pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin.

Gram-Positive Aerobes

Enterococcus faecalis¶
Staphylococcus epidermidis (ß-lactamase and non-ß-lactamase-producing)
Staphylococcus saprophyticus (ß-lactamase and non-ß-lactamase-producing)
Streptococcus pneumoniae¶**
Streptococcus pyogenes¶**
viridans group Streptococcus¶**

Gram-Negative Aerobes

Eikenella corrodens (ß-lactamase and non-ß-lactamase-producing)
Neisseria gonorrhoeae¶ (ß-lactamase and non-ß-lactamase-producing)
Proteus mirabilis¶ (ß-lactamase and non-ß-lactamase-producing)

Anaerobic Bacteria

Bacteroides species, including *Bacteroides fragilis* (ß-lactamase and non-ß-lactamase-producing)
Fusobacterium species (ß-lactamase and non-ß-lactamase-producing)
Peptostreptococcus species**

¶ Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to these organisms.

** These are non-ß-lactamase-producing organisms, and therefore, are susceptible to amoxicillin alone.

Susceptibility Testing

Dilution Techniques

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of 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:

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For gram-negative enteric aerobes:

MIC (mcg/mL)	Interpretation
≤ 8/4	Susceptible (S)
16/8	Intermediate (I)
≥ 32/16	Resistant (R)

For *Staphylococcus*†† and *Haemophilus* species:

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

†† Staphylococci which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

For *S. pneumoniae* from non-meningitis sources: Isolates should be tested using amoxicillin/clavulanic acid and the following criteria should be used:

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

Note: These interpretive criteria are based on the recommended doses for respiratory tract infections.

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)††
E. coli ATCC 25922	2 to 8
E. coli ATCC 35218	4 to 16
E. faecalis ATCC 29212	0.25 to 1.0
H. influenzae ATCC 49247	2 to 16
S. aureus ATCC 29213	0.12 to 0.5
S. pneumoniae ATCC 49619	0.03 to 0.12

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

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 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:

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For *Staphylococcus*§§ species and *H. influenzae*[a]:

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

For other organisms except *S. pneumoniae*[b] and *N. gonorrhoeae*[c]:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
14 to 17	Intermediate (I)
≤ 13	Resistant (R)

§§ Staphylococci which are resistant to methicillin/oxacillin must be considered as resistant to amoxicillin/clavulanic acid.

[a] A broth microdilution method should be used for testing *H. influenzae*. Beta-lactamase negative, ampicillin-resistant strains must be considered resistant to amoxicillin/clavulanic acid.

[b] 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. An amoxicillin/clavulanic acid MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤ 19 mm.

[c] A broth microdilution method should be used for testing *N. gonorrhoeae* and interpreted according to penicillin breakpoints.

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)
E. coli ATCC 25922	19 to 25 mm
E. coli ATCC 35218	18 to 22 mm
S. aureus ATCC 25923	28 to 36 mm

INDICATIONS AND USAGE

Amoxicillin and clavulanate potassium chewable tablets are indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections

Caused by ß-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

Otitis Media

Caused by ß-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

Sinusitis

Caused by ß-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

Skin and Skin Structure Infections

Caused by ß-lactamase-producing strains of *S. aureus, E. coli* and *Klebsiella* spp.

Urinary Tract Infections

Caused by ß-lactamase-producing strains of *E. coli, Klebsiella* spp. and *Enterobacter* spp.

While amoxicillin and clavulanate potassium chewable tablets are indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with amoxicillin and clavulanate potassium chewable tablets due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and ß-lactamase-producing organisms susceptible to amoxicillin and clavulanate potassium chewable tablets should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *S. pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and amoxicillin and clavulanate potassium chewable tablets. (See **Microbiology.**)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of amoxicillin and clavulanate potassium chewable tablets and other antibacterial drugs, amoxicillin and clavulanate potassium chewable tablets 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.

Bacteriological studies, to determine the causative organisms and their susceptibility to amoxicillin and clavulanate potassium chewable tablets, should be performed together with any indicated surgical procedures.

CONTRAINDICATIONS

Amoxicillin and clavulanate potassium chewable tablets are 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, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN AND CLAVULANATE POTASSIUM 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**

AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP, (CHEWABLE)

AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP, (CHEWABLE)

Iss. 12/2004

ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin and 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 *C. difficile* colitis.

Amoxicillin and clavulanate potassium should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin and 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

While amoxicillin and clavulanate potassium 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 during prolonged therapy.

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.

Prescribing amoxicillin and clavulanate potassium chewable tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for the Patient

Amoxicillin and clavulanate potassium may be taken every 8 hours or every 12 hours, depending on the strength of the product prescribed. Each dose should be taken with a meal or snack to reduce the possibility of gastrointestinal upset. Many antibiotics can cause diarrhea. If diarrhea is severe or lasts more than 2 or 3 days, call your doctor.

Patients should be counseled that antibacterial drugs including amoxicillin and clavulanate potassium chewable tablets, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When amoxicillin and clavulanate potassium chewable tablets are 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 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 chewable tablets or other antibacterial drugs in the future.

Phenylketonurics

Each amoxicillin and clavulanate potassium chewable tablet, 200 mg/28.5 mg contains 3.4 mg phenylalanine; each amoxicillin and clavulanate potassium chewable tablet, 400 mg/57 mg contains 6.7 mg phenylalanine. There are other amoxicillin and clavulanate potassium products that do not contain phenylalanine and can be used by phenylketonurics. Contact your physician or pharmacist.

Drug Interactions

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin and clavulanate potassium may result in increased and prolonged blood levels of amoxicillin. Coadministration 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 and allopurinol administered concurrently.

In common with other broad-spectrum antibiotics, amoxicillin and clavulanate potassium 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, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis

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.

Impairment of Fertility

Amoxicillin and clavulanate potassium at oral doses of up to 1,200 mg/kg/day (5.7 times the maximum human dose, 1,480 mg/m^2/day, 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, equivalent to 7,200 and 4,080 mg/m^2/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), 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 the milk; therefore, caution should be exercised when amoxicillin and clavulanate potassium is administered to a nursing woman.

Pediatric Use

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of amoxicillin and clavulanate potassium should be modified in pediatric patients younger than 12 weeks (3 months). (See **DOSAGE AND ADMINISTRATION**, **Pediatric**.)

ADVERSE REACTIONS

Amoxicillin and clavulanate potassium is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. From the original premarketing studies, where both pediatric and adult patients were enrolled, the most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: Abdominal discomfort, flatulence, and headache.

In pediatric patients (aged 2 months to 12 years), 1 U.S./Canadian clinical trial was conducted which compared amoxicillin and clavulanate potassium 45 mg/6.4 mg/kg/day (divided q12h) for 10 days versus amoxicillin and clavulanate potassium 40 mg/10 mg/kg/day (divided q8h) for 10 days in the treatment of acute otitis media. A total of 575 patients were enrolled, and only the suspension formulations were used in this trial. Overall, the adverse event profile seen was comparable to that noted above; however, there were differences in the rates of diarrhea, skin rashes/urticaria, and diaper area rashes. (See **CLINICAL STUDIES**.)

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. Crystalluria has also been reported (see **OVERDOSAGE**).

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 (brown, yellow, or gray staining) has been reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

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, 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 center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.[3]

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adult and pediatric patients. In case of overdosage, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin crystalluria.

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

Dosage

Pediatric Patients

Based on the amoxicillin component, amoxicillin and clavulanate potassium chewable tablets should be dosed as follows:

Neonates and infants aged < 12 weeks (3 months)

Due to incompletely developed renal function affecting elimination of amoxicillin in this age group, the recommended dose of amoxicillin and clavulanate potassium chewable tablets is 30 mg/kg/day divided q12h, based on the amoxicillin component. Clavulanate elimination is unaltered in this age group. Experience with the 200 mg/28.5 mg per 5 mL formulation in this age group is limited and, thus, use of the 125 mg/31.25 per 5 mL oral suspension is recommended.

Patients aged 12 weeks (3 months) and older

INFECTIONS	DOSING REGIMEN	
	q12h*	q8h
	200 mg/5 mL or 400 mg/5 mL oral suspension†	125 mg/5 mL or 250 mg/5 mL oral suspension
Otitis media‡, sinusitis, lower respiratory tract infections, and more severe infections	45 mg/kg/day q12h	40 mg/kg/day q8h
Less severe infections	25 mg/kg/day q12h	20 mg/kg/day q8h

* The q12h regimen is recommended as it is associated with significantly less diarrhea. (See **CLINICAL STUDIES**.) However, the q12h formulations (200 mg and 400 mg) contain aspartame and should not be used by phenylketonurics.

† Each strength of amoxicillin and clavulanate potassium suspension is available as a chewable tablet for use by older children.

‡ Duration of therapy studied and recommended for acute otitis media is 10 days.

Pediatric patients weighing 40 kg and more

Should be dosed according to the following adult recommendations

The usual adult dose is one amoxicillin and clavulanate potassium tablet, 500 mg/125 mg every 12 hours or one amoxicillin and clavulanate potassium tablet, 250 mg/125 mg every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one amoxicillin and clavulanate potassium tablet, 875 mg/125 mg every 12 hours or one amoxicillin and clavulanate potassium tablet, 500 mg/125 mg every 8 hours. Among adults treated with 875 mg/125 mg tablets every 12 hours, significantly fewer experienced severe diarrhea or withdrawals with diarrhea versus adults treated with 500 mg/125 mg tablets every 8 hours. For detailed adult dosage recommendations, please see complete prescribing information for amoxicillin and clavulanate potassium tablets.

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

Adults

Adults who have difficulty swallowing may be given the 125 mg/5 mL or 250 mg/5 mL suspension in place of the 500 mg tablet. The 200 mg/5 mL suspension or the 400 mg/5 mL suspension may be used in place of the 875 mg tablet. See dosage recommendations above for children weighing 40 kg or more.

The amoxicillin and clavulanate potassium 250 mg tablet and the 250 mg chewable tablet do not contain the same amount of clavulanic acid (as the potassium salt). The amoxicillin and clavulanate potassium 250 mg tablet contains 125 mg of clavulanic acid, whereas the 250 mg chewable tablet contains 62.5 mg of clavulanic acid. Therefore, the amoxicillin and clavulanate potassium 250 mg tablet and the 250 mg chewable tablet should *not* be substituted for each other, as they are not interchangeable.

Due to the different amoxicillin to clavulanic acid ratios in the amoxicillin and clavulanate potassium 250 mg tablet (250/125) versus the amoxicillin and clavulanate potassium 250 chewable tablet (250/62.5), the amoxicillin and clavulanate potassium 250 mg tablet should not be used until the child weighs at least 40 kg and more.

Administration

Amoxicillin and clavulanate potassium chewable tablets may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when amoxicillin and clavulanate potassium chewable tablets are administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, amoxicillin and clavulanate potassium chewable tablets should be taken at the start of a meal.

HOW SUPPLIED

Amoxicillin and clavulanate potassium tablets USP, (chewable) are available as follows:

200 mg/28.5 mg - mottled pink, oval, biconvex tablets, debossed with "93" on one side and "2270" on the other side in bottles of 20 tablets.

400 mg/57 mg - mottled pink, oval, biconvex tablets, debossed with "93" on one side and "2272" on the other side in bottles of 20 tablets.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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

CLINICAL STUDIES

In pediatric patients (aged 2 months to 12 years), 1 U.S./Canadian clinical trial was conducted which compared amoxicillin and clavulanate potassium 45 mg/6.4 mg/kg/day (divided q12h) for 10 days versus amoxicillin and clavulanate potassium 40 mg/10 mg/kg/day (divided q8h) for 10 days in the treatment of acute otitis media. Only the suspension formulations were used in this trial. A total of 575 patients were enrolled, with an even distribution among the two treatment groups and a comparable number of patients were evaluable (i.e., ≥ 84%) per treatment group. Strict otitis media-specific criteria were required for eligibility and a strong correlation was found at the end of therapy and follow-up between these criteria and physician assessment of clinical response. The clinical efficacy rates at the end of therapy visit (defined as 2 to 4 days after the completion of therapy) and at the follow-up visit (defined as 22 to 28 days post-completion of therapy) were comparable for the 2 treatment groups, with the following cure rates obtained for the evaluable patients: At end of therapy, 87.2% (n = 265) and 82.3% (n = 260) for 45 mg/kg/day q12h and 40 mg/kg/day q8h, respectively. At follow-up, 67.1% (n = 249) and 68.7% (n = 243) for 45 mg/kg/day q12h and 40 mg/kg/day q8h, respectively.

The incidence of diarrhea††† was significantly lower in patients in the q12h treatment group compared to patients who received the q8h regimen (14.3% and 34.3%, respectively). In addition, the number of patients with either severe diarrhea or who were withdrawn with diarrhea was significantly lower in the q12h treatment group (3.1% and 7.6% for the q12h/10 day and q8h/10 day, respectively). In the q12h treatment group, 3 patients (1.0%) were withdrawn with an allergic reaction, while 1 patient (0.3%) in the q8h group was withdrawn for this reason. The number of patients with a candidal infection of the diaper area was 3.8% and 6.2% for the q12h and q8h groups, respectively.

It is not known if the finding of a statistically significant reduction in diarrhea with the oral suspensions dosed q12h, versus suspensions dosed q8h, can be extrapolated to the chewable tablets. The presence of mannitol in the chewable tablets may contribute to a different diarrhea profile. The q12h oral suspensions are sweetened with aspartame only.

