CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-189

Name: Amoxicillin and Clavulanate Potassium Tablets USP 250 mg/125 mg (base)

Sponsor: Sandoz Inc.

Approval Date: August 23, 2005

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APPLICATION NUMBER:

ANDA 65-189

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APPLICATION NUMBER:

ANDA 65-189

APPROVAL LETTER

ANDA 65-189

AUG 23 2005

Sandoz Inc.
Attention: Beth Brannan
Director, Drug Regulatory Affairs
2555 W. Midway Blvd.
Broomfield, CO 80038

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated August 22, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg (base).

Reference is also made to your amendments dated April 12, and December 22, 2004; and January 20, March 29, April 13, May 25, and June 14, 2005.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Augmentin Tablets, 250 mg/125 mg (base), of GlaxoSmithKline). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

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

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

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

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

8/23/05

cc: ANDA 65-189
Division File
Field Copy
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Approved Electronic Labeling Located at:

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8/23/05

F/T by

APPROVAL

Conc satisfactory.
8/10/05.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

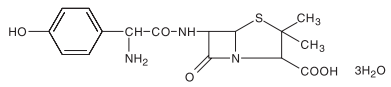
ANDA 65-189

LABELING

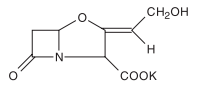
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Amoxicillin and Clavulanate Potassium Tablets and other antibacterial drugs, Amoxicillin and Clavulanate Potassium Tablets should be used only to treat or prevent infections that are proven or strongly suspected to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

DESCRIPTION

Amoxicillin and Clavulanate Potassium Tablets are an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the ß-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. 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 has the following structural formula:



Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a ß-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of ß-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated ß-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$, 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 has the following structural formula:



Each film coated tablet for oral administration contains 250 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt. Each Amoxicillin and Clavulanate Potassium Tablet 250 mg/125 mg contains 0.63 mEq potassium.

Inactive Ingredients: cetyl alcohol, colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulphate, sodium starch glycolate, talc, titanium dioxide and triethyl citrate.

CLINICAL PHARMACOLOGY

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

Mean* amoxicillin and clavulanate potassium pharmacokinetic parameters are shown in the table below:

Dose† and regimen	AUC_{0-24} (mcg·hr/mL)		C_{max} (mcg/mL)	
amoxicillin/ clavulanate potassium	amoxicillin (±S.D.)	clavulanate potassium (±S.D.)	amoxicillin (±S.D.)	clavulanate potassium (±S.D.)
250 mg/125 mg q8h	26.7 ± 4.56	12.6 ± 3.25	3.3 ± 1.12	1.5 ± 0.70
500 mg/125 mg q12h	33.4 ± 6.76	8.6 ± 1.95	6.5 ± 1.41	1.8 ± 0.61
500 mg/125 mg q8h	53.4 ± 8.87	15.7 ± 3.86	7.2 ± 2.26	2.4 ± 0.83
875 mg/125 mg q12h	53.5 ± 12.31	10.2 ± 3.04	11.6 ± 2.78	2.2 ± 0.99

* Mean values of 14 normal volunteers (n=15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.
† Administered at the start of a light meal.

Amoxicillin serum concentrations achieved with Amoxicillin and Clavulanate Potassium Tablets are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half-life of amoxicillin after the oral administration of Amoxicillin and Clavulanate Potassium Tablets is 1.3 hours and that of clavulanic acid is 1 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 a single Amoxicillin and Clavulanate Potassium 250 mg/125 mg and 500 mg/125 mg Tablet.

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

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

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

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

The formulation of amoxicillin and clavulanic acid in Amoxicillin and Clavulanate Potassium Tablets protects amoxicillin from degradation by ß-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other ß-lactam antibiotics. Thus, Amoxicillin and Clavulanate Potassium Tablets possess the properties of a broad-spectrum antibiotic and a ß-lactamase inhibitor.

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

Gram-Positive Aerobes:

Staphylococcus aureus (ß-lactamase and non-ß-lactamase-producing)**.

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

Gram-Negative Aerobes:

Enterobacter species (Although most strains of *Enterobacter* species are resistant in vitro, clinical efficacy has been demonstrated with Amoxicillin and Clavulanate Potassium Tablets in urinary tract infections caused by these organisms.)

Escherichia coli (ß-lactamase and non-ß-lactamase-producing)

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

Klebsiella species (All known strains are ß-lactamase-producing)

Moraxella catarrhalis (ß-lactamase and non-ß-lactamase-producing)

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

Amoxicillin/clavulanic acid exhibits in vitro minimal inhibitory concentrations (MICs) of 2 mcg/mL or less against most (≥90%) strains of *Streptococcus pneumoniae*#; MICs of 0.06 mcg/mL or less against most (≥90%) strains of *Neisseria gonorrhoeae*; MICs of 4 mcg/mL or less against most (≥90%) strains of staphylococci and anaerobic bacteria; and MICs of 8 mcg/mL or less against most (≥90%) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

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

Gram-Positive Aerobes:

*Enterococcus faecalis**

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

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

*Streptococcus pneumoniae**/**

*Streptococcus pyogenes**/**

viridans group *Streptococcus**/**

Gram-Negative Aerobes:

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

*Neisseria gonorrhoeae** (ß-lactamase and non-ß-lactamase-producing)

*Proteus mirabilis** (ß-lactamase and non-ß-lactamase-producing)

Anaerobic Bacteria:

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

Fusobacterium species (ß-lactamase and non-ß-lactamase-producing)

Peptostreptococcus species**

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

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

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

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

RECOMMENDED RANGES FOR AMOXICILLIN/ CLAVULANIC ACID SUSCEPTIBILITY TESTING

For Gram-Negative Enteric Aerobes:

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

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

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

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

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

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

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard amoxicillin/clavulanate potassium powder should provide the following MIC values:

Microorganism	MIC Range (mcg/mL)*
Escherichia coli ATCC 25922	2 to 8
Escherichia coli ATCC 35218	4 to 16
Enterococcus faecalis ATCC 29212	0.25 to 1
Haemophilus influenzae ATCC 49247	2 to 16
Staphylococcus aureus ATCC 29213	0.12 to 0.5
Streptococcus pneumoniae ATCC 49619	0.03 to 0.12

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

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

RECOMMENDED RANGES FOR AMOXICILLIN/ CLAVULANIC ACID SUSCEPTIBILITY TESTING

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

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

For Other Organisms Except *S. pneumoniae*[b] and N. *gonorrhoeae*[c]:

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

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

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

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

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

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

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

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	19 to 25
Escherichia coli ATCC 35218	18 to 22
Staphylococcus aureus ATCC 25923	28 to 36

INDICATIONS AND USAGE

Amoxicillin and Clavulanate Potassium Tablets are indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections – caused by ß-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

Otitis Media – caused by ß-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

Sinusitis – caused by ß-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

Skin and Skin Structure Infections – caused by ß-lactamase-producing strains of *S. aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections – caused by ß-lactamase-producing strains of *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.

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

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

Bacteriological studies, to determine the causative organisms and their susceptibility to Amoxicillin and Clavulanate Potassium Tablets, should be performed together with any indicated surgical procedures.

CONTRAINDICATIONS

Amoxicillin and Clavulanate Potassium Tablets are contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Amoxicillin and Clavulanate Potassium Tablets.

WARNINGS

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Amoxicillin and Clavulanate Potassium Tablets, and has ranged in severity from mild to life-threatening; therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a

toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

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

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

PRECAUTIONS

General: While Amoxicillin and Clavulanate Potassium Tablets possess the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

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

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

Prescribing Amoxicillin and Clavulanate Potassium Tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with Amoxicillin and Clavulanate Potassium Tablets may result in increased and prolonged blood levels of amoxicillin. Coadministration of probenecid cannot be recommended.

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

In common with other broad-spectrum antibiotics, Amoxicillin and Clavulanate Potassium Tablets may reduce the efficacy of oral contraceptives.

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

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

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

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

Mutagenesis: The mutagenic potential of Amoxicillin and Clavulanate Potassium Tablets was investigated in vitro with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and in vivo with mouse micronucleus tests and a dominant lethal test. All were negative apart from the in vitro mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.

Impairment of Fertility: Amoxicillin and Clavulanate Potassium Tablets at oral doses of up to 1,200 mg/kg/day (5.7 times the maximum human dose, 1,480 mg/m^2/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Teratogenic Effects: Pregnancy (Category B). Reproduction studies performed in pregnant rats and mice given Amoxicillin and Clavulanate Potassium Tablets at oral dosages up to 1,200 mg/kg/day, equivalent to 7,200 and 4,080 mg/m^2/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to Amoxicillin and Clavulanate Potassium Tablets. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions; however, it is not known whether the use of Amoxicillin and Clavulanate Potassium Tablets in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with Amoxicillin and Clavulanate Potassium Tablets may be associated with an increased risk of necrotizing enterocolitis in neonates.

Nursing Mothers: Ampicillin-class antibiotics are excreted in the milk; therefore, caution should be exercised when Amoxicillin and Clavulanate Potassium Tablets are administered to a nursing woman.

ADVERSE REACTIONS

Amoxicillin and Clavulanate Potassium Tablets are generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. 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.

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

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

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

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

Renal: Interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported (See **OVERDOSAGE**).

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

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

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occured in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

OVERDOSAGE

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

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

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

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

Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis. (See DOSAGE AND ADMINISTRATION for recommended dosing for patients with impaired renal function.)

DOSAGE AND ADMINISTRATION

Since both the Amoxicillin and Clavulanate Potassium 250 mg/125 mg and 500 mg/125 mg Tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two Amoxicillin and Clavulanate Potassium 250 mg/125 mg Tablets are not equivalent to one Amoxicillin and Clavulanate Potassium 500 mg/125 mg Tablet; therefore, two Amoxicillin and Clavulanate Potassium 250 mg/125 mg Tablets should not be substituted for one Amoxicillin and Clavulanate Potassium 500 mg/125 mg Tablet.

Dosage

Adults: The usual adult dose is one Amoxicillin and Clavulanate Potassium 500 mg/125 mg Tablet every 12 hours or one Amoxicillin and Clavulanate Potassium 250 mg/125 mg Tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one Amoxicillin and Clavulanate Potassium 875 mg/125 mg Tablet every 12 hours or one Amoxicillin and Clavulanate Potassium 500 mg/125 mg Tablet every 8 hours.

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/min. should not receive the 875 mg/125 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/ min. should receive 500 mg/125 mg or 250 mg/125 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/min. glomerular filtration rate should receive 500 mg/125 mg or 250 mg/125 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg/125 mg or 250 mg/125 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

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

Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

Due to the different amoxicillin to clavulanic acid ratios in the Amoxicillin and Clavulanate Potassium Tablets (250 mg/125 mg) versus the Amoxicillin and Clavulanate Potassium Chewable Tablets (250 mg/62.5 mg), the Amoxicillin and Clavulanate Potassium 250 mg/125 mg Tablets should not be used until the pediatric patient weighs at least 40 kg or more.

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

HOW SUPPLIED

Amoxicillin and Clavulanate Potassium Tablets, USP, 250 mg/125 mg: Each film coated tablet, for oral administration, is white, capsule-shaped, and debossed GGN5 on one side and contains 250 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

NDC 0781-1874-31 . . . . . bottles of 30

Amoxicillin and Clavulanate Potassium Tablets, USP are also supplied as:

Amoxicillin and Clavulanate Potassium Tablets, USP, 500 mg/125 mg: Each film coated tablet, for oral administration, is white, oval-shaped, debossed GGN6 on one side and plain on the reverse side, and contains 500 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

NDC 0781-1831-20 . . . . . bottles of 20
NDC 0781-1831-13 . . . . . Unit Dose (10 x 10) 100 film coated tablets

Amoxicillin and Clavulanate Potassium Tablets, USP, 875 mg/125 mg: Each film coated tablet, for oral administration, is white, capsule-shaped, scored and debossed GGN7 on one side and scored on the reverse side, and contains 875 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

NDC 0781-1852-20 . . . . . bottles of 20
NDC 0781-1852-13 . . . . . Unit Dose (4 x 25) 100 film coated tablets

Amoxicillin and Clavulanate Potassium for Oral Suspension, USP, 200 mg/5 mL: as a dry, white powder. Each 5 mL of reconstituted orange-flavored suspension contains 200 mg amoxicillin as the trihydrate and 28.5 mg clavulanic acid as the potassium salt.

NDC 0781-6102-46 . . . . . 100 mL bottle

Amoxicillin and Clavulanate Potassium for Oral Suspension, USP, 400 mg/5 mL: as a dry, white powder. Each 5 mL of reconstituted orange-flavored suspension contains 400 mg amoxicillin as the trihydrate and 57 mg clavulanic acid as the potassium salt.

NDC 0781-6104-46 . . . . . 100 mL bottle

Amoxicillin and Clavulanate Potassium Tablets, USP, (Chewable) 200 mg/28.5 mg: Each chewable tablet is round, pink, cherry-banana flavored, embossed GGN2 on one side and plain on the reverse side, and contains 200 mg amoxicillin as the trihydrate and 28.5 mg clavulanic acid as the potassium salt.

NDC 0781-1619-66 . . . . . Carton of 20 (4 x 5) tablets

Amoxicillin and Clavulanate Potassium Tablets, USP, (Chewable) 400 mg/57 mg: Each chewable tablet is round, pink, cherry-banana flavored, embossed GGN4 on one side and plain on the reverse side, and contains 400 mg amoxicillin as the trihydrate and 57 mg clavulanic acid as the potassium salt.

