

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-161

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

Sponsor: Ranbaxy Pharmaceuticals, Inc.

Approval Date: December 3, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 65-161

CONTENTS

Reviews / Information Included in this Review
--

Approval Letter	X
Approvable Letter	
Labeling	X
Labeling Reviews	X
Medical Review	
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Review	
Microbiology Review	
Administrative Documents	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-161

APPROVAL LETTER

ANDA 65-161

DEC 3 2003

Ranbaxy Pharmaceuticals, Inc.
Attention: Abha Pant
U.S. Agent for: Ranbaxy Laboratories Limited
600 College Road East
Princeton, NJ 08540

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 23, 2002, 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 August 25, August 27, and September 29, 2003.

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 and Augmentin Chewable Tablets, 400 mg, respectively, of GlaxoSmithKline). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

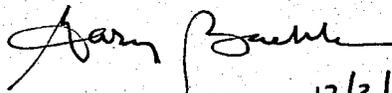
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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

Sincerely yours,



Gary Buehler 12/3/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 65-161
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-92

Endorsements:

HFD-643/S.Zuk/10/20/03 *Sam Zuk 10/24/03*
HFD-643/R.Adams/10/20/03 *R.C. Adams 10/22/03*
HFD-617/M.Anderson/10/21/03 *Mark Anderson 10/24/03*
HFD-613/A.Vezza/10/21/03 *A. Vezza 10/21/03*
HFD-613/L.Golson/10/21/03 *L. Golson 10/21/03*
V:\firmsnz\ranbaxy\ltrs&rev\65161apda.doc
F/T by: mda/10/21/03

APPROVAL

com satisfactory
Kilara Bay
10/27/03

Robert Pyle
10/27/2003
4 days satisfactory
BBS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 65-161

LABELING

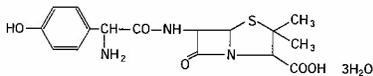
AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP (CHEWABLE)

Rx Only

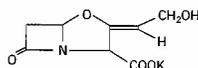
To reduce the development of drug-resistant bacteria and maintain the effectiveness of amoxicillin and clavulanate potassium chewable tablets and other antibacterial drugs, amoxicillin and clavulanate potassium chewable tablets should be used only to treat or prevent infections that are proven or strongly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

DESCRIPTION

Amoxicillin and clavulanate potassium is an oral chewable tablet and an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β -lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{15}H_{19}N_3O_5S \cdot 3H_2O$ and the molecular weight is 419.46. Chemically, amoxicillin is (2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(μ -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:



Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β -lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β -lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated β -lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_{14}H_{14}KNO_6$ and the molecular weight is 237.25. Chemically, clavulanate potassium is potassium (2Z)-2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate and may be represented structurally as:



Inactive Ingredients: aspartame, FD&C red No. 40 aluminum lake, glycine, povidone, magnesium stearate, mannitol, mint cream flavor, orange cream flavor, silicon dioxide, sodium starch glycolate, tropical blend flavor. *See **PRECAUTIONS-Information for Patients.**

Each 200 mg chewable tablet contains 0.15 mEq potassium. Each 400 mg chewable tablet contains 0.30 mEq of potassium.

CLINICAL PHARMACOLOGY

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of amoxicillin and clavulanate potassium chewable tablets. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin and clavulanate potassium chewable tablets can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In one study, the relative bioavailability of clavulanate was reduced when amoxicillin and clavulanate potassium chewable tablets was dosed at 30 and 150 minutes after the start of a high fat breakfast. The safety and efficacy of amoxicillin and clavulanate potassium chewable tablets have been established in clinical trials where amoxicillin and clavulanate potassium chewable tablets were taken without regard to meals. Oral administration of single doses of 400 mg amoxicillin and clavulanate potassium chewable tablets and 400 mg/5 mL suspension to 28 adult volunteers yielded comparable pharmacokinetic data.

Dose [†] (amoxicillin/clavulanate potassium)	AUC _{0-∞} (mcg·hr/mL)		C _{max} (mcg/mL) [‡]	
	amoxicillin (±S.D.)	clavulanate potassium (±S.D.)	amoxicillin (±S.D.)	clavulanate potassium (±S.D.)
400/57 mg (5 mL of suspension)	17.29 ± 2.28	2.34 ± 0.94	6.94 ± 1.24	1.10 ± 0.42
400/57 mg (one 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 250 mg/5 mL suspension or the equivalent dose of 10 mL amoxicillin and clavulanate potassium 125 mg/5 mL suspension 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 250 mg/5 mL suspension or equivalent dose of 10 mL of amoxicillin and clavulanate potassium 125 mg/5 mL suspension was administered to adult volunteers. One amoxicillin and clavulanate potassium 250 mg chewable tablet or 2 amoxicillin and clavulanate potassium 125 mg chewable tablets are equivalent to 5 mL of amoxicillin and clavulanate potassium 250 mg/5 mL suspension 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 hour. Time above the minimum inhibitory concentration of 1 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 250 mg/5 mL suspension.

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

Neither component in amoxicillin and clavulanate potassium chewable tablets 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 suspension to fasting children, average concentrations of 3 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 β -lactamases and, therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β -lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β -lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated β -lactamases frequently responsible for transferred drug resistance.

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

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

GRAM-POSITIVE AEROBES

Staphylococcus aureus (β -lactamase and non- β -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 (β -lactamase and non- β -lactamase producing)

Haemophilus influenzae (β -lactamase and non- β -lactamase producing)

Klebsiella species (All known strains are β -lactamase producing.)

Moraxella catarrhalis (β -lactamase and non- β -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 0.5 mcg/mL or less against most ($\geq 90\%$) strains of *Streptococcus pneumoniae*; MICs of 0.06 mcg/mL or less against most ($\geq 90\%$) strains of *Neisseria gonorrhoeae*; MICs of 4 mcg/mL or less against most ($\geq 90\%$) strains of staphylococci and anaerobic bacteria, and MICs of 8 mcg/mL or less against most ($\geq 90\%$) 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 *Streptococcus 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 ANAEROBES

Enterococcus faecalis[§]

Staphylococcus epidermidis (β -lactamase and non- β -lactamase producing)

Staphylococcus saprophyticus (β -lactamase and non- β -lactamase producing)

Streptococcus pneumoniae[‡]

Streptococcus pyogenes[‡]

viridans group *Streptococcus*[‡]

GRAM-NEGATIVE ANAEROBES

Eikenella corrodens (β -lactamase and non- β -lactamase producing)

Neisseria gonorrhoeae[‡] (β -lactamase and non- β -lactamase producing)

Proteus mirabilis[§] (β -lactamase and non- β -lactamase producing)

ANAEROBIC BACTERIA

Bacteroides species, including *Bacteroides fragilis* (β -lactamase and non- β -lactamase producing)

Fusobacterium species (β -lactamase and non- β -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- β -lactamase-producing organisms and, therefore, are susceptible to amoxicillin alone

SUSCEPTIBILITY TESTING

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method¹ (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*¹ and *Haemophilus* species:

MIC (mcg/mL) Interpretation

≤ 4/2 Susceptible (S)

≥ 8/4 Resistant (R)

¹ *Staphylococci* which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

For *Streptococcus pneumoniae*: Isolates should be tested using amoxicillin/clavulanic acid and the following criteria should be used:

MIC (mcg/mL) Interpretation

≤ 0.5/0.25 Susceptible (S)

1/0.5 Intermediate (I)

≥ 2/1 Resistant (R)

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)¹

Escherichia coli ATCC 25922 2 to 8

Escherichia coli ATCC 35218 4 to 16

Enterococcus faecalis ATCC 29212 0.25 to 1

Haemophilus influenzae ATCC 49247 2 to 16

Staphylococcus aureus ATCC 29213 0.12 to 0.5

Streptococcus pneumoniae ATCC 49619 0.03 to 0.12

¹ 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 procedure² 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*³ species and *H. influenzae*⁴:

Zone Diameter (mm) Interpretation

≥ 20 Susceptible (S)

≤ 19 Resistant (R)

For other organisms except *S. pneumoniae*⁵ and *N. gonorrhoeae*⁶:

Zone Diameter (mm) Interpretation

≥ 18 Susceptible (S)

14 to 17 Intermediate (I)

≤ 13 Resistant (R)

³ *Staphylococci* which are resistant to methicillin/oxacillin must be considered as resistant to amoxicillin/clavulanic acid.

⁴ 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.

⁵ 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.

⁶ 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)

Escherichia coli ATCC 25922 19 to 25 mm

Escherichia coli ATCC 35218 18 to 22 mm

Staphylococcus aureus ATCC 25923 28 to 36 mm

INDICATIONS AND USAGE

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.

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 β -lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

Otitis Media: caused by β -lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

Sinusitis: caused by β -lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

Skin and Skin Structure Infections: caused by β -lactamase-producing strains of *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella* spp.

Urinary Tract Infections: caused by β -lactamase-producing strains of *Escherichia 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 amoxicillin and clavulanate potassium chewable tablets treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β -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 *Streptococcus 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 clavulanate potassium chewable tablets. (See **Microbiology** subsection.)

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

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to amoxicillin and clavulanate potassium chewable tablets when there is reason to believe the infection may involve any of the β -lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

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

DEC - 3 2003

APPROVED

CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN AND CLAVULANATE POTASSIUM CHEWABLE TABLETS SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin and clavulanate potassium chewable tablets, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic associated colitis.*

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Amoxicillin and clavulanate potassium 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: 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.

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.

Information for the Patient: 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 is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of 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.

Amoxicillin and clavulanate potassium chewable tablets 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.

Make sure your child completes the entire prescribed course of treatment, even if he/she begins to feel better after a few days. Follow your doctor's instructions about the amount to use and the days of treatment your child requires.

Phenylketonurics: Each 200 mg amoxicillin and clavulanate potassium chewable tablet contains 3.5 mg phenylalanine, each 400 mg chewable tablet contains 7 mg phenylalanine. Contact your physician or pharmacist.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin and clavulanate potassium chewable tablets 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 chewable tablets and allopurinol administered concurrently.

In common with other broad-spectrum antibiotics, amoxicillin and clavulanate potassium chewable tablets may reduce the efficacy of oral contraceptives.

Drug/Laboratory Test Interactions: Oral administration of amoxicillin and clavulanate potassium chewable tablets 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 chewable tablets, 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 estril, estril-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore amoxicillin and clavulanate potassium chewable tablets.

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 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m²/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 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/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 chewable tablets are 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 **DOSE AND ADMINISTRATION-Pediatric**.)

ADVERSE REACTIONS

Amoxicillin and clavulanate potassium chewable tablets are 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), one U.S./Canadian clinical trial was conducted which compared amoxicillin and clavulanate potassium 45/6.4 mg/kg/day (divided q12h) for 10 days versus amoxicillin and clavulanate potassium 40/10 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 (Stevens-Johnson syndrome), acute generalized exanthematous pustulosis and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See **WARNINGS**.)

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

Renal: Interstitial nephritis and hematuria have been reported rarely.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with amoxicillin and clavulanate potassium. There have been reports of increased prothrombin time in patients receiving amoxicillin and clavulanate potassium and anticoagulant therapy concomitantly.

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

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

OVERDOSAGE

Following overdose, 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 overdose, discontinue amoxicillin and clavulanate potassium chewable tablets, treat symptomatically, and institute supportive measures as required. If the overdose 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 overdoses 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 overdose with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis.

DOSE AND ADMINISTRATION

Dosage:

Pediatric Patients: Based on the amoxicillin component, amoxicillin and clavulanate potassium 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 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/5 mL formulation in this age group is limited and, thus, use of the 125 mg/5 mL oral suspension is recommended.

Patients aged 12 weeks (3 months) and older

INFECTIONS	DOSING REGIMEN	
	q12h ¹⁾	q8h
	200 mg/5 mL or 400 mg/5 mL oral suspension ¹⁾	125 mg/5 mL or 250 mg/5 mL oral suspension ¹⁾
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

¹⁾ 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.

