CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

65-066

Generic Name:	Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200mg/28.5mg (base)/5mL and 400mg/57mg (base)/5mL
Sponsor:	Geneva Pharmaceuticals, Inc.
Approval Date:	June 5, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-066

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 65-066

JUN 5 2002

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 11, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 mg/28.5 mg (base)/5 mL, and 400 mg/57 mg (base)/5 mL. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated December 13, 2001; and January 23, February 28, May 8, May 17, and May 31, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 mg/28.5 mg (base)/5 mL, and 400 mg/57 mg (base)/5 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Augmentin® 200 mg/5 mL for Oral Suspension, and Augmentin® 400 mg/5 mL for Oral Suspension, 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.

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

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

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

Sincerely yours,

Gary Buehler 6/5/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-066

FINAL PRINTED LABELING

ANDA SUBMISSION

8037

AMOXICILLIN AND CLAVULANATE POTASSIUM

for Oral Suspension, USP

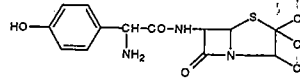
8037-3

℞ only

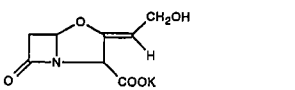
JUN - 5 2002

APPROVED

DESCRIPTION: Amoxicillin/clavulanate potassium is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$ and the molecular weight is 419.46. Chemically, amoxicillin is (2*S*,5*R*,6*R*)-6-((*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl) acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid trihydrate and may be represented structurally as:



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 $C_8H_9KNO_5$ and the molecular weight is 237.25. Chemically clavulanate potassium is potassium (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate and may be represented structurally as:



After reconstitution each teaspoon (5 mL) of suspension will contain 200 mg or 400 mg amoxicillin as the trihydrate and 28.5 or 57 mg clavulanic acid as the potassium salt. Each 5 mL of reconstituted amoxicillin/clavulanate potassium 200 mg/5 mL oral suspension contains 0.14 mEq potassium. Each 5 mL of reconstituted 400 mg/5 mL oral suspension contains 0.29 mEq of potassium.

Inactive Ingredients: Aspartame*, colloidal silicon dioxide, hydroxypropyl methylcellulose, mannitol, orange flavoring, precipitated silicon dioxide, succinic acid, xanthan gum, and golden syrup flavoring (carmel).

*See PRECAUTIONS-Information for Patients.

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

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

Dose† (amoxicillin/ clavulanate potassium)	$AUC_{0-\infty}$ (μg.hr./mL) amoxicillin (± S.D.)	$AUC_{0-\infty}$ (μg.hr./mL) clavulanate potassium (± S.D.)	C_{max} (μg/mL)‡ amoxicillin (± S.D.)	C_{max} (μg/mL)‡ 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/clavulanate potassium 250 mg/5mL suspension or the equivalent dose of 10 mL amoxicillin/clavulanate potassium 125 mg/5 mL suspension provides average peak serum concentrations approximately 1 hour after dosing of 6.9 μg/mL for amoxicillin and 1.6 μg/mL for clavulanic acid. The areas under the serum concentration curves obtained during the first 4 hours after dosing were 12.6 μg.hr./mL for amoxicillin and 2.9 μg.hr./mL for clavulanic acid when 5 mL of amoxicillin/clavulanate potassium 250 mg/5 mL suspension or equivalent dose of 10 mL of amoxicillin/clavulanate potasslum 125 mg/5 mL suspension was administered to adult volunteers. One amoxicillin/clavulanate potassium 250 mg chewable tablet or 2 amoxicillin/clavulanate potassium 125 mg chewable tablets are equivalent to 5 mL of amoxicillin/clavulanate potassium 250 mg/5 mL suspension and provide similar serum levels of amoxicillin and clavulanic acid.

Amoxicillin serum concentrations achieved with amoxicillin/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/clavulanate potassium is 1.3 hours and that of clavulanic acid is 1.0 hour. Time above the minimum inhibitory concentration of 1.0 μg/mL for amoxicillin has been shown to be similar after corresponding q12h and q8h dosing regimens of amoxicillin/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/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/clavulanate potassium is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

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

Two hours after oral administration of a single 35 mg/kg dose of amoxicillin/clavulanate potassium suspension to fasting children, average concentrations of 3.0 μg/mL of amoxicillin and 0.5 μg/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/clavulanate potassium 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/clavulanate potassium possesses the distinctive properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

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

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/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 μg/mL or less against most (≥90%) strains of *Streptococcus pneumoniae#*; MICs of 0.06 μg/mL or less against most (≥90%) strains of *Neisseria gonorrhoeae;* MICs of 4 μg/mL or less against most (≥90%) strains of staphylococci and anaerobic bacteria; and MICs of 8 μg/mL or less against most (≥90%) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Because amoxicillin has greater *in-vitro* activity against *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 AEROBES

*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 AEROBES

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 method (REF. 1) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

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

RECOMMENDED RANGES FOR AMOXICILLIN/ CLAVULANIC ACID SUSCEPTIBILITY TESTING

For gram-negative enteric aerobes:

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

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

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

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

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

MIC (μg/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 (μg/mL)*
Escherichia coli ATCC 25922	2 to 8
Escherichia coli ATCC 35218	4 to 16
Enterococcus faecalis ATCC 29212	0.25 to 1.0
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

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (REF. 2) requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 μg of amoxicillin/clavulanate potassium (20 μg amoxicillin plus 10 μg 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 μg amoxicillin/clavulanate potassium (20 μg amoxicillin plus 10 μg clavulanate potassium) disk should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

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

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

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

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

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

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

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

(c) A broth microdilution method should be used for testing *N. gonorrhoeae* and interpreted according to penicilin 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 μg amoxicillin/clavulanate potassium (20 μg amoxicillin plus 10 μg 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: Amoxicillin/clavulanate potassium for oral suspension is 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/clavulanate potassium is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to amoxicillin/clavulanate potassium treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to amoxicillin/clavulanate potassium 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 amoxicillin/clavulanate potassium. (See Microbiology subsection.)

Bacteriological studies, to determine the causative organisms and their susceptibility to amoxicillin/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/clavulanate potassium 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/clavulanate potassium is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of amoxicillin/clavulanate potassium-associated cholestatic jaundice/hepatic dysfunction.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AMOXICILLIN/CLAVULANATE POTASSIUM, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN/CLAVULANATE POTASSIUM SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

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

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

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

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

PRECAUTIONS:

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

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

Phenylketonurics: Each 5 mL of either the 200 mg/5 mL or 400 mg/5 mL oral suspension contains 7 mg phenylalanine. Contact your physician or pharmacist.

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

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

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

Drug/Laboratory Test Interactions: Oral administration of amoxicillin/clavulanate potassium will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore amoxicillin/clavulanate potassium, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore amoxicillin/clavulanate potassium.

Carcinogenesis, Mutagenesis, Impairment Of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis: The mutagenic potential of amoxicillin/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 vitro* 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/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/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/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/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.

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

Pediatric Use: Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing

(See Reverse)

of amoxicillin/clavulanate potassium should be modified in pediatric patients younger than 12 weeks (3 months). (See DOSAGE AND ADMINISTRATION-Pediatric.)

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

In pediatric patients (aged 2 months to 12 years), 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. 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, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness- like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome) 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/clavulanate potassium and, when reported has been more commonly in the elderly, and/or males, and/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/clavulanate potassium. There have been reports of increased prothrombin time in patients receiving amoxicillin/clavulanate potassium and anticoagulant therapy concomitantly.

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

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

In the case of overdosage, discontinue amoxicillin/clavulanate potassium, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying. (REF. 3)

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: All recommended dosages for Amoxicillin and Clavulanate Potassium for Oral Suspension are included in this section for informational purposes only. Some of the dosages may not be obtainable with the 400 mg/5 mL (57 mg*/5 mL) and 200 mg/5 mL (28.5 mg*/5 mL) strengths.

*(clavulanic acid equivalent)

Dosage:

Pediatric Patients: Based on the amoxicillin component, amoxicillin/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/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*	q8h
	200 mg/5 mL or 400 mg/5 mL oral suspension**	125 mg/5 mL or 250 mg/5 mL oral suspension**
Otitis media*/*, sinusitis, lower respiratory tract infections, and more severe infections	45 mg/kg/day q12h	40 mg/kg/day q8h
Less severe infections	25 mg/kg/day q12h	20 mg/kg/day q8h

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

** Each strength of amoxicillin/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/clavulanate potassium 500 mg tablet every 12 hours or 1 amoxicillin/clavulanate potassium 250 mg tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 amoxicillin/clavulanate potassium 875 mg tablet every 12 hours or 1 amoxicillin/clavulanate potassium 500 mg 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/clavulanate potassium tablets.

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

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

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

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

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

AMOXICILLIN/CLAVULANATE POTASSIUM 200 mg/5 mL SUSPENSION

Bottle Size	Amount of Water Required for Suspension
100 mL	88 mL

Each teaspoonful (5 mL) will contain 200 mg amoxicillin and 28.5 mg of clavulanic acid as the potassium salt.

AMOXICILLIN/CLAVULANATE POTASSIUM 400 mg/5 mL SUSPENSION

Bottle Size	Amount of Water Required for Suspension
100 mL	84 mL

Each teaspoonful (5 mL) will contain 400 mg amoxicillin and 57.0 mg of clavulanic acid as the potassium salt.

NOTE: SHAKE ORAL SUSPENSION WELL BEFORE USING.

Reconstituted suspension must be stored under refrigeration and discarded after 10 days.

Administration: Reconstituted amoxicillin/clavulanate potassium may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when amoxicillin/clavulanate potassium is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, amoxicillin/clavulanate potassium should be taken at the start of a meal.

HOW SUPPLIED: Amoxicillin and clavulanate potassium for oral suspension, USP is supplied as a dry white powder containing:

Amoxicillin/Clavulanate Potassium 200 mg/5 mL: Each 5 mL of reconstituted orange-flavored suspension contains 200 mg amoxicillin and 28.5 mg clavulanic acid as the potassium salt and is available in a 100 mL bottle.

Amoxicillin/Clavulanate Potassium 400 mg/5 mL: Each 5 mL of reconstituted orange-flavored suspension contains 400 mg amoxicillin and 57 mg clavulanic acid as the potassium salt and is available in a 100 mL bottle.

Store dry powder at or below 25ºC (77ºF). Dispense in tightly closed, moisture-proof containers. Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days.

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 2-4 days after the completion of therapy) and at the follow-up visit (defined as 22-28 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=265) and 82.3% (n=260) for 45 mg/kg/day q12h and 40 mg/kg/day q8h, respectively. At follow-up, 67.1% (n=249) and 68.7% (n=243) for 45 mg/kg/day q12h and 40 mg/kg/day q8h, respectively.

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

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

Diarrhea was defined as either: (a) 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

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

Rev. 02-2002M
8037-3

Manufactured By
Biochemie GmbH
Kundl, Austria

Distributed By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

65-066

RW

Amoxicillin and Clavulanate Potassium for Oral Suspension, USP

200 mg/5 mL

When reconstituted, each 5 mL contains:
AMOXICILLIN, 200 mg,
as the trihydrate
CLAVULANIC ACID, 28.5 mg,
as clavulanate potassium

100 mL (when reconstituted)

℞ only

DISTRIBUTED BY
Geneva
PHARMACEUTICALS
BROOMFIELD, CO 80020

N 3 0781-6102-46 2

Use only if inner seal is intact.
Net contents: Equivalent to 4 g amoxicillin and 0.57 g clavulanic acid. Each 5 mL of reconstituted amoxicillin/clavulanate potassium 200 mg/5 mL oral suspension contains 0.14 mEq potassium.
Store dry powder at or below 25°C (77°F).
Directions for mixing: Tap bottle until all powder flows freely. Add approximately 2/3 of total water for reconstitution (**total = 86 mL**); shake vigorously to wet powder. Add remaining water, again shake vigorously.
Dosage: Administer every 12 hours. See accompanying prescribing information.
Phenylketonurics: Contains phenylalanine 7 mg per 5 mL.
Keep tightly closed. Shake well before using.
Must be refrigerated. Discard after 10 days.
Rev. 02-2002M

Manufactured By
Biochemie GmbH
Kundl, Austria

APPROVED
JUN - 5 2002
Exp:
Lot:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-066

CSO LABELING REVIEW(S)

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

ANDA Number: 65-066

Date of Submission: February 11, 2000
November 14, 2000 [Amendment]

Applicant's Name: Biochemie GmbH [U.S. Agent: Geneva Pharmaceuticals, Inc.]

Established Name: Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 400 mg/5 mL (57 mg*/5 mL) and 200 mg/5 mL (28.5 mg*/5mL)
*(clavulanate acid equivalent)

Labeling Deficiencies:

1. CONTAINER:

   We encourage the inclusion of the potassium content, per 5 mL to be consistent with your DESCRIPTION section.