NDC 0781-1643-66 . . . . . Carton of 20 (4 x 5) tablets

Store at 20°-25 °C (68°-77°F) [See USP Controlled Room Temperature].
Dispense in tightly closed, moisture-proof containers.

CLINICAL STUDIES

Data from two pivotal studies in 1,191 patients treated for either lower respiratory tract infections or complicated urinary tract infections compared a regimen of 875 mg/125 mg Amoxicillin and Clavulanate Potassium Tablets q12h to 500 mg/125 mg Amoxicillin and Clavulanate Potassium Tablets dosed q8h (584 and 607 patients, respectively). Comparable efficacy was demonstrated between the q12h and q8h dosing regimens. There was no significant difference in the percentage of adverse events in each group. The most frequently reported adverse event was diarrhea; incidence rates were similar for the 875 mg/125 mg q12h and 500 mg/125 mg q8h dosing regimens (14.9% and 14.3%, respectively); however, there was a statistically significant difference ($p<0.05$) in rates of severe diarrhea or withdrawals with diarrhea between the regimens: 1% for 875 mg/125 mg q12h dosing versus 2.5% for the 500 mg/125 mg q8h dosing.

In 1 of these pivotal studies, 629 patients with either pyelonephritis or a complicated urinary tract infection (i.e., patients with abnormalities of the urinary tract that predispose to relapse of bacteriuria following eradication) were randomized to receive either 875 mg/125 mg Amoxicillin and Clavulanate Potassium Tablets q12h or 500 mg/125 mg Amoxicillin and Clavulanate Potassium Tablets q8h in the following distribution:

	875 mg/125 mg q12h	500 mg/125 mg q8h
Pyelonephritis	173 patients	188 patients
Complicated UTI	135 patients	133 patients
Total patients	308	321

The number of bacteriologically evaluable patients was comparable between the two dosing regimens. Amoxicillin and Clavulanate Potassium Tablets produced comparable bacteriological success rates in patients assessed 2 to 4 days immediately following end of therapy. The bacteriological efficacy rates were comparable at one of the follow-up visits (5 to 9 days post-therapy) and at a late post- therapy visit (in the majority of cases, this was 2 to 4 weeks post-therapy), as seen in the table below:

	875 mg/125 mg q12h	500 mg/125 mg q8h
2 to 4 days	81%, n=58	80%, n=54
5 to 9 days	58.5%, n=41	51.9%, n=52
2 to 4 weeks	52.5%, n=101	54.8%, n=104

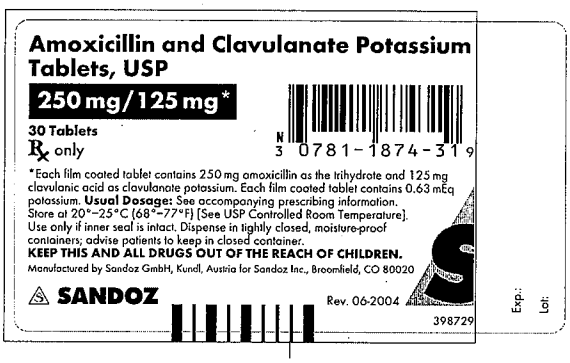
As noted before, though there was no significant difference in the percentage of adverse events in each group, there was a statistically sinificant difference in rates of severe diarrhea or withdrawals with diarrhea between the regimens.

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, December 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24. NCCLS, Villanova, PA, December 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. May 2005

Manufactured by
Sandoz GmbH, Kundl, Austria
for Sandoz Inc., Broomfield, CO 80020



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Print proof is not obligatory to the colours!

SANDOZ	PMP/PMD-textcontrol	
Bestellnr./order no.: 45688203	Materialnr./material no.: 398729-0	Draftnr./draft no.: 981614/1
Farben/colours: PMS 541 PMS 137	PMS 221 varnished area	Stanze
Grafik erstellt von/graphic made by: Kontrolliert von/controlled by:		
Grafik erstellt am/date of artwork: 01.12.2004 7:21 Uhr		
☐ Nochmalige Vorlage/new proof	☐ Druckreif/good for printing	Datum/date ..... Unterschrift/signature .....

Datum ..... Unterschrift .....

Der Auftraggeber bestätigt die Identität des Barcodes:
- Strichkombination
- Zeichenfolge unter dem Barcode

The customer confirms the identity of the barcode:
- combination of lines
- combination of characters below the barcode

Datum/date:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-189

LABELING REVIEWS

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

ANDA Number: 65-189

Dates of Submission: August 22, 2003

Applicant's Name: Sandoz, Inc. [formerly Geneva Pharmaceuticals, Inc.]

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg*
*(the potassium salt of clavulanic acid)

Labeling Deficiencies:

1. CONTAINER: 250 mg/125 mg – 30s

   a. Side Panel

      i. Revise the first paragraph to read as follows:

         ...acid as clavulanate potassium. Each film coated tablet contains ...

      ii. To be consistent with the innovator, revise the "USUAL DOSAGE" statement to read, "See accompanying prescribing information.

      iii. Revise the storage recommendations to read, "Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]".

      iv. If the container for your drug product has an inner seal, add the statement, "Use only if inner seal is intact".

      v. When printing final print, please assure that your container labels are differentiated from your other approved strengths for this drug product by using different colors, boxing and/or some other means.

      vi. Revise to include the new applicant name, "Sandoz, Inc.".

2. INSERT

   a. GENERAL COMMENTS

      i. Update your insert labeling to comply with the Federal Register final rule titled "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use". We refer you to 21 CFR 201.24.

      ii. Throughout the text revise your insert labeling as follows:

         - "Amoxicillin and Clavulanate Potassium Tablets" instead of "Amoxicillin/clavulante potassium"
         - "Amoxicillin and Clavulanate Potassium 250 mg/125 mg Tablets" instead of "Amoxicillin/clavulante potassium 250 mg/125 mg"
         - When referring to other strengths of this drug product include the strengths of

both active ingredients, "Amoxicillin and Clavulanate Potassium ___ mg/___mg Tablets".

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

iv. Use the abbreviation "mcg" for microorganisms instead of "*u*g" throughout the text of the insert.

v. To be consistent with the physical description of the finished dosage form of your tablets, as well as your container labels revise "tablet" to read "film coated tablet".

b. DESCRIPTION

i. Revise the last sentence of the first two paragraphs to read, "... and has the following structural formula:".

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

Each tablet for oral administration contains ___ mg amoxicillin as the trihydrate and ___ mg clavulanic acid as the potassium salt. Each Amoxicillin and Clavulanate Potassium tablet ___ mg/___mg contains ___ mEq potassium.

iii. Please note that the official title of "hydroxypropyl methylcellulose" is "hypromellose". We refer you to USP 26/NF21.

iv. We note that you list [redacted] as an inactive ingredient. However, it is not listed in your composition statement. Please comment.

c. INDICATIONS AND USAGE

i. Revise the first sentence to read, "...are indicated in...".

ii. Urinary Tract Infections

In the second paragraph revise the first sentence to read, "... are indicated only ...".

d. CONTRAINDICATIONS

Revise the first sentence to read, "... are contraindicated in ...".

e. ADVERSE REACTIONS

Revise the first sentence to read, "...are generally well...".

f. DOSAGE AND ADMINISTRATION

Pediatric Patients

In the second paragraph revise "250/125" to read "250 mg/125 mg" and "250/62.5" to read "250 mg/62.5 mg".

e. HOW SUPPLIED

i. In this section you indicate that your tablet is white and scored. This is not consistent with the physical description appearing in your application. Please comment.
In addition, please note that your tablet is required to be the same as the reference listed drug, "not scored".

ii. See comments 1(a)(iii and vi) under CONTAINER.

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

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

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

Adolph Vazza for

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

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert		X	

labeling?			
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths? *See comment to the firm.	*		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?	x		
Has the firm failed to describe the scoring in the HOW SUPPLIED section?*See comment under HOW SUPPLIED.	X*		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	X*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	x		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	

USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as RLD.	*		
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. The firm listed [redacted] as an inactive ingredient in the DESCRIPTION section. However, it is not listed the composition statement.

   Should [redacted] be listed as an inactive ingredient?

2. HOW SUPPLIED

   a. The firm indicates that the tablet is white and scored. This is not consistent with the physical description appearing in the application. We plan to request the firm to comment.

      Do you concur?

   b. We plan to inform the firm that the ANDA tablet is required to be the same as the reference listed drug, "not scored".

      Do you concur?

Chemist response:

I wrote to the firm regarding the listing of [redacted] on the label because this ingredient is not in the product formulation. In their response the firm said that the insert [redacted] I accepted this explanation.

The tablet is not scored.

[S.Z.]

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Reference Listed drug:

   Augmentin®/NDA 50564/S-043/approved 7/25/03

2. The inactive ingredients listed in the DESCRIPTION section are not consistent with the firm's components and composition statements.
   [See comment under DESCRIPTION].
   [B1.1, p. 6483, 6484]

3. Manufacturing Facility:

   Biochemie
   Kundl, Australia
   [Vol. 1.2, p. 6884]

4. Container/Closure:

   White transparent round HDPE round bottle with a CRC
   The closure contains a liner.
   [Vol. 1.2, p. 7047]

5. Storage/Dispense:

   NDA – Store at or below 25°C (77°F). Dispense in original container.

   ANDA – The firm will be requested to revise the storage statement to read, "Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

   USP - Packaging and storage— Preserve in tight containers.

6. Package Size:

   NDA – 30s and unit dose 100s
   ANDA – 30s

7. Patent/Exclusivity: None

8. The firm's physical description of the tablet in the HOW SUPPLIED section is not consistent with the physical description appearing on pages 7180 and 7177 in volume 1.2.
   [See comment to the firm and NOTE TO THE CHEMIST].

9. Scoring configuration:

   RLD – not scored
   ANDA – scored [See comment to the firm and NOTE TO THE CHEMIST]

APPEARS THIS WAY
ON ORIGINAL

Date of Review:	5/5/04
Date of Submission:	8/22/03
Primary Reviewer: Jacqueline Council, Pharm.D.	5-17-04 Date:
Team Leader: Captain Lillie Golson	A. Vega for L. Golson Date: 5-19-04

cc: ANDA: 65-189
DUP/DIVISION FILE
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Review

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

ANDA Number: 65-189

Dates of Submission: January 20, 2005

Applicant's Name: Sandoz, Inc. [formerly Geneva Pharmaceuticals, Inc.]

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg*
*(the potassium salt of clavulanic acid)

Labeling Deficiencies:

1. INSERT

   a. GENERAL COMMENTS

      i. Update your insert labeling to be in accord with the labeling of Augmentin® (amoxicillin/clavulanate potassium) by SmithKlineBeecham Pharmaceuticals, NDA 50-564/S-048 approved August 26, 2004. See attachment.

      ii. We note that your electronic "pdf" insert labeling is not true size. Please revise accordingly.

   b. CLINICAL PHARMACOLOGY /Table

      i. Add "mg" following each amoxicillin strength.

      ii. Replace "q8H" with "q8h".

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

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/cdernew/listserv.html or http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

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

APPEARS THIS WAY
ON ORIGINAL

Attachment: Augmentin® insert labeling

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels:
Carton Labeling:
Unit Dose Blister Label:
Unit Dose Carton Label:
Professional Package Insert Labeling:
Patient Package Insert Labeling:
Auxiliary Labeling:
Revisions needed post-approval:
BASIS OF APPROVAL:
Was this approval based upon a petition? Yes No
What is the RLD on the 356(h) form:
NDA Number:
NDA Drug Name:
NDA Firm:
Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA? Yes No
Was this approval based upon an OGD labeling guidance? Yes No
If yes, give date of labeling guidance:
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or		X	

NDA? If yes, describe in FTR.			
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths? *See comment to the firm.	*		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?	x		
Has the firm failed to describe the scoring in the HOW SUPPLIED section?*See comment under HOW SUPPLIED.	X*		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	X*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition	x		

statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as RLD.	*		
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: [January 20, 2005 submission]

1. In the DESCRIPTION section the firm added the potassium content, "0.63 mEq".

   Is the accurate?

NOTES/QUESTIONS TO THE CHEMIST:

1. The firm listed ' ——— ' as an inactive ingredient in the DESCRIPTION section. However, it is not listed the composition statement.

   Should ——— be listed as an inactive ingredient?

2. HOW SUPPLIED

   a. The firm indicates that the tablet is white and scored. This is not consistent with the physical description appearing in the application. We plan to request the firm to comment.

      Do you concur?

   b. We plan to inform the firm that the ANDA tablet is required to be the same as the reference listed drug, "not scored".

      Do you concur?

Chemist response:

I wrote to the firm regarding the listing of ——— on the label because this ingredient is not in the product formulation. In their response the firm said that the insert ———. I accepted this explanation.

The tablet is not scored.

[S.Z.]

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Reference Listed drug:

   Augmentin® (amoxicillin/clavulanate potassium) by SmithKlineBeecham Pharmaceuticals, NDA 50-564/S-048 approved August 26, 2004.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
   [B1.1, p. 6483, 6484]

   Previous comment to the firm:
   We note that you list "[redacted]" as an inactive ingredient. However, it is not listed in your composition statement. Please comment.
   Firm's response: [1/20/05]
   The originally submitted insert was [redacted] Therefore they deleted [redacted] from the list of inactive ingredients.
   [Also, refer to the chemist response].

3. Manufacturing Facility:

   Biochemie
   Kundl, Australia
   [Vol. 1.2, p. 6884]

4. Container/Closure:

   White transparent round HDPE round bottle with a CRC
   The closure contains a liner.
   [Vol. 1.2, p. 7047]

5. Storage/Dispense:

   NDA – Store at or below 25°C (77°F). Dispense in original container.