¹⁾ 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 1 amoxicillin 500 mg and clavulanate potassium tablet every 12 hours or 1 amoxicillin 250 mg and clavulanate potassium tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 amoxicillin 875 mg and clavulanate potassium tablet every 12 hours or 1 amoxicillin 500 mg and clavulanate potassium tablet every 8 hours. Among adults treated with 875 mg every 12 hours, significantly fewer experienced severe diarrhea or withdrawals with diarrhea vs. adults treated with 500 mg 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.

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 tablet is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, amoxicillin and clavulanate potassium chewable tablet should be taken at the start of a meal.

HOW SUPPLIED

Amoxicillin and Clavulanate Potassium Tablets USP (Chewable) are supplied in two strengths:

200 mg/28.5 mg Tablet

Amoxicillin and clavulanate potassium tablets (chewable) 200 mg/28.5 mg contain 200 mg of amoxicillin as the trihydrate and 28.5 mg of clavulanic acid as clavulanate potassium.

Each tablet is a pink colored, circular, biconvex, mottled tablet, debossed with "RX753" on one side and plain on the other side.

NDC 63304-753-03 Bottles of 10
NDC 63304-753-01 Bottles of 100
NDC 63304-753-21 Unit-Dose Blister Packs of 20

400 mg/57 mg Tablet

Amoxicillin and clavulanate potassium tablets (chewable) 400 mg/57 mg contain 400 mg of amoxicillin as the trihydrate and 57 mg of clavulanic acid as clavulanate potassium.

Each tablet is a pink colored, circular, biconvex, mottled tablet, debossed with "RX754" on one side and plain on the other side.

NDC 63304-754-03 Bottles of 10
NDC 63304-754-01 Bottles of 100
NDC 63304-754-21 Unit-Dose Blister Packs of 20

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

CLINICAL STUDIES

In pediatric patients (aged 2 months to 12 years), one U.S./Canadian clinical trial was conducted which compared amoxicillin/clavulanate potassium 45/6.4 mg/kg/day (divided q12h) for 10 days versus amoxicillin/clavulanate potassium 40/10 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 two treatment groups, with the following cure rates obtained for the evaluable patients: At end of therapy, 87.2% (n = 285) 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 diarrhea¹⁾ 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.

¹⁾ Diarrhea was defined as either: (a) three or more watery or four or more loose/watery stools in one day; OR (b) two watery stools per day or three loose/watery stools per day for two consecutive days.

REFERENCES

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

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32218 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

September 2003

FDA-3

3.88" x 1.77"

DEC - 3 2008

RANBAXY
NDC 63304-754-11

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)

400 mg/57 mg*
Rx only

10 Tablets

APPROVE

0803
 Usual Dosage: 1 tablet every 12 hours.
 See accompanying prescribing information.

633041754117
 00000000
 LOT:
 EXP:

EP

non varnish area

*Each chewable tablet contains 400 mg amoxicillin as the trihydrate, 57 mg clavulanate and as clavulanate potassium. Each chewable 400 mg tablet contains 0.30 mg potassium. **Contraindications:** Contains piperazine 7 mg per chewable tablet. Each chewable tablet equivalent to amoxicillin and clavulanate potassium 400 mg/57 mg tablet. Tablets may be chewed before swallowed or may be swallowed whole. Store at 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature. Protect from moisture. Manufactured for Ranbaxy Pharmaceuticals Inc. by Ranbaxy Laboratories, Inc., New Delhi - 110 013, India.

3.88" x 1.77"

DEC - 3 2003

RANBAXY
NDC 63304-754-01

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)

400 mg/57 mg*

Rx only

100 Tablets

0603

Usual Dosage: 1 tablet every 12 hours. See accompanying prescribing information.

00000000

6330417540118

LOT:
EXP:

FPO

non varnish area

*Each chewable tablet contains: 400 mg amoxicillin as the trihydrate, 57 mg clavulanic acid as clavulanate potassium.
Each chewable 400 mg tablet contains 630 mg potassium phenylethanolamine. Contains phenylethanolamine 7 mg per chewable tablet.
Each chewable tablet equivalent to amoxicillin and clavulanate potassium 400 mg/57 mg oral suspension.
Tablets are white to off-white and may be speckled while stored at 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature. Protect from moisture.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
A Division of Ranbaxy Laboratories Ltd.
New Delhi, 110 015, India

65761

RANBAXY
 NDC 63304-754-21
Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)
 400 mg/57 mg*
 Rx only

20 Unit-Dose Tablets
 (4 Blisters of 5 Unit-Dose Tablets)

* Each chewable tablet contains: 400 mg amoxicillin as the trihydrate, 57 mg clavulanic acid as clavulanate potassium. Each chewable 400 mg tablet contains 0.30 mEq potassium.

PHENYLKETONURICS: Contains phenylalanine 7 mg per chewable tablet.

Each chewable tablet equivalent to amoxicillin and clavulanate potassium 400 mg/57 mg oral suspension.

USUAL DOSAGE: 1 tablet every 12 hours. See accompanying prescribing information.

Tablets may be chewed before swallowed or may be swallowed whole.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Keep tablets in foil package until medication is to be taken.

This unit-dose package is not child resistant. This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.

AFFIX PHARMACY LABEL HERE

Manufactured for:
 Ranbaxy Pharmaceuticals Inc.
 Jacksonville, FL 32216 USA
 by: Ranbaxy Laboratories Ltd.
 New Delhi - 110 019, India

0803



NDC 63304-754-21

20 Unit-Dose Tablets
 (4 Blisters of 5 Unit-Dose Tablets)

400 mg/57 mg*

Rx only

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)

APPROVED



NDC 63304-754-21

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)

400 mg/57 mg*

Rx only

20 Unit-Dose Tablets
 (4 Blisters of 5 Unit-Dose Tablets)

DEC - 3 2009

LOT:
 EXP:

non varnish area



00000000

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)
 400 mg/57 mg*
 Rx only



Width 71.438 mm x Height 86.519 mm

<p>LOT: EXP:</p> <p>NDC 63304-754-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>400 mg/57 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 7 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>	<p>LOT: EXP:</p> <p>NDC 63304-754-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>400 mg/57 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 7 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>
<p>LOT: EXP:</p> <p>NDC 63304-754-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>400 mg/57 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 7 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>	<p>LOT: EXP:</p> <p>NDC 63304-754-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>400 mg/57 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 7 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>
<p>LOT: EXP:</p> <p>NDC 63304-754-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>400 mg/57 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 7 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>	<p>APPROVED</p> <p>DEC - 3 2009</p>

3.88" x 1.77"

0800

R **RANBAXY**
NDC 63304-753-01

**Amoxicillin and
Clavulanate Potassium
Tablets, USP (Chewable)**

200 mg/28.5 mg*

Rx only

100 Tablets

Usual Dosage: 1 tablet every 12 hours.
See accompanying prescribing information.

000000000

633041753011

LOT:
EXP:

EPO

non varnish area

Manufactured for:
Ranbaxy Pharmaceuticals, Inc.
Jacksonville, FL 32216 USA
Mumbai, India
Mn. Dsh#: 11019; India

*Each chewable tablet contains: 200 mg amoxicillin as the trihydrate, 28.5 mg clavulanic acid as clavulanate potassium.
Each chewable 200 mg tablet contains 0.15 mEq potassium.
Pharmaceuticals: Contains phenylalanine 3.5 mg per chewable tablet.
Each chewable tablet equivalent to amoxicillin and clavulanate potassium 200 mg/28.5 mg oral suspension.
Tablets are not for use in patients with known hypersensitivity to amoxicillin or clavulanate potassium or to any of the other ingredients.
Store at 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature. Protect from moisture.

DEC - 3 2003

APPROVED

3.88" x 1.77"

0000

RANBAXY

NDC 63304-753-01

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)

200 mg/28.5 mg*

Rx only

100 Tablets

00000000

1633041753011

LOT:

EXP:

non varnish area

APPROVED

Usual Dosage: 1 tablet, 4 times daily. See accompanying prescribing information.

*Each chewable tablet contains 200 mg amoxicillin, as the trihydrate, 28.5 mg clavulanic acid, as clavulanate potassium.

Each chewable 200 mg tablet contains 0.15 mg potassium pantothenate. Contains phenylalanine 3.9 mg per chewable tablet.

Each 200 mg tablet equivalent to amoxicillin and clavulanate potassium 200 mg/28.5 mg.

Tablets may be chewed before swallowed or fully swallowed whole.

Store at 20° to 25° C (68° to 77° F) (See USP Controlled Room Temperature). Protect from moisture.

Manufactured for:
 Ranbaxy Pharmaceuticals, Inc.
 Jaisowmi, 1132716 USA
 New Delhi, 110019, India

DEC

65-161

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)
200 mg/28.5 mg*
 Rx only

20 Unit-Dose Tablets
 (4 Blisters of 5 Unit-Dose Tablets)

RANBAXY
 NDC 63304-753-21

* Each chewable tablet contains: 200 mg amoxicillin as the trihydrate, 28.5 mg clavulanic acid as clavulanate potassium. Each chewable 200 mg tablet contains 0.15 mEq potassium. **PHENYLKETONURICS:** Contains phenylalanine 3.5 mg per chewable tablet.

Each chewable tablet equivalent to amoxicillin and clavulanate potassium 200 mg/5 mL oral suspension.

USUAL DOSAGE: 1 tablet every 12 hours. See accompanying prescribing information.

Tablets may be chewed before swallowed or may be swallowed whole.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Keep tablets in foil package until medication is to be taken.

This unit-dose package is not child resistant. This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.

0803

AFIX PHARMACY LABEL HERE

Manufactured for:
 Ranbaxy Pharmaceuticals, Inc.
 Jacksonville, FL 32216 USA
 by: Ranbaxy Laboratories Ltd.
 New Delhi - 110 019, India

RANBAXY
 NDC 63304-753-21

20 Unit-Dose Tablets
 (4 Blisters of 5 Unit-Dose Tablets)

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)
200 mg/28.5 mg*
 Rx only

DEC - 3 2003

RANBAXY
 NDC 63304-753-21

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)

200 mg/28.5 mg*
 Rx only

20 Unit-Dose Tablets
 (4 Blisters of 5 Unit-Dose Tablets)

APPROVED

LOT:
 EXP:

00000000
FPO

Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)
200 mg/28.5 mg*
 Rx only



Width 71.438 mm x Height 86.519 mm

<p>LOT: EXP:</p> <p>NDC 63304-753-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>200 mg/28.5 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 3.5 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>	<p>LOT: EXP:</p> <p>NDC 63304-753-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>200 mg/28.5 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 3.5 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>
<p>LOT: EXP:</p> <p>NDC 63304-753-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>200 mg/28.5 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 3.5 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>	<p>LOT: EXP:</p> <p>NDC 63304-753-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>200 mg/28.5 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 3.5 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>
<p>LOT: EXP:</p> <p>NDC 63304-753-56</p> <p>Amoxicillin and Clavulanate Potassium Tablet, USP (Chewable)</p> <p>200 mg/28.5 mg</p> <p>Rx only</p> <p>Each chewable tablet contains 3.5 mg phenylalanine.</p> <p>Manufactured by: Ranbaxy Laboratories Limited New Delhi - 110 019, India</p>	<p>APPROVED</p> <p>DEC - 3 2008</p>

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-161

LABELING REVIEWS

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

ANDA Number: **65-161** Dates of Submission: **August 25 and September 29, 2003**

Applicant's Name: **Ranbaxy Pharmaceuticals, Inc.**

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

BASIS OF APPROVAL:

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

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

Container Labels: 10s and 100s

Satisfactory in FPL as of August 25, 2003 submission [vol 2.1].

Unit Dose Blisters:

Satisfactory in FPL as of August 25, 2003 submission [vol 2.1].

Unit Dose Cartons: 20s (4 x 5s)

Satisfactory in FPL as of August 25, 2003 submission [vol 2.1].

Professional Package Insert Labeling:

Satisfactory in FPL as of September 29, 2003 submission [vol 3.1 - rev 9-03 - FDA-3].