2. INSERT

   a. DESCRIPTION

      Revise as follows:

      i. In the first sentence, revise " [redacted] to read "β-lactamase"

      ii. Prior to your list of inactive ingredients add the following statement.

      After reconstitution each teaspoonful (5 mL) of suspension will contain ___ mg or ___ mg amoxicillin as the trihydrate and ___ mg or ___ mg clavulanic acid as the potassium salt. If you prefer you may use separate sentences for each strength.

      iii. Relocate the last two sentences "... 0.___ mEq potassium" to immediately follow the statement in 4(a)(ii).

      iv. We note that you list "golden syrup flavoring (caramel)" as an inactive ingredient in your components and composition statement. However, it is not listed in your DESCRIPTION section. Please comment.

   b. INDICATIONS AND USAGE

      ... potassium for oral suspension is indicated...

   c. PRECAUTIONS (Drug/Laboratory Test)

      Revise the last sentence of the first paragraph to read, "... or be used".

d. DOSAGE AND ADMINISTRATION

i. Administration

A) First sentence

Reconstituted amoxicillin ...

B) Adults

We acknowledge that you have indicated the omission of the last two paragraphs referring to tablets and chewable tablets. However, we request that you add the last two paragraphs to be consistent with the reference listed drug insert labeling.

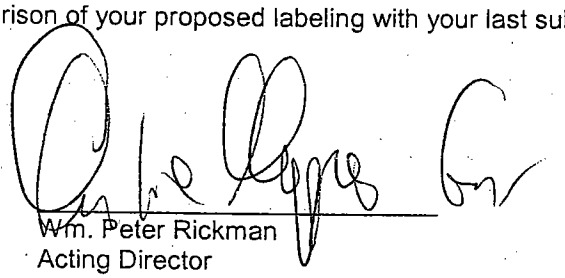
e. HOW SUPPLIED

Include the color or your drug product in your physical description statement. We refer you to 21 CFR 201.57 (k)(3).

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

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

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



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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-066

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

AADA: 65-066

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 mg + 28.5 mg/5 mL and 400 mg + 57 mg/5 mL

FIRM: Biochemie GmbH [U.S. Agent: Geneva Pharmaceuticals, Inc.]

DOSAGE FORM: Oral Suspension

STRENGTH: 200 mg + 28.5 mg/5 mL and 400 mg + 57 mg/5 mL

CGMP STATEMENT/EIR UPDATE STATUS: A signed cGMP certification from Biochemie GmbH was provided on page 409. An acceptable EER was issued 1/8/01.

BIO STUDY: The bio-study conducted on the applicant's product and SmithKline Beecham's Augmentin was found acceptable by the Division of Bioequivalence on 2/28/01.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substances and drug product are USP. The applicant is using USP methods in testing the bulk drugs and finished product.

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

LABELING: Labeling was found acceptable 3/13/02.

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

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): The bio-study was conducted using exhibit batch #103311, 400 mg + 57 mg. Exhibit batch #103311 was manufactured with Amoxicillin Trihydrate, USP from Biochemie S.A, Spain and Clavulanate Potassium, USP from Biochemie GmbH, Austria. The batch consisted of [redacted] bottles ([redacted] g/bottle)(theoretical). An exhibit batch of 200 mg + 28.5 mg, designated as batch 103310, was also manufactured. Batch #103310 consisted of [redacted] bottles ([redacted]/bottle)

(theoretical). Exhibit batches #103311 and #103310 were packaged and placed on stability study.

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

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch size for 200 mg + 28.5 mg is [redacted] bottles. The proposed production batch size is for 400 mg/57 mg tablets is [redacted] bottles. The commercial production batch records are the identical to the exhibit batch records.

CHEMIST: Susan Zuk **DATE:** 6/3/02 Susan Zuk

SUPERVISOR: Richard Adams **DATE:** 6/3/02 R.C. Adams

APPEARS THIS WAY
ON ORIGINAL

Bcg0004.004

1. CHEMISTRY REVIEW NO. 2. ANDA # 65066

3. NAME AND ADDRESS OF APPLICANT
Biochemie GmbH
Biochemiestr 10
Kundl, 6250

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Augmentin Powder for reconstitution 200, 400
Innovator Company: SmithKline Beecham
Patent Expiration Date:
Basis for ANDA Submission [314.94(a)(3)]

The basis of Biochemie's proposed ANDA for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg and 400 + 57 mg , is the approved, listed drug, Augmentin 200 and 400 Powder for reconstitution.

Section III.

Patent Certification [314.94(a)(12)] and Exclusivity Statement [314.94(a)(3)]

Paragraph I Certification:
In accordance with the Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our abbreviated new drug application for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg and 400 + 57 mg

Biochemie GmbH hereby certifies, in accordance with Section 505(j)(2)(A)(vii)(I) of Title 1 of the Food, Drug and Cosmetic Act, that in our opinion and to the best of our knowledge, patent information has not been submitted to the FDA.

According to information published in the list of Approved Drug Products, "Orange Book", 19th edition, "Augmentin Powder for reconstitution is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP

7. NONPROPRIETARY NAME
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200+28.5 , 400+57

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
02/11/00	Firm: Original
03/29/00	FDA: Refuse to Receive
06/01/00	Firm: Original Amendment
11/14/00	Firm: Original Amendment
12/21/00	FDA: Acceptable for Filing

10. PHARMACOLOGICAL CATEGORY
as on 356 h

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF #	DMF type	DMF holder	LOA(s)

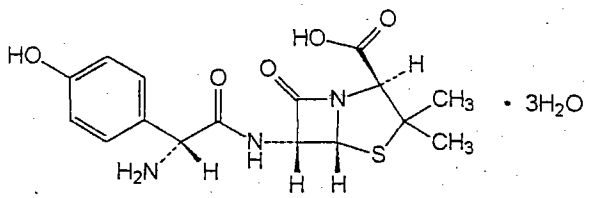
13. DOSAGE FORM
for oral suspension

14. POTENCY

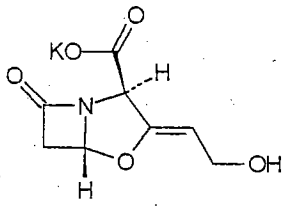
Strength	Strength units
200+28.5	mg
400+57	mg

15. CHEMICAL NAME AND STRUCTURE

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



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



16. RECORDS AND REPORTS
N/A

17. COMMENTS **Not Approvable-MINOR**
Biochemie has submitted four ANDA's for Amoxicillin + Clavulanate Potassium. These are 65-063 coated tablets, 65-064 coated tablets, 65-065 chewable tablets and 65-066 for oral suspension. Each ANDA represents a different strength or dosage form.

The following sections of the ANDA 65-066 were found to be deficient regarding chemistry, manufacturing and controls:

[ ]

• [ ]
•
•

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable-MINOR

19. REVIEWER:
Susan Zuk

DATE COMPLETED:
3/29/01

APPEARS THIS WAY
ON ORIGINAL

Redacted 33

pages of trade secret and /or confidential commercial information

Bcg0004.004

1. CHEMISTRY REVIEW NO. 2 2. ANDA # 65066

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2655 W. Midway Blvd.
Broomfield, CO 80038

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Augmentin Powder for reconstitution 200, 400
Innovator Company: SmithKline Beecham
Patent Expiration Date:
Basis for ANDA Submission [314.94(a)(3)]

The basis of Geneva's proposed ANDA for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg and 400 + 57 mg , is the approved, listed drug, Augmentin 200 and 400 Powder for reconstitution.

Section III.

Patent Certification [314.94(a)(12)] and Exclusivity Statement [314.94(a)(3)]

Paragraph I Certification:
In accordance with the Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our abbreviated new drug application for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg and 400 + 57 mg

Geneva hereby certifies, in a accordance with Section 505 (j)(2)(A)(vii)(I) of Title 1 of the Food, Drug, and Cosmetic Act, that in our opinion and to the best of our knowledge, patent information has not been submitted to the FDA.

According to information published in the list of Approved Drug Products, "Orange Book", 19th edition, "Augmentin Powder for reconstitution is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP

7. NONPROPRIETARY NAME
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200+28.5, 400+57

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
02/11/00	Firm: Original
03/29/00	FDA: Refuse to Receive
06/01/00	Firm: Original Amendment
11/14/00	Firm: Original Amendment
12/21/00	FDA: Acceptable for Filing
06/28/01	**Minor Amendment**

10. PHARMACOLOGICAL CATEGORY
as on 356 h

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF #	DMF type	DMF holder	LOA(s)

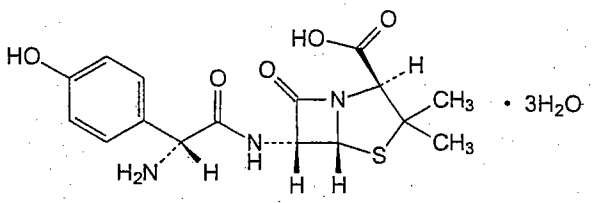
13. DOSAGE FORM
for oral suspension

14. POTENCY

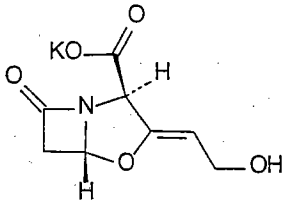
Strength	Strength units
200+28.5	mg
400+57	mg

15. CHEMICAL NAME AND STRUCTURE

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



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



16. RECORDS AND REPORTS
N/A

17. COMMENTS
Geneva has submitted four ANDA's for Amoxicillin + Clavulanate Potassium. These are 65-063 coated tablets, 65-064 coated tablets, 65-065 chewable tablets and 65-066 for oral suspension.

The applicant has adequately responded to most CMC comments resulting from the first cycle review. However, the finished drug product specifications and stability data are not yet satisfactory. The drug master file for clavulanate potassium is also not yet adequate. Therefore, a second MINOR deficiency letter has been issued.

18. CONCLUSIONS AND RECOMMENDATIONS: Not-Approvable

19. REVIEWER: Susan Zuk

DATE COMPLETED: 9/14/01

APPEARS THIS WAY
ON ORIGINAL

Redacted 42 pages of trade secret and /or confidential commercial information

Bcg0004.004

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 65066

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2655 W. Midway Blvd.
Broomfield, CO 80038

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Augmentin Powder for reconstitution 200, 400
Innovator Company: SmithKline Beecham
Patent Expiration Date:
Basis for ANDA Submission [314.94(a)(3)]

The basis of Geneva's proposed ANDA for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg and 400 + 57 mg , is the approved, listed drug, Augmentin 200 and 400 Powder for reconstitution.

Section III.

Patent Certification [314.94(a)(12)] and Exclusivity Statement [314.94(a)(3)]

Paragraph I Certification:
In accordance with the Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our abbreviated new drug application for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg and 400 + 57 mg

Geneva hereby certifies, in a accordance with Section 505 (j)(2)(A)(vii)(I) of Title 1 of the Food, Drug, and Cosmetic Act, that in our opinion and to the best of our knowledge, patent information has not been submitted to the FDA.

According to information published in the list of Approved Drug Products, "Orange Book", 19th edition, "Augmentin Powder for reconstitution is not entitled to a period of marketing exclusivity.

NDA 50-725

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP

7. NONPROPRIETARY NAME
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200+28.5, 400+57

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Submission date	*Submission type*
02/11/00	*Original*
03/29/00	*Refuse to Receive*
06/01/00	*Original Amendment*
11/14/00	*Original Amendment*
12/21/00	*Acceptable for Filing*
06/28/01	*Minor Amendment*
11/30/01	*Minor Amendment*
1/23/02	*Telephone Amendment*

10. PHARMACOLOGICAL CATEGORY
as on 356 h

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF #	DMF type	DMF holder	LOA(s)
—	—	—	—
—	—	—	—

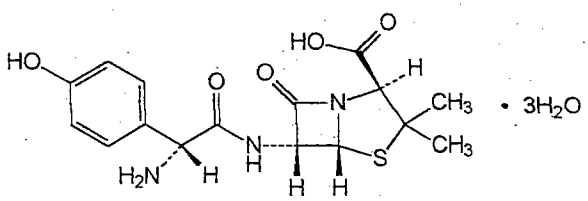
13. DOSAGE FORM
for oral suspension

14. POTENCY

Strength	Strength units
200+28.5	mg
400+57	mg

15. CHEMICAL NAME AND STRUCTURE

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



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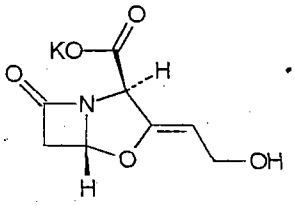

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Biochemie has submitted four ANDA's for Amoxicillin + Clavulanate Potassium. These are 65-063 coated tablets, 65-064 coated tablets, 65-065 chewable tablets and 65-066 for oral suspension. Each ANDA represents a different strength or dosage form.