   ANDA – The firm will be requested to revise the storage statement to read, "Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

   USP - Packaging and storage— Preserve in tight containers.

6. Package Size:

   NDA – 30s and unit dose 100s
   ANDA – 30s

7. Patent/Exclusivity: None

8. The firm's physical description of the tablet in the HOW SUPPLIED section is consistent with the physical description appearing on pages 7180 and 7177 in volume 1.2.

   Previous response to the firm:

   In this section you indicate that your tablet is white and scored. This is not consistent with the physical description appearing in your application. Please comment.
   In addition, please note that your tablet is required to be the same as the reference listed drug, "not scored".

   Firm's response: [1/20/05 submission].

   Their tablets are not scored and they revised the description in the HOW SUPPLIED section.
   [Also, refer to the chemist response].

9. Scoring configuration:

   RLD – not scored
   ANDA – scored [See comment to the firm and NOTE TO THE CHEMIST]

Date of Review: 3/8/05

Date of Submission: 2/20/05

Primary Reviewer:
Jacqueline Council, Pharm.D. Date: 3-10-05

Team Leader:
Captain Lillie Golson Date: 3/11/05

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cc: ANDA: 65-189
DUP/DIVISION FILE
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Review

~~APPROVAL SUMMARY~~

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

ANDA Number: 65-189

Dates of Submission: March 29, 2005

Applicant's Name: Sandoz, Inc.

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg*
*(the potassium salt of clavulanic acid)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 250 mg/125 mg – 30s
Satisfactory as of the March 29, 2005 submission.
[Electronic location: \\CDSESUBOGD\65189\N_000\2005-03-29]

Professional Package Insert Labeling:
Satisfactory in final print as of the March 29, 2005, submission.
[Insert code: 398730/Rev. March 2005]
[Electronic location: \\CDSESUBOGD\65189\N_000\2005-03-29]

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 50-564

NDA Drug Name: Amoxicillin and Clavulanate Potassium Tablets, USP

NDA Firm: SmithKlineBeecham Pharmaceuticals

Date of Approval of NDA Insert and supplement #S-048 approved August 26, 2004

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: RLD side by sides
Basis of Approval for the Carton Labeling: RLD side by sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?*See comment under HOW SUPPLIED.			
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as RLD.	*		
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. In the DESCRIPTION section the firm added the potassium content, "0.63 mEq".

   Is the accurate?

-----Original Message-----
From: Zuk, Susan
Sent: Thursday, March 10, 2005 10:06 AM
To: Council, Jacqueline
Cc: Park, Sarah Soojung
Subject: RE: 65-189

The firm must have calculated this based on the amount of Potassium Clavulanate they actually add to the tablet rather than based on the label claim. The label claim is 125 mg, but they add 149 mg. This is a permissible overage. So, 149 mg/(237.25 mg/mmol) x 1 mEq K+/mmol = 0.63 mEq. This figure is correct on the label.

Sue

NOTES/QUESTIONS TO THE CHEMIST:

1. The firm listed "[redacted]," as an inactive ingredient in the DESCRIPTION section. However, it is not listed the composition statement.

   Should "[redacted]" be listed as an inactive ingredient?

2. HOW SUPPLIED

   a. The firm indicates that the tablet is white and scored. This is not consistent with the physical description appearing in the application. We plan to request the firm to comment.

      Do you concur?

   b. We plan to inform the firm that the ANDA tablet is required to be the same as the reference listed drug, "not scored".

      Do you concur?

Chemist response:

I wrote to the firm regarding the listing of [redacted] on the label because this ingredient is not in the product formulation. In their response the firm said that the insert [redacted] I accepted this explanation.

The tablet is not scored.
[S.Z.]

NOTE: As of the March 29, 2005 submission
-The firm does not have "[redacted]" in the DESCRIPTION section.
-The firm does not have "scored" tablet in the HOW SUPPLIED section.

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Reference Listed drug:

   Augmentin® (amoxicillin/clavulanate potassium) by SmithKlineBeecham Pharmaceuticals, NDA 50-564/S-048 approved August 26, 2004.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
   [B1.1, p. 6483, 6484]

   Previous comment to the firm:
   We note that you list ' as an inactive ingredient. However, it is not listed in your composition statement. Please comment.
   Firm's response: [1/20/05]
   The originally submitted insert was
   [redacted]
   Therefore they deleted
   [redacted]' from the list of inactive ingredients.
   [Also, refer to the chemist response].

3. Manufacturing Facility:

   Biochemie
   Kundl, Australia
   [Vol. 1.2, p. 6884]

4. Container/Closure:

   White transparent round HDPE round bottle with a CRC
   The closure contains a liner.
   [Vol. 1.2, p. 7047]

5. Storage/Dispense:

   NDA – Store at or below 25°C (77°F). Dispense in original container.

   ANDA – The firm will be requested to revise the storage statement to read, "Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

   USP - Packaging and storage— Preserve in tight containers.

6. Package Size:

   NDA – 30s and unit dose 100s
   ANDA – 30s

7. Patent/Exclusivity: None

8. The firm's physical description of the tablet in the HOW SUPPLIED section is consistent with the physical description appearing on pages 7180 and 7177 in volume 1.2.

Previous response to the firm:

In this section you indicate that your tablet is white and scored. This is not consistent with the physical description appearing in your application. Please comment.
In addition, please note that your tablet is required to be the same as the reference listed drug, "not scored".

Firm's response: [1/20/05 submission].

Their tablets are not scored and they revised the description in the HOW SUPPLIED section.
[Also, refer to the chemist response].

9. Scoring configuration:

RLD – not scored
ANDA – not scored

10. Bioequivalency – Acceptable as of the 8/22/03 submission
[Fasting and fed studies]

Date of Review: 4/26/05

Date of Submission: 3/29/05

Primary Reviewer:
Jacqueline Council, Pharm.D. Date: 4.28.05

Team Leader:
Captain Lillie Golson Date: 5/4/05

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cc: ANDA: 65-189
DUP/DIVISION FILE
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Review

This supercedes the Labeling Approval Summary of 5/4/05

APPROVAL SUMMARY

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

ANDA Number: 65-189

Dates of Submission: June 14, 2005

Applicant's Name: Sandoz, Inc.

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg*
*(the potassium salt of clavulanic acid)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 250 mg/125 mg – 30s
Satisfactory as of the June 14, 2005 submission.
[Electronic location: <<**\\Cdsesubogd1\n65189\N_000\2005-06-14\Container label.pdf**>>

Professional Package Insert Labeling:
Satisfactory in final print as of the June 14, 2005 submission.
[Insert code: 398730/Rev. March 2005]
[Electronic location: <<**\\Cdsesubogd1\n65189\N_000\2005-06-14\Package insert_Bookmarks.pdf**>>

Revisions needed post-approval:
INSERT
At the end of your insert labeling add the following statements:
Clinitest is a registered trademark of Miles, Inc.
Clinistix is a registered trademark of Bayer Corporation

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 50-564

NDA Drug Name: Amoxicillin and Clavulanate Potassium Tablets, USP

NDA Firm: SmithKlineBeecham Pharmaceuticals

Date of Approval of NDA Insert and supplement #S-046 approved May 27, 2004[See FTR#1]
#S-047 approved August 30, 2004

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: RLD side by sides
Basis of Approval for the Carton Labeling: RLD side by sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	

Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?*See comment under HOW SUPPLIED.			
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as RLD.	*		
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. In the DESCRIPTION section the firm added the potassium content, "0.63 mEq".

   Is the accurate?

-----Original Message-----
From: Zuk, Susan
Sent: Thursday, March 10, 2005 10:06 AM
To: Council, Jacqueline
Cc: Park, Sarah Soojung
Subject: RE: 65-189

The firm must have calculated this based on the amount of Potassium Clavulanate they actually add to the tablet rather than based on the label claim. The label claim is 125 mg, but they add 149 mg. This is a permissible overage. So, 149 mg/(237.25 mg/mmol) x 1 mEq K+/mmol = 0.63 mEq. This figure is correct on the label.

Sue

NOTES/QUESTIONS TO THE CHEMIST:

1. The firm listed [redacted] as an inactive ingredient in the DESCRIPTION section. However, it is not listed the composition statement.

   Should '[redacted]' be listed as an inactive ingredient?

2. HOW SUPPLIED

   a. The firm indicates that the tablet is white and scored. This is not consistent with the physical description appearing in the application. We plan to request the firm to comment.

      Do you concur?

   b. We plan to inform the firm that the ANDA tablet is required to be the same as the reference listed drug, "not scored".

      Do you concur?

Chemist response:

I wrote to the firm regarding the listing of [redacted] on the label because this ingredient is not in the product formulation. In their response the firm said that the insert [redacted] I accepted this explanation.

The tablet is not scored.
[S.Z.]

NOTE: As of the March 29, 2005 submission
-The firm does not have '[redacted]' in the DESCRIPTION section.
-The firm does not have "scored" tablet in the HOW SUPPLIED section.

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Reference Listed drug:

   Augmentin® (amoxicillin/clavulanate potassium) by SmithKlineBeecham Pharmaceuticals, NDA 50-564/S-046 approved May 27, 2004 and S-047 approved August 30, 2004.

   Note: S-046 was used for the revisions to the ADVERSE REACTIONS and OVERDOSAGE sections.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
   [B1.1, p. 6483, 6484]

   Previous comment to the firm:
   We note that you list " ——— " as an inactive ingredient. However, it is not listed in your composition statement. Please comment.
   Firm's response: [1/20/05]
   The originally submitted insert
   [———
   Therefore they deleted ———— from the list of inactive ingredients.
   [Also, refer to the chemist response].

3. Manufacturing Facility:

   Biochemie [New company name: Sandoz]
   Kundl, Australia
   [Vol. 1.2; p. 6884]

4. Container/Closure:

   White transparent round HDPE round bottle with a CRC
   The closure contains a liner.
   [Vol. 1.2, p. 7047]

5. Storage/Dispense:

   NDA – Store at or below 25°C (77°F). Dispense in original container.

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

   USP - Packaging and storage— Preserve in tight containers.

6. Package Size:

NDA – 30s and unit dose 100s
ANDA – 30s

7. Patent/Exclusivity: None

8. The firm's physical description of the tablet in the HOW SUPPLIED section is consistent with the physical description appearing on pages 7180 and 7177 in volume 1.2.

Previous response to the firm:

In this section you indicate that your tablet is white and scored. This is not consistent with the physical description appearing in your application. Please comment.
In addition, please note that your tablet is required to be the same as the reference listed drug, "not scored".

Firm's response: [1/20/05 submission].

Their tablets are not scored and they revised the description in the HOW SUPPLIED section.
[Also, refer to the chemist response].

9. Scoring configuration:

RLD – not scored
ANDA – not scored

10. Bioequivalency – Acceptable as of the 8/22/03 submission
[Fasting and fed studies]

Date of Review: 6/28/05

Date of Submission: 6/14/05

Primary Reviewer: Jacqueline Council, Pharm.D. Date: 7-27-05

Team Leader: Captain Lillie Golson Date: 7/27/05

---

cc: ANDA: 65-189
DUP/DIVISION FILE
V:\FIRMSNZ\SANDOZ\LTRS&REV\65189.apl.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-189

CHEMISTRY REVIEWS

ANDA 65-189

Amoxicillin and Clavulanate Potassium Tablets, USP 250/125 mg

Geneva Pharmaceuticals, Inc.

Susan Zuk
Chemistry Division II, OGD

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-189

2. REVIEW #: 1

3. REVIEW DATE: 11/20/03

4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original ANDA	8/22/03

7. NAME & ADDRESS OF APPLICANT:

Name:	Geneva Pharmaceuticals, Inc.
Address:	2555 W. Midway Blvd. Broomfield, CO 80038
Representative:	Beth Brennan
Telephone:	(303) 438-4237

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: none
b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Potassium (Film-Coated) Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The basis for submission is the reference listed drug Augmentin 250 manufactured by GlaxoSmithKline Beecham, NDA #50-564. There are no unexpired patents or exclusivities for this product.

10. PHARMACOL. CATEGORY: antibiotic

11. DOSAGE FORM: solid oral tablets

12. STRENGTH/POTENCY: 250 mg/125 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

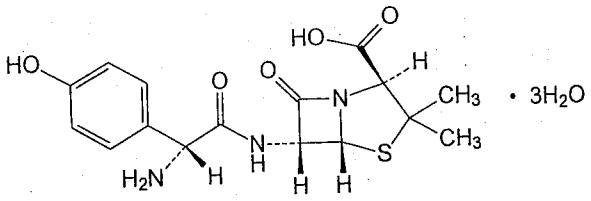
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

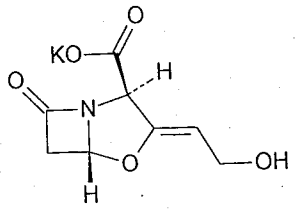
____X_Not a SPOTS product

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

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



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



17. RELATED/SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
13764	II	Biochemie S.A. Spain	Amoxicillin Trihydrate	3	A	6/28/03	Reviewer Y. Pan
14679	II	Biochemie S.p.A. Italy	Clavulanate Potassium	3	A	5/15/03	Reviewer S. Zuk
	IV			4			
	III			3, 4	A	4/18/96	
	III			3	A	4/29/02	
	III			3	A	4/25/02	
	III			3	A	5/27/03	
	III			3	A	5/28/03	
	III			3	A	8/5/03	
	III			3	A	10/8/02	
	III			3	A	1/10/01	

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-189

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is not recommended for approval.