††† Diarrhea was defined as either: (a) 3 or more watery or 4 or more loose/watery stools in 1 day; OR (b) 2 watery stools per day or 3 loose/watery stools per day for 2 consecutive days.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25. NCCLS, Villanova, PA, Dec. 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standard for Antimicrobial Disk Susceptibility Tests – Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24. NCCLS, Villanova, PA, Dec. 1993.
3. Swanson-Biearman B, Dean BS, Lopez G, Krenzelok EP. The effects of penicillin and cephalosporin ingestions in children less than six years of age. *Vet Hum Toxicol* 1988;30:66-67.

Manufactured In Canada By:
NOVOPHARM LIMITED
Toronto, Canada M1B 2K9

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 12/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-205

LABELING REVIEWS

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

ANDA Number: 65-205

Dates of Submission: December 15, 2003

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, (Chewable) 200 mg/28.5 mg (base) and 400 mg/57 mg (base)

Labeling Deficiencies:

1. CONTAINER: 200 mg/28.5 mg and 400 mg/57 mg - 20s

   a. Revise the name of your drug product to read, "Amoxicillin and Clavulanate Potassium Tablets USP, (Chewable)".

   b. Differentiate each strength by using contrasting colors, boxing and/or by some other means.

   c. Main Panel

      Print "Chewable Tablets" in the same font size as the active ingredients.

   d. Side Panel

      i. First sentence

         A) Revise to read, "Each chewable tablet ...".

         B) Include the clavulanic acid strength.

      ii. Immediately following the first sentence, include the potassium content per tablet.

      iii. Please revise your storage temperature recommendation to read: "Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

2. INSERT

   a. General Comments

      i. Update your insert labeling to be in accord with the reference listed drug, Augmentin® (Amoxicillin and Clavulanate Potassium Powder for Oral Suspension and Chewable Tablets USP) by GlaxoSmithKline/NDA 50-597/S-042 approved June 3, 2004. See attachment.

      ii. Delete the terminal zero appearing in the text, [i.e.,"1" instead of "1.0"].

iii. Throughout the text include the strength of both active ingredients following the drug product name, [i.e. "Amoxicillin and Clavulanate Potassium Chewable Tablets 200 mg/28.5 mg"].

iv. See comment 1(a) under CONTAINER.

b. DESCRIPTION

Add an asterisk following the inactive ingredient "aspartame*" and the statement "*See PRECAUTIONS – Information for the Patient" at the end of the paragraph.

c. CLINICAL PHARMACOLOGY

Table

Revise ——— to read "400 mg/57 mg".

b. HOW SUPPLIED

Please revise your storage temperature recommendation to read: "Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

Please revise you labels and labeling, as instructed above and submit in electronic format. The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the guidance for industry regarding electronic submissions (Providing Regulatory Submissions in Electronic Format - ANDAs, issued 6/2002) available at the following website: http://www.fda.gov/cder/guidance/5004fnl.htm.
Although the guidance specifies labeling to be submitted in PDF format, we request that labeling also be submitted in MS Word format to assist our review.

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 the reference listed drug with all differences annotated and explained.

Adolph Vezza for

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

Attachment: Augmentin® insert labeling

APPEARS THIS WAY
ON ORIGINAL

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 27		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?		X	
Is the corporate logo larger than 1/3 container label? (No regulation – see ASHP guidelines)		X	

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		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 ingredients differ from the RLD.	*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		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. Does the 200 mg/28.5 mg tablet contain 3.4 mg phenylalanine and the 400 mg/57 mg contain 6.7 mg phenylalanine?

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

3. Does the 200 mg/28.5 mg tablet contain 0.14 mEq potassium and the 400 mg/57 mg contain 0.29 mEq potassium?

4. We are requesting the firm to revise the name of the drug product to read, "Amoxicillin and Clavulanate Potassium Tablets USP, (Chewable)" instead of "Amoxicillin and Clavulanate Potassium Chewable Tablets, USP".

FOR THE RECORD:

1. Labeling model

   Augmentin® (Amoxicillin/clavulanate potassium powder for oral suspension and chewable tablets), NDA 50-597/S-042, approved June 3, 2004 by GlaxoSmithKline.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
   [Vol. B1.1, p 7796]

3. The firm's physical description of the tables in the DESCRIPTION section are consistent with the finished dosage statements.
   [Vol. B1.3, p. 8598 & 8607].

4. Manufacturing Facility

   -Manufacturing: Novopharm/Ontario Canada
   -Packaged and labeled product distributed through the warehouse location in North Wales, PA.
   -Analytical testing of raw materials: Novopharm & Teva
   [Vol. B1.2, p.7907, 7908]

5. Patent and exclusivity –none pending

6. Package Sizes

   RLD 20s
   ANDA 20s

7. Container/Closure

   Both strengths/20s – Round natural HDPE bottles with CRC
   [Vol. B1.3, p.8294, 8295]

8. Storage and/or Dispensing:

USP -Packaging and storage— Preserve in tight containers.

NDA – Store dry powder at or below 25°C (77°F). Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days.

ANDA - Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]
Reconstituted suspension must be stored under refrigeration and discarded after 10 days

9. The firm amended the application to include a new strength, 200 mg/28.5 mg per 5 mL.

Date of Review: 9/9/04

Date of Submission: 12/15/03

Jacqueline Council, Pharm.D.
Primary Reviewer

9-16-04
Date

Team Leader
Captain Lillie Golson

9-20-04
Date

cc:

ANDA: 65-205
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\65205na2.l..doc
Review

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

ANDA Number: 65-205

Dates of Submission: October 22, 2004

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, (Chewable) 200 mg/28.5 mg (base) and 400 mg/57 mg (base)

Labeling Deficiencies:

1. INSERT

   a. General Comment

      Retain the use of the name "Amoxicillin and Clavulanate Potassium Tablets USP, (Chewable)" in the TITLE and HOW SUPPLIED sections and wherever you use the "USP" designation. In all other sections of your insert labeling you may use "Amoxicillin and Clavulanate Potassium chewable tablets".

   b. PRECAUTIONS/Phenylketonurics

      Add the following as the two sentences:

         There are other Amoxicillin and Clavulanate Potassium products that do not contain phenylalanine and can be used by phenylketonurics. Contact your physician or pharmacist.

   c. ADVERSE REACTIONS

      Hemic and Lymphatic Systems

         Revise "leucopenia" to read "leukopenia".

   d. DOSAGE AND ADMINISTRATION

      We note that you deleted text previously included in your DOSAGE AND ADMINISTRATION section. Please note that you may omit the subsection, ". All other text should be retained.

Please revise you labels and labeling, as instructed above and submit in electronic format. The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the guidance for industry regarding electronic submissions (Providing Regulatory Submissions in Electronic Format - ANDAs, issued 6/2002) available at the following website: http://www.fda.gov/cder/guidance/5004fnl.htm.
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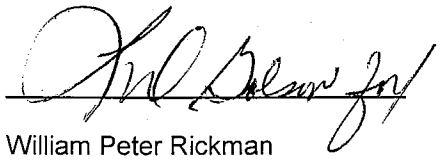
To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug with all differences annotated and explained.



William 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

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 27		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?		X	
Is the corporate logo larger than 1/3 container label? (No regulation – see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		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 ingredients differ from the RLD.	*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the		X	

difference acceptable?			
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.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		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. Yes. 200 mg tablets contain 3.4 mg phenylalanine and 400 mg tablets contain 6.7 mg pheylalanine.
2. Yes. Clavulanate potassium is produced by the fermentation of *Steptomyces clavuligerus.*
3. Yes. There are 0.14 mEq and 0.29 mEq in the tablets.
   [S.Z.]

-----Original Message-----
From: Nguyen, Ryan
Sent: Monday, November 01, 2004 2:39 PM
To: Zuk, Susan
Subject: FW: 65-205

1. Does the 200 mg/28.5 mg tablet contain 3.4 mg phenylalanine and the 400 mg/57 mg contain 6.7 mg phenylalanine?

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

3. Does the 200 mg/28.5 mg tablet contain 0.14 mEq potassium and the 400 mg/57 mg contain 0.29 mEq potassium?

4. We are requesting the firm to revise the name of the drug product to read, "Amoxicillin and Clavulanate Potassium Tablets USP, (Chewable)" instead of "Amoxicillin and Clavulanate Potassium Chewable Tablets, USP".

FOR THE RECORD:

1. Labeling model

   Augmentin® (Amoxicillin/clavulanate potassium powder for oral suspension and chewable tablets), NDA 50-597/S-042, approved June 3, 2004 by GlaxoSmithKline.

NOTE: The most current insert labeling, [S-043] provides for revised labeling to comply with the Final Rule entitled "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use" (68FR 6062, February 6, 2003). This supplement did not include the revisions approved in S-042. Therefore, S-042 was used as the labeling model. The firm has already included the "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use" in the insert labeling.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
[Vol. B1.1, p 7796]

3. The firm's physical description of the tables in the DESCRIPTION section are consistent with the finished dosage statements.
[Vol. B1.3, p. 8598 & 8607].

4. Manufacturing Facility

-Manufacturing: Novopharm/Ontario Canada
-Packaged and labeled product distributed through the warehouse location in North Wales, PA.
-Analytical testing of raw materials: Novopharm & Teva
[Vol. B1.2, p.7907, 7908]

5. Patent and exclusivity –none pending

6. Package Sizes

RLD 20s
ANDA 20s

7. Container/Closure

Both strengths/20s – Round natural HDPE bottles with CRC
[Vol. B1.3, p.8294, 8295]

8. Storage:

USP -Packaging and storage— Preserve in tight containers.

NDA – Store dry powder at or below 25°C (77°F). .

ANDA - Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]

9. Spoke w Vincent Andolina 10/5/04 regarding the Dec 22nd container labels. Teva wanted to use those labels in the validation batch. He said I OK'd this. Teva has made the revisions requested for after launch.

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 11/1/04

Date of Submission: 10/22/04

Primary Reviewer
Jacqueline Council, Pharm.D.

11/2/04
Date

Team Leader
Captain Lillie Golson

11/30/04
Date

cc:

ANDA: 65-205
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\65205na2.L.doc
Review

APPROVAL SUMMARY

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

ANDA Number: 65-205

Dates of Submission: December 16, 2004

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, (Chewable) 200 mg/28.5 mg (base) and 400 mg/57 mg (base)

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

Do you have 12 Final Printed Labels? Yes

1. CONTAINER: 200 mg/28.5 mg and 400 mg/57 mg - 20s
   Satisfactory as of the 10/22/04 submission. [Vol. 5.1]

2. Professional Package Insert Labeling:
   Satisfactory as of the 12/16/04 submission.
   Note: Insert labeling was submitted electronically. Insert code#: Revised 12/2004
   Electronic location: \\CDSESUBOGD1\N65205\N_000\2004-12-16
   [Vol. 6.1]

Revisions needed post-approval:
DOSAGE AND ADMINISTRATION/Adults/First paragraph.
Add the clavulanate strength.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Augmentin®

NDA Number: 50-597

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

NDA Firm: GlaxoSmithKline.

Date of Approval of NDA Insert and supplement #: S-042, approved June 3, 2004

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

Basis of Approval for the Carton Labeling: RLD

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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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 27		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?		X	
Is the corporate logo larger than 1/3 container label? (No regulation – see ASHP guidelines)		X	

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
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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.		X	
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Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

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NOTES/QUESTIONS TO THE CHEMIST

1. Yes. 200 mg tablets contain 3.4 mg phenylalanine and 400 mg tablets contain 6.7 mg pheylalanine.
2. Yes. Clavulanate potassium is produced by the fermentation of *Steptomyces clavuligerus.*
3. Yes. There are 0.14 mEq and 0.29 mEq in the tablets.
   [S.Z.]

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From: Nguyen, Ryan
Sent: Monday, November 01, 2004 2:39 PM
To: Zuk, Susan
Subject: FW: 65-205

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   NOTE: The most current insert labeling, [S-043] provides for revised labeling to comply with the Final Rule entitled "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use" (68FR 6062, February 6, 2003). This supplement did not include the revisions approved in S-042. Therefore, S-042 was used as the labeling model. The firm has already included the "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use" in the insert labeling.

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   [Vol. B1.1, p 7796]

3. The firm's physical description of the tablets in the DESCRIPTION section are consistent with the finished dosage statements.
   [Vol. B1.3, p. 8598 & 8607].

4. Manufacturing Facility

-Manufacturing: Novopharm/Ontario Canada
-Packaged and labeled product distributed through the warehouse location in North Wales, PA.
-Analytical testing of raw materials: Novopharm & Teva
[Vol. B1.2, p.7907, 7908]

5. Patent and exclusivity –none pending

6. Package Sizes

RLD 20s
ANDA 20s

7. Container/Closure

Both strengths/20s – Round natural HDPE bottles with CRC
[Vol. B1.3, p.8294, 8295]

8. Storage:

USP -Packaging and storage— Preserve in tight containers.

NDA – Store dry powder at or below 25°C (77°F). .

ANDA - Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]

9. The following was added as FTR#9 on the pink copy.

> "Spoke with Vincent Andolina on 10/5/04 regarding the December 22nd container labels. Teva wanted to use those labels in the validation batch. He said I Ok'ed this. Firm has made the revisions requested for after launch."
> [Per Team Leader, Lillie Golson].

10. Bioequivalence:

- The *in vivo* bioequivalence study conducted under fasting and fed conditions by Teva Pharmaceuticals comparing its amoxicillin-clavulanate potassium 400 mg/57 mg chewable tablet, USP to the reference product Augmentin® 400 mg/57 mg tablet (GlaxoSmithKline) was found to be acceptable by the Division of Bioequivalence.

- The formulation of Teva Pharmaceutical's amoxicillin clavulanate potassium 200 mg/28.5 mg chewable tablet, USP is proportional to the 400 mg/57 mg chewable tablet, which underwent *in vivo* testing. A waiver of bioequivalence study requirements for the 200 mg/28.5 mg chewable tablet was granted by the Division of Bioequivalence.