The CMC review is complete and approval is recommended. The following support drug approval:

- EER acceptable 1/8/01
- Bioequivalence acceptable 2/28/01
- Labeling acceptable 3/13/02

18. CONCLUSIONS AND RECOMMENDATIONS: Recommend Approval

19. REVIEWER: Susan Zuk
DATE COMPLETED: 1/29/02 revised 3/13/02

APPEARS THIS WAY
ON ORIGINAL

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pages of trade secret and /or confidential commercial information

Bcg0004.004

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 65-066

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2655 W. Midway Blvd.
Broomfield, CO 80038

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Augmentin Powder for reconstitution 200, 400
Innovator Company: SmithKline Beecham
Patent Expiration Date:
Basis for ANDA Submission [314.94(a)(3)]

The basis of Geneva's proposed ANDA for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg and 400 + 57 mg , is the approved, listed drug, Augmentin 200 and 400 Powder for reconstitution.

Section III.

Patent Certification [314.94(a)(12)] and Exclusivity Statement [314.94(a)(3)]

Paragraph I Certification:
In accordance with the Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our abbreviated new drug application for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg and 400 + 57 mg

Geneva hereby certifies, in a accordance with Section 505 (j)(2)(A)(vii)(I) of Title 1 of the Food, Drug, and Cosmetic Act, that in our opinion and to the best of our knowledge, patent information has not been submitted to the FDA.

According to information published in the list of Approved Drug Products, "Orange Book", 19th edition, "Augmentin Powder for reconstitution is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP

7. NONPROPRIETARY NAME
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200+28.5, 400+57

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Submission date	*Submission type*
02/11/00	*Original*
03/29/00	*Refuse to Receive*
06/01/00	*Original Amendment*
11/14/00	*Original Amendment*
12/21/00	*Acceptable for Filing*
06/28/01	*Minor Amendment*
11/30/01	*Minor Amendment*
1/23/02	*Telephone Amendment*
5/8/02	***Telephone Amendment***
5/17/02	***Telephone Amendment (gratuitous)***
5/31/02	***Telephone Amendment***

10. PHARMACOLOGICAL CATEGORY
as on 356 h

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF #	DMF type	DMF holder	LOA(s)
[redacted]	II, API	[redacted]	pp. 121
[redacted]	II, API	[redacted]	N/A

13. DOSAGE FORM
for oral suspension

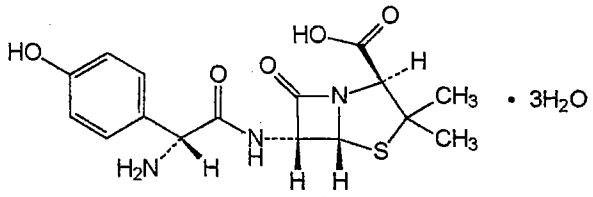
14. POTENCY

Strength	Strength units
200+28.5	mg
400+57	mg

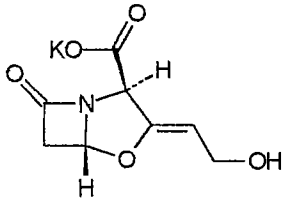
15. CHEMICAL NAME AND STRUCTURE

Amoxicillin and Clavulanate Potassium
Amoxicillin. 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino-(4-

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



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



16. RECORDS AND REPORTS
N/A

17. COMMENTS
Biochemie has submitted four ANDA's for Amoxicillin + Clavulanate Potassium. These are 65-063 coated tablets, 65-064 coated tablets, 65-065 chewable tablets and 65-066 for oral suspension. Each ANDA represents a different strength or dosage form.

The CMC review is complete and approval is recommended. The following support drug approval:

- EER acceptable 1/8/01
- Bioequivalence acceptable 2/28/01
- Labeling acceptable 3/13/02

18. CONCLUSIONS AND RECOMMENDATIONS: Recommend Approval

19. REVIEWER:

DATE COMPLETED:
Susan Zuk 1/29/02, revised 3/13/02 and 5/9/02, 6/3/02

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-066

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS

ANDA: 65-066 APPLICANT: Biochemie GmbH
U.S. Agent: Geneva Pharmaceuticals

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium Powder for Oral Suspension USP, 400 + 57 mg/5 mL & 200 + 28.5 mg/5 mL

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.

The dissolution testing is conducted in _____ 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 **20 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

#6

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-066

SPONSOR : Biochemie GmbH
(US Agent: Geneva Pharmaceuticals)

DRUG AND DOSAGE FORM : Amoxicillin and Clavulanate Potassium Powder for Oral Suspension, USP
STRENGTH(S) : 400 + 57 mg/5 mL & 200 + 28.5 mg/5 mL
TYPES OF STUDIES : Fasting Study & Non-Fasting Study
CINICAL STUDY SITE(S) :
ANALYTICAL SITE(S) :

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable
WAIVER: Acceptable

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic YES	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : ____ /S/ _____ DATE : 2/13/01

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : ____ /S/ DATE : 2/14/2001

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

INITIAL : ____ /S/ DATE : 2/28/2001

The Division of Chemistry should be aware that both ~~brand~~ test and reference formulations have overage in the 400 mg (Amoxicillin)/57 mg (Clavulanate K)/5 ml Strength Suspension.

	Biochemie	SmithKline Beecham
Amoxicillin	110	110
Clavulanate Potassium	110	110

Similar overage in the low strength formulation.

Mark 3.1

AMOXICILLIN & CLAVULANATE POTASSIUM Powder for Oral Suspension USP 400 mg + 57 mg/5 mL & 200 mg + 28.5 mg/5 mL
ANDA 65-066
Reviewer: Hoainhon Nguyen
W#65066sdw.200

Biochemie GmbH

(U.S. Agent: Gevena Pharmaceuticals Broomfield, CO)
Submission Date: ~~02/11/00,~~ ~~10/01/00~~ 11/14/00

Review of Bioequivalence Studies, Dissolution Data and Waiver Requests (Electronic Submission) First-Generic

I. Introduction

Indication: 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.)

Contents of Submission: a fasting bio study, a non-fasting bio study, dissolution data and waiver request for the lower strength, 200 mg + 28.5 mg.

RLD: Augmentin Powder for Oral Suspension, 400 mg + 57 mg, and 200 mg + 28.5 mg, 125 mg + 31.25 mg, 250 mg + 62.5 mg, manufactured by SmithKline Beecham

Recommended Dose: For neonates and infants aged <12 weeks, 30 mg/kg/day divided q12h; for patients aged 12 weeks and older, 25 to 45 mg/kg/day q12h, or 20 to 40 mg/kg/day q8h.

II. Background: The drug product is an oral antibacterial combination consisting of semisynthetic antibiotic amoxicillin and the (beta)-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid).

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of the drug product. 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. In one study, the relative bioavailability of clavulanate was reduced when the drug product was dosed at 30 and 150 minutes after the start of a high fat breakfast. The safety and efficacy of the drug product have been established in clinical trials where the drug product was taken without regard to meals.

Oral administration of single doses of 400 mg Augmentin chewable tablets to 28 adult volunteers yielded following pharmacokinetic data:

400 + 57 mg (5 mL suspension):	AUC(0-∞) μg.hr./mL	CMAX μg/mL
amoxicillin	17.29±2.28	6.94±1.24
clavulanate potassium	2.34±0.94	1.10±0.4

(The dose was administered at the start of a light meal. Peak concentrations occurred approximately 1 hour after the dose.)

Amoxicillin serum concentrations achieved with the combination drug product 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 the drug product is 1.3 hours and that of clavulanic acid is 1.0 hour. Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of 10 mL of Augmentin 250 mg/5 mL suspension. One Augmentin 250 mg chewable tablet or 2 Augmentin 125 mg chewable tablets are equivalent to 5 mL of Augmentin 250 mg/5 mL suspension and provide similar serum levels of amoxicillin and clavulanic acid.

Neither component of the drug product 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. Experiments in animals suggest clavulanic acid is also well distributed in body tissues.

The most common adverse events associated with the amoxicillin and clavulanate potassium drug products include diarrhea, nausea, vomiting, indigestion, rash, urticaria, candida vaginitis and stomatitis.

Financial Disclosure: p. 64-65, Vol. A1.1

III. Protocol No.: 99051, A Single Center, Open, Randomized, Two-way, Two-period, Two-sequence Crossover Study of the Bioequivalence of 459.2 mg Amoxicillin Trihydrate Equivalent to 400 mg Amoxicillin and 67.9 mg Potassium Salt of Clavulanic Acid Equivalent to 57 mg Clavulanic Acid of Amox C 400 + 57 mg/5 mL Powder for Oral Suspension (Test formulation) and Augmentin 400 mg/5 mL for Oral Suspension (Reference Formulation) Each Given as a Single Oral Dose to Fifty-Three Healthy Male and/or Female Volunteers in the Fasting State

1)Study Information

STUDY FACILITY INFORMATION

Clinical Facility: [redacted]
Medical Director: [redacted]
Clinical Study Dates: 09/12/99 to 9/19/99
Analytical Facility [redacted]

Principal Investigator: [redacted]
Analytical Study Dates: 10/08/99 to 10/20/99

Storage Period: 38 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Amoxicillin & Clavulanate Potassium (Amox C)	Amoxicillin & Clavulanate Potassium (Augmentin)
Manufacturer:	BIOCHEMIE GmbH, Kundl, Austria	SmithKline Beecham Pharmaceuticals, Philadelphia, USA
Manufacture Date:	6/99	N/A
Expiration Date:	N/A	7/00
ANDA Batch Size:	[redacted] (total weight)	
Batch/Lot Number:	103311	MA2143
Potency:	108.5% + 114.7%	110.8% + 118.1%
Strength:	400 + 57 mg	400 mg + 57 mg
Dosage Form:	suspension	Suspension
Dose Administered:	400 mg + 57 mg	400 mg + 57 mg
Study Condition:	fasting	Fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	N
No. of Treatments:	2	**Washout Period:**	7 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	53 19 females 34 males
Route of Administration:	oral	**No. of Subjects Completing:**	53
		No. of Subjects Plasma Analyzed:	46 (per protocol)
		No. of Dropouts:	0
		Sex(es) Included:	Both
		Healthy Volunteers Only:	Y
		Age: 18-45 yrs	
		Mean Height: 153-186 cm	
		Mean Weight: 49-86 kg	

Dietary Restrictions:	Subjects were instructed to abstain from food or beverages containing xanthine (e.g. coffee, tea, caffeine-containing sodas, colas and chocolate, etc.) and alcohol starting 48 hours prior to dosing and throughout the study period . No smoking was allowed at least 1 hour before dosing and up to 4 hours after dosing. Thereafter, the smoking activity was documented to ensure that the frequency of smoking is similar at Period I and II. Grapefruit products were not allowed starting 7 days prior to dosing until 10 hours post-dose.
Activity Restrictions:	Subjects engaged in normal activity for the first 4 hours after dosing avoiding complete rest. Subjects were not permitted to lie down for the first 4 hours after dosing, unless medically necessary, in which case, it was documented. No vigorous physical activity was allowed during confinement.
Drug Restrictions:	No concomitant drug therapy was allowed during the study except one to counteract an adverse event (e.g. occasional use of acetaminophen for headache). No prescription medication (including oral contraceptives) and no OTC medication was allowed for 14 days and 7days, respectively, prior to the study.
Confinement:	At least 10 hours pre-dose to 10 hours post-dose
Inclusion/Exclusion Criteria:	See pp. 369-371, Vol. A1.5
Blood Sampling:	Pre-dose, 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 7, 8 & 10 hours post-dose

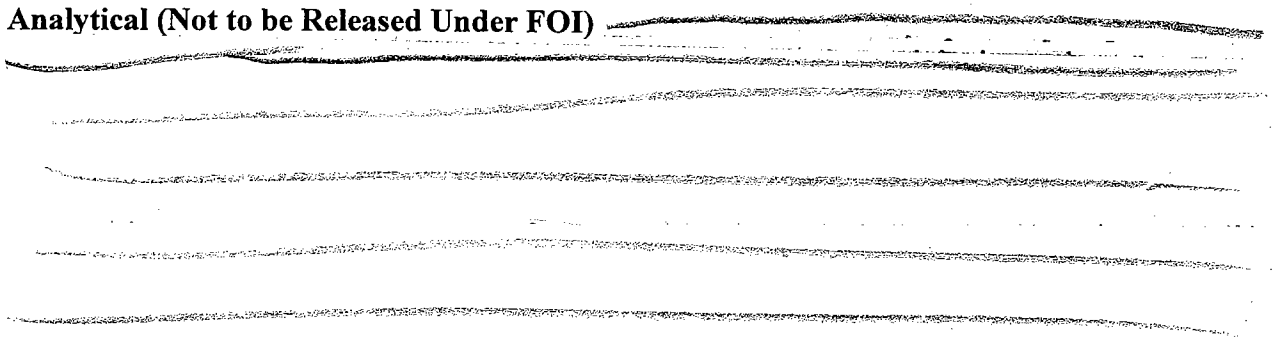
2)Study Results

Clinical Adverse Events: There was no serious adverse event reported. Three and none mild drug-related adverse reactions were reported during the Test and Referenct treatments, respectively. The reactions included abdominal cramps and heartburn.