Revisions needed post-approval: **None**

BASIS OF APPROVAL:

Was this approval based upon a petition? **NO**

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

NDA Number: **50-726**

NDA Drug Name: **Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)**

NDA Firm: **SMITHKLINE BEECHAM Pharmaceuticals**

Date of Approval of NDA Insert and supplement #: **5/12/03 (S-014)**

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: **side-by-sides**

Basis of Approval for the Unit Dose Carton Labeling: **side-by-sides**

Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		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	
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	
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) [THE TABLET IS CHEWABLE]	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? NEED TO STATE "UNSCORED"	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?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? ASPARTAME - PHENYLALANINE - PHENYLKETONURICS	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 dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		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:

The RLD's 200 mg tablet and 400 mg tablet have a potassium content of 0.14 mEq and 0.29 mEq respectively while this ANDA's 200 mg tablet and 400 mg tablet state that they have a potassium content of 0.15 mEq and 0.30 mEq respectively. I have asked S. Furness (chemist) regarding this and it is his belief that this difference is inconsequential.

FOR THE RECORD: (portions taken from previous review)

- Review based on the labeling of Augmentin-200 and Augmentin-400 Chewable Tablets - NDA 50-726/S-014 (in draft - rev 1-02); approved 5-12-03.

The firm has added the text regarding antibiotic resistance to the beginning of the insert and to the INDICATIONS AND USAGE and PRECAUTIONS sections as directed by 21 CFR 201.24.

- Patent/ Exclusivities

Patent Data - 50-726

No	Expiration	Use Code	Use	File
None				

Exclusivity Data - 50-726

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	

3. Storage Conditions:
NDA - Store at or below 25°C (77°F).
ANDA - Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
USP - Preserve in tight containers.
4. Dispensing Recommendations:
NDA - Keep tablets in foil package until medication is to be taken.
ANDA - This unit-dose package is not child resistant. This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.
USP -
5. Scoring:
NDA - unscored
ANDA - unscored
6. Product Line:
The innovator markets their product in unit dose cartons of 20s.
The applicant proposes to market their product in unit dose cartons of 20s and in bottles of 10s (CRC) and 100s (CRC). The blisters have foil backing [p 3464 B 1.3]
7. The tablet debossings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95) except that I have asked the firm to indicate the scoring configuration of the tablets.
8. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 3558, 3563 v B 1.3 section XIII.
9. Ranbaxy Laboratories Limited is the manufacturer [p 3030 v B 1.2 section IX].
10. The amounts of phenylalanine listed in the labeling for each tablet [3.5 mg - 200 mg tablet and 7 mg - 400 mg tablet] are accurate. The aspartame in the tablets [6.25 mg - 200 mg tablet and 12.5 mg - 400 mg tablet] is broken down in the body to phenylalanine. The ratio of the molecular weights [phenylalanine/aspartame] equals 0.561 thus 56.1% of the weight of aspartame becomes phenylalanine.
 $[200 \text{ mg tablet}] \quad 6.25 \text{ mg} \times 0.561 = 3.5 \text{ mg} \quad [400 \text{ mg tablet}] \quad 12.5 \text{ mg} \times 0.561 = 7 \text{ mg}$
11. USP labeling requirement for this drug product: Label chewable tablets to include the word "chewable" in juxtaposition to the official name - I have asked the firm to do this. The labeling must also indicate that the chewable tablets may be chewed being swallowing or may be swallowed whole - I have asked the firm to place this statement on all their labeling pieces - exception being the unit dose blisters because of space constraints.
12. Geneva's approved ANDA 65-065 (for chewable tablets) as well as the RLD's insert labeling were used as models. The Geneva application is the only approved generic for chewable tablets.

Date of Review: 10-16-03

Dates of Submission: 8-25-03 and 9-29-03

Primary Reviewer: Adolph Vezza

Date:

Team Leader: Lillie Golson

Date:

A. Vezza
L. Golson

10/20/03

10/20/03

cc:

ANDA: 65-161

DUP/DIVISION FILE

HFD-613/AVeZZa/LGolson (no cc)

aev/10/16/03|V:\FIRMSNZ\|RANBAXYLTRS&REV\65161.APL

Review

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-161

CHEMISTRY REVIEWS



ANDA 65-161

**Amoxicillin and Clavulanate Potassium Chewable Tablets
USP, 200 mg/28.5 mg and 400 mg/57 mg**

Ranbaxy Laboratories Limited

**Susan Zuk
OGD, Chemistry Division II**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary.....	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s).....	8
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative.....	9
A. Reviewer's Signature	9
B. Endorsement Block	9
C. CC Block.....	9
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	
S DRUG SUBSTANCE [Name, Manufacturer]	
P DRUG PRODUCT [Name, Dosage form]	
A APPENDICES	
R REGIONAL INFORMATION.....	
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	
A. Labeling & Package Insert.....	
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	
III. List Of Deficiencies To Be Communicated.....	



Chemistry Review Data Sheet

1. ANDA 65-161
2. REVIEW #: 1
3. REVIEW DATE: 6/12/03
4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original ANDA

12/23/02

7. NAME & ADDRESS OF APPLICANT:

Name: Ranbaxy Laboratories Limited

Address: Sector 18, Udyog Vihar Industrial Area

Representative: Gurgaon -- 122001, India

Telephone: 91-124-2343125



Chemistry Review Data Sheet

Name of US Agent: Ranbaxy Pharmaceuticals, Inc.
Address: 600 College Road East
Princeton, NJ 08540
Representative: Abha Pant
Telephone: (609) 720-5666
FAX (609) 720-1155

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: Basis for submission of the ANDA is reference listed drug Augmentin® (Amoxicillin and Clavulanate Potassium Chewable Tablets) manufactured by GlaxoSmithkline, NDA #50-726. There are no unexpired patents for the RLD.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Chewable tablet

12. STRENGTH/POTENCY: 200 mg/28.5 mg and 400 mg/57 mg
Amoxicillin / Clavulanate Potassium

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

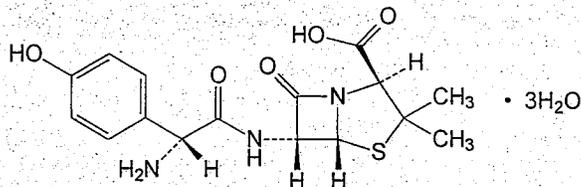
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

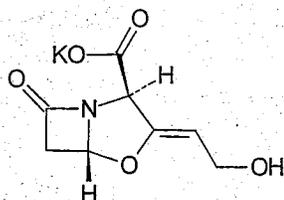
Not a SPOTS product

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*-[2 α ,5 α ,6 β (*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).



**APPEARS THIS WAY
ON ORIGINAL**



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
12895	II	Ranbaxy	Amoxicillin Trihydrate	3	A	12/10/02 info wrong in COMIS	M. Shih
	II			3	A	3/17/03	S. Zuk
	IV			4			
	IV			4			
	IV			4			
	III			3	A	4/29/02	
	III			3	A	4/29/02	
	III			3	A	4/3/01	
	III			3	A	10/8/02	
	III			3	A	7/17/02	
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4, 6	I	4/14/03 last review	Checked out to H. Hahn
	III			3	A	12/18/02	
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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	NA		
EES	Clavulanate K DS - Acceptable Amoxicillin THD - assigned DP Manufacturer - Acceptable	2/24/03 3/10/03 2/20/03	
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA 65-161

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Approval is not due to minor deficiencies.
- 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-aminopenicillic 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 _____ 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, glycine, povidone, magnesium stearate, mannitol, mint cream flavor, orange cream flavor, silicon dioxide, sodium starch glycolate and tropical blend flavor. Each 200 mg tablet contains 0.15 mEq potassium. Tablets are supplied in bottles of 100 and in blister packs 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 + Clavulanate Potassium Tablets (Chewable) are used in the treatment of a variety of both gram negative and gram positive bacterial infections. The recommended dosage is one tablet every 12 hours.



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is deficient due to the following omissions:

1. Description of _____ was omitted.
2. Identification of impurities in drug substance was omitted.
3. Blend Uniformity Analysis was not performed.
3. In-process sampling procedure (frequency) was not provided.

III. Administrative

A. Reviewer's Signature

Susan Zuk 6/25/03

B. Endorsement Block

Susan Zuk/6/12/03
Richard Adams/6/20/03
Mark Anderson/

C. CC Block

Redacted 19 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW # 1



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 65161
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SZUK/6/12/03 *Jan Zuh* 6/25/03

HFD-643/RADAMS/6/20/03 *R. C. Adams* 6/25/03

HFD-617/MANDERSON/6/24/03 *M Anderson* 6/25/03

F/T by: EW 6/25/03

V:\FIRMSNZ\ANBAXYLTRS&REV\65161R01.NA1

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 65-161

Amoxicillin and Clavulanate Potassium Chewable Tablets
USP, 200 mg/28.5 mg and 400 mg/57 mg

Ranbaxy Laboratories Limited

Susan Zuk
OGD, Chemistry Division II

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s).....	8
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block.....	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	
S DRUG SUBSTANCE [Name, Manufacturer].....	
P DRUG PRODUCT [Name, Dosage form]	
A APPENDICES	
R REGIONAL INFORMATION	
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	
A. Labeling & Package Insert	
B. Environmental Assessment Or Claim Of Categorical Exclusion	
III. List Of Deficiencies To Be Communicated.....	



Chemistry Review Data Sheet

1. ANDA 65-161
2. REVIEW #: 2
3. REVIEW DATE: 9/25/03
4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents

Original ANDA

Document Date

12/23/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Minor Amendment

8/27/03 - response to chemistry deficiency letter of
6/26/03

7. NAME & ADDRESS OF APPLICANT:

Name: Ranbaxy Laboratories Limited

Address: Sector 18, Udyog Vihar Industrial Area

Representative: Gurgaon – 122001, India



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Telephone: 91-124-2343125

Name of US Agent: Ranbaxy Pharmaceuticals, Inc.

Address: 600 College Road East
Princeton, NJ 08540

Representative: Abha Pant

Telephone: (609) 720-5666

FAX (609) 720-1155

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Potassium Chewable Tablets USP

9. LEGAL BASIS FOR SUBMISSION: Basis for submission of the ANDA is reference listed drug Augmentin® (Amoxicillin and Clavulanate Potassium Chewable Tablets) manufactured by GlaxoSmithkline, NDA #50-726. There are no unexpired patents for the RLD.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Chewable tablet

12. STRENGTH/POTENCY: 200 mg/28.5 mg and 400 mg/57 mg
Amoxicillin / Clavulanate Potassium

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed



CHEMISTRY REVIEW

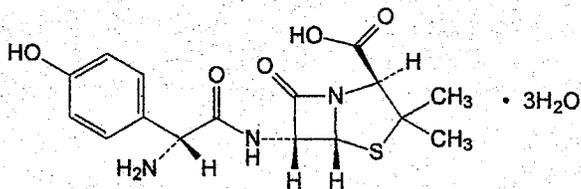


Chemistry Review Data Sheet

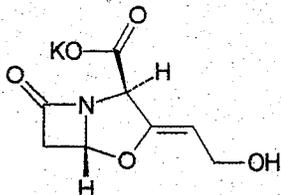
 X Not a SPOTS product

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 [2S-[2 α ,5 α ,6 β (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).