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 1/13/05

Date of Submission: 12/16/04

Primary Reviewer
Jacqueline Council, Pharm.D.

Jan 12-26-05
Date

Team Leader
Captain Lillie Golson

Jan 1/28/05
Date

cc:

ANDA: 65-205
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\65205..ap.L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-205

CHEMISTRY REVIEWS

ANDA 65-205

Amoxicillin and Clavulanate Potassium Chewable Tablets, USP

Teva Pharmaceuticals USA

Susan Zuk
Chemistry Division III, OGD

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-205

2. REVIEW #: 1

3. REVIEW DATE: 3/9/04

4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Gratuitous Amendment	02/23/04
Original ANDA	12/15/03

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road P.O. Box 1090 North Wales, PA 19454
Representative:	Philip Erickson
Telephone:	(215) 591-3000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Chewable Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The reference listed drug that is the basis for submission is Augmentin® Chewable Tablets manufactured by GlaxoSmithKline, NDA #50-726. There are no unexpired patents or exclusivities for this product.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Chewable tablet

12. STRENGTH/POTENCY: 200 + 28.5 mg and 400 + 57 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

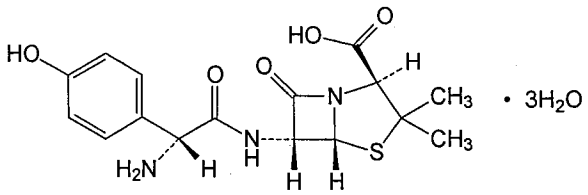
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

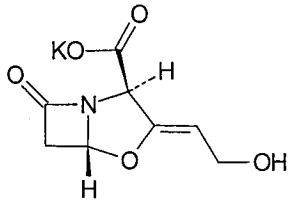
__X___Not a SPOTS product

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

Amoxicillin. 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	1/23/04	R. Ganunis
	II			3	A	3/17/03	S. Zuk
	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	1/7/04	
	III			4	A		
	III			3, 4	A	10/29/03	
	III			3, 4	A	1/21/04	

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	Novopharm acceptable DSM acceptable Fersinsa Pending	2/24/04 2/24/04	
Methods Validation	N/A		
Labeling	Pending		
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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-205

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is not recommended.
Minor Amendment required.

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)

Amoxicillin + Clavulanate Potassium Tablets (Chewable) contain the antibiotic Amoxicillin and the β-lactamase inhibitor Clavulanic acid. Amoxicillin is present as Amoxicillin Trihydrate. This antibacterial agent is a semi-synthetic analogue of ampicillin, derived from the basic penicillin nucleus 6-aminopenicillanic acid. Amoxicillin trihydrate is described as an off-white crystalline powder. Amoxicillin is degraded by exposure to acidic and oxidative environments.

Clavulanic Acid is present as Clavulanate Potassium. Clavulanic acid is a fermentation product of *Streptomyces clavuligerus*. The potassium salt is a white to off-white powder. It is highly hygroscopic and requires special care in handling. The ANDA holder purchases the [redacted]. Clavulanate Potassium is sensitive to degradation by base, oxidation and UV radiation.

The drug product is a chewable, flavored tablet. In addition to the active ingredients, Amoxicillin and Clavulanate Potassium, each tablet contains aspartame, FD&C Red No. 40 aluminum lake, magnesium stearate, mannitol, colloidal silicon dioxide, artificial banana and cherry flavors. Each 200 mg tablet contains 0.14 mEq potassium and 3.4 mg phenylalanine. Tablets are supplied in bottles of 20. Tablets should be stored at room temperature and protected from moisture.

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

Amoxicillin and Clavulanate Potassium Tablets are indicated for the treatment of infections caused by *H. influenza, M. catarrhalis, S. aureus, E. coli, Klebsiella spp., and Enterobacter spp.* The usual dosage is 1 tablet every 12 hours.

C. Basis for Approvability or Not-Approval Recommendation

The following deficiencies were found:

1.

2.

3.

4.

5.

6.

III. Administrative

A. Reviewer's Signature

Susan Zuk 3/16/04

B. Endorsement Block

Susan Zuk/3/9/04 Susan Zuk 3/16/04
Richard Adams/3/10/04 R.C. Adams 3/18/04
Mark Anderson/3/126/04 M Anderson 3/18/04

C. CC Block

Redacted 20 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 65-05
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SZuk/3/9/04 S Zuk 3/16/04

HFD-643/RAdams/3/10/04 R. C. Adams 3/18/04

HFD-617/MAnderson/3/16/04 M Anderson 3/18/04

F/T by mda/3/16/04

V:\FIRMSNZ\TEVA\LTRS&REV\65205.NA.R01

TYPE OF LETTER: NOT APPROVABLE -MINOR

ANDA 65-205

Amoxicillin and Clavulanate Potassium Chewable Tablets, USP

Teva Pharmaceuticals USA

Susan Zuk
Chemistry Division III, OGD

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-205

2. REVIEW #: 2

3. REVIEW DATE: 8/11/04

4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Gratuitous Amendment	02/23/04
Original ANDA	12/15/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	5/25/04
Telephone Amendment	7/23/04

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Address: 1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Representative: Philip Erickson

Telephone: (215) 591-3000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Chewable Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The reference listed drug that is the basis for submission is Augmentin® Chewable Tablets manufactured by

GlaxoSmithKline, NDA #50-726. There are no unexpired patents or exclusivities for this product.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Chewable tablet

12. STRENGTH/POTENCY: 200 + 28.5 mg and 400 + 57 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

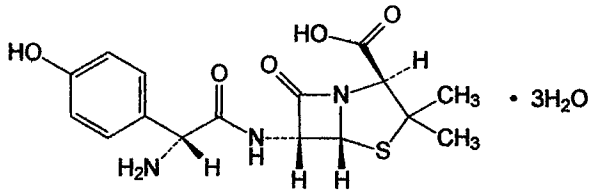
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

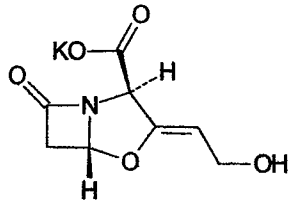
___X___Not a SPOTS product

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

Amoxicillin. 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	6/28/04	R. Ganunis
	II			3	A	3/17/03	S. Zuk
	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	1/7/04	
	III			4	A		
	III			3, 4	A	10/29/03	
	III			3, 4	A	1/21/04	

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	Overall acceptable	6/3/04	
Methods Validation	N/A		
Labeling	Pending		
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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-205

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Approval is recommended.

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)
Amoxicillin + Clavulanate Potassium Tablets (Chewable) contain the antibiotic Amoxicillin and the β-lactamase inhibitor Clavulanic acid. Amoxicillin is present as Amoxicillin Trihydrate. This antibacterial agent is a semi-synthetic analogue of ampicillin, derived from the basic penicillin nucleus 6-aminopenicillanic acid. Amoxicillin trihydrate is described as an off-white crystalline powder. Amoxicillin is degraded by exposure to acidic and oxidative environments.

Clavulanic Acid is present as Clavulanate Potassium. Clavulanic acid is a fermentation product of *Streptomyces clavuligerus.* The potassium salt is a white to off-white powder. It is highly hygroscopic and requires special care in handling. The ANDA holder purchases the [redacted]. Clavulanate Potassium is sensitive to degradation by base, oxidation and UV radiation.

The drug product is a chewable, flavored tablet. In addition to the active ingredients, Amoxicillin and Clavulanate Potassium, each tablet contains aspartame, FD&C Red No. 40 aluminum lake, magnesium stearate, mannitol, colloidal silicon dioxide, artificial banana and cherry flavors. Each 200 mg tablet contains 0.14 mEq potassium and 3.4 mg phenylalanine. Tablets are supplied in bottles of 20. Tablets should be stored at room temperature and protected from moisture.

B. Description of How the Drug Product is Intended to be Used
Amoxicillin and Clavulanate Potassium Tablets are indicated for the treatment of infections caused by *H. influenza, M. catarrhalis, S. aureus, E. coli, Klebsiella spp., and Enterobacter spp.* The usual dosage is 1 tablet every 12 hours.

C. Basis for Approvability or Not-Approval Recommendation

Approval is recommended based on the CMC review. Bio and Labeling approvals are still pending. The EER is acceptable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Susan Zuk/8/11/04

Scott Furness/8/11/04

Ryan Nguyen/

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 18 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 65-05
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SZuk/8/11/04

HFD-643/SFurness/8/11/04

HFD-617/RNguyen/

F/T by

V:\FIRMSNZ\TEVA\LTRS&REV\65205AP.R02.doc

TYPE OF LETTER: ANDA APPROVABLE

ANDA 65-205

Amoxicillin and Clavulanate Potassium Chewable Tablets, USP

Teva Pharmaceuticals USA

Susan Zuk
Chemistry Division III, OGD

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-205

2. REVIEW #: 3

3. REVIEW DATE: 12/7/04

4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Telephone Amendment	7/23/04
Amendment	5/25/04
Gratuitous Amendment	02/23/04
Original ANDA	12/15/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment	12/1/04
Telephone Amendment	11/19/04
Gratuitous Telephone Amendment	11/10/04

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Address: 1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Representative: Philip Erickson

Telephone: (215) 591-3000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Chewable Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The reference listed drug that is the basis for submission is Augmentin® Chewable Tablets manufactured by GlaxoSmithKline, NDA #50-726. There are no unexpired patents or exclusivities for this product.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Chewable tablet

12. STRENGTH/POTENCY: 200 + 28.5 mg and 400 + 57 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

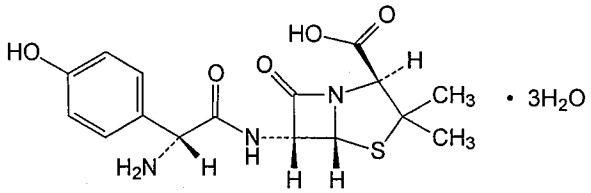
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

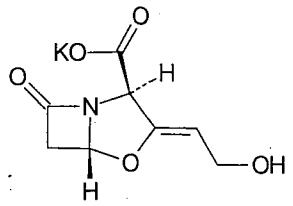
___X___Not a SPOTS product

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

Amoxicillin. 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
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	II			3	A	3/17/03	S. Zuk
	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	1/7/04	
	III			4	A		
	III			3, 4	A	10/29/03	
	III			3, 4	A	1/21/04	

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	Overall acceptable	6/3/04	S. Adams
Methods Validation	N/A		
Labeling	Acceptable	1/28/05	J. Council
Bioequivalence	Acceptable	9/23/04	E. Stier
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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-205

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Approval is recommended.

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)
Amoxicillin + Clavulanate Potassium Tablets (Chewable) contain the antibiotic Amoxicillin and the β-lactamase inhibitor Clavulanic acid. Amoxicillin is present as Amoxicillin Trihydrate. This antibacterial agent is a semi-synthetic analogue of ampicillin, derived from the basic penicillin nucleus 6-aminopenicillanic acid. Amoxicillin trihydrate is described as an off-white crystalline powder. Amoxicillin is degraded by exposure to acidic and oxidative environments.

Clavulanic Acid is present as Clavulanate Potassium. Clavulanic acid is a fermentation product of *Streptomyces clavuligerus.* The potassium salt is a white to off-white powder. It is highly hygroscopic and requires special care in handling. The ANDA holder purchases the [redacted]. Clavulanate Potassium is sensitive to degradation by base, oxidation and UV radiation.

The drug product is a chewable, flavored tablet. In addition to the active ingredients, Amoxicillin and Clavulanate Potassium, each tablet contains aspartame, FD&C Red No. 40 aluminum lake, magnesium stearate, mannitol, colloidal silicon dioxide, artificial banana and cherry flavors. Each 200 mg tablet contains 0.14 mEq potassium and 3.4 mg phenylalanine. Tablets are supplied in bottles of 20. Tablets should be stored at room temperature and protected from moisture.

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Amoxicillin and Clavulanate Potassium Tablets are indicated for the treatment of infections caused by *H. influenza, M. catarrhalis, S. aureus, E. coli, Klebsiella spp., and Enterobacter spp.* The usual dosage is 1 tablet every 12 hours.

C. Basis for Approvability or Not-Approval Recommendation

Approval is recommended based on the CMC review. The EER and labeling are acceptable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-643/SZuk/12/7/04/ 2/7/05

HFD-643/SFurness/ 2/7/05

HFD-617/RNguyen/

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 18 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

cc: ANDA 65-205
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SZuk/12/7/04 Sue Zuk 2/7/05

HFD-643/SFurness/ M Sue Furness 2/4/05

HFD-617/RNguyen/ R Nguyen 2/7/05

F/T by: RTN/02/03/05

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TYPE OF LETTER: ANDA APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-205

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-205
Drug Product Name	Amoxicillin and Clavulanate Potassium Chewable Tablets, USP
Strength	200 mg/28.5 mg and 400 mg/57 mg
Applicant Name	Teva Pharmaceuticals
Address	1090 Horsham Road P.O. Box 1090 North Wales, PA 19454
Submission Date(s)	12/15/03
Amendment Date(s)	09/07/04
Reviewer	**Ethan M. Stier**
First Generic	**No**
File Location	**V:\firms\Teva\ltrs&rev\65205N1203**

I. Executive Summary

This application references Augmentin® Tablets and includes one fasting and one fed BE study. The fasting study is a single-dose two-way crossover study using male and female healthy volunteers given a dose of 1X400 mg/57 mg. Bioequivalence is based on plasma levels of amoxicillin and clavulanic acid. The results (point estimate, 90% CI) of the fasting BE study for amoxicillin are: LAUCt of 0.98, 96.58-100.03, LAUC∞ of 0.98, 96.71-100.18, and LCmax of 1.03, 98.4-107.88. The results of the fasting BE study for clavulanic acid are LAUCt of 1.04, 95.76-113.52, LAUC∞ of 1.04, 95.75-112.50, and LCmax of 1.03, 95.33-111.64.