Protocol Deviations: None was judged likely to affect the bioavailability comparison by the study investigator.

Dropouts: None.

3) Analytical (Not to be Released Under FOI)



DURING STUDY ASSAY VALIDATION FOR AMOXICILLIN IN FASTING STUDY #99051

Parameter	Quality Control Samples	Standard Curve Samples
[redacted]		

DURING STUDY ASSAY VALIDATION FOR CLAVULANIC ACID FASTING STUDY #99051

Parameter	Quality Control Samples	Standard Curve Samples
[redacted]		

For clavulanic acid, there was no repeat sample.

4) Pharmacokinetic:

PARAMETER	CALCULATION METHOD
AUC0-t	Trapezoidal
AUC0-inf	AUC0-t + Observed CT/Kel
Cmax	Observed Data
Tmax	Observed Data
Residual Area	(1-(AUC0-t/AUC0-inf)) x 100
Kel	Ln-linear regression of the terminal elimination phase
Thalf	(ln2)/Kel

Results:

TABLE I

FASTING IN VIVO BIOEQUIVALENCE STUDY #99051
LEAST-SQUARES MEANS AND 90% GEOMETRIC CONFIDENCE INTERVALS
FOR PHARMACOKINETIC PARAMETERS, N=46
a) Amoxicillin

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)	90% C.I.
AUC(T) [µg.hr/mL] ---------- (Geometric mean)	20.32 *20.32**	20.10 *20.13**	1.01 *1.01**	0.99-1.03 *0.99-1.03**
AUC(I) [µg.hr/mL] ---------- (Geometric mean)	20.47 *20.47**	20.24 *20.27**	1.01 *1.01**	0.99-1.03 *0.99-1.03**
Cmax [µg/mL] ---------- (Geometric mean)	7.87 *7.87**	7.80 *7.90**	1.01 *1.00**	0.96-1.06 *0.94-1.05**

*Results of the re-analysis

TABLE II

b) Clavulanic acid

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)	90% C.I.
AUC(T) [µg.hr/mL] ---------- (Geometric mean)	2.82	2.49	1.13	1.04-1.23
AUC(I) [µg.hr/mL] ---------- (Geometric mean)	2.94	2.60	1.13	1.05-1.22
Cmax [µg/mL] ---------- (Geometric mean)	1.49	1.34	1.11	1.02-1.21

TABLE III

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99051 ARITHMETIC MEAN PLASMA CONCENTRATIONS (μG/ML) VERSUS TIME (CV%) IN 46 SUBJECTS

a) Amoxicillin

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)
Pre-dose	---- (----)	---- (----)	----
0.250	1.04 (61.59)	0.815 (73.94)	1.2732
0.500	4.29 (41.07)	3.84 (48.84)	1.1176
0.750	6.76 (32.77)	6.51 (35.15)	1.0391
1.00	7.70 (23.65)	7.38 (26.90)	1.0437
1.25	7.47 (20.50)	7.46 (22.72)	1.0017
1.50	6.95 (19.01)	6.99 (21.27)	0.9936
1.75	6.20 (17.88)	6.28 (23.81)	0.9878
2.00	5.51 (18.35)	5.52 (23.52)	0.9985
2.25	4.77 (20.19)	4.83 (24.53)	0.9877
2.50	4.20 (24.19)	4.18 (24.63)	1.0057
3.00	3.16 (29.67)	3.09 (29.57)	1.0232
4.00	1.71 (36.01)	1.73 (39.76)	0.9898
5.00	1.05 (40.28)	1.05 (42.78)	1.0031
6.00	0.577 (42.02)	0.613 (60.51)	0.9421
7.00	0.319 (46.17)	0.333 (71.74)	0.9560
8.00	0.187 (43.53)	0.198 (57.50)	0.9466
10.0	0.0739 (40.00)	0.0736 (48.51)	1.0032

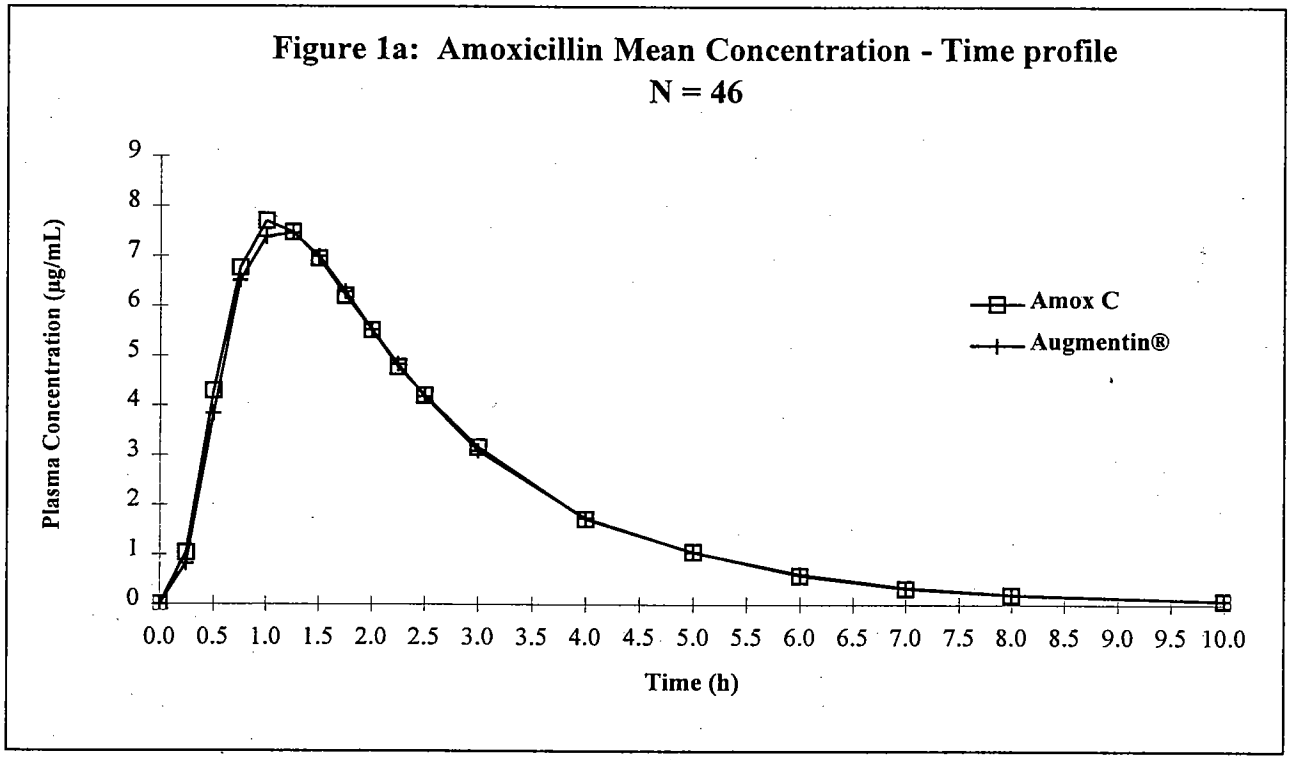
TABLE IV

b) Clavulanic acid

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)
Pre-dose	---- (----)	---- (----)	----
0.250	0.244 (63.51)	0.222 (71.45)	1.0986
0.500	1.03 (43.07)	0.937 (53.53)	1.1044
0.750	1.45 (32.95)	1.35 (41.96)	1.0678
1.00	1.49 (27.93)	1.34 (35.94)	1.1067
1.25	1.28 (30.36)	1.19 (36.88)	1.0769
1.50	1.08 (30.61)	1.00 (36.29)	1.0834
1.75	0.888 (31.51)	0.819 (37.06)	1.0849
2.00	0.739 (33.16)	0.684 (40.27)	1.0805
2.25	0.613 (34.54)	0.571 (42.29)	1.0737
2.50	0.519 (36.64)	0.474 (45.10)	1.0936
3.00	0.360 (39.17)	0.323 (47.30)	1.1134
4.00	0.185 (43.43)	0.175 (50.76)	1.0573
5.00	0.112 (41.55)	0.100 (49.53)	1.1200
6.00	0.771 (31.65)	0.0709 (51.24)	1.0865
7.00	0.0739 (32.97)	0.893 (58.23)	0.8276
8.00	0.0518 (----)	0.0684 (----)	0.7573
10.0	---- (----)	---- (----)	----

FIGURE 1

PLASMA CONCENTRATION (µg/mL) VERSUS TIME
SINGLE-DOSE FASTING STUDY #99051



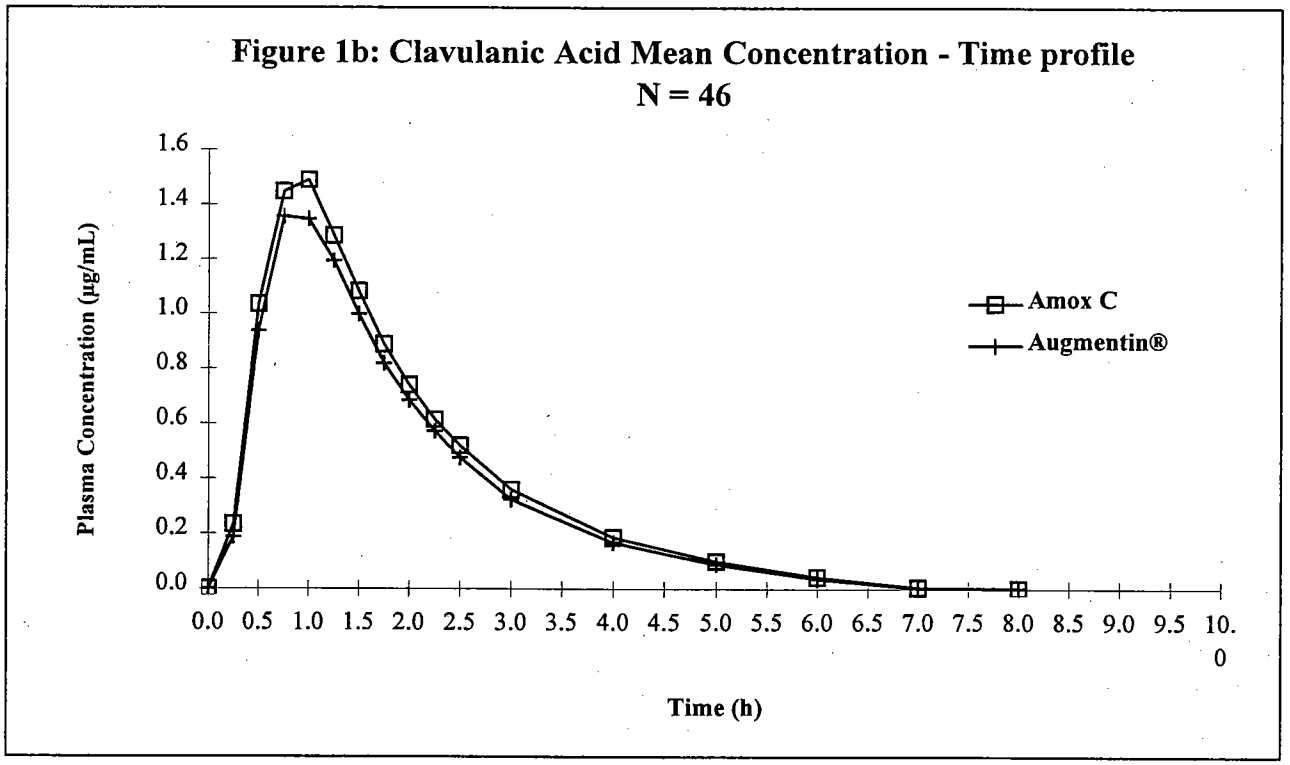


TABLE V

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99051 ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS IN 46 SUBJECTS

a) Amoxicillin

PK PARAMETER	N	TEST TREATMENT A	N	REFERENCE TREATMENT B	RATIO (A/B)
AUCT [µg.hr/mL]	46	20.64 (17.74)	46	20.40 (17.36)	1.0115
AUCI [µg.hr/mL]	46	20.78 (17.81)	46	20.54 (17.41)	1.0117
Cmax [µg/mL]	46	8.07 (22.15)	46	8.01 (22.35)	1.0069
Tmax [hr]	46	1.14 (24.34)	46	1.22 (32.57)	0.9333
Kel [1/hr]	46	0.5070 (9.76)	46	0.5164 (10.48)	0.9816
T½ [hr]	46	1.38 (9.94)	46	1.36 (10.64)	1.0173

TABLE VI

b) Clavulanic acid

PK PARAMETER	N	TEST TREATMENT A	N	REFERENCE TREATMENT B	RATIO (A/B)
AUCT [µg.hr/mL]	46	2.97 (33.13)	46	2.71 (40.03)	1.0954
AUCI [µg.hr/mL]	46	3.08 (31.92)	46	2.81 (38.72)	1.0960
Cmax [µg/mL]	46	1.55 (28.16)	46	1.45 (35.59)	1.0691
Tmax [hr]	46	0.886 (18.48)	46	0.935 (22.81)	0.9473
Kel [1/hr]	46	0.6305 (14.23)	46	0.6526 (15.29)	0.9662
T½ [hr]	46	1.12 (13.70)	46	1.08 (13.78)	1.0336

APPEARS THIS WAY
ON ORIGINAL

5) Statistical Analysis: Fifty-three subjects entered completed the study. Per protocol, data from the first completing 46 subjects were used in the statistical analysis for this study.