APPEARS THIS WAY
ON ORIGINAL



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
12895	II	Ranbaxy	Amoxicillin Trihydrate	3	A	12/10/02 info wrong in COMIS	M. Shih
	II			3	A	3/17/03	S. Zuk
	IV			4			
	IV			4			
	IV			4			
	III			3	A	4/29/02	
	III			3	A	4/29/02	
	III			3	A	4/3/01	
	III			3	A	10/8/02	
	III			3	A	7/17/02	
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			3	A	9/5/03	B. Wu
	III			3	A	12/18/02	
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Clavulanate K DS - Acceptable Amoxicillin THD - assigned DP Manufacturer - Acceptable	2/24/03 3/10/03 2/20/03	
Methods Validation	NA		
Labeling	Acceptable	10/20/03	A. Vezza
Bioequivalence	Acceptable	7/24/03	M. Makary
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

**APPEARS THIS WAY
ON ORIGINAL**



The Chemistry Review for ANDA 65-161

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-aminopenicillic 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 _____ 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, glycine, povidone, magnesium stearate, mannitol, mint cream flavor, orange cream flavor, silicon dioxide, sodium starch glycolate and tropical blend flavor. Each 200 mg tablet contains 0.15 mEq potassium. Tablets are supplied in bottles of 10 and 100 and in blister packs 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 + Clavulanate Potassium Tablets (Chewable) are used in the treatment of a variety of both gram negative and gram positive bacterial infections. The recommended dosage is one tablet every 12 hours.



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is recommended for approval when labeling and EER are found acceptable.

The following supports approval:

- Bioequivalence review - acceptable
- CMC - acceptable

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Susan Zuk/9/25/03; 10/20/03 (updated upon completion of label review)
Richard Adams/9/30/03; 10/20/03

Susan Zuk 10/22/03

R.C. Adams 10/27/03

C. CC Block

Redacted 20 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW # 2



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 65-161
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SZUK/9/25/03; 10/20/03 (updated upon completion of label review) *San Zule 10/22/03*

HFD-643/RADAMS/9/30/03; 10/20/03 *R-C Adams 10/22/03*

F/T by: mda/10/22/03

V:\FIRMSNZ\ANBAXYLTRS&REV\65161R02.AP

TYPE OF LETTER: ANDA Approval



ANDA APPROVAL SUMMARY

ANDA: 65-161

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)

FIRM: Ranbaxy Pharmaceuticals, Inc.

DOSAGE FORM: Oral Solid **STRENGTH:** 200 + 28.5 mg and 400 + 57 mg

CGMP STATEMENT/EIR UPDATE STATUS: A signed cGMP was provided on page 3033 for Ranbaxy's drug product manufacturing facility. Ranbaxy received an acceptable EER dated 2/20/03. _____ supplier of Clavulanate, received acceptable EER dated 2/24/03. Ranbaxy Laboratories Ltd, supplier of Amoxicillin THD, has not yet received an EER report.

BIO STUDY: The bio-study comparing the applicant's product to GlaxoSmithKline's Augmentin was found to be acceptable on 7/24/03.

METHOD VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substances and drug product are compendial products. Method validation is not required.

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

LABELING: Acceptable 10/20/03

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

SIZE OF BIO BATCH (FORM'S SOURCE OF NDS OK?): Exhibit batches 1236227 (200 + 28.5 mg) and 1237790 (400 + 57 mg), used for stability and bio-studies, were manufactured with bulk drug substance supplied by Ranbaxy and _____. The exhibit batches were manufactured to produce theoretical yields of _____ tablets each.

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

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch sizes are _____ tablets of 200 + 28.5 mg



CHEMISTRY REVIEW



Chemistry Assessment Section

dosage, and — tablets of 400 + 57 mg dosage strength. The manufacturing process described in the blank master record is the same as that described in the exhibit batch records.

CHEMIST: Susan Zuk

DATE: 9/25/03; 10/20/03

SUPERVISOR: Richard Adams

DATE: 10/20/03

Susan Zuk
10/20/03

R.C. Adams 10/22/03

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-161

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-161
Drug Product Name	Amoxicillin and Clavulanate Potassium Chewable Tablets, USP
Strength	400 mg/EQ 57 mg Base and 200 mg/EQ 28.5 mg Base
Applicant Name	Ranbaxy Laboratories Limited.
Address	Gurgaon, India
Submission Date(s)	December 23, 2002
Reviewer	Moheb H. Makary
File Location	V:\FIRMSNZ\LANBAXY\LTRS&REV\65161N1202.doc

I. Executive Summary

This submission consisted of two BE studies, one under fasting and the other nonfasting conditions and dissolution data on all strengths of the test and reference products. The studies conducted on the 400 mg/EQ 57 mg Base chewable tablets comparing them with Augmentin^R chewable tablets, 400 mg/EQ 57 mg Base, of GlaxoSmithKline. The study design for each of the BE studies is a two-way, crossover study in normal male and female subjects (n=39 each study). Statistical analyses of the plasma concentration data for amoxicillin and clavulanic acid demonstrate bioequivalence in both studies.

For the fasting BE study, amoxicillin results are (point estimate, 90% CI): LAUC_t of 94.1, 88.9-99.5%; LAUC_i of 97.0, 94.0-100.0% and LCmax of 98, 90.7-106.3%. Clavulanic acid results are (point estimate, 90% CI): LAUC_t of 103.3, 93.8-113.9%; LAUC_i of 103.5, 94.2-113.7% and LCmax of 103.1, 93.7-113.6%.

For the nonfasting BE study, amoxicillin results are (point estimate, 90% CI): LAUC_t of 93.8, 86.6-101.7%; LAUC_i of 94.4, 88.8-100.6% and LCmax of 99.3, 89.4-110.4%. Clavulanic acid results are (point estimate, 90% CI): LAUC_t of 106.9, 100.6-113.5%; LAUC_i of 106.9, 100.8-113.4% and LCmax of 106.0, 97.4-115.3%.

The products meet the FDA dissolution specifications. Waiver of in vivo study requirements is granted for the 200 mg/28.5 mg strength. The application is acceptable with no deficiencies.

II. Table of Contents

I. Executive Summary.....	1
II. Table of Contents	2
III. Submission Summary.....	2
A. Drug Product Information.....	2
B. Contents of Submission.....	3
C. Bioanalytical Method Validation.....	4
D. In Vivo Studies.....	4
1. Single-dose Fasting Bioequivalence Study.....	5
2. Single-dose Fed Bioequivalence Study	6
E. Formulation.....	6
In Vitro Dissolution.....	6
G. Waiver Requests	7
H. Deficiency Comments.....	7
I. Recommendations.....	7
IV. Appendix.....	9
A. Individual Study Reviews.....	9
1. Single-dose Fasting Bioequivalence Study.....	9
2. Single-dose Fed Bioequivalence Study	14
B. Attachments.....	19

III. Submission Summary

A. Drug Product Information

Test Product:

Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 400 mg/ 57 mg and 200 mg/ 28.5 mg, are pink, colored, circular, biconvex, mottled tablets.

Reference Product:

Augmentin[®] (amoxicillin and clavulanate potassium) chewable tablets are available in three strengths: 400 mg/ 57 mg, 250 mg/62.5 mg and 200 mg/ 28.5 mg. The Orange Book (Electronic 2003) lists Augmentin[®] 400 mg/ 57 mg and 250 mg/62.5 mg chewable tablets manufactured by GlaxoSmithKline as the reference listed drug (NDA 50726 and 50597, approved in May 31, 1996 and July 22, 1985, respectively). Lot #RT1576 (EXP. 5/03) of the 400 mg/ 57 mg Augmentin^R chewable tablet was used in the BE studies.

Indication:

Augmentin[®] is indicated for the treatment of infections caused by susceptible (beta)-lactamase-producing strains of organisms in the following conditions: lower respiratory tract infections, otitis media and sinusitis (caused by *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*, skin and skin structure infections (caused by *Staphylococcus aureus*, *Escherichia coli* and

Klebsiella spp.) and urinary tract infections (caused by *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp.).

PK/PD Information

Bioavailability: Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of the drug product.

Half Life: The half-life of amoxicillin after the oral administration of the drug product is 1.3 hours and that of clavulanic acid is 1.0 hour.

Tmax: 1.4 and 1 hours for amoxicillin and clavulanic acid, respectively.

Excretion: Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours.

Food Effect: Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While the drug product can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state.

Relevant DBE History

The Division of Bioequivalence requests the following for documentation of bioequivalence of amoxicillin and clavulanate potassium chewable tablets USP, 400 mg/ 57 mg and 200 mg/ 28.5 mg (Geneva Pharmaceuticals, approved product: April 18, 2002, ANDA 65-065):

- 1). Both fasting and non-fasting studies on the 400 mg/ 57 mg chewable tablets to establish bioequivalence.
- 2). Biowaiver for the generic amoxicillin and clavulanate potassium chewable tablets USP, 200 mg/ 28.5 mg, may be considered if the following conditions are met:
 - a. Results of both fasting and non-fasting bioequivalence studies conducted on the 400 mg/ 57 mg chewable tablets are acceptable.
 - b. Dissolution testing conducted on the two strengths of the generic amoxicillin and clavulanate potassium chewable tablets is acceptable.
 - c. Formulations among the two strengths of generic chewable tablets are proportionally similar.

B. Contents of Submission

		How many?
Single-dose fasting study	Yes	1
Single-dose fed study	Yes	1
Steady-state study	No	0
In vitro dissolution testing	Yes	2 (one for each strength)
Waiver requests	Yes	1

Freeze-thaw stability (cycles)	4
Long-term storage stability (days)	198 @ -80°C
Specificity	Yes
Bioanalytical method is acceptable	Yes
20% Chromatograms included	Yes

Comments on the Analytical Method: The analytical method utilized a direct injection technique. It was determined that there was no scientifically viable approach to obtain conventional recovery data. The analytical method and data are acceptable.

D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study No.	AA02872
Study Design:	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	40
No. of subjects completing	39
No. of subjects analyzed	39
Sex(es) included (how many?)	Male (22) Female (18)
Test product	Amoxicillin and Clavulanate Potassium Chewable Tablets USP
Reference product	Augmentin® (amoxicillin and clavulanate potassium) chewable tablets of GlaxoSmithKline.
Strength tested	400 mg/57 mg
Dose	2 x 400 mg/57 mg chewable tablets

Summary of Statistical Analysis for Amoxicillin

Parameter	Point Estimate	90% Confidence Interval
LnAUCt	0.94	88.9 – 99.5
LnAUCi	0.97	93.96 – 99.9
LnCmax	0.98	90.7 – 106.3

Summary of Statistical Analysis for Clavulanic Acid

Parameter	Point Estimate	90% Confidence Interval
LnAUCt	1.03	93.8 – 113.9
LnAUCi	1.03	94.2 – 113.7
LnCmax	1.03	93.7 – 113.6

The study is acceptable. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCt, AUCi and Cmax for a amoxicillin and clavulanic acid. The reviewer's calculations are similar to those submitted by the firm.

2. Single-dose Fed Bioequivalence Study

Study No. AA02873
Study Design: A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled 40
No. of subjects completing 39
No. of subjects analyzed 39
Sex(es) included (how many?) Male (20) Female (20)
Test product Amoxicillin and Clavulanate Potassium Chewable Tablets USP
Reference product Augmentin® (amoxicillin and clavulanate potassium) chewable tablets of GlaxoSmithKline.
Strength tested 400 mg/57 mg
Dose 2 x 400 mg/57 mg chewable tablets

Summary of Statistical Analysis for Amoxicillin

Parameter	Point Estimate	90% Confidence Interval
LnAUCt	0.94	86.6 – 101.7
LnAUCi	0.94	88.8 – 100.6
LnCmax	0.99	89.4 – 110.4

Summary of Statistical Analysis for Clavulanic Acid

Parameter	Point Estimate	90% Confidence Interval
LnAUCt	1.07	100.6 – 113.5
LnAUCi	1.07	100.8 – 113.4
LnCmax	1.06	97.4 – 115.3

The study is acceptable. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCt, AUCi and Cmax for a amoxicillin and clavulanic acid. The reviewer's calculations are similar to those submitted by the firm.

E. Formulation

The test product formulations are shown in Table 1 of the Appendix.

Inactive Ingredients within IIG limits Yes

The formulation is acceptable Yes

F. In Vitro Dissolution (FDA Method, ANDA #65-065)

Dissolution studies were conducted in 900 mL of water at 37°C using USP apparatus II (paddle) at 75 rpm. The dissolution testing conducted by Ranbaxy Laboratories Limited. on its amoxicillin/clavulanate potassium chewable tablets, 400 mg/57 mg and 200 mg/28.5 mg, is acceptable.