The fed study is a single-dose two way crossover study using male and female healthy volunteers given a dose of 1X400 mg/57 mg. The results (point estimate, 90% CI) of the fed BE study for amoxicillin are LAUCt of 0.98, 96.12-99.19, LAUC∞ of 0.99, 97.09-101.53, LCmax of 0.98, 93.19-102.43. The results of the fed BE study for clavulanic acid are LAUCt of 0.94, 87.19-101.52, LAUC∞ of 0.94, 87.83-101.54, and LCmax of 0.95, 85.64-104.47.

The applicant requests a waiver of in vivo BE study requirements for the 200 mg/28.5 mg strength. The formulation of the 200 mg/28.5 mg is proportional to the 400 mg/57 mg strength, which underwent in vivo testing. The dissolution testing for this product is acceptable. The waiver is granted.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Amoxicillin-Clavulanate Potassium Chewable Tablets, USP
Reference Product	Augmentin®
RLD Manufacturer	Glaxo Smith Kline
NDA No.	50-726
RLD Approval Date	May 31, 1996
Indication	Used to treat beta-lactamase and non beta-lactamase producing bacteria.

B. PK/PD Information

Bioavailability	Approximately 74-92% of a dose of amoxicillin is absorbed. Clavulanic acid is well absorbed.
Food Effect	Dosing in the fasted or the fed state has minimal effect on the pharmacokinetics of amoxicillin; however, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. High-fat meals decrease the absorption of clavulanic acid.
Tmax	Peak plasma concentrations of amoxicillin and clavulanic acid occur within 1-2.5 hours following oral administration.
Metabolism	Approximately 10% of an amoxicillin dose is metabolized to inactive derivatives. Clavulanic acid appears to be extensively metabolized, although the exact metabolism is not fully established.
Excretion	Approximately 50 to 70% of the amoxicillin and 25 to 40% of the clavulanic acid are excreted unchanged in the urine.
Half-life	The half lives of amoxicillin and clavulanic acid are 1.3 h and 1.0 h, respectively.
Relevant OGD or DBE History	DBE has previously approved two ANDAs (65-161 and 65-065) for amoxicillin/clavulanate potassium chewable tablets. Both ANDAs included fasting and fed studies.
Agency Guidance	None
Drug Specific Issues (if any)	NA

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	NA
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	NA
Vasoconstrictor Studies	No	NA
Clinical Endpoints	No	NA
Failed Studies	No	NA
Amendments	Yes	1

D. Pre-Study Bioanalytical Method Validation

	Amoxicillin	Clavulanic Acid
Analyte name	amoxicillin	clavulanic acid
Internal Standard	[redacted]	[redacted]
Method description	LC/MS	LC/MS
QC range	120.48 to 8433.60 ng/ml	90.19 to 1127.4 ng/ml
Standard curve range	40.08 to 12024.00 ng/ml	29.96 to 1497.800 ng/ml
Limit of quantitation	40.08 ng/ml	29.96 ng/ml
Average recovery of Drug (%)	77.05 to 78.95	Not Provided (see below)
Average Recovery of Int. Std (%)	84.27	Not Provided (see below)
QC Intraday precision range (%)	0.5 to 4.61	0.65 to 4.15
QC Intraday accuracy range (%)	97.57 to 103.99	95.16 to 108.15
QC Interday precision range (%)	2.7 to 4.78	4.42 to 6.62
QC Interday accuracy range (%)	99.15 to 103.79	96.02 to 100.77
Bench-top stability (hrs)	24 hours	7 hours
Stock stability (days)	6 hours	6 hours
Processed stability (hrs)	69 hours	dry stability: 71 hours reconstituted stability: 22 hours
Freeze-thaw stability (cycles)	at -20°C: 4 cycles at -80°C: 4 cycles	at -20°C: 4 cycles at -80°C: 4 cycles
Long-term storage stability (days)	at -80°C: 229 days	at -80°C: 60 days
Dilution integrity (Accuracy/C.V.)	101.49 to 105.79 (1.09 to 1.22)	97.64 to 104.18 (2.27 to 2.33)
Specificity	Yes	Yes
SOPs submitted	Yes	
Bioanalytical method is acceptable	Yes	

Reviewer's Comment: The firm did not submit the absolute recovery of clavulanic acid or the internal standard, because the derivatization interfered with measuring absolute recovery of both compounds (see telephone amendment).

E. In Vivo Studies

Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	30073
Study Design	single-dose, randomized, two-way crossover
No. of subjects enrolled	52
No. of subjects completing	50
No. of subjects analyzed	50
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male 18 Female 32
Test product	Amoxicillin/Clavulanate Potassium Chewable Tablet, USP
Reference product	Augmentin®
Strength tested	400 mg/57 mg of Amoxicillin/Clavulanate Potassium Chewable Tablet, USP
Dose	1x400 mg/57 mg of Amoxicillin/Clavulanate Potassium Chewable Tablet, USP

Summary of Statistical Analysis of Amoxicillin		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC0-t	0.98	96.58-100.03
LAUC∞	0.98	96.71-100.18
LCmax	1.03	98.40-107.88

Summary of Statistical Analysis of Clavulanic Acid		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC0-t	1.04	95.76-113.52
LAUC∞	1.04	95.75-112.50
LCmax	1.03	95.33-111.64

Reanalysis of Amoxicillin 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**
Unacceptable Internal Standard response	2	2	0.11	0.11	2	2	0.11	0.11
Incomplete Analysis	11	7	0.61	0.39	11	7	0.61	0.39
Sample Concentration Above Upper Limit of Quantitation	5	5	0.28	0.28	5	5	0.28	0.28
Sample Reanalyzed to Obtain Confirming Value	1	2	0.06	0.11	1	2	0.06	0.11
Total	**19**	**16**	**1.06**	**0.89**	**19**	**16**	**1.06**	**0.89**

Reanalysis of Clavulanic Acid 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**
Poor Chromotography	1	0	0.06	0	1	0	0.06	0
Unacceptable Internal Standard Response	1	0	0.06	0	1	0	0.06	0
Incomplete Analysis	12	7	0.67	0.39	12	7	0.67	0.39
Sample Concentration Above Upper Limit of Quantitation	16	11	0.89	0.61	16	11	0.89	0.61
Sample Stability Exceeding Validation Data	0	1	0	0.06	0	1	0	0.06
Total	**30**	**19**	**1.68**	**1.06**	**30**	**19**	**1.68**	**1.06**

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

Single-dose Fed Bioequivalence Study

Study No.	30074
Study Design	single-dose, randomized, two-way crossover
No. of subjects enrolled	52
No. of subjects completing	51
No. of subjects analyzed	51
Subjects (Healthy or Patients?)	healthy
Sex(es) included (how many?)	Male: 16 Female: 35
Test product	Amoxicillin/Clavulanate Potassium Chewable Tablet, USP
Reference product	Augmentin®
Strength tested	400 mg/57 mg of Amoxicillin/Clavulanate Potassium Chewable Tablet, USP
Dose	1x400 mg/57 mg of Amoxicillin/Clavulanate Potassium Chewable Tablet, USP

Summary of Statistical Analysis of Amoxicillin		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC0-t	0.98	96.12-99.19
LAUC∞	0.99	97.09-101.53
LCmax	0.98	93.19-102.43

Summary of Statistical Analysis of Clavulanic Acid		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC0-t	0.94	87.19-101.54
LAUC∞	0.94	87.83-101.52
LCmax	0.95	85.64-104.47

Reanalysis of Amoxicillin Study Samples Additional information in Appendix, Table 17								
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**
Poor Chromotography	9	9	0.49	0.49	9	9	0.49	0.49
Unacceptable Internal Standard Response	9	4	0.49	0.22	9	4	0.49	0.22
Incomplete Analysis	2	2	0.11	0.11	2	2	0.11	0.11
Total	**20**	**15**	**1.09**	**0.82**	**20**	**15**	**1.09**	**0.82**

Reanalysis of Clavulanic Acid Study Samples Additional information in Appendix, Table 17								
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**
Unacceptable Internal Standard Response	3	0	0.16	0	3	0	0.16	0
Incomplete Analysis	11	6	0.60	0.33	11	6	0.60	0.33
Sample Concentration Above Upper Limit of Quantitation	1	2	0.05	0.11	1	2	0.05	0.11
Sample Reanalyzed to Obtain Confirming Value	35	36	1.91	1.97	35	36	1.91	1.97
Total	**50**	**44**	**2.72**	**2.41**	**50**	**44**	**2.72**	**2.41**

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

F. Formulation

Location in appendix	Section B, Page 37
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	NA
If a tablet, is the product scored?	No
If yes, which strengths are scored?	NA
Is scoring of RLD the same as test?	NA (RLD is not scored)
Is the formulation acceptable?	Yes
If not acceptable, why?	NA

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	USP
Medium	Water
Volume (mL)	900
USP Apparatus type	II
Rotation (rpm)	75 RPM
Firm's proposed specifications	NLT 80% (Q) of amoxicillin in 45 minutes NLT 80% (Q) of clavulanic acid in 45 minutes
FDA-recommended specifications	NLT 80% (Q) of amoxicillin in 45 minutes NLT 80% (Q) of clavulanic acid in 45 minutes
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapid Dissolution
Is method acceptable?	Yes

H. Waiver Request(s)

Strengths for which waivers are requested	200 mg/28.5 mg
Regulation cited	21 CFR 320.22(d)(2)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	Yes
If not then why?	NA

I. Deficiency Comments

None

J. Recommendations

1. The in vivo bioequivalence study under fed conditions by Teva Pharmaceuticals comparing its amoxicillin-clavulanate potassium 400 mg/57 mg chewable tablet, USP to the reference product Augmentin® 400 mg/57 mg tablet (GlaxoSmithKline) is acceptable.

2. The in vivo bioequivalence study conducted under fasting conditions by Teva Pharmaceuticals comparing its amoxicillin-clavulanate potassium 400 mg/57 mg chewable tablet, USP to the reference product Augmentin® 400 mg/57 mg tablet (GlaxoSmithKline) is acceptable.

3. The dissolution testing conducted by Teva on its amoxicillin-clavulanate potassium chewable tablets, 200 mg/28.5 mg and 400 mg/57 mg, is acceptable. The dissolution testing should be conducted in 900 mL of water using USP

Apparatus II (Paddle) at 75 RPM. The test product should meet the following specifications:

Not less than 80% (Q) of the labeled amount of amoxicillin in the dosage form is dissolved in 45 minutes.

Not less than 80% (Q) of the labeled amount of clavulanic acid in the dosage form is dissolved in 45 minutes.

4. The formulation of Teva Pharmaceutical's amoxicillin clavulanate potassium 200 mg/28.5 mg chewable tablet, USP is proportional to the 400 mg/57 mg chewable tablet, which underwent in vivo testing. A waiver of bioequivalence study requirements for the 200 mg/28.5 mg chewable tablet is granted.

Ethan M Stier 9/23/04

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

IV. Appendix

A. Individual Study Reviews

Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	R30073
Study Title	Randomized, 2-Way Crossover, Bioequivalence Study of Amoxicillin-Clavulanic Acid 400 mg-57 mg Chewable Tablets and Augmentin 400 mg-57 mg Chewable Tablets Administered as 1X400 mg/57 mg Chewable Tablet in Healthy Subjects Under Fasting Conditions
Clinical Site	[redacted]
Principal Investigator	[redacted], M.D.
Study/Dosing Dates	Clinical Period 1: September 20, 2003 Clinical Period 2: September 21, 2003
Analytical Site	[redacted]
Analytical Director	[redacted] M.Sc.
Analysis Dates	Amoxicillin: 11/05/03 to11/20/03 Clavulanic Acid: 09/23/03 to 10/24/03
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	Amoxicillin: 61 days Clavulanic Acid: 34 days

Treatment ID	A	B
Test or Reference	**Test**	**Reference**
Product Name	Amoxicillin-Clavulanate Potassium Chewable Tablet, USP	Augmentin®
Manufacturer	Teva	Glaxo Smith Kline
Batch/Lot No.	11146P1	TS2508
Manufacture Date	08/06/03	NA
Expiration Date	NA	03/04
Strength	400 mg/57 mg	400 mg/57 mg
Dosage Form	Tablet	Tablet
Batch Size	[redacted]	NA
Production Batch Size	[redacted]	NA
Potency	Amoxicillin: 102.4 Clavulanic Acid: 100.7	Amoxicillin: 104.2 Clavulanic Acid: 102.3
Content Uniformity (mean, %CV)	Amoxicillin: 104.1 (1.2) Clavulanic Acid: 102.0 (1.0)	Amoxicillin: 103.7 (1.3) Clavulanic Acid: 100.4 (1.7)
Formulation	See Appendix B	
Dose Administered	1x400 mg/57 mg	1x400 mg/57 mg
Route of Administration	Oral	

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No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	1 day
Randomization Scheme	AB: 3,4,5,8,9,13,14,16,17,20,23,25,28,33,34,35,36,37,40,41,46,48,50,52 BA:1,2,6,7,10,11,12,15,18,19,21,22,24,26,27,29,30,31,32,38,39,42,43,44,45,47,49,51
Blood Sampling Times (collected post dose)	pre-dose, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0
Blood Volume Collected/Sample	2x5 ml
Blood Sample Processing/Storage	Blood samples were processed and stored at -80°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours prior to and 4 hours after dosing
Length of Confinement	from at least 10 hours before drug administration until the 10h hour blood draw in period 2
Safety Monitoring	subjects monitored throughout study