There were statistically significant differences (alpha=0.05) between treatment for clavulanic acid LAUC(0-T) (p=0.0126), LAUC(0-Inf) (p=0.0105) and LCMAX (p=0.0361). There was no statistically significant difference between treatment for LAUC(0-T), LAUC(0-Inf) or LCMAX of amoxicillin.

The results of the re-analyses using the original assayed values where appropriate are given in the PK parameter summary tables.

Conclusion: The study is acceptable.

IV. Protocol No.: 131, A Single Center, Open, Randomized, Three-way, Three-period, Six-sequence Crossover Study of the Bioequivalence of 459.2 mg Amoxicillin Trihydrate Equivalent to 400 mg Amoxicillin and 67.9 mg Potassium Salt of Clavulanic Acid Equivalent to 57 mg Clavulanic Acid of Amox C 400 + 57 mg/5 mL Powder for Oral Suspension (Test Formulation) and Augmentin 400 mg/5 mL Oral Suspension (Reference Formulation) Each Given as a Single Oral Dose to Twenty-Four Healthy Male and/or Female Volunteers in the Fasting and Fed Conditions

1)Study Information

STUDY FACILITY INFORMATION

Clinical Facility: [redacted]
Medical Director: [redacted]
Clinical Study Dates: 06/12/00 to 06/26/00
Analytical Facility [redacted]

Principal Investigator: [redacted]
Analytical Study Dates: 08/16/00 to 09/05/00

Storage Period: 85 days

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TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	T	R	T
Product Name:	Amoxicillin & Clavulanate Potassium	Augmentin	Amoxicillin & Clavulanate Potassium
Manufacturer:	BIOCHEMIE GmbH, Kundl, Austria	SmithKline Beecham Pharmaceuticals, Philadelphia, USA	BIOCHEMIE GmbH, Kundl, Austria
Manufacture Date:	6/1/99	N/A	6/1/99
Expiration Date:	N/A	7/00	N/A
ANDA Batch Size:	[redacted] (total weight)	N/A	[redacted] total weight)
Batch/Lot Number:	103311	MA2143	103311
Potency:	108.5% + 114.7%	110.8% + 118.1%	108.5% + 114.7%
Strength:	400 + 57 mg	400 + 57 mg	400 + 57 mg
Dosage Form:	Suspension	Suspension	Suspension
Dose Administered:	400 mg	400 mg	400 mg
Study Condition:	fed	fed	Fasted
Length of Fasting:	At least 10 hours	At least 10 hours	at least 10 hours
Breakfast Specifics:	1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 240 mL of whole milk, 180 mL of orange juice.	1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 240 mL of whole milk, 180 mL of orance juice.	N/A

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	6		
No. of Periods:	3	**Balanced:**	N
No. of Treatments:	3	**Washout Period:**	7 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
		Informed Consent :	Y
Volume of Liquid Intake:	180 mL	**No. of Subjects Enrolled:**	30
Route of Administration:	oral	**No. of Subjects Completing:**	30
		No. of Subjects Plasma Analyzed (per protocol):	24
		No. of Dropouts:	0
		Sex(es) Included:	both
		Healthy Volunteers Only:	Y
		Age range: 20-45 yrs	
		Mean Height: 154-189 cm	
		Mean Weight: 50-86 kg	

Dietary/Drug/Activity Restrictions: See the Fasting Study above.

Blood Sampling: See the Fasting Study above.

2)Study Results

Clinical Adverse Events: There was no serious adverse event reported. None, two and two mild to moderate, drug-related adverse reactions were reported during the Test (Fed), Reference (Fed) and Test (Fasted) treatments, respectively. These reactions included abdominal cramps, rash and diarrhea.

Protocol Deviations: None was considered by the investigator as likely to affect the study results.
Dropouts: None

3) Analytical (Not to be Released Under FOI)

DURING STUDY ASSAY VALIDATION FOR AMOXICILLIN IN NON-FASTING STUDY #00131

Parameter	Quality Control Samples	Standard Curve Samples
[redacted]		

DURING STUDY ASSAY VALIDATION FOR CLAVULANIC ACID NON-FASTING STUDY #00131

Parameter	Quality Control Samples	Standard Curve Samples
[redacted]		

[redacted]

4) Pharmacokinetic: For calculation method, see the Fasting Study above.

TABLE VII
FOOD EFFECTS IN VIVO BIOEQUIVALENCE STUDY # 00131
LEAST-SQUARES MEANS (n= 24) FOR PHARMACOKINETIC PARAMETERS
a) Amoxicillin

PK PARAMETER	FED TEST TREATMENT A	FED REFERENCE TREATMENT B	FASTING TEST TREATMENT C	RATIO (A/B)	RATIO (A/C)
AUC(T) [µg.hr/mL] ---------- (Geometric mean)	20.60	20.46	21.33	1.01	0.97
AUC(I) [µg.hr/mL] ---------- (Geometric mean)	20.79	20.64	21.49	1.01	0.97
Cmax [µg/mL] ---------- (Geometric mean)	5.80	6.06	8.19	0.96	0.71

TABLE VIII

b) Clavulanic acid

PK PARAMETER	FED TEST TREATMENT A	FED REFERENCE TREATMENT B	FASTING TEST TREATMENT C	RATIO (A/B)	RATIO (A/C)
AUC(T) [µg.hr/mL] ---------- (Geometric mean)	1.31	1.21	3.11	1.08	0.42
AUC(I) [µg.hr/mL] ---------- (Geometric mean)	1.43	1.32	3.23	1.08	0.44
Cmax [µg/mL] ---------- (Geometric mean)	0.61	0.58	1.66	1.06	0.37

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ON ORIGINAL

TABLE IX

LIMITED FOOD EFFECTS SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #00131
ARITHMETIC MEAN PLASMA CONCENTRATIONS (μg/mL) VERSUS TIME (CV%) IN 24 SUBJECTS

a) Amoxicillin

TIME (HR)	NON-FASTING TEST TREATMENT A	NON-FASTING REFERENCE TREATMENT B	FASTING TEST TREATMENT C	RATIO (A/B)	RATIO (A/C)
Pre-dose	---- (----)	---- (----)	---- (----)	----	----
0.250	0.371 (123.63)	0.178 (80.19)	0.938 (66.40)	2.0888	0.3952
0.500	1.10 (100.78)	0.817 (74.77)	4.23 (34.13)	1.3448	0.2594
0.750	2.03 (78.33)	1.53 (59.60)	6.75 (26.59)	1.3319	0.3013
1.00	3.01 (55.09)	2.46 (47.75)	7.93 (25.84)	1.2241	0.3799
1.25	3.66 (44.87)	3.36 (38.82)	7.72 (27.04)	1.0885	0.4739
1.50	4.38 (34.56)	4.25 (35.12)	7.04 (23.83)	1.0299	0.6218
1.75	5.00 (28.24)	4.99 (27.96)	6.67 (21.97)	1.0027	0.7491
2.00	5.27 (22.99)	5.35 (23.81)	5.85 (23.69)	0.9847	0.9018
2.25	5.04 (18.38)	5.36 (25.85)	5.08 (24.49)	0.9395	0.9916
2.50	5.29 (17.90)	5.53 (17.00)	4.70 (20.67)	0.9556	1.1246
3.00	4.93 (17.14)	5.22 (18.04)	3.59 (29.22)	0.9450	1.3731
4.00	3.15 (29.84)	3.29 (27.95)	1.84 (44.16)	0.9566	1.7137
5.00	2.03 (38.00)	2.00 (33.39)	0.964 (41.82)	1.0186	2.1072
6.00	1.28 (56.13)	1.17 (35.08)	0.545 (33.95)	1.0886	2.3430
7.00	0.632 (48.03)	0.598 (35.85)	0.301 (33.29)	1.0579	2.0997
8.00	0.351 (60.39)	0.324 (38.79)	0.177 (29.98)	1.0826	1.9770
10.0	0.112 (49.87)	0.109 (43.27)	0.0777 (38.28)	1.0292	1.4465

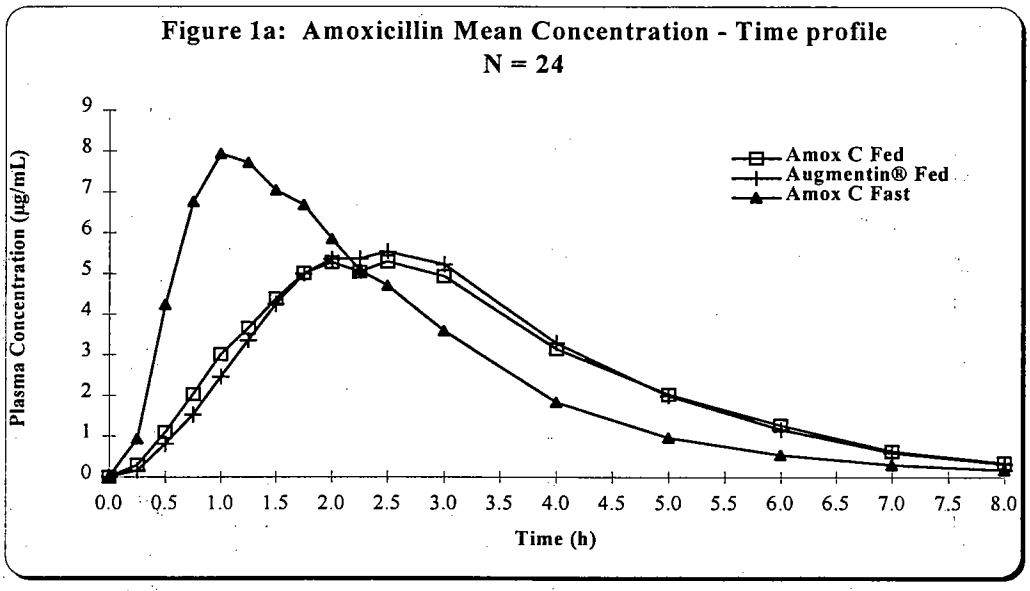
TABLE X

b) Clavulanic acid

TIME (HR)	NON-FASTING TEST TREATMENT A	NON-FASTING REFERENCE TREATMENT B	FASTING TEST TREATMENT C	RATIO (A/B)	RATIO (A/C)
Pre-dose	---- (----)	---- (----)	---- (----)	----	----
0.250	0.109 (57.02)	0.0768 (22.68)	0.264 (58.66)	1.4156	0.4115
0.500	0.209 (88.08)	0.175 (74.68)	1.12 (39.53)	1.1903	0.1857
0.750	0.375 (65.92)	0.274 (65.06)	1.64 (32.44)	1.3665	0.2288
1.00	0.546 (52.32)	0.420 (53.52)	1.62 (28.45)	1.2975	0.3373
1.25	0.598 (44.02)	0.522 (42.83)	1.42 (26.86)	1.1470	0.4223
1.50	0.616 (40.33)	0.564 (33.82)	1.17 (26.09)	1.0916	0.5242
1.75	0.611 (39.69)	0.559 (35.10)	0.997 (25.23)	1.0932	0.6133
2.00	0.536 (44.39)	0.501 (36.25)	0.813 (28.52)	1.0696	0.6597
2.25	0.458 (47.39)	0.432 (40.99)	0.648 (27.57)	1.0612	0.7073
2.50	0.386 (54.78)	0.368 (44.51)	0.540 (30.60)	1.0502	0.7151
3.00	0.271 (58.07)	0.256 (48.53)	0.381 (35.20)	1.0574	0.7125
4.00	0.133 (52.00)	0.127 (44.20)	0.195 (36.36)	1.0519	0.6825
5.00	0.0808 (42.97)	0.0814 (33.59)	0.110 (31.93)	0.9929	0.7317
6.00	0.0678 (25.54)	0.0692 (21.65)	0.0754 (25.52)	0.9811	0.8995
7.00	0.0540 (0.79)	---- (----)	0.0637 (16.53)	----	0.8482
8.00	---- (----)	---- (----)	---- (----)	----	----
10.0	---- (----)	---- (----)	---- (----)	----	----