G. Waiver Requests

The applicant requests a waiver of in vivo bioequivalence testing under 21 CFR 320.22(d)(2) for the 200 mg/28.5 mg chewable tablets.

The formulations are proportionally similar to that of the strength, which underwent acceptable in vivo testing: Yes

Acceptable dissolution testing, all strengths: Yes

H. Deficiency Comment None

I. Recommendations

1. The single-dose fasting and non-fasting bioequivalence studies conducted by Ranbaxy Laboratories Limited. on its amoxicillin/clavulanate potassium chewable tablets, 400 mg/EQ 57 mg Base, Lot # 1237790, comparing it to Augmentin^R chewable tablets, 400 mg/EQ 57 mg Base, Lot #RT1576, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Ranbaxy's amoxicillin/clavulanate potassium 400 mg/EQ 57 mg Base chewable tablets are bioequivalent to the reference product Augmentin^R 400 mg/EQ 57 mg Base chewable tablets, manufactured by GlaxoSmithKline.

2. The dissolution testing conducted by Ranbaxy Laboratories Limited. on its amoxicillin/clavulanate potassium chewable tablets, 400 mg/EQ 57 mg Base and 200 mg/EQ 28.5 mg Base, lots #1237790 and 1236227, respectively, is acceptable. The formulation for the 200 mg/28.5 mg amoxicillin/clavulanate potassium chewable tablet strength is proportionally similar to that of the 400 mg/EQ 57 mg Base amoxicillin/clavulanate potassium chewable tablet of the test product, which underwent acceptable bioequivalency testing. Waiver of in-vivo bioequivalence study requirements for the 200 mg/EQ 28.5 mg Base chewable tablet of amoxicillin/clavulanate potassium is granted per 21 CFR 320.22(d)(2).

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 26 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than —% (Q) of the labeled amount of amoxicillin and —% (Q) of the labeled amount of clavulanic acid in the dosage form are dissolved in 30 minutes.

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

The firm should be informed of the above recommendations.

Moheb H. Makary
Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED

FT INITIALED GJP SINGH

[Signature]

Date

7-24-03

Concur:

Barbara M. Savit

Date:

7/24/03

for

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 7-17-03, 7-24-03, 65161N1202.doc

cc: ANDA #65-161, original, HFD-658 (Makary), Drug File, Division File.

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information

Study Number: #AA02872
 Clinical Site: []
 Dosing Dates: Group A
 period I: 10/22/2002 (Subjects 1-20)
 period II: 10/29/2002 (Subjects 1-20)
 Group B
 period I: 10/23/2002 (Subjects 21-40)
 period II: 10/30/2002 (Subjects 21-40)
 Analytical Site: []
 Analysis Dates: 11/8/2002-11/13/2002
 Storage Period: 21 days

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Amoxicillin/Clavulanate Potassium Chewable Tablets	Augmentin [®] Chewable Tablets
Manufacturer:	Ranbaxy Laboratories Limited.	GlaxoSmithKline
Manufacture Date:	9/02	N/A
Expiration Date:	N/A	5/03
Strength	400 mg/57 mg	400 mg/EQ 57 mg Base
Dosage Form	Chewable Tablets	Chewable Tablets
Bio Batch Size:	[] Tablets	N/A
Batch/Lot Number:	1237790	RT1576
Potency	99.5%/102.2%	103.2%/102.1%
Content Uniformity	98.6%/102.1%	104.7%/104.3%
Formulation	See Table #1	N/A
Dose Administered:	2x400 mg/EQ 57 mg Base Chewable Tablets	2x400 mg/EQ 57 mg Base Chewable Tablets
Route of Administration	Oral	Oral
Study Condition:	Fasting	Fasting

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
Washout Period	7 days

Randomization Scheme	AB for subjects #2, 3, 4, 7, 8, 12, 13, 14, 15, 19, 21, 22, 24, 25, 29, 31, 32, 33, 36, 37 and BA for the rest of subjects.
Blood Sampling Times	0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7 and 8 hours
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Under conditions with minimal UV exposure
IRB Approval	Yes, on 10/11/2002
Informed Consent	Yes, 10/15/2002
Subjects Demographics	See Table #3
Length of Fasting:	10 hours pre-dose and 4 hours post-dose.
Length of Confinement	From at least 11 hours pre-dose to 8 hours post-dose.
Safety Monitoring	Subjects were instructed to inform the study physician and /or nurses of any adverse events that occurred during the study.

Study Results

Clinical: The firm's clinical summary is provided on Page 421, Vol. 1.2.

Dropout Information	
Subject Nos.	8
Reason	Subject #8 was dropped by the principal investigator on Day 1 of period 2 because of failed drug screen.
Adverse Events	A total of 10 adverse events were reported in the study, three were either probably or possibly related to study medication. 2 following administration of Treatment A 1 following administration of Treatment B For additional information see Vol. 1.2, page #445
Protocol Deviations	No significant deviations from the protocol were documented.

Comments:

The adverse events occurred similar frequency for both treatments.

DURING STUDY ASSAY VALIDATION FOR AMOXICILLIN (Vol.1.2, page 481)

Parameter	
QC Conc. (ug/mL)	0.301, 8.017, 15.533
Standard Curve Conc. (ug/mL)	0.1, 0.2, 0.95, 3.0, 9.504, 14.006, 17.007, 19.008
Between-Batch Precision for Standards (%CV)	2.9-7.2
Between-Batch Accuracy for Standards (% Actual)	95.0-104.9
Between-Batch Precision for QC (%CV)	1.2-6.2
Between-Batch Accuracy for QC (% Actual)	101.1-104.3

DURING STUDY ASSAY VALIDATION FOR CLAVULANIC ACID (Vol.1.4, page 481)

Parameter	
QC Conc. (ng/mL)	150.7, 2008.7, 4017.4
Standard Curve Conc. (ng/mL)	50.0, 99.9, 249.8, 749.3, 2497.6, 3746.4, 4495.6, 4995.1
Between-Batch Precision for Standards %CV)	2.1-4.9
Between-Batch Accuracy for Standards (% Actual)	96.3-111.6
Between-Batch Precision for QC (%CV)	0.2-4.7
Between-Batch Accuracy for QC (% Actual)	102.9-106.8

Repeat Assays

There were no reported repeat assays.

Chromatograms: Acceptable

Comments: The analytical method and data for amoxicillin and clavulanic acid are acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

Pharmacokinetic/Statistical Analysis for Amoxicillin

Mean Plasma Concentrations	Table #4, Figure #1
----------------------------	---------------------

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

a. Arithmetic Mean Pharmacokinetic Parameters (N=39)

PK Parameter	Test Treatment A	Reference Treatment B	T/R
AUC _t [ug-hr/mL]	35.41 (21%)	36.91 (17%)	0.96
AUC _i [ug-hr/mL]	36.66 (17%)	37.44 (18%)	0.98
C _{max} [ug/mL]	13.61 (27%)	13.44 (21%)	1.01
T _{max} [hr]	1.38	1.67	
K _{el} [1/hr]	0.596	0.607	
T _½ [hr]	1.20	1.16	

b. 90% Confidence Intervals (N=39)

Parameter	RMSE	Point Estimate	90% Confidence Interval
LnAUC _t	0.147	0.94	88.9 – 99.5
LnAUC _i	0.078	0.97	93.96 – 99.9
LnC _{max}	0.207	0.98	90.7 – 106.3

Comments: (on pharmacokinetic analysis)

- Ke and AUC_i were determined for 38 subjects
- Measurable drug concentrations at 0 hr: None
- First scheduled post-dose sampling time as T_{max}: None
- First measurable drug concentration as C_{max}: None
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for AUC_t, AUC_i, C_{max} are within the acceptable limits of 80-125%.

Pharmacokinetic/Statistical Analysis for Clavulanic Acid

Mean Plasma Concentrations	Table #5, Figure #2
----------------------------	---------------------

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

a. Arithmetic Mean Pharmacokinetic Parameters (N=39)

PK Parameter	Test Treatment A	Reference Treatment B	T/R
AUCt [ng-hr/mL]	6630.2 (34%)	6233.9 (31%)	1.06
AUCi [ng-hr/mL]	6758.1 (34%)	6357.0 (31%)	1.06
Cmax [ng/mL]	3154.7 (40%)	2942.6 (34%)	1.07
Tmax [hr]	1.19	1.05	
Kei [1/hr]	0.55	0.55	
T½ [hr]	1.30	1.30	

b. 90% Confidence Intervals (N=39)

Parameter	RMSE	Point Estimate	90% Confidence Interval
LnAUCt	0.25	1.03	93.8 – 113.9
LnAUCi	0.25	1.03	94.2 – 113.7
LnCmax	0.25	1.03	93.7 – 113.6

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for all 39 subjects
- Measurable drug concentrations at 0 hr: None
- First scheduled post-dose sampling time as Tmax: None
- First measurable drug concentration as Cmax: None
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for AUCt, AUCi, Cmax are within the acceptable limits of 80-125%.

Conclusion:

The single-dose fasting bioequivalence study is acceptable.

2. Single-dose Fed Bioequivalence Study**Study Information**

Study Number: #AA02873
 Clinical Site: []
 Dosing Dates: Group A
 period I: 10/19/2002 (Subjects 1-20)
 period II: 10/26/2002 (Subjects 1-20)
 Group B
 period I: 10/20/2002 (Subjects 21-40)
 period II: 10/27/2002 (Subjects 21-40)
 Analytical Site: []
 Analysis Dates: 11/18/2002-11/22/2002
 Storage Period: 33 days

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Amoxicillin/Clavulanate Potassium Chewable Tablets	Augmentin [®] Chewable Tablets
Manufacturer:	Ranbaxy Laboratories Limited.	GlaxoSmithKline
Manufacture Date:	9/02	N/A
Expiration Date:	N/A	5/03
Strength	400 mg/EQ 57 mg Base	400 mg/EQ 57 mg Base
Dosage Form	Chewable Tablets	Chewable Tablets
Bio Batch Size:	Tablets	N/A
Batch/Lot Number:	1237790	RT1576
Potency	99.5%/102.2%	103.2%/102.1%
Content Uniformity	98.6%/102.1%	104.7%/104.3%
Formulation	See Table #1	N/A
Dose Administered:	2x400 mg/EQ 57 mg Base Chewable Tablets	2x400 mg/EQ 57 mg Base Chewable Tablets
Route of Administration	Oral	Oral
Study Condition:	Fed	Fed

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
Washout Period	7 days

Randomization Scheme	AB for subjects #1, 3, 4, 5, 7, 9, 11, 14, 15, 17, 22, 23, 27, 29, 30, 33, 34, 35, 36, 39 and BA for the rest of subjects.
Blood Sampling Times	0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7 and 8 hours
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Under conditions with minimal UV exposure
IRB Approval	Yes, on 10/11/2002
Informed Consent	Yes, 10/15/2002
Subjects Demographics	See Table #4
Length of Fasting:	10 hours pre-dose until 30 minutes prior to dosing when a standard breakfast (same as the one recommended by the DBE) was given.
Length of Confinement	From at least 11 hours pre-dose to 8 hours post-dose.
Safety Monitoring	Subjects were instructed to inform the study physician and /or nurses of any adverse events that occurred during the study.

Study Results

Clinical: The firm's clinical summary is provided on Page 1778, Vol. 1.5.

Dropout Information	
Subject Nos.	20
Reason	Subject #20 did not check in for period 2
Adverse Events	A total of 7 adverse events were reported in the study, three were either probably or possibly related to study medication. 2 following administration of Treatment A 1 following administration of Treatment B For additional information see Vol. 1.5, page #1800
Protocol Deviations	No significant deviations from the protocol were documented.

Comments:

The adverse events occurred with similar frequency for both treatments.