Comments on Study Design:
Acceptable

a) Clinical Results

Table 1 Demographics of Study Subjects

Age		**Weight**		**Age Groups**		**Gender**		**Race**	
				Range	**%**	**Sex**	**%**	**Category**	**%**
				<18	0.0			Caucasian	98.0
Mean	33.2	Mean	67.7	18-40	82.0	Male	36.0	Afr. Amer.	2.0
SD	8.86	SD	11.16	41-64	18.0	Female	64.0	Hispanic	0.0
Range	20-54	Range	48.6-88.8	65-75	0.0			Asian	0.0
				>75	0.0			Others	0.0

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
5	subject withdrew after the 2.25 hour post-dose blood draw in Period 1 due to difficulty with vein	1	**no**
33	subject withdrew after the 1.0 hour post-dose blood draw in Period 2 due to difficulty with vein	2	**no**

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Pain at Catheter Site/Arm/Wrist	6	6
High Potassium	0	1
Loose Stools	0	1
Low Glucose	0	1
Nausea	0	1
Pain in Both Legs	0	1
Total:	**6**	**11**

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Particles of drug (chewable tablet)in oral cavity after ingesting drug	All (1-52)	All (1-52)
During transfer of reference drug between sites the temperature rose to 29.3°C	0	All (1-52)
Unknown if the subject's 2.5 h post-dose plasma and derivatization solution aliquots for clavulanic acid were stirred	1,2,6,7,10, 11,12,15,18 ,19,21,22, 24,26	3,4,8,9,13,1 4,16,17,20, 23,25
Some water spilled at time of drug administration.	2	37
Subject's 10.0 h post-dose ——— plasma proportion and derivatization solution was not respected for aliquot 2/2. The tome point was excluded from analysis.	37	None
question regarding a depot injection or an implant of any drugs 3 months prior to administration of study medication	NA	NA
Total	68	117

Comments on Dropouts/Adverse Events/Protocol Deviations:

The protocol deviations did not compromise the outcome of this study. The number of adverse events following test product administration was less than in the RLD group.

b) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

Amoxicillin								
QC. (ng/mL)	118.92	3567.60	8324.4	1189.2				
Inter day Precision (%CV)	4.9	3.6	4.5	5.7				
Inter day Accuracy (%)	100.3	100.8	97.4	101.9				
Cal. Standards (ng/mL)	40.08	80.16	601.2	2404.8	4809.6	7214.4	9619.2	12024.0
Inter day Precision (%CV)	6.2	4.2	3.5	3.3	3.5	4.1	2.9	3.3
Inter day Accuracy (%)	99.8	100.1	102.3	102.5	98.9	98.6	98.6	99.2
Linearity Range (range of R^2 values)	.9952-.9998							

Comments on Study Assay Quality Control:
Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	yes
Were chromatograms serially or randomly selected?	serially

Clavulanic Acid								
QC Conc. (ng/mL)	90.19	450.96	1127.40	375.8				
Inter day Precision (%CV)	6.8	8.1	4.5	8.9				
Inter day Accuracy (%)	95.8	97.7	99.4	98.0				
Cal. Standards Conc. (ng/mL)	29.96	59.91	149.78	299.56	599.12	898.68	1198.2	1497.8
Inter day Precision (%CV)	4.8	5.2	4.7	4.8	4.0	3.8	5.3	4.9
Inter day Accuracy (%)	101.6	97.6	98.8	97.6	100.5	101.4	100.9	101.8
Linearity Range (range of R^2 values)	.9960-.9995							

Comments on Study Assay Quality Control:
Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:
None

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

SOP No.	Date of SOP	SOP Title
SOP 156.08	2003-07-01	Sample Reassay and Reporting of Final Concentration

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Acceptable

c) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

A. Amoxicillin – Fasting Study

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	19089.36	18.02	19395.97	18.93	0.98
AUC_{0-t}	ng·hr/mL	18939.13	18.17	19263.26	18.90	0.98
CMAX	ng/mL	7800.48	27.10	7599.29	29.25	1.03
KE	$hour^{-1}$	0.56	18.13	0.58	15.19	0.97
LAUCI	ng·hr/mL	18801.27	0.00	19080.81	0.00	0.99
LAUCT	ng·hr/mL	18648.61	0.00	18950.98	0.00	0.98
LCMAX	ng/mL	7556.64	0.00	7290.19	0.00	1.04
THALF	hour	1.28	18.77	1.22	15.22	1.04
TMAX	hour	1.20	21.53	1.30	28.25	0.92

B. Clavulanic Acid– Fasting Study

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	2876.99	35.54	2833.74	36.40	1.02
AUC_{0-t}	ng·hr/mL	2798.69	36.15	2749.12	37.04	1.02
CMAX	ng/mL	1483.32	34.30	1449.68	34.29	1.02
KE	$hour^{-1}$	0.64	15.14	0.64	13.91	1.00
LAUCI	ng·hr/mL	2704.82	0.01	2593.98	0.02	1.04

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
LAUCT	ng·hr/mL	2624.56	0.01	2504.49	0.02	1.05
LCMAX	ng/mL	1398.72	0.03	1348.86	0.03	1.04
THALF	hour	1.11	16.00	1.10	13.39	1.01
TMAX	hour	0.90	23.94	0.94	22.56	0.95

Table 9 Geometric Means and 90% Confidence Intervals

Amoxicillin – Fasting Study

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$AUC_{0-\infty}$	19131.68	19454.23	0.98	96.69	100.00
AUC_{0-t}	18978.56	19320.51	0.98	96.58	99.88
CMAX	7789.51	7632.84	1.02	97.85	106.25
LAUCI	18846.91	19147.72	0.98	96.71	100.18
LAUCT	18691.12	19016.86	0.98	96.58	100.03
LCMAX	7553.78	7331.52	1.03	98.40	107.88

Clavulanic Acid – Fasting Study

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$AUC_{0-\infty}$	2872.97	2839.29	1.01	95.65	106.73
AUC_{0-t}	2793.75	2754.58	1.01	95.74	107.10
CMAX	1477.05	1449.90	1.02	95.53	108.21
LAUCI	2695.71	2597.26	1.04	95.75	112.50
LAUCT	2614.31	2507.45	1.04	95.76	113.52
LCMAX	1388.91	1346.36	1.03	95.33	111.64

Table 10 Additional Study Information

Amoxicillin Fasting-Study

Root mean square error, AUCT	0.0519
Root mean square error, AUC∞	0.0521
Root mean square error, Cmax	0.1359
Ke and AUCi determined for how many subjects?	50
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	NA
Were the subjects dosed as more than one group?	No

Clavulanic Acid Fasting-Study

Root mean square error, AUCT	0.2518
Root mean square error, AUC∞	0.2386
Root mean square error, Cmax	0.2337
Ke and AUCi determined for how many subjects?	50
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	NA
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis:
Acceptable

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
Complete.

Table 11 A Mean Amoxicillin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time	Test (ng/ml)		Reference (ng/ml)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
0.25	953.59	81.36	886.85	75.06	1.08
0.5	3862.10	51.55	3686.28	52.77	1.05
0.75	6436.24	37.31	5902.89	40.94	1.09
1	7240.61	30.88	6953.32	35.79	1.04
1.25	7246.21	24.29	7102.83	30.47	1.02
1.5	5859.09	19.24	6015.21	24.57	0.97
1.75	6786.13	21.40	6561.15	26.56	1.03
2	5128.25	18.48	5306.65	23.41	0.97
2.25	4420.15	21.68	4716.42	23.04	0.94
2.5	3832.27	24.16	4141.20	23.89	0.93
2.75	3364.94	28.90	3578.24	26.28	0.94
3	2922.85	31.27	3161.39	25.90	0.92
4	1589.24	42.58	1720.81	36.93	0.92
5	790.05	44.47	858.78	39.10	0.92
6	444.22	50.22	465.13	36.42	0.96
8	141.58	49.12	142.84	40.33	0.99
10	50.87	110.37	44.32	84.53	1.15

Table 11 B Clavulanic Acid Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time	Test (ng/ml)		Reference (ng/ml)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
0.25	267.82	82.41	268.51	89.80	1.00
0.5	977.87	56.90	952.36	52.66	1.03
0.75	1374.24	36.80	1303.85	42.14	1.05
1	1382.18	34.12	1334.83	36.06	1.04
1.25	1210.04	33.24	1184.02	33.90	1.02
1.5	820.06	34.32	836.59	35.28	0.98
1.75	1030.15	32.71	999.63	34.52	1.03
2	704.38	37.18	712.39	36.27	0.99
2.25	559.18	36.15	546.92	40.83	1.02
2.5	474.45	40.55	474.87	41.54	1.00
2.75	397.38	39.70	401.46	44.54	0.99
3	331.48	48.51	329.77	43.41	1.01
4	170.27	50.97	171.79	48.46	0.99
5	90.63	53.67	91.47	50.81	0.99
6	45.85	76.18	47.14	66.91	0.97
8	4.83	283.00	2.87	345.79	1.68
10	0.00	.	0.00	.	.

Plasma Amoxicillin Levels
Tablets, 400 mg/57 mg mg, ANDA 65-205
Under Fasting Conditions

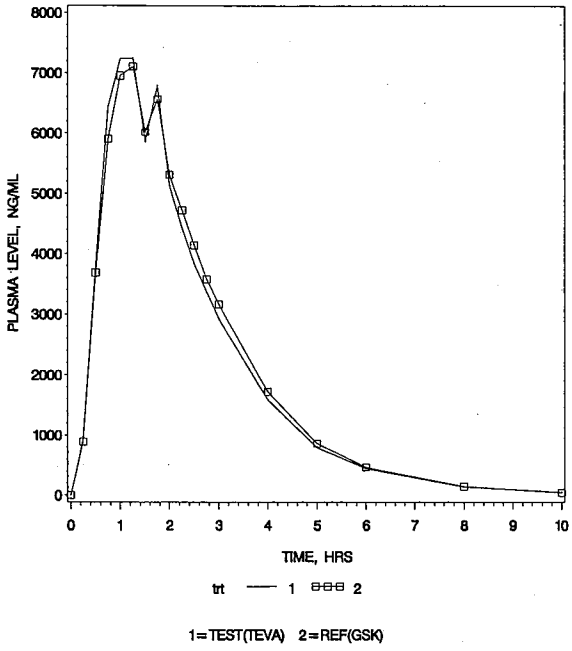

Figure 1 Mean Amoxicillin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

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PLASMA CLAVULANATE LEVELS

Plasma Clavulanic Acid Levels
Tablets, 400 mg/57mg, ANDA 65-205
Under Fasting Conditions

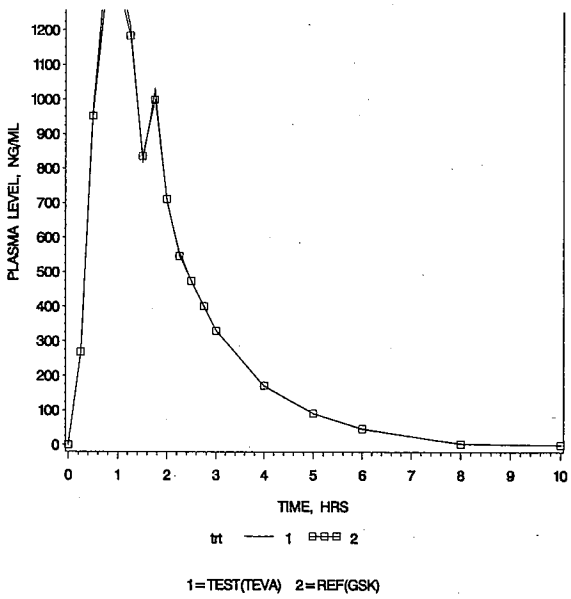

Figure 2 Mean Clavulanic Acid Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

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Single-dose Fed Bioequivalence Study

1. Study Design

Study Information	
Study Number	30074
Study Title	Single Dose, 2-Way Crossover, Fed, BE Study of Amoxicillin-Clavulanic Acid 1x 400 mg-57 mg Chewable Tablet Administered as 1X400 mg/57 mg Chewable Tablet in Healthy Subjects under Fed Conditions
Clinical Site	[redacted]
Principal Investigator	[redacted] M.D.
Study/Dosing Dates	Period 1: 09/20/03 Period 2: 09/21/03
Analytical Site	[redacted]
Analytical Director	[redacted] M.Sc.
Analysis Dates	Amoxicillin: 11/08/03 to 11/21/03 Clavulanic Acid: 09/30/03 to 11/03/03
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	Amoxicillin: 62 days Clavulanic Acid: 44 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Amoxicillin/Clavulanate Potassium Chewable Tablet, USP	Augmentin®
Manufacturer	Teva	Glaxo Smith Kline
Batch/Lot No.	11146P1	TS2508
Manufacture Date	08/06/03	NA
Expiration Date	NA	03/04
Strength	400 mg/57 mg	400 mg/57 mg
Dosage Form	Tablet	Tablet
Batch Size		NA
Production Batch Size		NA
Potency	Amoxicillin: 102.4 Clavulanic Acid: 100.7	Amoxicillin: 104.2 Clavulanic Acid: 102.3
Content Uniformity	Amoxicillin: 104.1 (1.2) Clavulanic Acid: 102.0 (1.0)	Amoxicillin: 103.7 (1.3) Clavulanic Acid: 100.4 (1.7)
Formulation	See Appendix B	
Dose Administered	1x400 mg/57 mg	1x400 mg/57 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	1 day
Randomization Scheme	AB:1,6,9,10,11,13,15,16,18,20,21,24,27,28,30,31,32,33,40,43,45,46,49,52 BA:2,3,4,5,7,8,12,14,17,19,22,23,25,26,29,34,35,36,37,38,39,41,42,44,47,48,50,51
Blood Sampling Times	pre-dose,0.25,0.5,0.75,1.0,1.25,1.5,1.75,2.0,2.25,2.5,2.75,3.0,4.0,5.0,6.0,8.0,10.0
Blood Volume Collected/Sample	2x5 ml
Blood Sample Processing/Storage	stored at -80°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 12**
Length of Fasting before Meal	at least 10 hours
Length of Confinement	from at least 10 hours before drug administration until the 10h hour blood draw in period 2
Safety Monitoring	Subjects were monitored throughout study
Standard FDA Meal Used?	Yes
If no, then meal is listed in	NA

table below	

Comments on Study Design: Acceptable

Clinical Results

Table 12 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	**%**	**Sex**	**%**	**Category**	**%**
				<18	0.0			Caucasian	78.8
Mean	32.38	Mean	70.01	18-40	76.9	Male	29.4	Afr. Amer.	5.8
SD	9.52	SD	12.74	41-64	23.1	Female	70.6	Hispanic	15.4
Range	19-59	Range	48.3-93.3	65-75	0			Asian	0
				>75	0			Others	0