FIGURE 2

PLASMA CONCENTRATION (µg/mL) VERSUS TIME
SINGLE-DOSE FOOD EFFECTS STUDY #00131



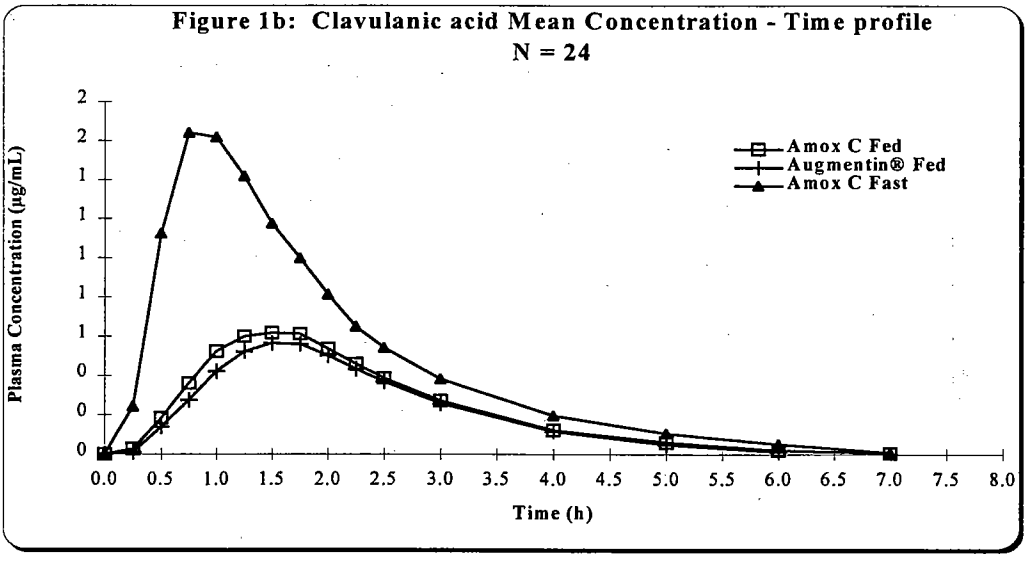


TABLE XI

FOOD EFFECTS SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #00131 ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS IN 24 SUBJECTS

c) Amoxicillin

PK PARAMETER	N	FED TEST TREATMENT A	N	FED REFERENCE TREATMENT B	N	FASTING TEST TREATMENT C	RATIO (A/B)	RATI (A/C)
AUCT [µg.hr/mL]	24	20.85 (15.94)	24	20.73 (16.40)	24	21.51 (13.33)	1.0062	0.969
AUCI [µg.hr/mL]	24	21.04 (16.13)	24	20.92 (16.57)	24	21.67 (13.30)	1.0061	0.971
Cmax [µg/mL]	24	5.90 (19.24)	24	6.20 (21.01)	24	8.38 (22.28)	0.9522	0.703
Tmax [hr]	24	2.37 (20.89)	24	2.44 (22.07)	24	1.40 (36.24)	0.9713	1.697
Kel [1/hr]	24	0.6026 (11.06)	24	0.5963 (12.88)	24	0.5049 (15.31)	1.0105	1.193
T½ [hr]	24	1.16 (11.09)	24	1.18 (13.15)	24	1.41 (16.13)	0.9852	0.828

TABLE XII

d) Clavulanic acid

PK PARAMETER	N	FED TEST TREATMENT A	N	FED REFERENCE TREATMENT B	N	FASTING TEST TREATMENT C	RATIO (A/B)	RATI (A/C)
AUCT [µg.hr/mL]	24	1.50 (48.63)	24	1.32 (40.05)	24	3.23 (25.41)	1.1343	0.464
AUCI [µg.hr/mL]	24	1.60 (45.48)	24	1.43 (37.46)	24	3.35 (24.72)	1.1197	0.476
Cmax [µg/mL]	24	0.670 (41.16)	24	0.618 (36.01)	24	1.73 (26.66)	1.0850	0.388
Tmax [hr]	24	1.50 (20.89)	24	1.59 (19.52)	24	0.917 (31.14)	0.9417	1.637
Kel [1/hr]	24	0.6863 (14.89)	24	0.7363 (14.16)	24	0.6083 (12.20)	0.9321	1.128
T½ [hr]	24	1.03 (15.56)	24	0.96 (16.12)	24	1.16 (12.59)	1.0737	0.893

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5) Statistical Analysis: All thirty enrolled subjects completed the study. Per protocol, samples from the first 24 completing subjects were analyzed and used for the pharmacokinetic and statistical analyses. Standard three-way crossover ANOVA models were used.

For amoxicillin, there were statistically significant differences (alpha=0.05) between treatments for LAUC(0-T) (p=0.0424) and LCMAX (p=0.0001). For clavulanic acid, there was statistically significant difference between treatments for LAUC(0-T) (p=0.0001), LAUC(0-Inf) (p=0.0001) and LCMAX (p=0.0001).

Conclusion: The study is acceptable.

V. Dissolution(Not to be released under FOI)

Dissolution Method: FDA
Dissolution Medium:
Apparatus:
Speed:
Sample Times: @ 2, 6, 10, 15 and 30 minutes
Limits: NLT (Q) of amoxicillin in 20 minutes
NLT (Q) of clavulanic acid in 20 minutes
NOTE: Currently, the USP monograph does not contain dissolution method and specification for this drug product. The Agency recommends the same dissolution method (see above) as that used for Amoxicillin/Clavulanate Potassium Chewable Tablets, but different specification of "NLT (Q) of amoxicillin and (Q) of clavulanic acid dissolved in **20 minutes**".

Results:

Amoxicillin Mean Dissolution Data

TEST: Biochemie's Amox C Powder for Oral Suspension

Lot No.: 103311
Strength: 400 + 57 mg
No. of Units: 12

REFERENCE: SmithKline Beecham's Augmentin Powder for Oral Suspension
Lot No.: MA2143
Strength: 400 + 57 mg
No. of Units: 12

Time(min.)	Mean	Range	Mean	Range
2	105.3		101.6	
6	105.2		107.5	
10	104.7		108.1	
15	104.3		107.5	
30	103.7		106.9	

Clavulanic Acid Mean Dissolution Data

TEST: Biochemie's Amox C
Powder for Oral Suspension

Lot No.: 103311
Strength: 400 + 57 mg
No. of Units: 12

Time(min.)	Mean	Range
2	111.8	
6	111.0	
10	109.9	
15	109.1	
30	107.9	

REFERENCE: SmithKline
Beecham's Augmentin Powder for
Oral Suspension
Lot No.: MA2143
Strength: 400 + 57 mg
No. of Units: 12

Mean	Range
115.6	
115.3	
114.7	
112.7	
111.2	

Amoxicillin Mean Dissolution Data

TEST: Biochemie's Amox C
Powder for Oral Suspension

Lot No.: 103310
Strength: 200 + 28.5 mg
No. of Units: 12

Time(min.)	Mean	Range
2	108.3	
6	107.9	
10	107.3	
15	106.5	
30	106.0	

REFERENCE: SmithKline
Beecham's Augmentin Powder for
Oral Suspension
Lot No.: MM2609
Strength: 200 + 28.5 mg
No. of Units: 12

Mean	Range
104.8	
107.4	
108.1	
107.6	
107.3	

Clavulanic Acid Mean Dissolution Data

TEST: Biochemie's Amox C
Powder for Oral Suspension

Lot No.: 103310
Strength: 200 + 28.5 mg
No. of Units: 12

Time(min.)	Mean	Range
2	111.7	
6	110.5	
10	109.5	
15	108.4	
30	107.7	

REFERENCE: SmithKline
Beecham's Augmentin Powder for
Oral Suspension
Lot No.: MM2609
Strength: 200 + 28.5 mg
No. of Units: 12

Mean	Range
114.6	
114.1	
113.2	
111.8	
110.5	

Comments: The dissolution data are acceptable.

VII. Formulation: See Review Attachment I. The formulation of Biochemie's Amoxicillin and Clavulanate Potassium Powder for Oral Suspension, 200 mg + 28.5 mg is proportionally similar to that of the 400 mg + 57 mg strength of the test product, which underwent *in vivo* bioequivalence testing.

VIII. Recommendations:

1. The single-dose, fasting bioequivalence study and the single-dose post-prandial bioequivalence study conducted by Biochemie on the test product, Amoxicillin and Clavulanate Potassium Powder for Oral Suspension USP, 400 + 57 mg/5 mL, lot # 103311, comparing it with the reference product, SmithKline Beecham's Augmentin for Oral Suspension, 400 + 57 mg/5 mL, lot # MA2143, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Biochemie's Amoxicillin and Clavulanate Potassium Powder for Oral Suspension USP, 400 + 57 mg/5 mL, is bioequivalent to the reference product, SmithKline Beecham's Augmentin 400 + 57 mg/5 mL amoxicillin and clavulanate potassium oral suspension, under fasting and non-fasting conditions.

2. The in-vitro dissolution testing conducted by Biochemie on its Amoxicillin and Clavulanate Potassium Powder for Oral Suspension USP, 400 + 57 mg/5 mL and 200 mg + 28.5 mg/5 mL, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in [redacted] The test product should meet the following specifications:

Not less than [redacted] of the labeled amount of amoxicillin and [redacted] of the labeled amount of clavulanic acid in the dosage form are dissolved in 20 minutes.

3. The firm has demonstrated that the formulation of its Amoxicillin and Clavulanate Potassium Powder for Oral Suspension USP, 200 + 28.5 mg/5 mL, is proportionally similar to that of the 400 + 28.5 mg/5 mL strength that underwent complete, acceptable *in vivo* bioequivalence testing. The request for waiver of *in vivo* bioequivalence study requirements for the 200 + 28.5 mg/5 mL is granted. The firm's Amoxcillin and Clavulanate Potassium Powder for Oral Suspension USP, 200 + 28.5 mg/5 mL, is deemed bioequivalent to SmithKline Beecham's Augmentin 200 + 28.5 mg/5 mL amoxicillin and clavulanate potassium oral suspension.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 2/14/2001

Concur: /S/ Date: 2/28/2001
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 65-066 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/01-22-01/W #65066sdw.200
Also as V:\firmsam\biochemi\ltrs&rev\65066sdw.200
Attachment: 1 page

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BIOEQUIVALENCY COMMENTS

ANDA: 65-066 APPLICANT: Biochemie GmbH
U.S. Agent: Geneva Pharmaceuticals

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium Powder for Oral Suspension USP, 400 + 57 mg/5 mL & 200 + 28.5 mg/5 mL

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.

The dissolution testing is conducted in [redacted]. The test product should meet the following specifications:

Not less than [redacted] of the labeled amount of amoxicillin and [redacted] of the labeled amount of clavulanic acid in the dosage form are dissolved in **20 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,

/S/

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

CC:ANDA 65-066
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen /s/ 2/28/2001
HFD-652/ YHuang /s/ 3/1/01
HFD-617/ K. Scardina
HFD-650/ D. Conner for lwe 2/28/2001

V:\FIRMSAM\biochemi\ltrs&rev\65066SDW.200
Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE

Submission date: ~~02-11-00~~ ~~10-01-00~~ 11/14/00

1. FASTING STUDY (STF) olc
   Clinical:
   Analytical:
   Strength: 400 + 57 MG
   Outcome: AC

2. NON-FASTING STUDY (STP) olc
   Clinical: /
   Analytical:
   Strength: 400 + 57 MG
   Outcome: AC

3. DISSOLUTION WAIVER (DIW) olc
   Strenth: 200 + 28.5 MG
   Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-066

SPONSOR : Biochemie GmbH
(US Agent: Geneva Pharmaceuticals)

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

STRENGTH(S) : 400 + 57 mg/5 mL & 200 + 28.5 mg/5 mL

TYPES OF STUDIES : Fasting Study & Non-Fasting Study

CINICAL STUDY SITE(S) : —

ANALYTICAL SITE(S) : —

STUDY SUMMARY : Acceptable

DISSOLUTION : Acceptable

WAIVER: Acceptable

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
YES		Acceptable
First Generic YES	Inspection requested: (date)	
New facility ____	Inspection completed: (date) 4/6/01	
For cause ____		
Other ____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I

INITIAL : /S/ DATE : 2/13/01

TEAM LEADER : Yih-Chain Huang BRANCH : I

INITIAL : /S/ DATE : 2/14/2001

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

INITIAL : /S/ DATE : 2/28/2001

The Division of Chemistry should be aware that both test and reference formulations have overage in the 400 mg (Amoxicillin)/57 mg (Clavulanate K)/5 ml Strength Suspension.