DURING STUDY ASSAY VALIDATION FOR AMOXICILLIN (Vol.1.5, page 1828)

Parameter	
QC Conc. (ug/mL)	0.301, 8.017, 15.533
Standard Curve Conc. (ug/mL)	0.1, 0.2, 0.95, 3.0, 9.504, 14.006, 17.007, 19.008
Between-Batch Precision for Standards %CV)	2.6-7.1
Between-Batch Accuracy for Standards (% Actual)	96.3-104.6

Between-Batch Precision for QC (%CV)	4.5-7.9
Between-Batch Accuracy for QC (% Actual)	101.3-102.9

DURING STUDY ASSAY VALIDATION FOR CLAVULANIC ACID (Vol.1.7, page 2330)

Parameter	
QC Conc. (ng/mL)	150.7, 2008.7, 4017.4
Standard Curve Conc. (ng/mL)	50.0, 99.9, 249.8, 749.3, 2497.6, 3746.4, 4495.6, 4995.1
Between-Batch Precision for Standards %CV)	1.9-7.4
Between-Batch Accuracy for Standards (% Actual)	95.9-107.4
Between-Batch Precision for QC (%CV)	4.2-5.5
Between-Batch Accuracy for QC (% Actual)	103.4-106.6

Repeat Assays

There were no reported repeat assays.

Chromatograms: Acceptable

Comments: The analytical method and data for amoxicillin and clavulanic acid are acceptable.

Pharmacokinetic/Statistical Analysis for Amoxicillin

Mean Plasma Concentrations	Table #6, Figure #3
----------------------------	---------------------

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

a. Arithmetic Mean Pharmacokinetic Parameters (N=39)

PK Parameter	Test Treatment A	Reference Treatment B	T/R
AUC _t [ug-hr/mL]	34.33 (20%)	35.83 (16%)	0.96

AUCi [ug-hr/mL]	35.42 (19%)	37.02 (16%)	0.96
Cmax [ug/mL]	10.29 (27%)	10.05 (23%)	1.02
Tmax [hr]	2.12	2.37	
K_{el} [1/hr]	0.586	0.601	
T_½ [hr]	1.27	1.18	

b. 90% Confidence Intervals (N=39)

Parameter	RMSE	Point Estimate	90% Confidence Interval
LnAUCt	0.21	0.94	86.6 – 101.7
LnAUCi	0.16	0.94	88.8 – 100.6
LnCmax	0.28	0.99	89.4 – 110.4

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for all 39 subjects
- Measurable drug concentrations at 0 hr: None
- First scheduled post-dose sampling time as Tmax: None
- First measurable drug concentration as Cmax: None
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for AUCt, AUCi, Cmax are within the acceptable limits of 80-125%.

Pharmacokinetic/Statistical Analysis for Clavulanic Acid

Mean Plasma Concentrations	Table #7, Figure #4
-----------------------------------	---------------------

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

a. Arithmetic Mean Pharmacokinetic Parameters (N=39)

PK Parameter	Test Treatment A	Reference Treatment B	T/R
AUCt [ng-hr/mL]	4815.0 (32%)	4489.1 (34%)	1.07
AUCi [ng-hr/mL]	4931.7 (31%)	4597.7 (33%)	1.07
Cmax [ng/mL]	1933.6 (33%)	1786.7 (32%)	1.08
Tmax [hr]	1.61	1.53	
Ke _{el} [1/hr]	0.60	0.63	
T _½ [hr]	1.20	1.14	

b. 90% Confidence Intervals (N=39)

Parameter	RMSE	Point Estimate	90% Confidence Interval
LnAUCt	0.16	1.07	100.6 – 113.5
LnAUCi	0.15	1.07	100.8 – 113.4
LnCmax	0.22	1.06	97.4 – 115.3

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for all 39 subjects
- Measurable drug concentrations at 0 hr: None
- First scheduled post-dose sampling time as Tmax: None
- First measurable drug concentration as Cmax: None
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for AUCt, AUCi, Cmax are within the acceptable limits of 80-125%.

Conclusion:

The single-dose fed bioequivalence study is acceptable.

B. Attachments

Fig I - Fasting Study- Amoxicillin

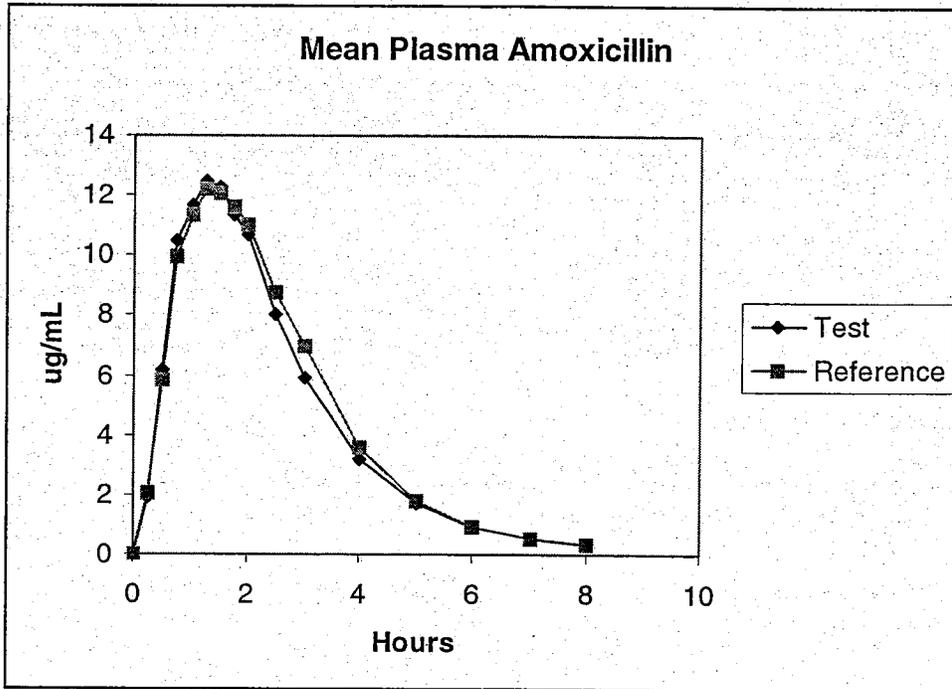


Fig 2 - Fasting Study - Clavulanic Acid

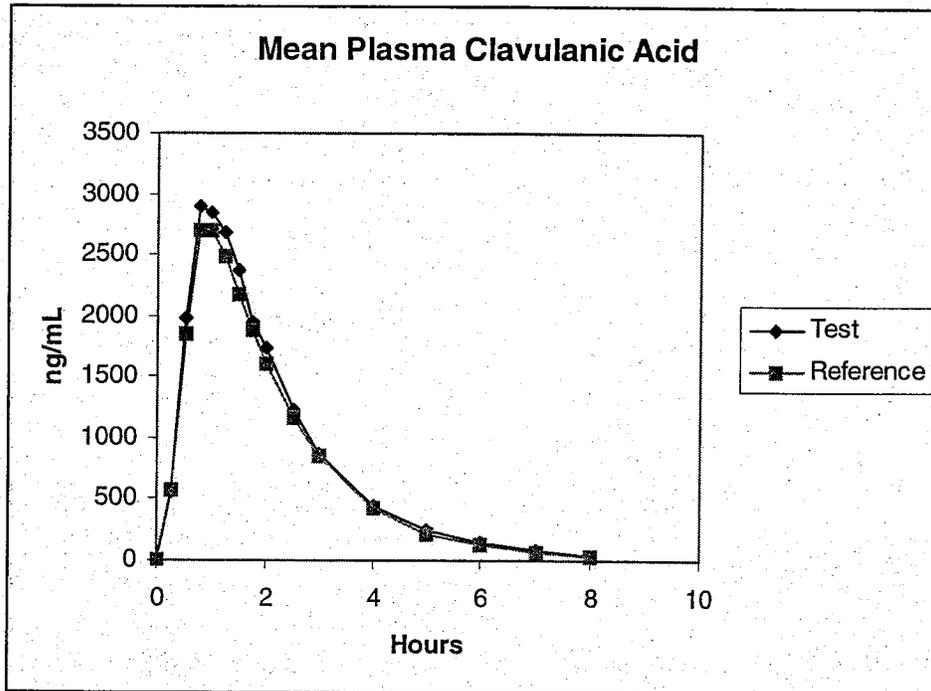


Fig 3 - Fed Study- Amoxicillin

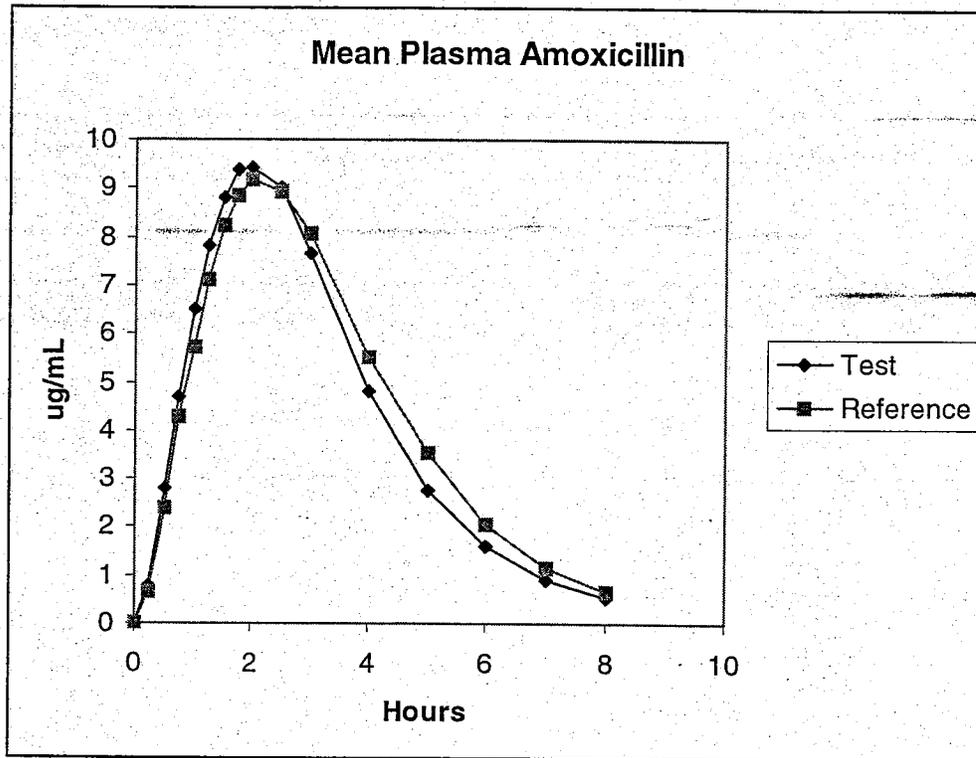
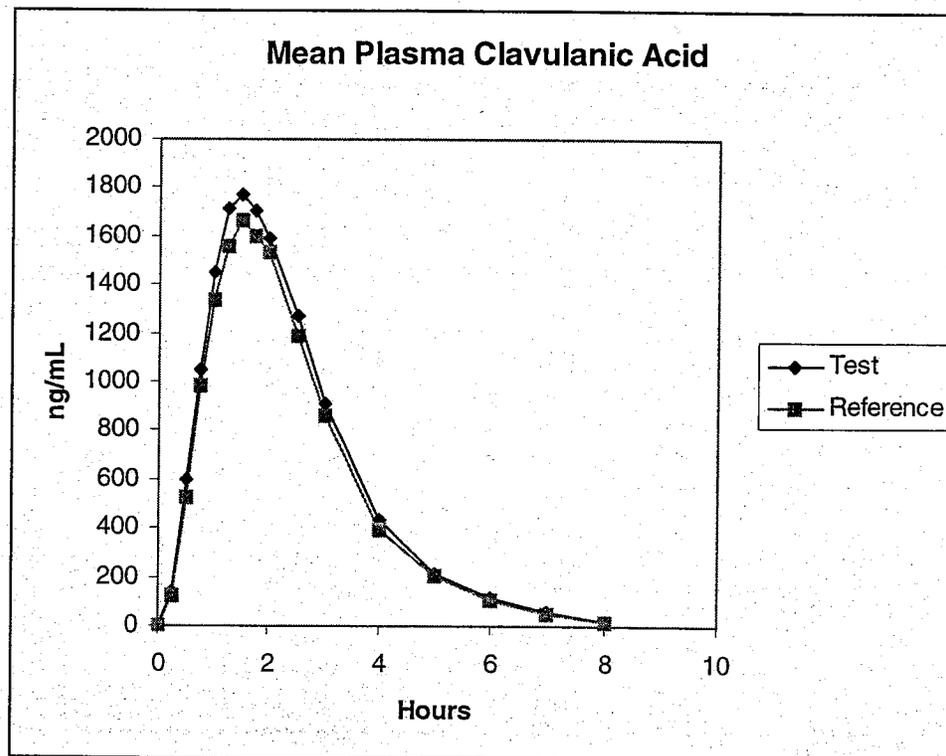