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
21	not reported	2	**no**

Table 14 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
pain at catheter site	3	2
low hemoglobin	4	4
protein in urine	1	0
red blood cells in urine	1	0
feels weak	1	0
hot flashes	0	2
nausea	0	1
high ALT	0	1
low hematocrit	1	1
dizziness	0	3
headache	2	0
fainting	0	1
dry skin/lips	0	3
pain in both legs	1	0
Total:	**14**	**18**

Table 15 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
it can not be confirmed if subject 3 h to 6 h blood samples were flash frozen in period I	1,6,9,10,11,13,15, 16,18,20,21,24,27, 28,30,31,32,33,40 43,45,46,49,52	2,3,4,5,7,8,12,14, 17,19,22,23,25,26, 29,34,35,36,37,38, 39,41,42,44,47,48,50,51
these subject's 8 h plasma derivitzation samples for clavulanic acid were kept on ice bath for 1 hour before being shaken for 30 minutes. However, there is a 7 hour room temperature stability once the analyte is derivatized in Period I.	1,6,9,10,11,13,15, 16,18,20,21,24,27, 28,30,31,32,33,40 43,45,46,49,52	2,3,4,5,7,8,12,14, 17,19,22,23,25,26, 29,34,35,36,37,38, 39,41,42,44,47,48,50,51
These subject's pre-dose to 1.25 hour blood samples were shaken 10 minutes instead of 30 minutes as specified in the protocol in Period II.	2,3,4,5,7,8,12,14, 17,19,22,23,25,26, 29,34,35,36,37,38, 39,41,42,44,47,48,50,51	1,6,9,10,11,13,15, 16,18,20,21,24,27, 28,30,31,32,33,40 43,45,46,49,52
These subject's 1.5, 1.75, and 2.0 hours post-dose blood samples were shaken 10 minutes, 11 minutes, and 23 minutes, respectively, instead of 30 minutes as specified in the protocol in Period II.	2,3,4,5,7,8,12,14, 17,19,22,23,25,26	1,6,9,10,11,13,15, 16,18,20,21,24
The washout was 1-96 minutes less than the stated 24 hour washout period.	33,43,45,49,52	14,48,50,51
These subjects 1 hour water restriction was not respected for approximately 19 minutes due to modifications in drug administration.	25,26	24,27,30,31,32
These subjects clavulanic acid 8.0 hour blood sample collections were performed with 3 ml instead of 5 ml tubes as specified in the protocol.	22,25,26,28	24,27,30,31,32
These subjects were dosed 31 minutes and 32 minutes, respectively, after being served their critical meals.	5	43
In addition to the 240 ml administered with the study drug at the time of dosing, this subject drank an additional 42 ml to finish swallowing the medication.	1	none
This subject did not respect the 10 hour post-dose confinement.	21	none
Total:	107	104

Comments on Adverse Events/Protocol Deviations:
The protocol deviations did not compromise the outcome of this study. The number of adverse events following test product administration were less than those in the RLD-treated group.

2. Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Amoxicillin							
QC Conc. (ng/mL)	118.92	3567.6	8324.4	1189.2				
Inter day Precision (%CV)	5.85	4.44	4.2	4.7				
Inter day Accuracy (%)	100.85	100.54	97.39	101.69				
Cal. Standards Conc. (ng/mL)	40.08	80.16	601.2	2404.8	4809.6	7214.4	9619.2	12024
Inter day Precision (%CV)	5.52	4.9	3.44	2.62	2.53	3.24	3.94	4.3
Inter day Accuracy (%)	99.52	100.4	103.97	102.24	98.32	98.88	97.9	98.51
Linearity Range (range of R^2 values)	.9956-.9997							

Comments on Study Assay Quality Control:

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

	Clavulanic Acid							
QC Conc. (ng/mL)	90.19	450.96	1127.4	375.8				
Inter day Precision (%CV)	9.3	10.7	14.1	7.0				
Inter day Accuracy (%)	93.7	98.2	95.5	100.5				
Cal. Standards Conc. (ng/mL)	29.96	59.91	149.78	299.56	599.12	898.68	1198.2	1497.8

Inter day Precision (%CV)	4.7	4.7	6.9	5.5	5.8	5.2	5.1	5.4
Inter day Accuracy (%)	100.7	99.5	98.3	98.8	99.3	99.8	100.9	102.9
Linearity Range (range of R^2 values)	.9956-.9994							

Comments on Chromatograms:
Acceptable

Comments on Study Assay Quality Control:

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Randomly

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
SOP — 156.08	2003-07-01	Sample Reassay and Reporting of Final Concentration

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:
Acceptable

3. Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

A. Amoxicillin – Fed Study

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	19403.12	20.63	19518.22	18.31	0.99
AUC_{0-t}	ng·hr/mL	18299.44	17.20	18746.55	17.77	0.98
CMAX	ng/mL	4482.26	25.83	4549.67	24.53	0.99
KE	$hour^{-1}$	0.45	30.01	0.44	27.03	1.02
LAUCI	ng·hr/mL	19013.16	0.00	19197.69	0.00	0.99
LAUCT	ng·hr/mL	18020.94	0.00	18457.31	0.00	0.98
LCMAX	ng/mL	4339.31	0.01	4425.39	0.01	0.98
THALF	hour	1.83	63.99	1.71	34.95	1.07
TMAX	hour	1.89	45.58	1.93	43.39	0.98

B. Clavulanic Acid – Fed Study

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	1772.85	37.48	1864.33	36.27	0.95
AUC_{0-t}	ng·hr/mL	1693.67	38.67	1785.27	37.05	0.95
CMAX	ng/mL	734.20	40.94	766.38	39.06	0.96
KE	$hour^{-1}$	0.65	16.12	0.68	15.85	0.96
LAUCI	ng·hr/mL	1650.46	0.02	1744.86	0.02	0.95
LAUCT	ng·hr/mL	1569.21	0.03	1665.16	0.02	0.94
LCMAX	ng/mL	672.80	0.06	707.52	0.06	0.95
THALF	hour	1.09	18.83	1.05	15.97	1.04
TMAX	hour	1.39	41.37	1.33	42.37	1.05

Table 20 Geometric Means and 90% Confidence Intervals

Amoxicillin – Fed Study

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$AUC_{0-\infty}$	19429.61	19492.46	1.00	97.09	102.26
AUC_{0-t}	18277.95	18727.53	0.98	96.08	99.12
CMAX	4471.57	4561.19	0.98	93.19	102.88
LAUCI	19028.86	19166.42	0.99	97.09	101.53
LAUCT	17999.30	18433.94	0.98	96.12	99.19
LCMAX	4332.82	4434.74	0.98	93.19	102.43

Clavulanic Acid – Fed Study

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$AUC_{0-\infty}$	1785.48	1883.46	0.95	88.63	100.96
AUC_{0-t}	1705.56	1803.18	0.95	88.23	100.95
CMAX	738.51	775.84	0.95	86.92	103.45
LAUCI	1665.38	1763.49	0.94	87.83	101.54
LAUCT	1583.34	1682.95	0.94	87.19	101.52
LCMAX	677.48	716.25	0.95	85.64	104.47

Table 21 Additional Study Information

Amoxicillin Fed-Study

Root mean square error, AUCT	0.0470
Root mean square error, AUC∞	0.0669
Root mean square error, Cmax	0.1417
Ke and AUCi determined for how many subjects?	51
Do you agree or disagree with firm's decision?	yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	1
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

Clavulanic Acid Fed-Study

Root mean square error, AUCT	0.2279
Root mean square error, AUC∞	0.2174
Root mean square error, Cmax	0.2979
Ke and AUCi determined for how many subjects?	51
Do you agree or disagree with firm's decision?	yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis:
Acceptable

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:
Complete.

Table 22 A Mean Amoxicillin Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Time	Test (ng/ml)		Reference (ng/ml)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	1.01	714.14	0.00	.	.
0.25	591.16	81.21	646.87	79.41	0.91
0.5	1974.82	74.10	2016.55	54.45	0.98
0.75	2843.94	51.46	3095.30	46.87	0.92
1	3326.35	45.52	3634.10	41.25	0.92
1.25	3513.85	42.37	3878.08	37.92	0.91
1.5	3541.58	31.04	3788.57	29.02	0.93
1.75	3527.69	34.43	3908.28	33.80	0.90
2	3566.76	26.73	3778.34	25.16	0.94
2.25	3530.56	24.39	3661.80	21.68	0.96
2.5	3470.08	22.79	3587.59	20.58	0.97
2.75	3425.59	22.59	3509.99	19.33	0.98
3	3329.10	22.15	3391.79	19.76	0.98
4	2750.79	27.73	2737.77	25.86	1.00
5	1869.41	32.00	1819.96	28.09	1.03
6	1258.48	34.74	1225.49	35.36	1.03
8	541.80	53.70	514.37	50.40	1.05
10	268.08	94.92	257.36	71.85	1.04

Table 22 B Mean Clavulanic Acid Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Time	Test (ng/ml)		Reference (ng/ml)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
0.25	105.70	100.05	120.29	100.10	0.88
0.5	346.29	77.32	390.39	66.85	0.89
0.75	549.70	61.99	587.88	53.42	0.94
1	619.66	50.16	680.00	46.28	0.91
1.25	605.30	49.40	664.30	43.23	0.91
1.5	570.91	38.64	591.37	38.67	0.97
1.75	579.39	42.62	615.81	40.11	0.94
2	484.56	37.63	517.86	35.80	0.94
2.25	436.47	36.60	456.75	36.07	0.96
2.5	383.77	38.15	405.34	39.79	0.95
2.75	340.89	45.49	339.70	39.12	1.00
3	291.37	44.32	303.84	41.95	0.96
4	154.93	51.26	158.04	47.25	0.98
5	79.12	61.63	78.94	57.20	1.00
6	34.86	94.57	35.45	93.04	0.98
8	3.19	303.16	2.18	400.35	1.46
10	0.00	.	0.00	.	.

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ON ORIGINAL

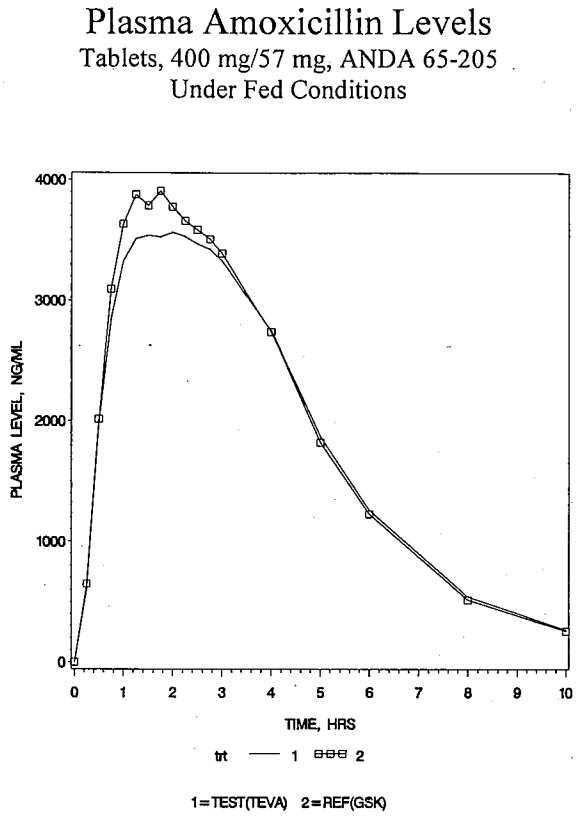

Figure 3 Mean Amoxicillin Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Plasma Clavulanic Acid Levels
Tablets, 400 mg/57 mg, ANDA 65-205
Under Fed Conditions

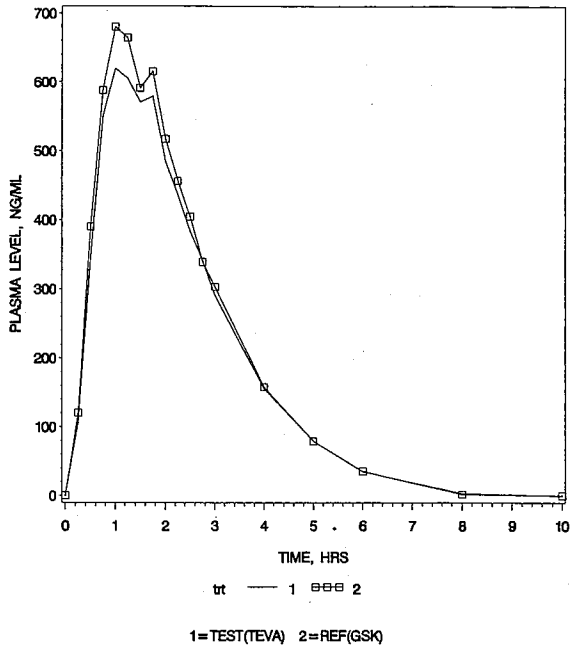

Figure 4 Mean Clavulanic Acid Plasma Concentrations, Single-Dose Fed Bioequivalence Study