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

II. Summary of Chemistry Assessments

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

The drug substances are amoxicillin supplied as amoxicillin trihydrate and clavulanic acid supplied as clavulanate potassium. Amoxicillin is a semi-synthetic antibiotic related to penicillin. Clavulanic acid is a fermentation product that acts as a B-lactamase inhibitor.

The drug product is a film-coated tablet containing the 250 mg of amoxicillin and 125 mg of clavulanic acid along with the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, sodium starch glycolate, microcrystalline cellulose, triethyl citrate, hypromellose, talc, ———————————. and titanium dioxide. The maximum proposed commercial batch size is ——— tablets. One exhibit batch of ——— tablets was manufactured for the ANDA.

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

Amoxicillin + Clavulanate Potassium Film-Coated Tablets USP, 250 + 125 mg are indicated for the treatment of infections caused by susceptible organisms. The typical dosage is one tablet every 8 hours. The drug product is supplied in bottles of 30 tablets.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA was found to be deficient in the following areas:

1. composition statement
2. COA from suppliers and manufacturer
3. Calculation of active in batch records
4. Identification of ownership
5. Analytical methods
6. Release test results
7. Inactive ingredient list on the label

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Susan Zuk/11/20/03 Susan Zuk 12/3/03
Richard Adams/12/1/03 R. C. Adams 12/4/03
Mark Anderson/

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 16 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 65189
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-643/SZUK/11/20/03 Susan Zuk 12/3/03

HFD-643/RADAMS/12/1/03 R. C. Adams 12/4/03

HFD-617/MANDERSON/12/2/03 M Anderson 12/5/03

F/T by: EW 12/3/03

V:\FIRMSAM\GENEVA\LTRS&REV\65189NA.R01

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 65-189

Amoxicillin and Clavulanate Potassium Tablets, USP 250/125 mg

Geneva Pharmaceuticals, Inc.

Susan Zuk
Chemistry Division II, OGD

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-189

2. REVIEW #: 2

3. REVIEW DATE: 4/26/04

4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original ANDA	8/22/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	3/5/04 response to 12/5/03 deficiency letter
Telephone Amendment	4/21/04 response to 3/18/04 Tecon

7. NAME & ADDRESS OF APPLICANT:

Name: Geneva Pharmaceuticals, Inc.

Address: 2555 W. Midway Blvd.
Broomfield, CO 80038

Representative: Beth Brennan

Telephone: (303) 438-4237

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: none
b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Potassium (Film-Coated) Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The basis for submission is the reference listed drug Augmentin 250 manufactured by GlaxoSmithKline Beecham, NDA #50-564. There are no unexpired patents or exclusivities for this product.

10. PHARMACOL. CATEGORY: antibiotic

11. DOSAGE FORM: solid oral tablets

12. STRENGTH/POTENCY: 250 mg/125 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

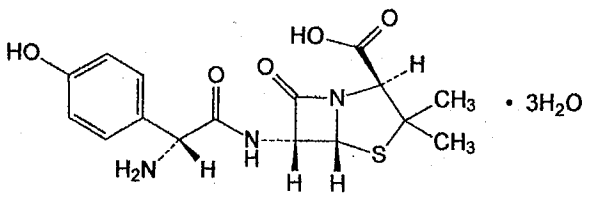
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

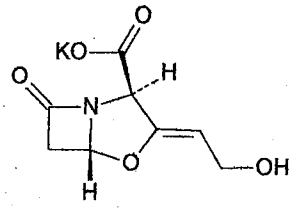
_____X_Not a SPOTS product

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

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



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



17. RELATED/SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
13764	II	Biochemie S.A. Spain	Amoxicillin Trihydrate	3	A	6/28/03	Reviewer Y. Pan
14679	II	Biochemie S.p.A. Italy	Clavulanate Potassium	3	A	2/4/04	Reviewer S. Zuk
	IV			4			
	III			3, 4	A	4/18/96	
	III			3	A	4/29/02	
	III			3	A	4/25/02	
	III			3	A	5/27/03	
	III			3	A	5/28/03	
	III			3	A	8/5/03	
	III			3	A	10/8/02	
	III			3	A	1/10/01	

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Acceptable		M. Makay
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-189

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability Approval is recommended.

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

II. Summary of Chemistry Assessments

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

The drug substances are amoxicillin, supplied as amoxicillin trihydrate and clavulanic acid, supplied as clavulanate potassium. Amoxicillin is a semi-synthetic antibiotic related to penicillin. Clavulanic acid is a fermentation product that acts as a B-lactamase inhibitor.

The drug product is a film-coated tablet containing the 250 mg of amoxicillin and 125 mg of clavulanic acid along with the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, sodium starch glycolate, microcrystalline cellulose, triethyl citrate, hypromellose, talc, ——————————— and titanium dioxide. The maximum proposed commercial batch size is ——— tablets. One exhibit batch of ——— tablets was manufactured for the ANDA.

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

Amoxicillin + Clavulanate Potassium Film-Coated Tablets USP, 250 + 125 mg are indicated for the treatment of infections caused by susceptible organisms. The typical dosage is one tablet every 8 hours. The drug product is supplied in bottles of 30 tablets.

C. Basis for Approvability or Not-Approval Recommendation

Approval is recommended once the Labeling Division completes their review and EER is acceptable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Susan Zuk/4/26/04
Richard Adams/ R-C. adams 4/27/04
Mark Anderson/

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 17 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

ANDA 65189
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-643/SZUK/4/26/04

HFD-643/RADAMS/ R. C. Adams 4/27/04

HFD-617/MANDERSON/

F/T by:

V:\FIRMSAM\GENEVA\LTRS&REV\65189AP.R02

TYPE OF LETTER: ANDA Approval

ANDA 65-189

Amoxicillin and Clavulanate Potassium Tablets, USP 250/125 mg

Sandoz, Inc.

Susan Zuk
Chemistry Division II, OGD

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-189

2. REVIEW #: 2a

3. REVIEW DATE: 6/8/04

4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original ANDA	8/22/03
Minor Amendment	3/5/04, response to 12/5/03 deficiency letter
Telephone Amendment	4/21/04, response to 3/18/04 Tecon

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment	6/2/04, response to 4/28/04 Tecon

7. NAME & ADDRESS OF APPLICANT:

Name: Geneva Pharmaceuticals, Inc.
Address: 2555 W. Midway Blvd.
Broomfield, CO 80038
Representative: Beth Brennan
Telephone: (303) 438-4237

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: none
b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Potassium (Film-Coated) Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The basis for submission is the reference listed drug Augmentin 250 manufactured by GlaxoSmithKline Beecham, NDA #50-564. There are no unexpired patents or exclusivities for this product.

10. PHARMACOL. CATEGORY: antibiotic

11. DOSAGE FORM: solid oral tablets

12. STRENGTH/POTENCY: 250 mg/125 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

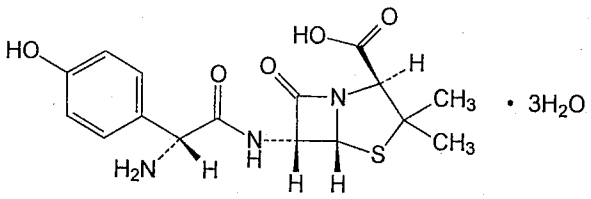
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

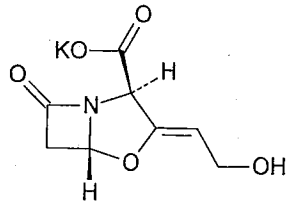
____X_Not a SPOTS product

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

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



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



17. RELATED/SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
13764	II	Biochemie S.A. Spain	Amoxicillin Trihydrate	3	A	6/28/03	Reviewer Y. Pan
14679	II	Biochemie S.p.A. Italy	Clavulanate Potassium	3	A	2/4/04	Reviewer S. Zuk
	IV			4			
	III			3, 4	A	4/18/96	
	III			3	A	4/29/02	
	III			3	A	4/25/02	
	III			3	A	5/27/03	
	III			3	A	5/28/03	
	III			3	A	8/5/03	
	III			3	A	10/8/02	
	III			3	A	1/10/01	

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Acceptable	5/6/04	M. Makay
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-189

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not-Approvable (MINOR)

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

II. Summary of Chemistry Assessments

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

The drug substances are amoxicillin, supplied as amoxicillin trihydrate and clavulanic acid, supplied as clavulanate potassium. Amoxicillin is a semi-synthetic antibiotic related to penicillin. Clavulanic acid is a fermentation product that acts as a B-lactamase inhibitor.

The drug product is a film-coated tablet containing the 250 mg of amoxicillin and 125 mg of clavulanic acid along with the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, sodium starch glycolate, microcrystalline cellulose, triethyl citrate, hypromellose, talc, [redacted] and titanium dioxide. The maximum proposed commercial batch size is [redacted] tablets. One exhibit batch of [redacted] tablets was manufactured for the ANDA.

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

Amoxicillin + Clavulanate Potassium Film-Coated Tablets USP, 250 + 125 mg are indicated for the treatment of infections caused by susceptible organisms. The typical dosage is one tablet every 8 hours. The drug product is supplied in bottles of 30 tablets.

C. Basis for Approvability or Not-Approval Recommendation

Not-Approvable (MINOR)

III. Administrative

A. Reviewer's Signature

Susan Zuk

B. Endorsement Block

Susan Zuk/6/8/04/ Susan Zuk 6/30/04
SFurness/6/28/04/ M. Scott Furness 6/30/04
MAnderson/ RWGyllen for MAnderson 6/30/04

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 17 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2A

ANDA 65189
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-643/SZUK/6/8/04/ [signature] 6/30/04

HFD-643/SFURNESS/6/28/04/ [signature] 6/30/04

HFD-617/MANDERSON/ [signature] for MAnderson 6/30/04

F/T by: RTN/06/30/04

V:\FIRMSAM\SANDOZ\LTRS&REV\65189NA.R02a

TYPE OF LETTER: Not-Approvable (MINOR)

ANDA 65-189

Amoxicillin and Clavulanate Potassium Tablets, USP 250/125 mg

Sandoz, Inc.

Susan Zuk
Chemistry Division III, OGD

Table of Contents

Chemistry Review Data Sheet

1. ANDA 65-189

2. REVIEW #: 3

3. REVIEW DATE: 2/22/05

4. REVIEWER: Susan Zuk

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original ANDA	8/22/03
Minor Amendment	3/5/04, response to 12/5/03 deficiency letter
Telephone Amendment	4/21/04, response to 3/18/04 Tecon
Telephone Amendment	6/2/04, response to Tecon 4/28/04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	12/22/04, response to deficiency letter 6/30/04

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz, Inc.
Address:	2555 W. Midway Blvd. Broomfield, CO 80038
Representative:	Beth Brennan
Telephone:	(303) 438-4237

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: none
b) Non-Proprietary Name (USAN): Amoxicillin and Clavulanate Potassium (Film-Coated) Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The basis for submission is the reference listed drug Augmentin 250 manufactured by GlaxoSmithKline Beecham, NDA #50-564. There are no unexpired patents or exclusivities for this product.

10. PHARMACOL. CATEGORY: antibiotic

11. DOSAGE FORM: solid oral tablets

12. STRENGTH/POTENCY: 250 mg/125 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

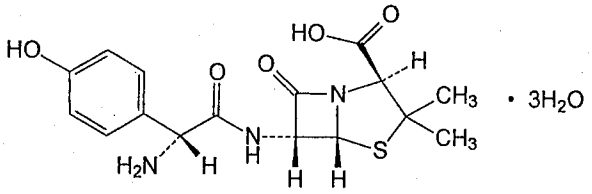
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

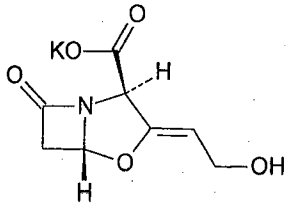
____X_Not a SPOTS product

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

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



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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
13764	II	Biochemie S.A. Spain	Amoxicillin Trihydrate	3	A	9/2/04	Reviewer Y. Pan
14679	II	Biochemie S.p.A. Italy	Clavulanate Potassium	3	A	2/4/04	Reviewer S. Zuk
	IV			4			
	III			3, 4	A	4/18/96	
	III			3	A	4/29/02	
	III			3	A	4/25/02	
	III			3	A	5/27/03	
	III			3	A	5/28/03	
	III			3	A	8/5/03	
	III			3	A	10/8/02	
	III			3	A	1/10/01	

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	1/31/05	S. Adams
Methods Validation	NA		
Labeling	Acceptable	7/27/05	J. Council
Bioequivalence	Acceptable	5/6/04	M. Makay
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-189

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended.

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

II. Summary of Chemistry Assessments

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

The drug substances are amoxicillin, supplied as amoxicillin trihydrate and clavulanic acid, supplied as clavulanate potassium. Amoxicillin is a semi-synthetic antibiotic related to penicillin. Clavulanic acid is a fermentation product that acts as a B-lactamase inhibitor.

The drug product is a film-coated tablet containing the 250 mg of amoxicillin and 125 mg of clavulanic acid along with the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, sodium starch glycolate, microcrystalline cellulose, triethyl citrate, hypromellose, talc, ———————————— and titanium dioxide. The maximum proposed commercial batch size is ——— tablets. One exhibit batch of ———tablets was manufactured for the ANDA.

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

Amoxicillin + Clavulanate Potassium Film-Coated Tablets USP, 250 + 125 mg are indicated for the treatment of infections caused by susceptible organisms. The typical dosage is one tablet every 8 hours. The drug product is supplied in bottles of 30 tablets.