Fig 4 - Fed Study- Clavulanic Acid



Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW (TABLE 1 - FORMULATION)

Table 2

Dissolution Method: FDA

Dissolution Medium: Water, 900mL @ 37°C ± 0.5°C

Apparatus: 2 (Paddles)

Speed: 75 rpm

Sample Times: @ 2, 6, 10, 15 and 30 minutes

Limits: NLT — % (Q) of amoxicillin in 30 minutes

NLT — % (Q) of clavulanic acid in 30 minutes

Results:

TEST: Ranbaxy Laboratories Limited

Chewable Tablets

Lot No.: 1237790

Strength: 400 / 57 mg

No. of Units: 12

Amoxicillin Mean Dissolution Data

Time(min.)	Mean	Range	%CV
10	71		11.1
20	100		1.0
30	101		1.0
45	101		1.0

Clavulanic Acid Mean Dissolution Data

Time(min.)	Mean	Range	%CV
10	62		13
20	104		1.3
30	105		1.1
45	105		1.1

REFERENCE: GSK

Augmentin Chewable Tablets

Lot No.: RT1576

Strength: 400 / 57 mg

No. of Units: 12

Time(min.)	Mean	Range	%CV
10	52		10.8
20	84		5.5
30	99		2.4
45	102		1.3

TEST: Ranbaxy Laboratories Limited

Chewable Tablets

Lot No.: 1236227

Strength: 200 / 28.5 mg

No. of Units: 12

Amoxicillin Mean Dissolution Data

Time(min.)	Mean	Range	%CV
10	83		7.7
20	99		2.4
30	100		2.2
45	100		2.6

Clavulanic Acid Mean Dissolution Data

Time(min.)	Mean	Range	%CV
10	79		10.5
20	103		1.7
30	104		1.8
45	104		1.6

REFERENCE: GSK

Augmentin Chewable Tablets

Lot No.: RM1313

Strength: 200 / 28.5 mg

No. of Units: 12

Time(min.)	Mean	Range	%CV
10	63		5.9
20	99		2.5
30	103		1.7
45	103		1.3

Time(min.)	Mean	Range	%CV
10	67		5.8
20	101		2.1
30	104		1.7
45	104		1.2

Table 3: Subject Demographics for Fasting Study									
Age		Age Groups		Gender		Race		Weight (kg)	
		Range	%	Sex	%	Category	%		
		<18	0			Caucasian	70.0		
Mean	30	18-40	82.5	Male	55	Black.	5.0	Mean	70.4
SD	10	41-64	17.5	Female	45	Asian	0	SD	11.0
Range	19-52	65-75	0			Other	0	Range	46.8-94.9
		>75	0			Hispanic	25.0		
Table 4: Subject Demographics for Fed Study									
Age		Age Groups		Gender		Race		Weight (kg)	
		Range	%	Sex	%	Category	%		
		<18	0			Caucasian	52.5		
Mean	28	18-40	92.5	Male	50	Black.	2.5	Mean	67.9
SD	6	41-64	7.5	Female	50	Asian	5.0	SD	8.9
Range	18-52	65-75	0			Hispanic	17.5	Range	49.0-84.4
		>75	0			Other	0		

**APPEARS THIS WAY
ON ORIGINAL**

Table 5: Mean Plasma Concentration (ug/mL) of Amoxicillin – Fasting Study

Time (Hrs)	Test Treatment A	Test Treatment B	Ratio (A vs B)
pre-dose	0.00	0.0	
0.25	1.94 (64)	2.08 (64)	0.93
0.5	6.17 (49)	5.87 (40)	1.05
0.75	10.49 (41)	9.93 (32)	1.06
1.0	11.71 (36)	11.37 (30)	1.03
1.25	12.50 (32)	12.20 (28)	1.02
1.5	12.28 (29)	12.07 (28)	1.02
1.75	11.34 (27)	11.63 (25)	0.98
2.0	10.69 (24)	10.99 (20)	0.97
2.5	8.05 (25)	8.79 (22)	0.92
3.0	5.91 (31)	6.96 (33)	0.85
4.0	3.18 (56)	3.58 (52)	0.89
5.0	1.74 (75)	1.80 (67)	0.97
6.0	0.92 (68)	0.95 (67)	0.97
7.0	0.51 (73)	0.51 (66)	1.00
8.0	0.33 (91)	0.31 (70)	1.06

Table 6: Mean Plasma Concentration (ng/mL) of Clavulanic Acid – Fasting Study

Time (Hrs)	Test Treatment A	Test Treatment B	Ratio (A vs B)
pre-dose	0.00	0.0	
0.25	559.60 (93)	578.95 (91)	0.97
0.5	1984.48 (65)	1840.95 (50)	1.08
0.75	2888.47 (51)	2704.81 (44)	1.07
1.0	2850.53 (47)	2701.23 (41)	1.06
1.25	2679.26 (42)	2487.21 (36)	1.08
1.5	2369.67 (38)	2168.22 (37)	1.09
1.75	1949.30 (38)	1876.28 (32)	1.04
2.0	1728.93 (32)	1598.39 (35)	1.08
2.5	1227.62 (35)	1157.53 (45)	1.06
3.0	871.60 (36)	853.10 (44)	1.02
4.0	443.71 (46)	430.50 (49)	1.03
5.0	247.12 (81)	208.96 (47)	1.18
6.0	141.48 (70)	131.17 (54)	1.08
7.0	74.49 (82)	70.32 (69)	1.06
8.0	32.54 (130)	30.42 (123)	1.07

Table7: Mean Plasma Concentration (ug/mL) of Amoxicillin – Fed Study

Time (Hrs)	Test Treatment A	Test Treatment B	Ratio (A vs B)
pre-dose	0.00	0.0	
0.25	0.79 (90)	0.64 (94)	1.23
0.5	2.79 (58)	2.37 (65)	1.18
0.75	4.70 (51)	4.29 (50)	1.10
1.0	6.52 (47)	5.72 (42)	1.14
1.25	7.82 (41)	7.12 (40)	1.10
1.5	8.79 (34)	8.23 (36)	1.07
1.75	9.37 (31)	8.85 (33)	1.06
2.0	9.44 (28)	9.17 (29)	1.03
2.5	9.01 (24)	8.94 (22)	1.01
3.0	7.65 (24)	8.06 (18)	0.95
4.0	4.81 (29)	5.51 (26)	0.87
5.0	2.75 (46)	3.52 (42)	0.78
6.0	1.59 (54)	2.07 (50)	0.77
7.0	0.92 (67)	1.14 (59)	0.81
8.0	0.53 (73)	0.65 (67)	0.82

Table 8: Mean Plasma Concentration (ng/mL) of Clavulanic Acid – Fed Study

Time (Hrs)	Test Treatment A	Test Treatment B	Ratio (A vs B)
pre-dose	0.00	0.0	
0.25	142.38 (118)	126.04 (127)	1.130
0.5	600.41 (75)	523.63 (81)	1.147
0.75	1052.21 (58)	981.28 (57)	1.072
1.0	1449.00 (49)	1332.84 (43)	1.087
1.25	1709.44 (40)	1554.94 (40)	1.099
1.5	1772.58 (33)	1660.19 (40)	1.068
1.75	1702.23 (33)	1601.41 (33)	1.063
2.0	1587.32 (35)	1530.51 (33)	1.037
2.5	1266.64 (35)	1189.39 (40)	1.065
3.0	910.97 (38)	863.33 (43)	1.055
4.0	436.59 (40)	396.27 (42)	1.102
5.0	211.41 (40)	201.77 (44)	1.048
6.0	114.28 (40)	105.51 (50)	1.083
7.0	59.65 (64)	48.69 (88)	1.225
8.0	17.27 (165)	17.53 (165)	0.985

BIOEQUIVALENCY COMMENTS

ANDA: 65-161

APPLICANT: Ranbaxy Laboratories Limited.

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium Chewable Tablets
USP, 400 mg /EQ 57 mg Base and 200 mg/EQ 28.5 mg Base

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

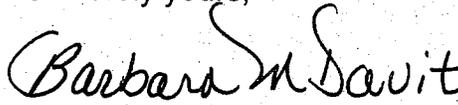
We acknowledge the following dissolution testing has been incorporated into your stability and quality control programs as recommended by the Agency.

The dissolution testing is conducted in 900 mL of water at 37°C using USP 26 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than —% of the labeled amount of amoxicillin and
—% of the labeled amount of clavulanic acid in the dosage form
are dissolved in 30 minutes.

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

Sincerely yours,

for 

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

CC: ANDA #65-161
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

V:\FIRMSNZ\ANBAXY\LTRS&REV\65161N1202.doc
Printed in final on 7/24/03

Endorsements: (Final with Dates)

HFD-658/ Reviewer M. Makary

HFD-658/ Bio team Leader G. Singh

HFD-650/ D. Conner

MMM

CDPS

7-24-03

Brw 7/24/03

Ja

BIOEQUIVALENCY - ACCEPTABLE

submission date: 12-23-02

1. **FASTING STUDY (STF)**

Strengths: 400 mg/57 mg

Clinical:

Analytical: [

] Outcome: AC

2. **FOOD STUDY (STF)**

Strengths: 400 mg/57 mg

Clinical:

Analytical: [

] Outcome: AC

3. **DISSOLUTION WAIVER (DIW)**

Strengths: 200mg/28.5 mg

Outcome: AC

Outcome Decisions: **AC** – Acceptable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-161

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 65-161 Applicant Ranbaxy Laboratories Limited
Drug Amoxicillin + Clavulanate Potassium Tablets USP (Chewable) Strength ~~200mg~~ 200mg / 28.5mg and 400mg / 57mg

PROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

1. Project Manager, M Anderson
Review Support Br Team 6

DRAFT Package
Date 10/20/03
Initials MSA

FINAL Package
Date 10/24/03
Initials MSA

Application Summary:

Original Rec'd date 12/30/02
Date Acceptable for Filing 12/30/02 ✓
Patent Certification (type) -
Date Patent/Exclus. expires -
Citizens' Petition/Legal Case Yes No
(If YES, attach email from PM to CP coord)
First Generic Yes No
(If YES, Pediatric Exclusivity Tracking System (PETS))
RLD =
Date checked _____ NDA# _____
Nothing Submitted
Written request issued
Study Submitted

EER Status Pending Acceptable OAI
Date of EER Status _____
Date of Office Bio Review 7/29/03
Date of Labeling Approv. Sum 10/20/03
Date of Sterility Assur. App. _____
Methods Val. Samples Pending Yes No
Commitment Rcd. from Firm Yes No
Modified-release dosage form: Yes No

Previously reviewed and tentatively approved Date _____
Previously reviewed and CGMP def./N/A Minor issued Date _____
Comments:

Gregg Davis PPIV ANDAs Only
Deputy Director, DLPS

Date 10/21/03
Initials [Signature]

Date 10/27/03
Initials [Signature]

Contains GDEA certification: Yes No
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes No
If Para. IV Certification- did applicant I
Notify patent holder/NDA holder Yes No
Was applicant sued w/in 45 days: Yes No
Has case been settled: Yes No
Date settled: N/A
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No

Determ. of Involvement? Yes No
Pediatric Exclusivity System
Date Checked N/A
Nothing Submitted
Written request issued
Study Submitted

RD = Augmentin 200mg and Augmentin 400mg Chewable Tablets
GlaxoSmithKline NDA 50-726 (03/002)

There are no unexpired patents or exclusivity currently listed in the Orange Book for this former "507" drug product.