B. Formulation Data

Ingredient	mg/Tablet	%w/w	mg/Tablet	%w/w
Amoxicillin Trihydrate				
Clavulanate Potassium				
Microcrystalline Cellulose				
Colloidal Silicon Dioxide				
Mannitol				
Aspartame				
FD&C Red #40 Aluminum Lake				
Magnesium Stearate				
S.D. Artificial Cherry Flavor				
SA84 Artificial Ripe Banana Flavor				
Total Tablet Weight	500	100%	1000	100%

C. Dissolution Data

Table 23 A. Release of Amoxicillin from 400 mg/57 mg tablet

Sampling Time	Amoxicillin/Clavulanate Potassium Chewable Tablet, USP, Strength 400 mg/57 mg Lot No. 11146P1			AUGMENTIN®, Strength 400 mg/57 mg Lot No. TS2508		
	Mean	%CV	Range	Mean	%CV	Range
10	56	11.4	46.2-65.6	35	25.0	15.7-43.8
20	97	3.4	90.6-101.9	63	13.1	46.6-74.9
30	103	1.1	100.7-105.5	84	9.5	63.8-91.6
45	103	1.4	100.4-106.1	101	4.8	88.1-105.6

Table 23 B. Release of Clavulanic Acid from 400 mg/57 mg tablet

Sampling Time	Amoxicillin/Clavulanate Potassium Chewable Tablet, USP, Strength 400 mg/57 mg Lot No. 11146P1			AUGMENTIN®, Strength 400 mg/57 mg Lot No. TS2508		
	Mean	%CV	Range	Mean	%CV	Range
10	56	10.8	47.0-63.9	40.0	10.0	32.0-44.2
20	94	4.2	87.2-100.6	65.0	6.4	57.9-71.8
30	101	1.0	99.4-102.3	84.0	5.4	74.5-89.7
45	101	1.1	99.2-102.7	98.0	2.6	92.8-101.7

Table 24 A. Release of Amoxicillin from 200 mg/28.5 mg tablet

Sampling Time	Amoxicillin/Clavulanate Potassium Chewable Tablet, USP, Strength 200 mg/28.5 mg Lot No. 11145P1			AUGMENTIN®, Strength 200 mg/28.5 mg Lot No. WH0025		
	Mean	%CV	Range	Mean	%CV	Range
10	59	9.5	47.9-65.8	24	24.6	11.0-31.9
20	101	1.5	98.1-102.5	60	10.3	44.8-67.7
30	104	0.8	102.5-105.5	86	6.9	70.3-93.1
45	104	0.7	102.3-104.8	103	2.2	96.7-105.1

Table 24 B. Release of Clavulanic Acid from 200 mg/28.5 mg tablet

Sampling Time	Amoxicillin/Clavulanate Potassium Chewable Tablet, USP, Strength 200 mg/28.5 mg Lot No. 11145P1			AUGMENTIN®, Strength 200 mg/28.5 mg Lot No. WH0025		
	Mean	%CV	Range	Mean	%CV	Range
10	62	7.6	51.4-66.7	38	8.2	32.6-44.3
20	99	1.6	97.0-101.6	68	6.6	59.8-75.0
30	102	0.8	101.1-103.8	89	4.3	79.6-93.9
45	102	0.7	100.6-102.9	102	1.6	98.2-103.1

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ON ORIGINAL

Figure 5 a) Release of Amoxicillin from 400 mg/57 mg tablet

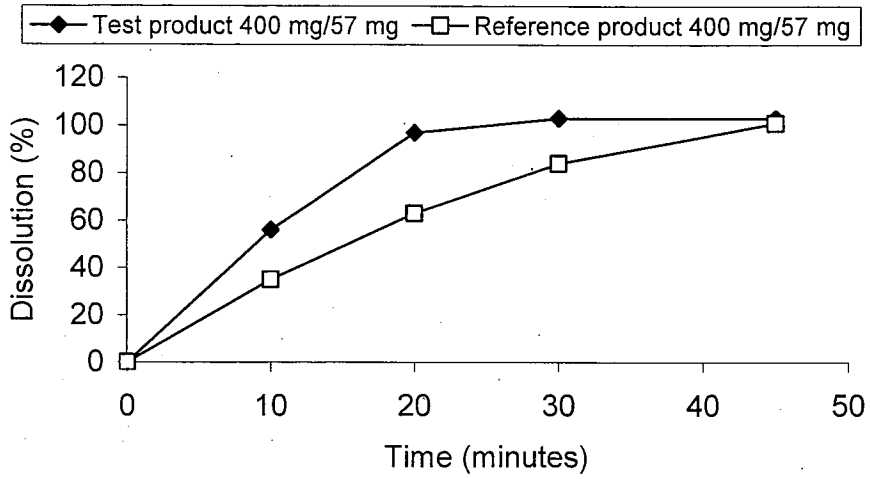
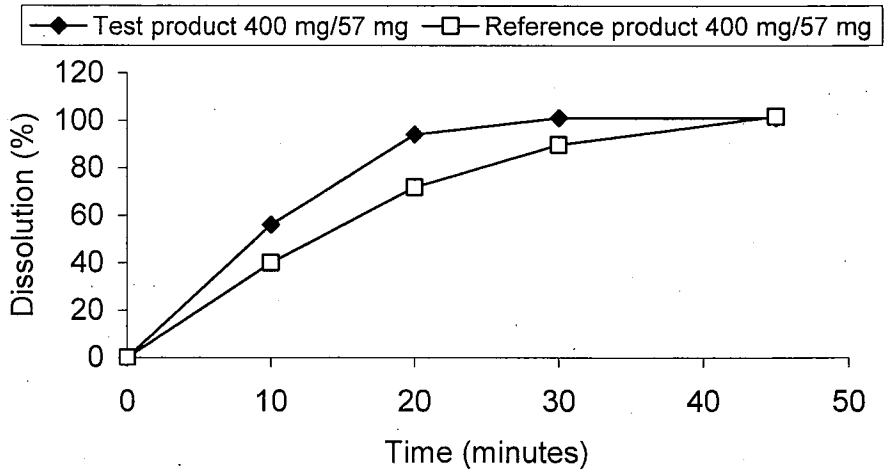


Figure 5 b) Release of Clavulanic Acid from 400 mg/57 mg tablet



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ON ORIGINAL

Figure 5 c) Release of Amoxicillin from 200 mg/28.5 mg tablet

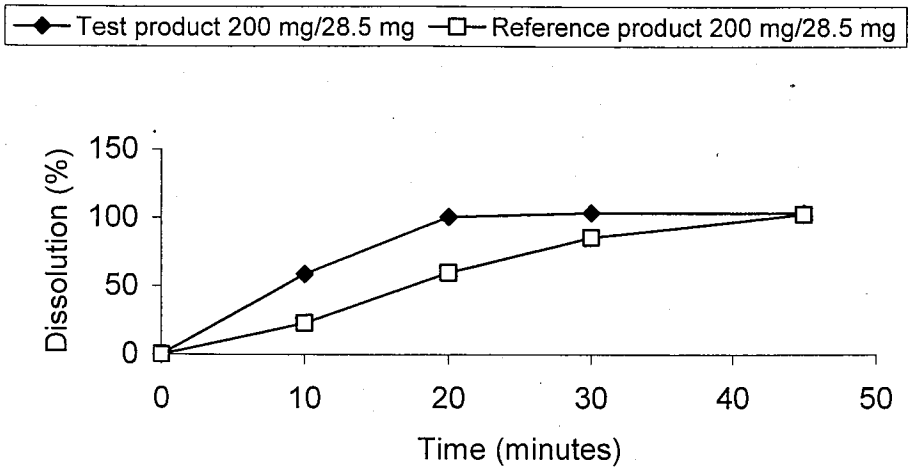
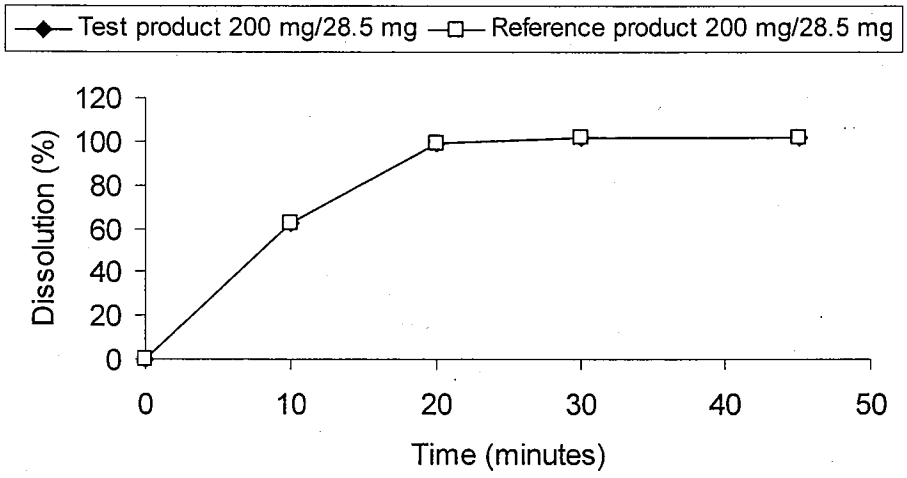


Figure 5 d) Release of Clavulanic Acid from 200 mg/28.5 mg tablet



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ON ORIGINAL

E. SAS Output

Statistical Analysis	Program file	Output file
Single dose fasting study/Amoxicillin	fasting amox program.txt	fasting amox list
Single dose fasting study/Clavulanic Acid	fasting clav program.txt	fasting clav list
Single dose fed study/Amoxicillin	fed amox program.txt	fed amox list
Single dose fed study/Clavulanic acid	fed clav program.txt	fed clav list

F. Additional Attachments

NA

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:65-205 APPLICANT: Teva

DRUG PRODUCT: Amoxicillin/Clavulanic Acid Chewable Tablets, USP

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

Since this is a USP product, the dissolution testing should be conducted as specified in USP 27.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence 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 65-205
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-655/Ethan M. Stier 9/23/04
HFD-655/Gur-Jai Pal Singh 9-23-04
HFD-617/Beth Fabian-Fritsch
HFD-650/Dale Conner 9/23/04

V:\firmsnz\teva\ltrs&rev\65205N1203.doc
Printed in final on 09/23/2004

BIOEQUIVALENCY - ACCEPTABLE Submission Date: 12/15/03

1. **FASTING STUDY (STF)** **Strengths: 400 mg/57 mg**
Outcome: AC

Clinical:
Analytical: [ ]

2. **FOOD STUDY (STP)** **Strengths: 400 mg/57 mg**
Outcome: AC

Clinical:
Analytical: [ ]

3. **DISSOLUTION WAIVER (DIW)** **Strengths: 200 mg/28.5 mg**
Outcome: AC

Outcome Decisions: AC - Acceptable
IC - Incomplete

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-205 SPONSOR : Teva

DRUG AND DOSAGE FORM : Amoxicillin and Clavulanate Potassium Chewable Tablets, USP

STRENGTH(S) : 200 mg/28.5 mg and 400 mg/57 mg

TYPES OF STUDIES : fasting and fed

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : Acceptable

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic No New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes___X___ No_____
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Spec acknowledged by firm: Yes _____

PROJECT MANAGER: _____ DATE:_____

PRIMARY REVIEWER : Ethan M. Stier, Ph.D. BRANCH: II

INITIAL : _____ DATE : 9/23/04

TEAM LEADER : Gur-Jai Pal Singh, Ph.D. BRANCH: II

INITIAL : _____ DATE : 9-23-04

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

INITIAL : _____ DATE : 9/23/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-205

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 65-205 Applicant TEVA Pharmaceuticals USA
Drug Amox/Clav Potassium Chewable Tab Strength(s) 200 mg/28.5 mg and 400 mg/57 mg

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 3Feb2005 Initials MMS	Date 2/9/05 for Initials

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 50-726
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Type of Letter:
Comments: no patents/exclusivities ∴ eligible for Final Approval

2. Project Manager, RYAN NGUYEN Team 6 Review Support Branch	Date 2/2/05 Initials RN	Date 2/7/05 Initials RN

Original Rec'd date 12/16/03
Date Acceptable for Filing 12/16/03 ✓
Patent Certification (type) 1
Date Patent/Exclus.expires N/A
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 06/03/04
Date of Office Bio Review 09/23/04
Date of Labeling Approv. Sum 1/28/05
Citizens' Petition/Legal Case Yes ☐ No ☒ Date of Sterility Assur. App. N/A
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☒
First Generic Yes ☐ No ☒ MV Commitment Rcd. from Firm Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☒ No ☐ Modified-release dosage form: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐ OGD Regulatory Counsel, Post-MMA Language Included ☐ Comments: N/A.		Date Initials

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments: cmc satisfactory.	2/8/05	Date 2/8/05 Initials

REVIEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date
Assoc. Dir. For Chemistry Initials
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this drug product.