	Biochemie	SmithKline Beecham
Amoxicillin	—	—
Clavulanate Potassium	—	—

Similar overage in the low strength formulation.

Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml **Section VI. Bioavailability/Bioequivalence**	ANDA-No.: Edition: Date: January 2000 DRE/Szb/sch

5.1. Formulation Data

Comparison of Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml with Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 400 + 57 mg/5 ml used for Bioavailability/Bioequivalence testing.

	Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml		**Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 400 + 57 mg/5 ml**	
	g/dose	**%**	**g/dose**	**%**
Ingredient				
Clavulanate Potassium corresponding to 28.5 mg respectively 57 mg Clavulanic Acid, USP				
Amoxicillin Trihydrate corresponding to 200 mg respectively 400 mg Amoxicillin, USP				
Succinic Acid				
Xanthan Gum				
Aspartame				
Orange Flavouring,				
Golden Syrup Flavouring, (Caramel)				
Silicon Dioxide, Colloidal				
Hydroxypropyl Methylcellulose (synonym:				
Mannitol				
Silicon Dioxide, Precipitated				
Total	**0.800**	**100**	**1.080**	**100**

1)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-066

CORRESPONDENCE

Beth Brannar
Director

Geneva Pharmaceuticals, Inc.
Drug Regulatory Affairs
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4237
Fax +1 303 438 4600
Internet: Beth.Brannan
@gx.novartis.com

Geneva pharmaceuticals, inc.

RPS 3/10/00

FEDERAL EXPRESS

ORIGINAL ANDA

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

February 11, 2000

RE: Original – Abbreviated New Drug Application
Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml

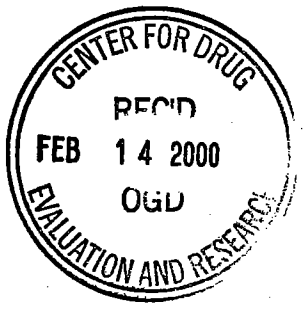
Dear Director:

On behalf of Biochemie Gmbh in Kundl, Austria, Geneva Pharmaceuticals, Inc. is hereby submitting an Abbreviated New Drug Application for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.92 and 314.94.

As stated in our Electronic Submission Declaration (provided in Section XXI of this application), the information contained in this application will also be provided separately in an electronic submission.

A comprehensive table of contents is provided in each volume, which shows the page number of our submission's contents, as required by the regulations Part 314.94(a)(2).

The name, title and address of the applicant is presented below:



Biochemie GmbH
Biochemie Strasse 10
A-6250 Kundl/Austria

Contact Person: Ingrid Schwarzenberger, DRE/Registration Manager
Telephone No.: 43-5338-200-2450
Telefax No.: 43-5338-200-2959

The U.S. Agent for this Abbreviated New Drug Application is:

Geneva Pharmaceuticals, Inc.
2555 West Midway Boulevard
Broomfield, CO 80038-0446

Contact Name: Beth Brannan, Director, Drug Regulatory Affairs
Telephone No.: (303) 438-4237
Telefax No.: (303) 438-4600

Enclosed in this package is the blue archival copy (10 volumes) containing the complete ANDA application. The red review copy (3 volumes) containing the Chemistry, Labeling, Manufacturing, and Controls sections. The orange pharmacokinetic section review copy (7 volumes) containing the bioequivalence information.

Per the Guidance for Industry on the "Organization of an ANDA" dated February 1999 (Rev. 1), Geneva Pharmaceuticals is submitting the field copy to the Office of Generic Drugs. The field copy, which is contained in 3 maroon binders, is also contained in this same package.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan,
Director, Drug Regulatory Affairs

Enclosures

BB/jep

ANDA 65-066

Geneva Pharmaceuticals, Inc.
U.S. Agent for: Biochemi GmbH
Attention: Beth Brannan
2655 W. Midway Blvd.
Broomfield, CO 80036-0446

MAR 29 2000

Dear Madam

Please refer to your abbreviated new drug application (ANDA) dated February 11, 2000 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Amoxicillin; Clavulanate Potassium for Oral Suspension, 200 mg/5 mL (28.5 mg base/5 mL); 400 mg/5 mL (57 mg base/5 mL).

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

The bioequivalence study submitted to support the approval of your application has been determined to be incomplete. You have failed to provide a non-fasting *in vivo* bioequivalence study for your proposed product.

It appears that your proposed formulation contains inactive ingredients, Golden Syrup Flavor [redacted] and Natural and Artificial Orange Flavor [redacted] which have not been approved in a drug product for human use by the same route of administration [21 CFR 314.127(a)(8)(ii)]. There is reasonable basis to conclude that the inactive ingredients in your proposed product may raise safety questions because of the lack of information that you have provided regarding their use. The Office of Generic Drugs (OGD) will not receive this application as an ANDA since new inactive ingredients must be the subject of a new drug application. Please provide additional information to support the safety of the use of these inactive ingredients in your proposed drug product. The information to demonstrate safety should include, but is not limited to, examples of approved drug products administered by the same route of administration

which contains the same inactive ingredients within the same concentration range.

Please note that DMF authorization and composition alone are not sufficient data to prove safety. If you choose to provide the composition instead of pharmacology toxicology data, you must provide supporting data showing that **each** component and composition was used in an approved drug product.

Although considered supportive, please note that the qualifications listed below for an inactive ingredient may not be enough to demonstrate safety:

- GRAS Certification
- FEMA Certification
- DMF Authorization
- Composition

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act. In addition, please submit the following:

Three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

A financial certification/disclosure statement. This information must be provided using FDA form 3454 and/or 3455. A copy of these forms may be obtained by calling the Regulatory Support Branch at (301) 827-5862.

You have failed to provide original signature on your debarment certification/list of convictions statement. Please provide this document with an original signature.

We note that you have failed to provide a Field Copy Certification with an original signature. Please provide this certification with an original signature.

Please provide a list of addresses of the suppliers of your inactive ingredients.

Please provide a list of addresses of the suppliers of your container/closure systems.

It is not clear whether you want to provide an environmental assessment or file for categorical exclusion of an environmental assessment. Please revise this section of your application to include a categorical exclusion per 21 CFR 25.30 or 31 or an environmental assessment in the format suggested in 21 CFR 25.40.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Saundra T. Middleton
Project Manager
(301) 827-5862

Sincerely yours,

/S/

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

ANDA 65-066
cc: DUP/Jacket
Division File
HFD-92
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-615/MBennett

Endorsement: HFD-615/NMahmud, Chief, /S/ date 3/28/00
HFD-615/SMiddleton, CS /S/ date 3/27/00
Word File
V:/FIRMSAM/BIOCHEMI/LTRS&REV/65066.RTF
F/T File mjl/3/22/00
ANDA Refuse to Receive!

Beth Brannan
Director

Geneva Pharmaceuticals, Inc.
Drug Regulatory Affairs
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4237
Fax +1 303 438 4600
Internet: beth.brannan
@gx.novartis.com

Geneva pharmaceuticals, inc.

FEDERAL EXPRESS

65-066

Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

EVA SUBMISSION – CMC and BIO

NEW CORRESP

NC

March 13, 2000

RE: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200+28.5 mg/5 ml and 400+57 mg/5 ml
EVA Submission for Original Abbreviated New Drug Application

Dear Mr. Buehler:

On behalf of Biochemie GMBH, Geneva Pharmaceuticals, Inc. is hereby submitting an electronic version of its Abbreviated New Drug Application for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200+28.5 mg/5 ml and 400+57 mg/5 ml

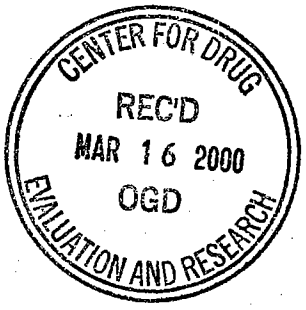
Enclosed you will find a CD, containing copies of the CMC portion of our electronic submission (EVA- 1 document) and the companion document (Word 6.0- 1document) as well as the Bio portion consisting of the EVA, the companion document and the data files.

If you have any questions regarding the data that was entered, please contact:

Jean Pederson, Drug Regulatory Affairs
Geneva Pharmaceuticals, Inc.
2555 West Midway Boulevard
Broomfield, CO 80028
Phone: (303) 438-4242
Fax: (303) 438-4600

Or

Ingrid Schwarzenberger
Biochemie GmbH
Biochemiestrasse 10
A-6250 Kundl/Austria
Phone: 43 5338 200 2450



APPEARS THIS WAY
ON ORIGINAL

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Ingrid Silvestri Berger

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures:
CD
356h
Original ANDA cover letter dated Feb. 11th, 2000
Electronic Submission declaration

Beth Brannan, Director

Geneva Pharmaceuticals, Inc.
Drug Regulatory Affairs
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4238
Fax +1 303 438 4609
Internet: Beth.Brannan
@gx.novartis.com

Geneva pharmaceuticals, inc.

7/24/00 Spoke with Jean data submitted is incomplete, will await response. /S/

FEDERAL EXPRESS

Sandra T. Middleton, Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

INACTIVE INGREDIENT INFORMATION

NDA ORIG AMENDMENT
N/AC

June 1, 2000

RE: ANDA 65-065; Amoxicillin; Clavulanate Potassium Tablets (Chewable), 200 mg (28.5 mg base); 400 mg (57 mg base)
ANDA 65-066; Amoxicillin; Clavulanate Potassium for Oral Suspension, 200 mg/5 mL (28.5 mg base/5 mL); 400 mg/5 mL (57 mg base/5 mL)

Dear Ms. Middleton:

On behalf of Biochemie GmbH in Kundl, Austria, Geneva Pharmaceuticals, Inc. is hereby submitting information on four inactive ingredients used in its Abbreviated New Drug Application, 65-065, for Amoxicillin; Clavulanate Potassium Tablets (Chewable), 200 mg/5 mL (28.5 mg base/5 mL); 400 mg/5 mL (57 mg base/5 mL) and Abbreviated New Drug Application, 65-066, for Amoxicillin; Clavulanate Potassium for Oral Suspension, 200 mg/5 mL (28.5 mg base/5 mL); 400 mg/5 mL (57 mg base/5 mL). This information is being submitted per your request.

Reference is made to FDA's Refuse to File letters dated March 29, 2000, for the above referenced products. In these letters, it was noted that the proposed formulations contain inactive ingredients: Golden Syrup Flavor [illegible], Natural and Artificial Orange Flavor [illegible] [illegible] and [illegible] which have not been approved in a drug product for human use by the same route of administration [21 CFR 314.127 (a) (8) (ii)]. A request for additional information to support the safety of the use of these inactive ingredients in the proposed drug products was requested.

In response to this request, we are providing, for each of the inactive ingredients in question, the following documents:

- A qualitative comparison between Biochemie's and SmithKline Beecham's products.
- A page from SmithKline Beecham's Abbreviated Environmental Assessment for each ADA submitted listing the inactive ingredient used in SmithKline Beecham's Augmentin.

Geneva pharmaceuticals, inc.

- A page from the Inactive Ingredient guide, which shows the inactive ingredient, is approved for use.
- A full list of the articles used as components in Biochemie's Amoxicillin/Clavulanate products.
- A formulation summary for Biochemie's products.
- A list of addresses for the inactive ingredients used in Biochemie's products.
- A DMF referral letter from each inactive ingredient manufacturer.
- Certificates of Analysis from the manufacturer for the inactive ingredient.
- Biochemie's Certificate of Analysis for each inactive ingredient.
- Biochemie's Specifications and Methods for each inactive ingredient.

Please note that the code number for the inactive ingredient, as referenced on SmithKline Beecham's Abbreviated Environmental Assessment and used by SmithKline Beecham for its Augmentin products, is the same code number used by the inactive ingredient manufacturer where Biochemie purchased its inactive ingredient for its Amoxicillin/Clavulanate products. Since these code numbers are the same, we believe SmithKline Beecham used the same inactive ingredients in its Augmentin products as Biochemie used in its Amoxicillin/Clavulanate products.

In addition, we are providing DMF referral letters from each inactive ingredient manufacturer. These DMFs will aid in reviewing the component/composition data for each ingredient.

We are also provided information from Biochemie on the specifications and tests for each ingredient. Please note that Biochemie provides the composition of each ingredient in its specification and method document.