C. Basis for Approvability or Not-Approval Recommendation

All disciplines are acceptable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Susan Zuk/2/22/05 Susan Zuk 8/18/05

Scott Furness/2/24/05 S.H. Liu 8/18/05

~~Ryan Nguyen~~/ L. Kim 8/18/05

C. CC Block

Redacted 16 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: N/A

APPEARS THIS WAY
ON ORIGINAL

ANDA 65189
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-643/SZUK/2/22/05/ 8/8/05

HFD-630/SLIU/ S.H.Liu 8/8/05

HFD-617/LKIM/ 8/8/05

F/T by: EW 8/4/05

V:\FIRMSNZ\SANDOZ\LTRS&REV\65189AP.R03

TYPE OF LETTER: ANDA Approval

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-189

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-189
Drug Product Name	Amoxicillin and Clavulanate Potassium Tablets, USP
Strength	250/125 mg
Applicant Name	Geneva Pharmaceuticals, Inc.
Address	Broomfield, Colorado
Submission Date(s)	August 22, 2003
Amendment Date(s)	N/A
Reviewer	Moheb H. Makary
First Generic	No
File Location	V:\FIRMSAM\GENEVA\LTRS&REV\65189N0803.doc

I. Executive Summary

This submission consisted of two BE studies, one under fasting and the other nonfasting conditions and dissolution data on the test and reference products. The studies conducted on the 250/125 mg tablets comparing them with Augmentin^R tablets, 250/125 mg, of GlaxoSmithKline. The study design for each of the BE studies is a two-way, crossover study in normal male and female subjects (n=42 each study). Statistical analyses of the plasma concentration data for amoxicillin and clavulanic acid demonstrate bioequivalence in both studies.

For the fasting BE study, amoxicillin results (point estimate, 90% CI) are: $LAUC_t$ of 92.97, 89.6-96.5%; $LAUC_i$ of 93.0, 89.63-96.49% and LCmax of 98.56, 92.6-104.91%. Clavulanic acid results (point estimate, 90% CI) are: $LAUC_t$ of 106.87, 96.69-118.12%; $LAUC_i$ of 106.24, 96.20-117.33% and LCmax of 109.59, 99.09-121.19%.

For the nonfasting BE study, amoxicillin results (point estimate, 90% CI) are: $LAUC_t$ of 93.55, 89.02-98.32%; $LAUC_i$ of 93.54, 89.06-98.25% and LCmax of 90.99, 83.93-98.64%. Clavulanic acid results (point estimate, 90% CI) are: $LAUC_t$ of 99.63, 85.12-116.60%; $LAUC_i$ of 99.75, 86.00-115.70% and LCmax of 98.50, 82.66-117.39%.

The product meets the USP dissolution specifications. The application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Amoxicillin and Clavulanate Potassium Tablets, 250/125 mg
Reference Product	Augmentin® (amoxicillin and clavulanate potassium) tablets, 250/125 mg
RLD Manufacturer	GlaxoSmithKline
NDA No.	50564
RLD Approval Date	August 6, 1984
Indication	It is indicated in the treatment of lower respiratory tract infections, ottis media, sinusitis, skin and skin structure infections, and urinary tract infections.

B. PK/PD Information

Bioavailability	Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of the drug product.
Food Effect	Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While the drug product can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state.
Tmax	1.4 and 1 hours for amoxicillin and clavulanic acid, respectively.
Excretion	Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours.
Half-life	1-1.5 hours for both amoxicillin and clavulanic acid
Relevant OGD or DBE History	Currently, Geneva Pharmaceuticals holds an approved application (AADA #65064-Sandoz) for the 500 mg/125 tablet strength.
Agency Guidance	BA/BE General Guidance
Drug Specific Issues (if any)	None

C. Contents of Submission

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

D. Pre-Study Bioanalytical Method Validation

	Parent	Parent
Analyte name	Amoxicillin	Clavulanic Acid
Internal Standard	[redacted]	[redacted]
Method description	LC-MS/MS	LC-MS/MS
QC range (ug/mL)	0.06 to 10	0.05 to 8.00
Standard curve range (ug/mL)	0.02 to 10	To ?
Limit of quantitation (ug/mL)	0.02	0.05
Average recovery of Drug (%)	103.7	89.6
Average Recovery of Int. Std (%)	104.4	98.4
QC Intraday precision range (%)	2.1 to 9.1	0.7 to 2.6
QC Intraday accuracy range (%)	93.9-105.0	99.5 to 106.8
QC Interday precision range (%)	3.6 to 9.2	2.7 to 5.4
QC Interday accuracy range (%)	95.7 to 106.7	98.7 to 106.2
Bench-top stability (hrs)	4	4
Stock stability (days)	NR	NR
Processed stability (hrs)	120	120
Freeze-thaw stability (cycles)	3	3
Long-term storage stability (days)	90	90
Dilution integrity	98%	101.2%
Specificity	Yes	Yes
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes
20% Validation Chromatograms included (Y/N)	Yes	Yes
Random or Serial Selection of Chrom	Serial	Serial

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	02285
Study Design	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	46
No. of subjects completing	44
No. of subjects analyzed	42 as per protocol
Subjects (Healthy or Patients?)	Healthy subjects
Sex(es) included (how many?)	Male:26 Female:20
Test product	Amoxicillin and Clavulanate Potassium Tablets
Reference product	Augmentin® (amoxicillin and clavulanate potassium) tablets
Strength tested	250/125 mg
Dose	1x250/125 mg tablet

Summary of Statistical Analysis (Amoxicillin)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	92.97%	89.58-96.50%
AUC∞	93.00%	89.63-96.49%
Cmax	98.56%	92.60-104.91%
Summary of Statistical Analysis (Clavulanic Acid)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	106.87%	96.69-118.2%
AUC∞	106.24%	96.20-117.33%
Cmax	109.59%	99.09-121.19%

Reanalysis of Study Samples Additional information in Appendix, Table 6 and Table 17				
Reason why assay was repeated	**Number of samples reanalyzed**		**Number of recalculated values used after reanalysis**	
	Actual number	**% of total assays**	**Actual number**	**% of total assays**
Sample below quantification limit (amoxicillin)	17	1.125	Same	Same
Samples which did not fit in the plasma vs. time curve (Clavulanic Acid)	2	0.1324	Same	Same
Total	19	1.25	Same	Same

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

2. Single-dose Fed Bioequivalence Study

Study No.	02286
Study Design	A single-dose, two-period, two-treatment, two- sequence crossover
No. of subjects enrolled	46
No. of subjects completing	46
No. of subjects analyzed	42 as per protocol
Subjects (Healthy or Patients?)	Healthy subjects
Sex(es) included (how many?)	Male 26 Female 16
Test product	Amoxicillin and Clavulanate Potassium Tablets
Reference product	Augmentin® (amoxicillin and clavulanate potassium) tablets
Strength tested	250/125 mg
Dose	1x250/125 mg tablet

Summary of Statistical Analysis (Amoxicillin)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	93.55%	89.02-98.32%
AUC∞	93.54%	89.06-98.25%
Cmax	90.99%	83.93-98.64%

Summary of Statistical Analysis (Clavulanic Acid)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	99.63%	85.12-116.60%
AUC∞	99.75%	86.00-115.70%
Cmax	98.50%	82.66-117.39%

Reanalysis of Study Samples Additional information in Appendix, Table 6 and Table 17				
Reason why assay was repeated	**Number of samples reanalyzed**		**Number of recalculated values used after reanalysis**	
	Actual number	**% of total assays**	**Actual number**	**% of total assays**
System errors (amoxicillin)	2	0.13	Same	Same
Sample preparation error (amoxicillin)	1	0.066	Same	Same
Peak interference (amoxicillin)	1	0.066	Same	Same
Sample which fit not in the plasma vs. time curve (amoxicillin)	1	0.066	Same	Same
Sample preparation error (Clavulanic Acid)	1	0.006	Same	Same
Samples which did not fit in the plasma vs. time curve (Clavulanic Acid)	5	0.33	Same	Same
Total	11	0.72	Same	Same

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

F. Formulation

Location in appendix	Section IV.B, Page 28
Are inactive ingredients within IIG limits?	Yes
If yes, list ingredients outside of limits	
If a tablet, is the product scored?	Yes
If yes, which strengths are scored?	
Is scoring of RLD the same as test?	No
Is the formulation acceptable?	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	USP
Medium	Water
Volume (mL)	900
USP Apparatus type	2
Rotation (rpm)	75
Firm's proposed specifications	Amoxicillin: NLT 85% (Q) of the labeled amount of amoxicillin in the dosage form is dissolved in 30 minutes. Clavulanic Acid: NLT 80% (Q) of the labeled amount of clavulanic acid in the dosage form is dissolved in 30 minutes.
USP-recommended specifications	Same as above
F2 metric calculated?	N/A
Is method acceptable?	Yes

H. Waiver Request(s)

N/A

I. Deficiency Comments

None

J. Recommendations

1. The bioequivalence study conducted under fasting conditions by Geneva Pharmaceuticals, Inc. on its amoxicillin/clavulanate potassium 250 /125 mg tablets, lot #120472, comparing it to Augmentin® 250/125 mg tablets, lot #Tb1838, manufactured by GlaxoSmithKline is acceptable to the Division of Bioequivalence. The study demonstrates that Geneva's amoxicillin/clavulanate potassium 250 /125 mg tablets are bioequivalent to the reference product, Augmentin® 250/125 mg tablets manufactured by GlaxoSmithKline.

2. The bioequivalence study conducted under nonfasting conditions by Geneva Pharmaceuticals, Inc. on its amoxicillin/clavulanate potassium 250 /125 mg tablets, lot #120472, comparing it to Augmentin® 250/125 mg tablets, lot #Tb1838, manufactured by GlaxoSmithKline is acceptable to the Division of Bioequivalence. The study demonstrates that Geneva's amoxicillin/clavulanate potassium 250 /125 mg tablets are bioequivalent to the reference product, Augmentin® 250/125 mg tablets manufactured by GlaxoSmithKline.

3. The dissolution testing conducted by the firm on its test product is acceptable. The dissolution testing should be conducted in 900 mL of water at 37^0C using apparatus 2 (paddle) at 75 rpm. The test product should meet the following specifications:

Amoxicillin: NLT 85% (Q) of the labeled amount of amoxicillin in the dosage form is dissolved in 30 minutes.
Clavulanic acid: NLT 80% (Q) of the labeled amount of clavulanic acid in the dosage form is dissolved in 30 minutes.

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

The Division of chemistry should note that the test product is scored, whereas the reference product is not scored. The sponsor should be requested to match the unscoring pattern of the RLD. The firm should submit dissolution data comparing its newly manufactured unscored tablets with the RLD unscored tablets.

Moheb H. Makary

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

Dhariwal. 5/6/2004

Kuldeep R. Dhariwal, Ph.D
Team Leader, Review Branch IV
Division of Bioequivalence

Dale P. Conner 5/6/04

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

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	02285
Study Title	A single center, open, randomized, two-way, two-period, two-sequence crossover study of the bioequivalence of 250 mg amoxicillin and 125 mg clavulanic acid of Amox C FCT 250+125 mg film-coated tablets (Test) and Augmentin® 250 mg tablets (Reference) each given as a single oral dose to 46 healthy male and/or female volunteers in the fasting state.
Clinical Site	[redacted]
Principal Investigator	[redacted] M.D.
Study/Dosing Dates	Period 1: December 23, 2002 Period 2: January 06, 2003
Analytical Site	[redacted]
Analytical Director	[redacted] Ph.D.
Analysis Dates	January 31, 2003 to February 12, 2003
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	50

Treatment ID	Test	Reference
Test or Reference	T	R
Product Name	Amoxicillin/Clavulanate Potassium Tablets	Augmentin^{R} Tablets
Manufacturer	Geneva Pharmaceuticals, Inc.	GlaxoSmithKline
Batch/Lot No.	120472	TB1838
Manufacture Date	11/2002	N/A
Expiration Date	N/A	06/04
Strength	250/125 mg	250/125 mg
Dosage Form	Tablets	Tablets
Batch Size		N/A
Production Batch Size		N/A
Potency	98.0/100.8%	101.6/96.8%
Content Uniformity (mean, %CV)	99.2/101.3%	NR
Formulation	See Appendix Section B	
Dose Administered	1x250/125 mg tablet	1x250/125 mg tablet
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	N/A
Washout Period	14 days
Randomization Scheme	AB for subjects #2, 5, 6, 7, 10, 12, 13, 15, 17, 19, 20, 22, 27, 29, 30, 31, 34, 35, 38, 40, 41, 43, 45 and BA for the rest of subjects.
Blood Sampling Times	Prior to dosing and at 0.25,0.50,0.75,1.0,1.25,1.50,1.75,2.0,2.25,2.50, 3.0, 4.0, 5.0, 6.0, 8.0, 10 and 12 hours after dosing
Blood Volume Collected/Sample	1x7 mL
Blood Sample Processing/Storage	Under conditions with minimal UV exposure
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours pre-dose and 6 hours post-dose.
Length of Confinement	From at least 11 hours pre-dose to 12 hours post-dose.
Safety Monitoring	Subjects were instructed to inform the study physician and /or nurses of any adverse events that occurred during the study.

Comments on Study Design:

The study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	95.65
Mean	33	Mean	67.5	18-40	67.4	Male	65.2	Afr. Amer.	0
SD	11	SD	10.8	41-64	32.6	Female	34.8	Hispanic	4.35
Range	18-54	Range	51.6-89	65-75	0			Asian	0
				>75	0			Others	0

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
14	Positive urine drug test	Prior to period 2	No
15	Fainting	After period 1	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Runny nose	3	0
Abdominal pain	1	1
High level of potassium	0	2
Fainting	1	0
Soft Stools	2	0
Dizziness	1	1
Vaginal infection	0	1
Pain (back or both thighs)	0	1
Nausea	0	1
Vomiting	1	0
Feels confused	0	1
Headache	1	1
Total:	10	9

Table 4 Protocol Deviations

No significant deviations from the protocol were documented.