6. Vacant Date
Deputy Dir., DLPS Initials

7. Peter Rickman Date 2/9/05
Director, DLPS Initials for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Bioequivalence studies (fasting and non-fasting) on the 400mg strength found acceptable 9/23/04. Dissolution testing on both strengths found acceptable. Bio waiver granted to the 200mg strength under 21 CFR 320.22(d)(2). Bio study/test sites have acceptable OSI inspection histories. Office-level bio endorsed 9/23/04. FRL found acceptable for approval 1/28/05. CMC found acceptable for approval 2/7/05. Methods validation was not requested.

RLD = Augmentin, 200mg (200mg, 28.5mg (base)) Chewable Tablets NDA 50-726 (001, 002)
Augmentin, 400mg (400mg, 57mg (base))
GlaxoSmithKline

Robert L. West Date 2/9/2005
Deputy Director, OGD Initials
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☐
Comments: Acceptable CES dated 6/30/04 (verified 2/9/05). No O.A.I. sites noted. There are no unexpired patents or exclusivity listed in the current "Orange Book" for this drug product.

this ANDA is recommended for approval.

9. Gary Buehler Date 2/9/05
Director, OGD Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team 6 Ryan Nguyen Date 2/9/05
Review Support Branch Initials SRP for Ryan
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
2:10 pm Time notified of approval by phone 11:16 am Time approval letter faxed
FDA Notification:
2/9/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/9/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-205

CORRESPONDENCE

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

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

December 15, 2003

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 CHEWABLE TABLETS USP,
200 mg/28.5 mg and 400 mg/57 mg

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 200 mg/28.5 mg and 400 mg/57 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 35 volumes; 17 for the archival copy and 18 for the review copy.

The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 400 mg/57 mg manufactured by TEVA Pharmaceuticals USA to the reference listed drug, Augmentin® Chewable Tablets, 400 mg/57 mg under both fasting and post-prandial conditions.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

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) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/ke
Enclosures

RECEIVED
DEC 16 2003
OGD/CDER

ANDA 65-205

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

JAN 28 2004

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.

NAME OF DRUG: Amoxicillin and Clavulanate Potassium Tablets USP (Chewable), 200 mg/28.5 mg (base), and 400 mg/57 mg (base)

DATE OF APPLICATION: December 15, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 16, 2003

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,

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

ANDA 65-205
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92

Endorsement:
HFD-615/M. Shimer, Chief, RSB _____ date 28 JAN 2004
HFD-615/S. Middleton, CSO _____ date 1/26/04
Word File
V:/FIRMSNZ\TEVA\LTRS&REV\65205.ACK
FT/StM 1/26/04

ANDA Acknowledgment Letter!

TEVA

21

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

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

February 23, 2004

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

UNSOLICITED AMENDMENT

ORIG AMENDMENT
N/AA

ANDA #65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP, 200 mg/28.5 mg and 400 mg/57 mg
UNSOLICITED AMENDMENT – INCLUSION OF ROOM TEMPERATURE STABILITY DATA

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced pending Abbreviated New Drug Application for Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 200 mg/28.5 mg and 400 mg/57 mg. The purpose of this submission is to provide the now available room temperature stability data for pivotal batches #1145P1 and #11146P1. Please see **Attachment 1**. Please also find, enclosed in **Attachment 2**, an updated Finished Product Stability Protocol that reflects a correction to the *appearance* specification. The *appearance* specification had inadvertently stated that there should be no observation of "mottling" when the tablet *description* stated that the product was indeed "mottled" pink. For this reason, the accelerated stability report submitted in the original application has likewise been updated to correct the *appearance* specification and is enclosed in **Attachment 3**.

This information is submitted for your continued review and approval of ANDA 65-205. Should there be any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/ke
Enclosures

FEB 2 4 2004

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Administrative Offices:
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March 24, 2004

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

UNSOLICITED BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N/AB

ANDA #65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP,
200 mg/28.5 mg and 400 mg/57 mg
UNSOLICITED BIOEQUIVALENCY AMENDMENT – EXTENSION OF LONG-TERM STABILITY OF ANALYTE AND INTERNAL STANDARD IN SOLUTION

Dear Mr. Buehler:

We submit herewith an unsolicited bioequivalency amendment to the above-referenced pending Abbreviated New Drug Application to provide for an extension of the long-term stability of analyte and internal standard in solution at a nominal temperature of -80°C. The expiration date of the amoxicillin ——————— at a nominal temperature of -80°C was extended from — days to 229 days for the analyte and internal standard in solution. Please find enclosed the amended final report from ———————. reflecting this update.

This information is submitted for your continued review and approval of ANDA #65-205. Should there be any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/RS

PE/ke
Enclosure

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MAR 25 2004
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21

Administrative Offices:
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May 25, 2004

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

MINOR AMENDMENT

DRUG AMENDMENT
N/AM

ANDA # 65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP,
200 mg/28.5 mg and 400 mg/57 mg
MINOR AMENDMENT – RESPONSE TO MARCH 18, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending Abbreviated New Drug Application for Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 200 mg/28.5 mg and 400 mg/57 mg, in response to a review letter dated March 18, 2004 from the Division of Chemistry III. For ease of your review, please find a copy of this letter provided in **Attachment I**. Comments in the review letter are addressed in the order presented.

A. Chemistry Deficiencies

1. [
2.
]

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MAY 26 2004
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Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

5/25/2004 TEVA LETTER

TEVA

ORIGINAL

4.1

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
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July 23, 2004

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

TELEPHONE AMENDMENT

ORIG AMENDMENT

ANDA # 65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP,
200 mg/28.5 mg and 400 mg/57 mg
TELEPHONE AMENDMENT – RESPONSE TO JULY 13, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending Abbreviated New Drug Application for Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 200 mg/28.5 mg and 400 mg/57 mg. This amendment is in response to a July 13, 2004 telephone request made by Dr. Susan Zuk of your office. Dr. Zuk requested the [redacted] of this product.

Per your request, please find enclosed the [redacted]
200 mg/28.5 mg and 400 mg/57 mg strengths. Please note, these

[redacted]

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JUL 26 2004
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The information provided herein represents, in our opinion, a complete response to your July 13, 2004 telephone request. This information is submitted towards the continued review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me by phone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ke
Enclosures

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

31

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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July 23, 2004

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

BIOEQUIVALENCY
TELEPHONE AMENDMENT

ORIG AMENDMENT
N/AB

ANDA # 65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP, 200 mg/28.5 mg and 400 mg/57 mg
BIOEQUIVALENCY TELEPHONE AMENDMENT – RESPONSE TO JULY 22, 2004 REQUEST

Dear Mr. Buehler:

We submit herewith a bioequivalency telephone amendment to the above-referenced pending Abbreviated New Drug Application for Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 200 mg/28.5 mg and 400 mg/57 mg. The information contained herein is submitted in accord with a request made by Ms. Beth Fritsch of the Division of Bioequivalence for a copy of the diskette containing the postprandial study data. Please find enclosed the diskette containing the postprandial study data.

This information is submitted towards the continued review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me by phone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ke
Enclosure

RECEIVED
JUL 26 2004
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Administrative Offices:
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September 7, 2004

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

BIOEQUIVALENCY
TELEPHONE AMENDMENT

ORIG AMENDMENT
N/AB

ANDA # 65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP,
200 mg/28.5 mg and 400 mg/57 mg
BIOEQUIVALENCY TELEPHONE AMENDMENT – RESPONSE TO AUGUST 23, 2004
REQUEST

Dear Mr. Buehler:

We submit herewith a bioequivalency telephone amendment to the above-referenced pending Abbreviated New Drug Application for Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 200 mg/28.5 mg and 400 mg/57 mg in response to a request made by Ms. Beth Fritsch of the Division of Bioequivalence. Specifically, Ms. Fritsch requested the absolute recovery for both ——— and clavulanic acid. The recovery test for clavulanic acid and the internal standard ——— did not meet the acceptance criteria for the coefficient of variation, causing out of specification CVs. The derivatization step used prior to sample storage to stabilize clavulanic acid is the main reason for the variability in the detector response for clavulanic acid and internal standard. This derivatization procedure may affect the ionization of both compounds in the mass spectrometry detector and produce variable peak detector responses. In order to correct this phenomenon, an addition of the internal standard during sample extraction gives reproducible analyte/internal standard peak response ratios and clavulanic acid concentrations as demonstrated for all the precision results obtained during bioanalytical method validation.

Based on these facts and that all other validation tests were in compliance with their acceptance criteria, it is our opinion that the out of specification CVs observed for the recovery test are not critical for the accurate and precise determination of clavulanic acid in study samples. The enclosed validation report has been revised to include this clarification.

This information is submitted towards the continued review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me by phone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ke
Enclosure

APPEARS THIS WAY
ON ORIGINAL

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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October 22, 2004

ORIG AMENDMENT
N/HF

LABELING AMENDMENT

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

ANDA #65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP,
200 mg/28.5 mg and 400 mg/57 mg
LABELING AMENDMENT – REPSONSE TO A REVIEW LETTER DATED SEPTEMBER 20, 2004

Dear Mr. Buehler:

We submit herewith an Labeling Amendment to the above-referenced pending Abbreviated New Drug Application in response to a review letter dated September 20, 2004 from the Labeling Review Branch of the Office of Generic Drugs. For ease of review, a copy of this review letter is provided in **Attachment 1.**

Please note, as we recognize the Agency's request to delete terminal zeros from our package insert, we would prefer to continue to use the terminal zero to prevent misleading data tables and to remain consistent with the significant figures represented in the Innovator labeling.

In accord with the requested revisions we have provided in **Attachment 2,** 12 copies of final print container labeling for each strength and a comparison to our previous revision. In addition, we have enclosed in **Attachment 3** the electronic version of the updated package insert, along with a comparison to our previously submitted revision.

This information is submitted for your continued review and approval of ANDA #65-205. Should there be any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/st
Enclosures

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OCT 25 2004
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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

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ORIG AMENDMENT
N/HF

November 4, 2004

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

ADDENDUM TO
LABELING AMENDMENT

ANDA #65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP, 200 mg/28.5 mg and 400 mg/57 mg
ADDENDUM TO OCTOBER 22, 2004 LABELING AMENDMENT

Dear Mr. Buehler:

We submit herewith an addendum to our labeling amendment submitted on October 22, 2004. According to an October 5, 2004 telephone conversation with Lillie Golson of your office and Rob Vincent of TEVA Pharmaceuticals USA, an agreement was made that it would be acceptable to utilize initial launch quantities of the drug product with the unrevised container label. This agreement was based on the fact that the container label revisions were of a clarification/editorial nature and that the labeling as submitted was not incorrect. The unrevised labeling will be utilized for the validation lots only. Please note, the product outsert will include the revisions submitted in the October 22, 2004 labeling amendment for all commercial lots, including the validation lots.

TEVA Pharmaceuticals USA commits to implement the revised labeling submitted in the October 22, 2004 labeling amendment on all lots manufactured/released after the initial validation lots.

This information is submitted for your continued review and approval of ANDA #65-205. If there are any questions regarding this information contained herein, please do not hesitate to contact me at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/RS

PE/ke
Enclosure

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

Philip Erickson, R.Ph.
Director, Regulatory Affairs
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philip.erickson@tevausa.com

ORIG AMENDMENT
N/AM

November 10, 2004

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

TELEPHONE AMENDMENT

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ANDA #65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP, 200 mg/28.5 mg and 400 mg/57 mg
TELEPHONE AMENDMENT – RESPONSE TO NOVEMBER 8, 2004 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA. This amendment is in response to a November 8, 2004 telephone conversation with Mr. Ryan Nguyen of your office. As requested by Mr. Nguyen, please find in **Attachment 1**,

This information is submitted towards the continued review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/rsv/ke
Enclosures

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

Philip Erickson, R.Ph.
Director, Regulatory Affairs
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ORIG AMENDMENT
N/AM

November 19, 2004

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

TELEPHONE AMENDMENT

ANDA #65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS USP,
200 mg/28.5 mg and 400 mg/57 mg
TELEPHONE AMENDMENT – RESPONSE TO NOVEMBER 16, 2004 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA. This amendment is in response to a November 16, 2004 telephone conversation with Ms. Susan Zuk of your office. As requested by Ms. Zuk, TEVA commits to tighten the — specification for

[ ]

This information is submitted towards the continued review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/ke

PE/ke
Enclosure

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Administrative Offices:
TEVA PHARMACEUTICALS USA
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ORIG AMENDMENT
N-000-AM

December 1, 2004

TELEPHONE AMENDMENT

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

ANDA #65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP (CHEWABLE),
200 mg/28.5 mg and 400 mg/57 mg
TELEPHONE AMENDMENT – RESPONSE TO NOVEMBER 23, 2004 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA. This amendment is in response to a November 23, 2004 telephone conversation with Ms. Susan Zuk of your office. As requested by Ms. Zuk, TEVA commits to develop, validate and submit a method that tightens the — specification from NMT—————————————————— ——— by April 2005.

This information is submitted towards the continued review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ke
Enclosure

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Administrative Offices:
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December 16, 2004

N-000-AF
LABELING AMENDMENT
ORIG AMENDMENT

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

ANDA #65-205
AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP (CHEWABLE),
200 mg/28.5 mg and 400 mg/57 mg
LABELING AMENDMENT – RESPONSE TO A REVIEW LETTER DATED DECEMBER 6, 2004

Dear Mr. Buehler:

We submit herewith a Labeling Amendment to the above-referenced pending Abbreviated New Drug Application in response to a review letter dated December 6, 2004 from the Division of Labeling and Program Support. For ease of review, a copy of this review letter is provided in **Attachment 1.**

In accord with the requested revisions we have provided in **Attachment 2** the electronic version of the updated package insert, along with a comparison to our previously submitted revision.

It is TEVA's belief that this is the final outstanding item for this application. As such, this information is submitted for your continued review and approval of ANDA #65-205. Should there be any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/RS

PE/ke
Enclosures

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DEC 17 2004
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