Although additional documentation is being provided, it may not necessarily support the safety of the inactive ingredients in questions. However, we are providing the additional documents to ease the review process.

This information is being submitted for your review. If you have any questions, please don't hesitate to contact me at (303) 438-4237.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

BB/jep
Enclosures

8/14/00
LH

Redacted ____|____

pages of trade secret and /or confidential commercial information

Beth Brannan
Director

Geneva Pharmaceuticals, Inc.
Drug Regulatory Affairs
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4237
Fax +1 303 438 4600
Internet: Beth.Brannan
@gx.novartis.com

Geneva pharmaceuticals, inc.

FEDERAL EXPRESS

BIOAVAILABILITY

Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

EVA SUBMISSION – BIO

NEW CORRESP
NC

December 7, 2000

RE: ANDA 65-066: Amoxicillin & Clavulanate Potassium Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml
EVA Submission; Non-Fasting Bio Information filed in Amendment dated 11/14/00

Dear Mr. Buehler:

On behalf of Biochemie GmbH in Kundl, Austria, Geneva Pharmaceuticals, Inc. is hereby submitting an electronic version of its Non-Fasting Bioequivalency information that was provided in its amendment dated November 14, 2000, for its Abbreviated New Drug Application 65-066: Amoxicillin & Clavulanate Potassium Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml

Enclosed you will find one CD, containing the ESD, Companion Document and Data Files for the non-fasting bioequivalency study that was performed.

The name, title and address of the applicant and U.S. agent are presented below. If you have any questions regarding the data that were entered, please contact Ingrid Schwarzenberger at Biochemie or Beth Brannan at Geneva.

	Applicant	U.S. Agent
Address	Biochemie GmbH Biochemie Strasse 10 A-6250 Kundl/Austria	Geneva Pharmaceuticals, Inc. 2555 West Midway Boulevard Broomfield, CO 80038 – 0446
Contact	Ingrid Schwarzenberger DRE/Registration Manager	Beth Brannan, Director Drug Regulatory Affairs
Phone	43-5338-200-2450	303-438-4237
Fax	43-5338-200-2959	303-438-4600

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 0 8 2000
OGD

This information is submitted for your review.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures

BB/jep

APPEARS THIS WAY
ON ORIGINAL

ANDA 65-066

Geneva Pharmaceuticals, Inc.
U.S. Agent for: Biochemie GmbH
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield, CO 80038

DEC 21 2000

Dear Madam:

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

Reference is made to the refuse to receive letter dated March 29, 2000 and your amendment dated November 14, 2000.

NAME OF DRUG: Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 mg/28.5 mg(base) per 5 mL and 400 mg/57 mg(base) per 5 mL

DATE OF APPLICATION: February 11, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 15, 2000

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

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

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

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

Beth Brannan
Director

Geneva Pharmaceuticals, Inc.
Drug Regulatory Affairs
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4237
Fax +1 303 438 4600
Internet: Beth.Brannan
@gx.novartis.com

Geneva
PHARMACEUTICALS

NC
NEW CORRESP

FEDERAL EXPRESS

Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TRANSFER OF OWNERSHIP

May 4, 2001

RE: ANDA 65-066: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP **200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml**
Transfer of Ownership

Dear Mr. Buehler:

On behalf of Biochemie GmbH in Kundl, Austria, Geneva Pharmaceuticals, Inc. is hereby submitting a Transfer of Ownership letter to its Abbreviated New Drug Application 65-066, Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml, effective May 4, 2001 .

As the recipient of said ANDA, Geneva Pharmaceuticals, Inc. hereby advises you that we have received a complete copy of ANDA 65-066 for Amoxicillin and Clavulanate for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml, including amendments and records that are required to be kept under 21 CFR 314.72. Therefore, correspondence relating to this ANDA should be forwarded to:

Ms. Beth Brannan, Director
Drug Regulatory Affairs
2655 West Midway Boulevard
Broomfield, CO 80038

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures

BB/jep

Beth Brannan
Director

Geneva Pharmaceuticals, Inc.
Drug Regulatory Affairs
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4237
Fax +1 303 438 4600
Internet: Beth.Brannan
@gx.novartis.com

Geneva
PHARMACEUTICALS

FEDERAL EXPRESS

NC
NEW CORRESP

Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

June 4, 2001

RE: ANDA 65-066: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP
200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml
Acceptance of Ownership 356h Form

Dear Mr. Buehler:

Reference is made to our submission dated May 4th, 2001, and to a phone conversation between Jean Pederson (Geneva) and Nadine Warren (FDA) on June 4th, 2001. In this phone conversation, Ms. Warren requested Geneva provide a 356h Form accepting transfer of ownership to correspond with its "Acceptance of Ownership" letter that was dated May 4th, 2001. The 356h Form is enclosed. As requested, the 356h Form is dated May 4th, 2001, which is the same date the ANDA was accepted for ownership by Geneva.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 07 2001
OGD

Enclosures
BB/jep

ANDA 65-066

JUL 11 2001

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield, CO 80038

Dear Madam:

We acknowledge receipt of your communications dated May 4, and June 4, 2001, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 mg/28.5 mg (base) per 5 mL and 400 mg/57 mg (base) per 5 mL.

Your letter details the transfer of ownership of the ANDA, from Biochemie GmbH to Geneva Pharmaceuticals, Inc.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the pending application.

The material submitted is being retained as part of your application.

Sincerely yours,

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

Beth Brannan
Director

Geneva Pharmaceuticals, Inc.
Drug Regulatory Affairs
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4237
Fax +1 303 438 4600
Internet: Beth.Brannan
@gx.novartis.com

Geneva
PHARMACEUTICALS

Noted. To Sue Z 12/20/01

N/AM

ORIG AMENDMENT

EXPRESS MAIL

MINOR AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

DEC 13 2001

RE: ANDA 65-066: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP **200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml**
Minor Amendment - Response to FDA Letter dated October 18, 2001
Chemistry, Manufacturing, Controls and Labeling

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting a Minor Amendment to its Abbreviated New Drug Application 65-066, Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

A response to your comments is provided in the following letter from Biochemie dated November 30, 2001.

In addition, Geneva is providing 12 copies each of computer-generated final printed container labels. The container labels have been updated to Geneva's current format and logo. No other changes were made. Copies of the final printed labeling for the 200 mg/5 mL and the 400 mg/5 mL Amoxicillin and Clavulanate Potassium for Oral Suspension, USP are provided in **ENCLOSURE 5**. Also provided directly in front of the final printed labeling is a copy of the red-line showing the changes that were made to the label since it was last submitted for approval.

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 14 2001
OGD

12/18/01

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This information is submitted for your review.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures

BB/jep

APPEARS THIS WAY
ON ORIGINAL

Beth Brannan, Director
Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Internet:
Beth.Brannan@gx.novartis.com

Geneva
PHARMACEUTICALS

EXPRESS MAIL

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

N/AM

ORIG AMENDMENT

January 23, 2002

RE: ANDA 65-066: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml
Telephone Amendment – Response to FDA Call Received January 9, 2002

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 65-066 for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone call received from Mark Anderson (FDA) dated January 9, 2002. In this call, Mr. Anderson raised two questions. A summary of these questions, as well as a response from Geneva is provided below.

FDA Question #1:
In your December 13, 2001, letter, why did you mention new dosages? Do you want them reviewed or were they provided for informational purposes? Adding these new dosages will not be considered a CBE submission, but rather a prior approval supplement.

Geneva's Response:
The new dosages were included for informational purposes only, and will be submitted for approval at a later date.

FDA Question #2:
In FDA's May 1, 2001, letter, we asked that the microbial count test be added to the stability protocol. It was added and submitted in your July 19, 2001, response, but was removed from the protocol submitted in your December 13, 2001, response. Please explain.

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Geneva's Response:
Please note that we have two stability commitments for the suspensions: one for the dry powder and one for the Ready-for-Use suspension. Only the stability protocol for the Ready-for-Use suspension contained the microbial count test parameter since this test can only be done on the reconstituted solution.

In our amendment filed December 13, 2001, we only provided the stability protocol for the dry powder, which referenced our new, proposed filling volumes. The stability commitment for the Ready-for-Use suspension was, therefore, not included in the December amendment and has since not been revised.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures
BB/jep

Beth Brannan, Director
Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Internet:
Beth.Brannan@gx.novartis.com

Geneva
PHARMACEUTICALS

UPS EXPRESS MAIL

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

LABELING AMENDMENT

ORIG AMENDMENT
N/AF

FEB 28 2002

RE: ANDA 65-066; Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml
Labeling Amendment – Response to FDA Communicated Received 1/31/02 and 2/23/02

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 65-066; Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml, in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your communication received 1/31/02 and 2/23/02 regarding changes to our labeling. We have made the requested changes and also corrected the reconstitution information on the insert and the 400 mg/5 mL container label. Twelve copies each of the final printed container and insert labeling are provided. Also provided is a red-line showing changes made to the insert and the label since its last submission to the ANDA.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

BB/jep
Enclosures

Beth Brannan, Director
Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Internet:
Beth.Brannan@gx.novartis.com

Geneva
PHARMACEUTICALS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/Am

MAY 0 8 2002

RE: ANDA 65-066: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml
Telephone Amendment – Response to FDA Call Received May 6, 2002

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 65-066 for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone call received from Mark Anderson (FDA) and Susan Zuk (FDA) dated May 6, 2002. In this call, Mr. Anderson and Ms. Zuk made two requests. A summary of these requests, as well as a response from Geneva is provided below.

FDA Request #1:

Please add dissolution specifications to finished product release and stability requirements. The dissolution conditions were proposed by FDA in a letter from the division of Bioequivalaece.

Geneva's Response:

Biochemie has added the dissolution specifications to its finished product release and stability requirements. Provided is a copy of the updated finished product release specifications (i.e. Control Procedure No. 5189.9) and an updated Post-Approval Commitment which indicates dissolution testing will be done on the Powder for Oral Suspension and Ready-for-Use Suspension.

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FDA Request #2:

There is no in-process test for [redacted] Please provide us with a commitment and specifications for [redacted] testing.

Geneva's Response:

Biochemie has committed to performing [redacted] on future batches of Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml. Enclosed is a copy of their commitment with proposed specifications.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures
BB/jep

Beth Brannan, Director
Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Internet:
Beth.Brannan@gx.novartis.com

Geneva
PHARMACEUTICALS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

ORIG AMENDMENT
N|AM

MAY 17 2002

RE: ANDA 65-066: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml
Telephone Amendment – Correction to [redacted] Commitment Page

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 65-066 for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone call between Jean Pederson (Geneva) and Mark Anderson (FDA) dated May 17, 2002. In this call, Mr. Anderson was informed that the [redacted] Commitment page that was provided to them in a Telephone Amendment dated May 8, 2002, contained incorrect specification ranges. The ranges did not allow for the overages in the Amoxicillin and the Clavulanic Acid. This page has been corrected and is being submitted for review.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

BBran

Beth Brannan, Director
Drug Regulatory Affairs

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BB/jep

Beth Brannan, Director
Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438-4237
Fax +1 303 438-4600
Internet:
Beth.Brannan@gx.novartis.com

Geneva
PHARMACEUTICALS

N/Rm

ORIG AMENDMENT

Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

MAY 31 2002

RE: ANDA 65-066; Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml
Telephone Amendment – Post Approval Commitments

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 65-066; Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml, in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a telephone conversation between Mark Anderson (FDA), Richard Aimes (FDA) and Beth Brannan (Geneva) on Tuesday, May 28th, 2002. During this conversation, it was discussed that the ANDA batch for Amoxicillin and Clavulanate Potassium for Oral Suspension, USP, 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml was manufactured using Clavulanate Potassium manufactured by Biochemie in Austria and that production size batches of Clavulanate Potassium will be made by Biochemie SpA in Rovereto, Italy. In response to this change, Geneva commitments to providing the following information in a CBE-0 once the product is approved:

1. Provide Certificates of Analysis from 3 batches of the clavulanate potassium manufactured at the old and new manufacturing site.
2. Put the first batch of Amoxicillin and Clavulanate Potassium for Oral Suspension, USP, 200 + 28.5 mg/5 ml and 400 + 57 mg/5 ml manufactured up on accelerated stability.
3. Provide comparative dissolution data from the ANDA bio batch versus the first batch of the finished product manufactured using the new site API.
4. Provide accelerated stability data on the Bio Batch of the finished drug product, versus the accelerated stability data on the first commercial batch of the finished drug product.

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We also commit to putting the first commercial batch into the room temperature stability program and providing the results in the annual report, as the data become available.

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Overall, we will provide data to show that the clavulanate potassium manufactured by Biochemie in Austria is equivalent to that manufacturing by Biochemie SpA in Rovereto, Italy.

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Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan/jep

Beth Brannan, Director
Drug Regulatory Affairs

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