Comments on Dropouts/Adverse Events/Protocol Deviations:

The firm has indicated that fainting of subject #15 was unrelated to study drug. The adverse events occurred with similar frequency for both treatments.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Amoxicillin										
QC Conc. (mcg/mL)	0.0546	0.518	2.67	8.17	20.5						
Inter day Precision (%CV)	7.3	6.8	6.5	5.8	5.3						
Inter day Accuracy (%)	98.9	103.6	102.2	101.2	98.3						
Cal. Standards Conc. (mcg/mL)	0.02	0.04	0.06	0.13	0.26	0.52	1.26	2.52	4.96	7.48	9.97
Inter day Precision (%CV)	9.2	6.4	6.1	5.9	5	4.9	4	4.4	3.1	2	2.3
Inter day Accuracy (%)	95.3	95.4	100	99.9	101	102	104	103	101	100	98
Linearity Range (range of R^2 values)	0.999										

	Clavulanic Acid								
QC Conc. (mcg/mL)	0.0532	0.505	2.60	7.96					
Inter day Precision (%CV)	7.7	3.8	5.4	5.6					
Inter day Accuracy (%)	98.8	98.1	99	99.3					
Cal. Standards Conc. (mcg/mL)	0.05	0.1	0.2	0.4	1	2	3.96	5.97	7.96
Inter day Precision (%CV)	5.3	3.4	2.0	2.7	2.5	2.2	1.9	2.1	1.8
Inter day Accuracy (%)	100.5	101.5	100	100.3	99	99.3	98.2	99.3	101.6
Linearity Range (range of R^2 values)	0.999								

Comments on Study Assay Quality Control:

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

Comments on Chromatograms: The chromatograms are acceptable.

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

SOP No.	Date of SOP	SOP Title
SOP QA-35	June 2000	[redacted] SOP QA-35

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes

Summary/Conclusions, Study Assays:

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

Amoxicillin

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ug.hr/mL	12.36	31.82	13.15	28.36	0.94
AUC∞	ug.hr/mL	12.44	31.81	13.24	28.39	0.94
Cmax	ug/mL	4.82	35.45	4.897	35.19	0.98
Tmax	hr	1.51		1.73		
T1/2	hr	1.39		1.37		
Kel	1/hr	0.519		0.521		

Clavulanic Acid

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ug.hr/mL	6.85	44.55	6.44	45.87	1.06
AUC∞	ug.hr/mL	7.01	43.77	6.62	44.88	1.06
Cmax	ug/mL	3.23	44.32	2.97	44.30	1.09
Tmax	hr	1.21		1.26		
T1/2	hr	1.15		1.17		
Kel	1/hr	0.614		0.61		

Table 9 Geometric Means and 90% Confidence Intervals (Amoxicillin)

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	11.81	12.71	92.97	89.58-96.50
AUC∞	11.90	12.79	93.00	89.63-96.49
Cmax	4.53	4.60	98.56	92.60-104.91

Geometric Means and 90% Confidence Intervals (Clavulanic Acid)

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	6.27	5.87	106.9	96.69-118.1
AUC∞	6.43	6.06	106.2	96.20-117.33
Cmax	2.93	2.67	109.6	99.09-121.19

Table 10 Additional Study Information (Amoxicillin & Clavulanic Acid)

Root mean square error, AUCt	0.10 (amoxicillin), 0.27 (clavulanic acid)
Root mean square error, Cmax	0.17 (amoxicillin), 0.27 (clavulanic acid)
Ke and AUCi determined for how many subjects?	All subjects
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	N/A

Comments on Pharmacokinetic Analysis:

The 90% confidence intervals for AUCt, AUCi and Cmax are within the acceptable limits of 80-125% for amoxicillin and clavulanic acid.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study is acceptable.

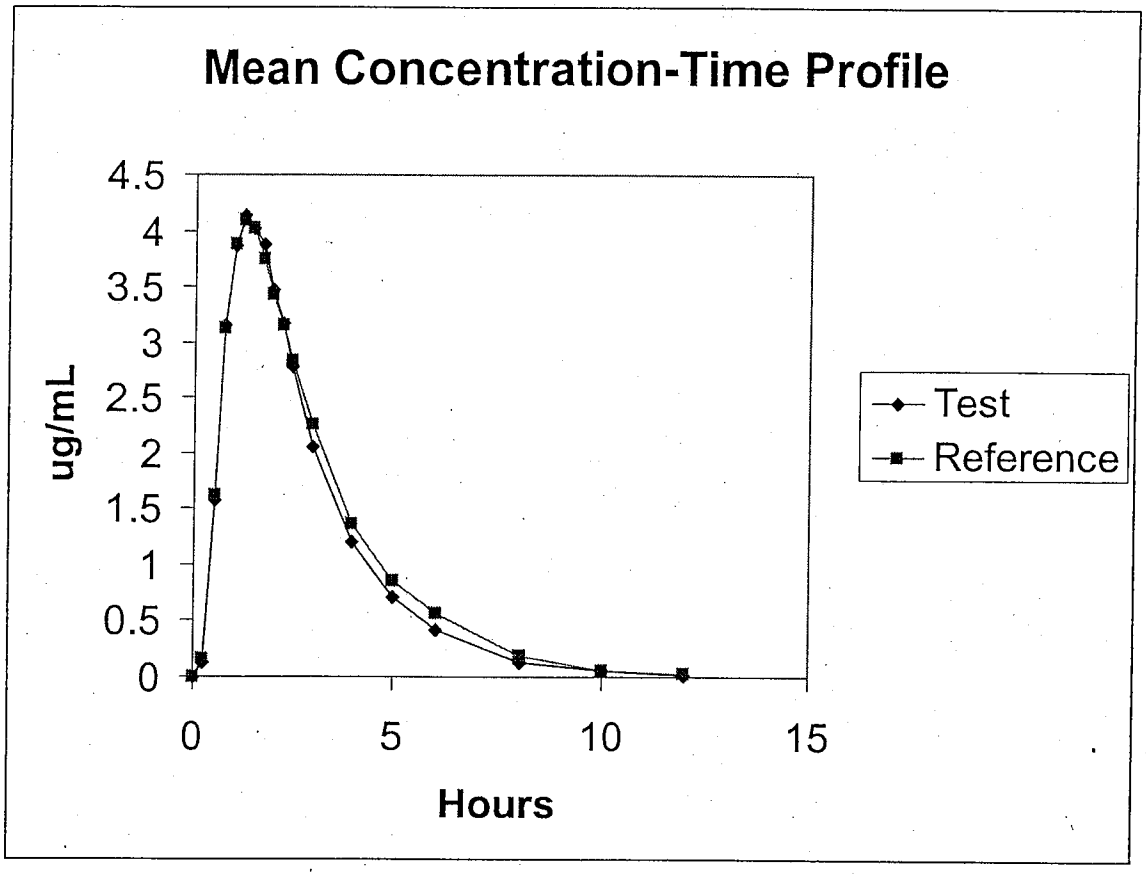
Table 11 Mean Amoxicillin Plasma Concentrations (ug/mL), Single-Dose Fasting Bioequivalence Study

Time	Test (n=42)		Reference (n=42)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	.	0	.	.
0.25	0.12	122.21	0.16	128.70	0.76
0.5	1.58	74.22	1.62	85.28	0.98
0.75	3.15	60.21	3.13	68.41	1.01
1	3.87	47.49	3.88	56.94	1.00
1.25	4.13	41.32	4.09	48.54	1.01
1.5	4.02	36.28	4.03	38.69	1.00
1.75	3.88	39.04	3.74	38.96	1.04
2	3.47	40.51	3.42	40.93	1.01
2.25	3.17	39.57	3.16	43.28	1.00
2.5	2.78	38.49	2.83	42.06	0.98
3	2.06	46.93	2.26	49.55	0.91
4	1.21	66.85	1.37	57.91	0.88
5	0.70	72.90	0.85	67.94	0.83
6	0.42	79.39	0.56	110.95	0.75
8	0.14	82.41	0.19	106.67	0.71
10	0.05	101.15	0.06	100.23	0.90
12	0.02	152.94	0.02	126.01	0.75

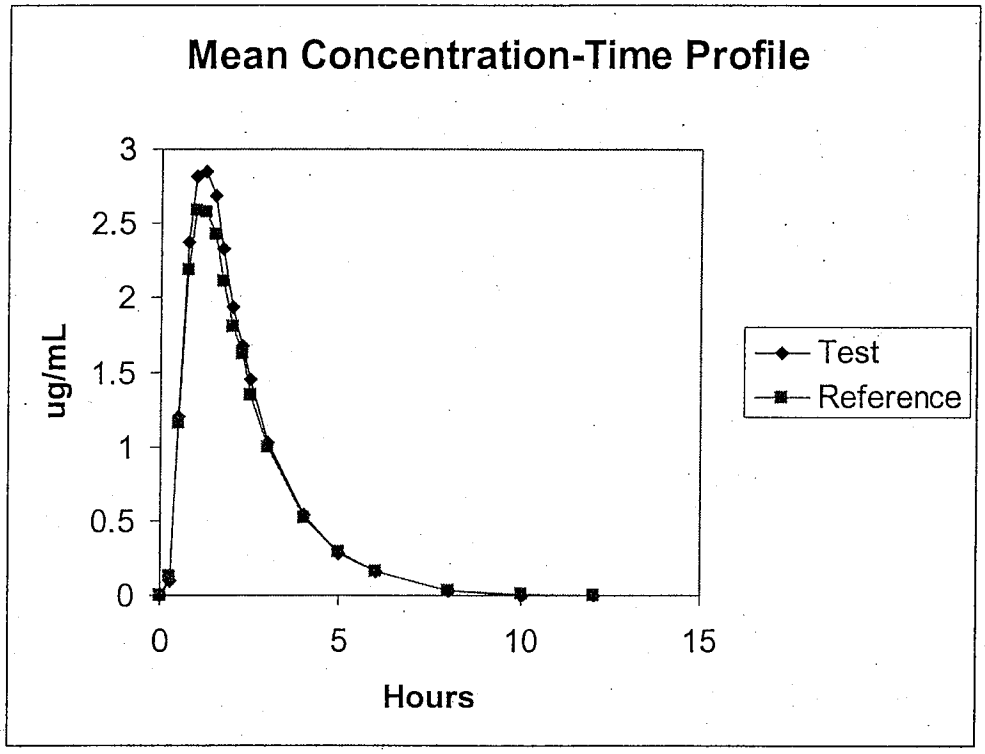
Mean Clavulanic Acid Plasma Concentrations (ug/mL), Single-Dose Fasting Bioequivalence Study

Time	Test (n=42)		Reference (n=42)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	.	0	.	.
0.25	0.10	128.08	0.13	143.11	0.80
0.5	1.20	71.75	1.16	81.27	1.03
0.75	2.37	52.26	2.19	59.57	1.08
1	2.82	40.78	2.59	46.82	1.09
1.25	2.85	37.75	2.58	40.38	1.11
1.5	2.68	50.11	2.42	40.75	1.11
1.75	2.32	51.70	2.11	48.30	1.10
2	1.94	52.77	1.81	52.76	1.07
2.25	1.67	52.18	1.62	66.51	1.03
2.5	1.45	61.44	1.34	67.28	1.08
3	1.03	62.25	1.00	72.30	1.03
4	0.54	59.46	0.52	62.27	1.03
5	0.28	58.93	0.29	64.90	0.97
6	0.16	75.24	0.16	75.95	1.01
8	0.03	140.16	0.03	175.83	1.12
10	0.00	648.07	0.01	379.13	0.35
12	0.00	.	0.00	.	.

Figure 1 Mean Amoxicillin Plasma Concentrations (ug/mL), Single-Dose Fasting Bioequivalence Study



Mean Clavulanic Acid Plasma Concentrations (ug/mL), Single-Dose Fasting Bioequivalence Study



Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	02286
Study Title	A single center, open, randomized, two-way, two-period, two-sequence crossover study of the bioequivalence of 250 mg amoxicillin and 125 mg clavulanic acid of Amox C FCT 250+125 mg film-coated tablets (Test) and Augmentin 250 mg tablets (Reference) each given as a single oral dose to 46 healthy male and/or female volunteers in the fed state.
Clinical Site	[redacted]
Principal Investigator	[redacted] M.D.
Study/Dosing Dates	Period 1: December 21, 2002 Period 2: January 4, 2003
Analytical Site	[redacted]
Analytical Director	[redacted] Ph.D.
Analysis Dates	January 21, 2003 to January 29, 2003
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	38

Treatment ID	Test Product	Reference Product
Test or Reference	T	R
Product Name	Amoxicillin/Clavulanate Potassium Tablets	Augmentin® Tablets
Manufacturer	Geneva Pharmaceuticals, Inc.	GlaxoSmithKline
Batch/Lot No.	120472	TB1838
Manufacture Date	11/2002	N/A
Expiration Date	N/A	06/04
Strength	250/125 mg	250/125 mg
Dosage Form	Tablets	Tablets
Batch Size		N/A
Production Batch Size		N/A
Potency	98.0/100.8%	101.6/96.8%
Content Uniformity	99.2/101.3%	NR
Formulation	See Appendix Section B	
Dose Administered	1x250/125 mg tablet	1x250/125 mg tablet
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	N/A
Washout Period	14 days
Randomization Scheme	AB for subjects #3, 5, 6, 10, 12, 13, 17, 18, 19, 20, 22, 27, 28, 29, 32, 33, 36, 38, 41, 42, 43, and BA for the rest of subjects.
Blood Sampling Times	Prior to dosing and at 0.25,0.50,0.75,1.0,1.25,1.50,1.75,2.0,2.25,2.50, 3.0, 4.0, 5.0, 6.0, 8.0, 10 and 12 hours after dosing
Blood Volume Collected/Sample	Same as fasting study
Blood Sample Processing/Storage	Same as fasting study
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 12**
Length of Fasting before Meal	10 hours pre-dose until 30 minutes prior to dosing when a breakfast was given.
Length of Confinement	From at least 11 hours pre-dose to 12 hours post-dose.
Safety Monitoring	Same as fasting study
Standard FDA Meal Used?	No
If no, then meal is listed in table below	The breakfast consisted of two pats of butter, two large waffles, 32 mL of syrup, 42 g of mild cheddar cheese, 128 g of hash brown potatoes, and 400 mL of whole milk.