3. Div. Dir./Deputy Dir.
Chemistry Div. I
Comments:

Date 10/24/03
Initials [Signature]

Date 10/27/03
Initials [Signature]

CMC satisfactory.

REVIEWER:

DRAFT Package

FINAL Package

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date _____
Initials _____

Date _____
Initials _____

IA ANDA 165-065 (Genera) was approved for this drug product on 4/18/02

5. Peter Rickman
Director, DLPS
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: EES is pending. Awaiting completion of inspection of Ranbaxy

Date 10/27/03
Initials [Signature]

Date 12/3/03 [Signature]
Initials [Signature]

ARC manufacturing site up for job. Spc. scheduled for November 3-6 2003. All other facilities currently acceptable. Bioequivalence studies (fasting and non-fasting) of 400mg/50mg strength found acceptable. Dissolution studies for both strengths found acceptable. However, wanted to 200 mg/25 mg strength under 350.22(d)(2). Bio studies conducted by [Signature] (analytical). These facilities have acceptable DSZ inspectional histories.

Office of Compliance has recommended this application for approval - see E-Mail dated 12/24/03 from L. Dietrick et al. L acceptable for approval 10/24/03. Methods validation is not required.

5. Robert L. West
Deputy Director, OGD

Date 10/27/03
Initials [Signature]

Date 12/3/2003
Initials [Signature]

Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments:

Office of Compliance has recommended this application for approval - see E-Mail dated 12/24/03 from L. Dietrick et al. L acceptable for approval 10/24/03.

This ANDA is recommended for approval.

6. Gary Buehler
Director, OGD
Comments:

Date 12/3/03
Initials GB

Date 12/3/03
Initials GB

First Generic Approval PD or Clinical for BE Special Scientific or Reg. Issue

7. Project Manager, Mark Anderson
Review Support Br Team

Date 12/3/03
Initials MA

Date 12/3/03
Initials MA

NA Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:45 Time notified of approval by phone 2:45 Time approval letter faxed

FDA Notification:
12/3 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/3 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-161

CORRESPONDENCE

RANBAXY

LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

December 23, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

505(j)(2)(A) OK
UPS
06 FEB 2003
Supriya D. Chandra

**Reference: Amoxicillin and Clavulanate Potassium Chewable Tablets USP
200 mg/28.5 mg and 400 mg/57 mg
Abbreviated New Drug Application**

Dear Sir/Madam:

Ranbaxy Laboratories Limited herewith submits an abbreviated new drug application (ANDA) for Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 200 mg/28.5 mg and 400 mg/57 mg pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA refers to the listed drugs, Augmentin® (amoxicillin and clavulanate potassium chewable tablets) 200 mg/28.5 mg and 400 mg/57 mg, which are manufactured by GlaxoSmithKline, the holder of the approved application, and which are listed in the 2002 Approved Drug Products with Therapeutic Equivalence Evaluations, 22nd Edition.

In the applicant's opinion and to the best of applicant's knowledge, no patent claims have been submitted to the FDA. In addition, the applicant is not aware of any marketing exclusivity.

The drug product manufacturer is Ranbaxy Laboratories Limited. Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 200 mg/28.5 mg and 400 mg/57 mg, will be manufactured at Ranbaxy Laboratories Limited's FDA registered and inspected Dewas, India facility in accordance with 21 CFR 210 and 211.

The drug product will also be packaged in bulk, bottles and blister packs at the Dewas, India facility.

The manufacturer of the Amoxicillin trihydrate drug substance used to produce the ANDA batches of drug product is Ranbaxy Laboratories Limited, Toansa, India. The Drug Master File (DMF) No. 12895 was filed on March 11, 1998. A sample of the bulk raw material is available and will be provided to the Agency upon request.

RECEIVED

DEC 30 2002

REGISTERED OFFICE: SAHIBZADA AJIT SINGH NAGAR-160 055. DISTT.ROPAR (PUNJAB) OGD / CDER

Food and Drug Administration
Amoxicillin and Clavulanate Potassium Chewable Tablets USP,
200 mg/28.5 mg and 400 mg/57 mg
Abbreviated New Drug Application
Page 2

_____ filed the Drug Master File (DMF) No. _____ for Potassium
Clavulanate _____ with US FDA. The sample of the bulk
raw material is available and will be provided to the Agency upon request.

The required bioavailability/bioequivalence study was conducted on Amoxicillin and
Clavulanate Potassium Chewable Tablets 400 mg/57 mg and Augmentin® chewable tablets
400 mg by _____.

_____. The study indicates that Amoxicillin and Clavulanate Potassium
Chewable Tablets 400 mg/57 mg are bioequivalent to Augmentin® chewable tablets 400
mg. The in-vitro dissolution profiles for Ranbaxy's Amoxicillin and Clavulanate Potassium
Chewable Tablets 200 mg/28.5 mg and 400 mg/57 mg are comparable to
GlaxoSmithkline's Augmentin chewable tablets 200 mg and 400 mg.

Amoxicillin and Clavulanate Potassium Chewable Tablets 200 mg/28.5 mg and 400 mg/57
mg are stable and a two year expiration dating is requested. The two year expiration dating
for these products is supported by one, two and three months accelerated stability data
(40°C/75% relative humidity).

The route of administration, indications and usage, dosage, active ingredient, potency and
labeling (except DESCRIPTION and HOW SUPPLIED sections) for Amoxicillin and
Clavulanate Potassium Chewable Tablets 200 mg/28.5 mg and 400 mg/57 mg are the same
as those for Augmentin® chewable tablets 200 mg and 400 mg.

This ANDA is submitted in 11 volumes:

Volume I:	Sections I through V
Volume II: Through Volume VII:	VI
Volume VIII:	Sections VII through XI
Volume IX:	Sections XII - XIV
Volume X:	Sections XV
Volume XI:	Sections XVI through XXII

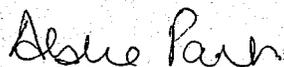
Food and Drug Administration
Amoxicillin and Clavulanate Potassium Chewable Tablets USP,
200 mg/28.5 mg and 400 mg/57 mg
Abbreviated New Drug Application
Page 3

Ranbaxy Laboratories Limited commits to resolve any issues identified in the method validation process after approval.

Please contact the undersigned at (609)720 5666 if you have any questions regarding this submission.

Field Copy : We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs.

Sincerely,



Abha Pant
US Agent for Ranbaxy Laboratories Limited

FEB 20 2002

ANDA 65-161

Ranbaxy Pharmaceuticals, Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Abha Pant
600 College Road East
Princeton, NJ 08540

Dear Madam:

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

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

DATE OF APPLICATION: December 23, 2002

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

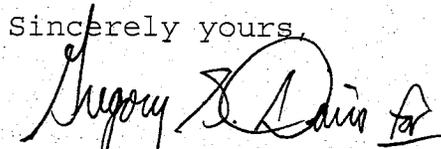
We will correspond with you further after we have had the opportunity to review the application.

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

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5848

Sincerely yours,



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

ANDA 65-161

cc: DUP/Jacket

Division File

Field Copy

HFD-610/R.West

HFD-610/P.Rickman

HFD-92

HFD-615/M.Bennett

HFD-600/

Endorsement:

HFD-615/GDavis, Chief, RSB *Davis* 19-FEB-2003 date

HFD-615/ACamphire, CSO *Siamee Camphire* date 2/19/03

Word File

V:\FIRMSNZ\Ranbaxy\LTRS&REV\65161.ACK

F/T EEH 02/07/03

ANDA Acknowledgment Letter!

RANBAXY
PHARMACEUTICALS INC.

*Labeling review
drafted 10/16/03
A. Vozze*

August 25, 2003

ORIGINAL

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

**MINOR LABELING
AMENDMENT**

**Reference: Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)
200mg/28.5mg (base) and 400mg/57 (base)
ANDA - 65-161**

ORIG AMENDMENT

Dear Sir/Madam,

N/A

Reference is made to our pending ANDA 65-161 for 200mg/28.5mg (base) and 400mg/57 (base) Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable) and to a labeling deficiency of August 15, 2003 in which Ranbaxy was asked to further revise the labels and package insert for the above referenced product.

Provided on the following pages are the agency's deficiencies followed by Ranbaxy's responses. The labeling has been revised as requested. Twelve sets of the final printed labeling are included in the "original" copy and an additional 6 sets of the labeling are in the duplicate copy in **Attachment 1**. To facilitate review we have provided a side-by-side comparison with Ranbaxy's revised labeling and previously submitted, with all differences shown with the use of color, in **Attachment 2**.

Please contact the undersigned at 609-720-5390, or Abha Pant at 609-720-5666, if you have any questions regarding this labeling amendment.

Sincerely,

Richard Leone (for)

Richard Leone
Regulatory Affairs Associate (*for*)
Abha Pant, US Agent, Regulatory Affairs Director

RECEIVED

AUG 26 2003

OGD/CDEH

RANBAXY
PHARMACEUTICALS INC.

August 27, 2003

ORIG AMENDMENT
N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

MINOR
AMENDMENT (CMC)

**Reference: Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable)
200mg/28.5mg (base) and 400mg/57 (base)
ANDA - 65-161**

Dear Sir/Madam,

Reference is made to our pending ANDA 65-161 for 200mg/28.5mg (base) and 400mg/57 (base) Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable) submitted to the Agency on December 23, 2002.

Reference is also made to the Minor Amendment, CMC comments, received June 26, 2003.

Reference is also made to our Labeling Amendment sent to the Agency on August 25, 2003.

The comments received June 26, 2003 and the response to each comment are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this response has been provided to the International Operations Group.

Please contact me at 609-720-5390, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Richard Leone (for)

Richard Leone
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED

AUG 28 2003

OGD/CDEH

*MLW
9/9/03*

RANBAXY

PHARMACEUTICALS INC.

ORIG AMENDMENT

September 29, 2003

*Labeling review
drafted 10/16/03
A. Loge*

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**UPS/FAX
LABELING AMENDMENT***N/AF***FPL****ANDA 65-161****Amoxicillin and Clavulanate Potassium Tablets, USP (Chewable) 200 mg/28.5 mg (base) and 400 mg/57 mg (base)**

Dear Sir/Madam:

Reference is made to ANDA 65-161 for Amoxicillin and Clavulanate Potassium Tablets USP (Chewable), 200 mg/28.5 mg and 400 mg/57 mg. Reference is also made to the labeling deficiency dated August 15, 2003 and our response dated August 25, 2003 in which we submitted final printed labeling.

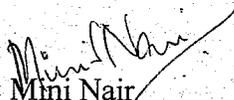
At this time we wish to withdraw the Package Insert labeling and side-by-side comparison package insert portions of the labeling amendment response sent on 8/25/03 and replace it with the attached Package Insert and side-by-side comparison package insert.

Please note, that we have also amended the package insert to include the labeling requirements as per the Federal Register /Vol 68, No 25/Thursday-February 6, 2003/ Rules and Regulations, #201.24 "Labeling for Systemic Antibacterial Drug Products".

Twelve copies of the replacement Final Printed Package Insert are included in **Attachment 1**. An additional six copies of the Final Printed Package Insert are provided in the duplicate copy. To facilitate review we are also providing a replacement side-by-side comparison package insert with Ranbaxy's revised labeling along with the previously submitted labeling, with all differences shown by use of color, in **Attachment 2**.

If you have any questions about this submission, please contact the undersigned at 609-720-5328, or Abha Pant at 609-720-5666

Sincerely,


Mini NairManager, Regulatory Affairs (for)
Abha Pant

US Agent for Ranbaxy Laboratories Limited

RECEIVED

SEP 30 2003

OGD/CDER