Composition of Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat	50%	500
Carbohydrate		
Protein		
Total		1000

Comments on Study Design:

The study design is acceptable.

Clinical Results

Table 12 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	100
Mean	33	Mean	71.5	18-40	78.3	Male	65.2	Afr. Amer.	0
SD	9	SD	11.5	41-64	21.7	Female	34.8	Hispanic	0
Range	19-53	Range	51.4-95.4	65-75				Asian	0
				>75				Others	0

Table 13 Dropout Information

N/A

Table 14 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Low platelet count	0	1
Burning sensation both eyes	0	1
High potassium	0	1
Soft stools	0	1
Headache	0	2
Erythrocytes in urine	1	1
Hot flushes	1	0
Total:	2	7

Table 15 Protocol Deviations

No significant deviations from the protocol were documented.

Comments on Adverse Events/Protocol Deviations:

No serious, severe, or significant adverse events were reported during the study. Most of adverse events were reported as unrelated to the study drug.

b) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Amoxicillin										
QC Conc. (ug/mL)	0.0546	0.518	2.67	8.17	20.5						
Inter day Precision (%CV)	8.2	5.8	5.3	5.4	6.1						
Inter day Accuracy (%)	97.6	99.0	97.3	97.1	94.6						
Cal. Standards Conc. (ug/mL)	0.02	0.04	0.06	0.13	0.26	0.52	1.26	2.52	4.96	7.48	9.97
Inter day Precision (%CV)	9.4	5.8	5.5	4.4	6.5	4.5	4.2	5.1	3.0	2.8	3.5
Inter day Accuracy (%)	99.2	98.3	94.6	102	99	101	103	101	102	99.8	98.2
Linearity Range (range of R^2 values)	0.999										

	Clavulanic Acid								
QC Conc. (ug/mL)	0.0532	0.505	2.60	7.96					
Inter day Precision (%CV)	6.5	4.1	4.9	3.9					
Inter day Accuracy (%)	105	96.0	96	97.9					
Cal. Standards Conc. (ug/mL)	0.05	0.1	0.2	0.4	1	2	3.96	5.97	7.96
Inter day Precision (%CV)	5.8	3.1	2.3	1.8	2.1	1.5	1.2	2.1	1.6
Inter day Accuracy (%)	102.8	101.5	99.8	99.2	98.2	99.2	98.2	99.6	101.6
Linearity Range (range of R^2 values)	0.999								

Comments on Study Assay Quality Control:

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

Comments on Chromatograms:

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
SOP QA-35	June 2000	[redacted] SOP QA-35

Table 18 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

c) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 22and Figure

Amoxicillin

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ug.hr/mL	10.60	18.91	11.20	14.11	0.95
AUC∞	ug.hr/mL	10.66	18.82	11.27	13.96	0.95
Cmax	ug/mL	4.04	34.31	4.29	26.42	0.94
Tmax	hr	2.15		2.27		
T1/2	hr	1.24		1.20		
Kel	1/hr	0.576		0.588		

Clavulanic Acid

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ug.hr/mL	4.36	49.5	4.18	41.5	1.04
AUC∞	ug.hr/mL	4.51	48.1	4.34	40.3	1.04
Cmax	ug/mL	1.98	55.3	1.88	46.4	1.05
Tmax	hr	2.00		2.05		
T1/2	hr	1.06		1.04		
Kel	1/hr	0.675		0.681		

Table 20 Geometric Means and 90% Confidence Intervals

Amoxicillin

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	10.91	11.08	0.94	89.02-98.32
AUC∞	10.44	11.16	0.94	89.06-98.25
Cmax	3.78	4.16	0.91	83.93-98.64

Clavulanic Acid

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	3.75	3.77	1.00	85.12-116.6
AUC∞	3.93	3.94	1.00	86.00-115.70
Cmax	1.65	1.67	0.99	82.66-117.39

Table 21 Additional Study Information

Root mean square error, AUCt	0.135 (amoxicillin), 0.4298(clavulanic acid)
Root mean square error, Cmax	0.219 (amoxicillin), 0.477 (clavulanic acid)
Ke and AUCi determined for how many subjects?	All subjects
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	N/A

Comments on Pharmacokinetic Analysis:

The 90% confidence intervals for AUCt, AUCi and Cmax are within the acceptable limits of 80-125% for amoxicillin and clavulanic acid.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study is acceptable.

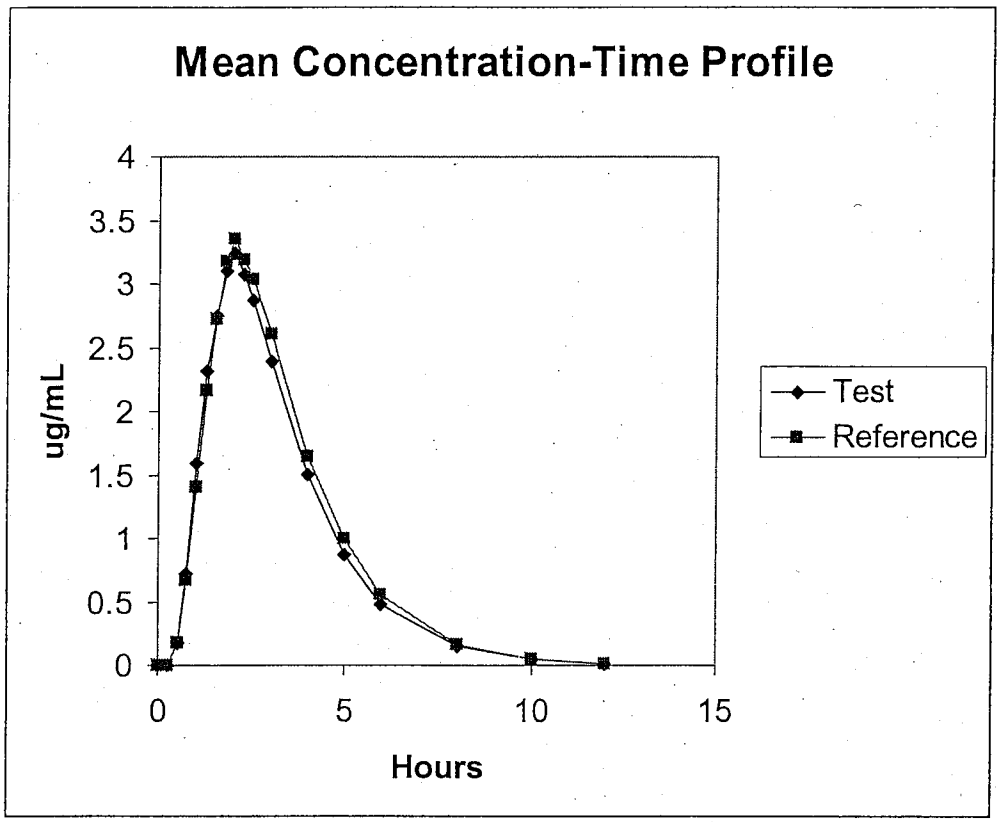
Table 22 Mean Amoxicillin Plasma Concentrations (ug/mL), Single-Dose Fed Bioequivalence Study

Time (hrs)	Test (n=42)		Reference (n=42)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	.	0	0	.
0.25	0.003	21.08	0.004	24.30	0.75
0.5	0.18	56.52	0.18	59.64	1.00
0.75	0.72	82.80	0.67	78.13	1.08
1	1.60	104.13	1.41	98.05	1.14
1.25	2.32	118.63	2.17	114.68	1.07
1.5	2.75	162.03	2.72	146.06	1.01
1.75	3.10	210.84	3.18	199.18	0.98
2	3.25	238.78	3.35	243.28	0.97
2.25	3.07	259.33	3.19	265.65	0.96
2.5	2.87	313.01	3.04	304.08	0.95
3	2.40	328.54	2.60	357.31	0.92
4	1.51	255.20	1.64	235.16	0.92
5	0.87	224.79	1.00	189.27	0.87
6	0.49	201.59	0.56	163.15	0.87
8	0.15	182.23	0.17	185.09	0.87
10	0.05	151.18	0.05	173.23	0.93
12	0.01	78.01	0.01	70.03	1.13

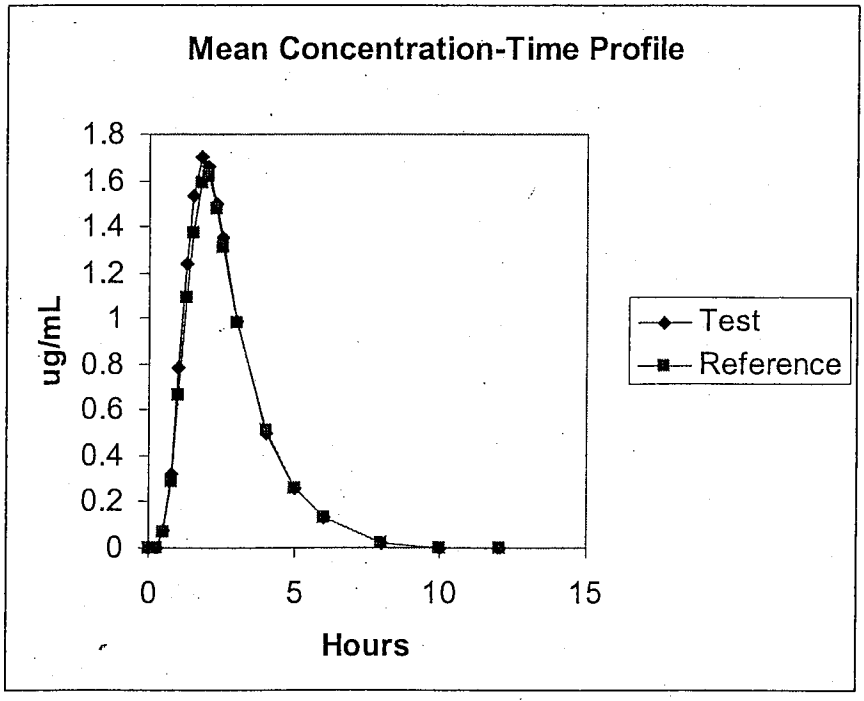
Mean Clavulanic Acid Plasma Concentrations (ug/mL), Single-Dose Fed Bioequivalence Study

Time (hrs)	Test (n=42?)		Reference (n=42?)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	.	0	.	.
0.25	0	.	0.00	15.43	.
0.5	0.08	65.66	0.07	53.06	1.11
0.75	0.32	82.76	0.28	67.15	1.13
1	0.79	92.61	0.66	92.29	1.19
1.25	1.24	105.16	1.09	109.86	1.14
1.5	1.53	135.00	1.38	134.03	1.11
1.75	1.70	165.90	1.59	172.74	1.07
2	1.66	181.32	1.62	198.07	1.03
2.25	1.50	181.76	1.48	210.22	1.02
2.5	1.35	191.61	1.31	230.53	1.03
3	0.99	198.63	0.98	256.55	1.01
4	0.50	199.25	0.51	203.16	0.98
5	0.26	184.61	0.26	177.52	0.97
6	0.14	147.11	0.14	158.61	1.00
8	0.02	53.84	0.02	53.22	1.28
10	0.00	15.43	0	.	.
12	0.00	.	0	.	.

Figure 2 Mean Amoxicillin Plasma Concentrations (ug/mL), Single-Dose Fed Bioequivalence Study



Mean Clavulanic Acid Plasma Concentrations (ug/mL), Single-Dose Fed Bioequivalence Study



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of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW (FORMULATION DATA)

C. Dissolution Data

Table 1

Sampling Time (min)	Test Product, Amoxicillin/Clavulanate Potassium Strength 250/125 mg Lot No. 120472			Reference Product, Augmentin^{R} Strength 250/125 mg Lot No. TB 1838		
	Amoxicillin					
	Mean	%CV	Range	Mean	%CV	Range
10	57.8	18.3	33.9-71.3	62.7	4.8	56.3-67.1
15	83.5	10.8	64.4-93.5	86.2	1.7	84.4-88.4
30	97.3	3.7	90.7-102.4	98.3	1.0	96.7-99.7
	Clavulanic Acid					
	Mean	%CV	Range	Mean	%CV	Range
10	58.7	14.5	39.0-70.5	62.1	4.6	55.9-66.2
15	84.2	9.7	67.2-94.7	83.4	1.5	81.4-85.2
30	98.9	2.7	94.0-102.7	94.6	1.1	92.5-96.6

D. SAS Output

Study	Data	SAS Code	SAS Output
Fasting Study	clav.prn	amoxcod.txt	clavsasoutput.txt
	amox.prn	amoxcod.txt	amoxsasoutput.txt
Fed Study	amoxfed.prn	amoxfedcod.txt	amoxfedsasoutput.txt
	clavfed.prn	clavfedcod.txt	clavfedsasoutput.txt

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-189 APPLICANT: Geneva Pharmaceuticals, Inc.

DRUG PRODUCT: Amoxicillin; Clavulanate Potassium Tablets, USP 250 mg/125 mg

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

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

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

Sincerely yours,

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

CC: ANDA 65-189
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

V:\FIRMSAM\GENEVA\LTRS&REV\65189N0803.doc
Printed in final on 4/30/2004

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader K. Dhariwal 5/6/04
HFD-650/ D. Conner 5/6/04

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 8/22/03

✓ 1. **FASTING STUDY** (STF)
Clinical:
Analytical:

Strengths: 250 mg/125 mg
Outcome: AC

✓ 2. **FOOD STUDY** (STP)
Clinical:
Analytical:

Strengths: 250 mg/125 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 65-189 SPONSOR : Geneva Pharmaceuticals, Inc.
DRUG AND DOSAGE FORM : Amoxicillin and Clavulanate Potassium Tablets USP
STRENGTH(S) : 250 mg /125 mg
TYPES OF STUDIES : Fasting Study & Non-Fasting Study
CINICAL STUDY SITE(S) : [ ]
ANALYTICAL SITE(S) :

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable
WAIVER REQUEST: N/A

DSI INSPECTION STATUS

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

PRIMARY REVIEWER :Moheb H. Makary, Ph.D. BRANCH : IV
INITIAL : MHM DATE : 5/6/04

TEAM LEADER : Kuldeep Dhariwal, Ph.D. BRANCH : IV
INITIAL : KD DATE : 5/6/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : DPC DATE : 5/6/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-189

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

DA # 65-189 Applicant Sandoz Inc.
ug Amoxicillin and Clavulanate Potassium, USP Strength(s) 250/125 mg
tablets

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

REVIEWER: | **DRAFT Package** | **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch

Date 20 May 05 Initials MS
Date 8/23/05 Initials for MS

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 50-564
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked N/A
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Date of latest Labeling Review/Approval Summary
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter:
Comments: no patents/exclusivities ∴ eligible for Full Approval

2. Project Manager, Lisa Kim Team 11
Review Support Branch

Date 5/19/05 Initials LK
Date 8/3/05 Initials LK

Original Rec'd date 8/22/03
Date Acceptable for Filing 8/25/03 ✓
Patent Certification (type) I
Date Patent/Exclus.expires
EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 1/31/05
Date of Office Bio Review 5/6/04
Date of Labeling Approv. Sum 5/4/05
Citizens' Petition/Legal Case Yes ☐ No ☑
Labeling Acceptable Email Rec'd Yes ☑ No ☐
(If YES, attach email from PM to CP coord)
Labeling Acceptable Email filed Yes ☑ No ☐
First Generic Yes ☐ No ☑
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☐ NA
MV Commitment Rcd. from Firm Yes ☐ No ☐

Acceptable Bio reviews tabbed Yes ☑ No ☐
Modified-release dosage form: Yes ☐ No ☑
Suitability Petition/Pediatric Waiver
Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

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

Date
Initials

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments:

Date 8/10/05
Initials

cmc satisfactory.

VIEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date _____
Assoc. Dir. For Chemistry Initials _____
Comments: (First generic drug review)
NA. Multiple ANDAs have been approved for this drug product. Sandoz currently has ANDAs approved for the 500mg and 875mg strengths.

6. Vacant RLD = Augmentin Tablets 250mg/125mg (base) Date _____
Deputy Dir., DLPS GlaxoSmithKline NDA 50-564 (001) Initials _____

7. Peter Rickman Date 8/23/05
Director, DLPS Initials _____
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable ES dated 1/31/05 (verified 8/23/05). No OAI alerts noted. Bioequivalence studies (fasting and non-fasting) found acceptable 6/6 pt. Dissolution data also found acceptable. Bio study test sites have acceptable GCP inspection histories. Office-level biowaiver issued 5/6/04. FPI found acceptable for approval 7/21/05. CMC found acceptable for approval 8/23/05. Methods validation was not required - compendial.

8. Robert L. West Date 8/23/2005
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☐
Comments: There are no unexpired patents or exclusivity listed in the current "Orange Book" for this drug product.
This ANDA is recommended for approval.

9. Gary Buehler Date 8/23/05
Director, OGD Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team NSA Kwok Date 8/23/05
Review Support Branch Initials _____
_____ Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
10:17 Time notified of approval by phone 10:19 Time approval letter faxed
FDA Notification:
8/23/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
8/23/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Approval Letter Faxed to Orange Book Staff @ 301-827-7337: Date/Time: _____

File V:/division/dlps/approvreq9.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-189

CORRESPONDENCE

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 4609
Internet: Beth.Brannan
@gx.novartis.com

Geneva
PHARMACEUTICALS

505(b)(2)
Motion
30 Sept 2003

65-189
N-000

UPS OVERNIGHT MAIL

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

ORIGINAL ANDA
SUBMISSION

AUG 2 2 2003

RE: Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg
Original Abbreviated New Drug Application

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting an Abbreviated New Drug Application for Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg 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 required by 21 CFR 314.94(a)(2), a comprehensive table of contents is provided in each volume which shows the page number of our submission's contents.

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

Contact:	Beth Brannan, Director of Drug Regulatory Affairs
Phone #:	(303) 438-4237
Fax #:	(303) 438-4600
Name:	Geneva Pharmaceuticals, Inc.
Address:	2555 West Midway Boulevard Broomfield, CO 80038

RECEIVED
AUG 2 5 2003
OGD/CDER

Geneva
PHARMACEUTICALS

Attached please find a

[ ]

Enclosed is this package is the blue archival copy (18 volumes) containing the complete ANDA application. The red chemistry review copy (3 volumes) contains the Chemistry, Labeling, Manufacturing and Controls sections. The orange pharmacokinetic review copy (15 volumes) contains bioequivalence information.

The two additional copies of the Methods Validation package are provided in two brown binders. They contain duplicate copies of the raw material and finished product specifications, methods, analytical results and validation reports. Geneva commits to resolve any issues identified in the methods validation process after approval.

The firm has submitted an additional copy of the Chemistry, Manufacturing and Controls section [as required under 314.50 (d)(1)] to the U.S. Food and Drug Administration, Denver District Office.

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

BB/jep

Enclosures

Jean Pederson
Associate

Geneva Pharmaceuticals, Inc.
Development
Drug Regulatory Affairs
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4242
Fax +1 303 438 4600
Internet: jean.pederson
@gx.novartis.com

Geneva
PHARMACEUTICALS

. NEW CORRESP

NC

Fax

Attention: Paras Patel
Office of Generic Drugs
Food and Drug Administration

Fax no. 301-594-1174
Number of pages 3 including cover page

Date 25 September 2003

Concerning ANDA 65-189 for Amoxicillin and Cavulanate Potassium Tablets, USP 250/125 mg

Dear Mr. Patel,

Per your telephone call received September 24, 2003, following you will find a 356h form for ANDA 65-189 for Amoxicillin and Cavulanate Potassium Tablets, USP 250/125 mg, which has been revised to reflect the established USP name as well as the correct holder of the approved reference application.

In addition, I wanted to confirm with you that the grade of hydroxypropyl methylcellulose used in manufacturing this product is the USP grade Hypromellose. — C J - Called

If you have additional questions or concerns, please call me at (303) 438-4242.

Sincerely,

Jean Pederson

Jean Pederson, Sr. Associate
Drug Regulatory Affairs

/jep

ANDA 65-189

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

OCT - 7 2003

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 telephone conversations dated September 24, 2003 and September 26, 2003 and to your correspondence dated September 25, 2003 and September 26, 2003.

NAME OF DRUG: Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg

DATE OF APPLICATION: August 22, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 25, 2003

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

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

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

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

ANDA 65-189
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92
Endorsement:
HFD-615/MShimer,Chief/ RSB _____ date 20 Sept 200
HFD-615/PPatel,CSO _____ date 9/29/03
Word File V:\Firmsam\Geneva\ltrs&rev\65189.ACK
F/T
ANDA Acknowledgment Letter!

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

NEW CORRESP
(NC)

OVERNIGHT 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

OCT 2 4 2003

RE: ANDA 65-189: Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg
Telephone Amendment - Clarification of the ——— Manufacturing Site Address

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting a Telephone Amendment to its Abbreviated New Drug Application 65-189, Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96. Geneva would like to provide clarification of the —— manufacturing site for the ———————

Reference is made to a conversation between Mark Anderson (FDA) and Beth Brannan (Geneva). During this conversation, Mr. Anderson noted that the address provided for —— in the ——————— that was filed in our Original ANDA Submission dated August 22, 2003, was the office address. Mr. Anderson asked that we provide them with the —— manufacturing site address. Therefore, we are providing ——— manufacturing site address for ———. It is as noted below:

[ ]

RECEIVED
OCT 2 7 2003
OGD/CDER

Geneva
PHARMACEUTICALS

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**

Geneva
PHARMACEUTICALS

Beth Brannan, Director
Regulatory Affairs

Geneva Pharmaceuticals, Inc.
2555 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

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

NEW INFORMATION

XS

November 26, 2003

Re: ANDA 65-189 Amoxicillin and Clavulanate Potassium Tablets USP, 250 / 125 mg
New Information – Company Name Change to Sandoz, Inc.

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting new information to its Abbreviated New Drug Application 65-189 for Amoxicillin and Clavulanate Potassium Tablets USP, 250 / 125 mg. Geneva would like to inform you that its name will be changed to Sandoz, Inc., effective December 1, 2003. This is a company name change only; the address remains the same.

Please incorporate this information into our ANDA 65-189 for Amoxicillin and Clavulanate Potassium Tablets USP, 250 / 125 mg and 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.

BBrannan

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures
BB/jep

Beth Brannan, Director
Regulatory Affairs

Sandoz 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

SANDOZ

MA Noted NAP

UPS EXPRESS MAIL

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

WITHDRAWAL
OF _____
NEW CORRESP
MC

MAR - 1 2004

RE: ANDA 65-189; Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg

Withdrawal of _____

Dear Mr. Buehler:

(— MA)

In accord with 21 CFR 314.120, Sandoz Inc. (formerly Geneva Pharmaceuticals, Inc.) requests to withdraw the _____ The purpose of the _____ was to add _____ This withdrawal notice is being submitted without preduce to future filings.

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 yours,

SANDOZ INC.

Beth Brannan/jep

Beth Brannan, Director
Regulatory Affairs

/jep
Enclosures

RECEIVED
MAR - 2 2004
OGD/CDER

2.1

SANDOZ

Beth Brannan, Director
Regulatory Affairs

Sandoz 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

UPS OVERNIGHT MAIL

Gary Buehler, Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockeville, MD 20855

MINOR AMENDMENT

ORIG AMENDMENT
N/AM

MAR - 5 2004

RE: ANDA 65-189; Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg
Minor Amendment – Chemistry Deficiencies
Response to FDA Letter dated December 05, 2003

Dear Mr. Buehler,

In response to your deficiency letter dated December 05, 2003, asking for additional information with regards to the Chemistry, Manufacturing and Controls section we are providing a minor amendment to the ANDA mentioned above.

All items of your letter have been addressed.

A. DEFICIENCIES

1. Please justify the [redacted]

RECEIVED
MAR 0 8 2004
OGD/CDER

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

3/5/2004 SANDOZ LETTER

B. ADDITIONAL INFORMATION

10. Current stability data of the ongoing stability study.

Please find enclosed the updated stability report including the 9 months long term stability data. All results are within the limits.

ENCLOSURE 7

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,

SANDOZ INC.

Beth Brannan/jep

Beth Brannan, Director
Drug Regulatory Affairs

/jep

Enclosures

SANDOZ

Beth Brannan, Director
Regulatory Affairs

Sandoz 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

UPS OVERNIGHT MAIL

Gary Buehler, Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockeville, MD 20855

BIOEQUIVALENCY
TELEPHONE AMENDMENT

ORIG AMENDMENT
N/A3

April 12, 2004

RE: ANDA 65-189; Amoxicillin/Clavulanate Potassium Tablets USP, 250 mg/125 mg
Telephone Amendment – Bioequivalency Deficiency
Submission of Bioequivalency Data Diskettes in SAS Transport Format

Dear Mr. Buehler,

Sandoz, Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 65-189 for Amoxicillin/Clavulanate Potassium Tablets USP, 250 mg/125 mg 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 Aaron Zeigler on March 17, 2004, requesting the diskettes for the Amoxicillin Clavulanate Potassium Tablets USP bioequivalaency study data on a CD in SAS Transport format. In response to this request, we are providing the requested data on the enclosed (1) diskette.

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,

SANDOZ INC.

Beth Brannan, Director
Drug Regulatory Affairs

/jep
Enclosures

RECEIVED
APR 1 3 2004
OGD / CDER

ORIGINAL

1

SANDOZ

Beth Brannan, Director
Drug Regulatory Affairs

Sandoz Inc.
2555 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

ORIG AMENDMENT

N/AM

UPS OVERNIGHT 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

April 21, 2004

RE: ANDA 65-189; Amoxicillin/Clavulanate Potassium Tablets USP, 250 mg/125 mg
Telephone Amendment – Chemistry Deficiencies
Response to Telephone Conversation dated March 18, 2004

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an Amendment to its unapproved Abbreviated New Drug Application 65-189; Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg, 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 and Susan Zuk (FDA) March 18, 2004. Mr. Anderson and Ms. Zuk raised several questions regarding chemistry, manufacturing and control issues. A response to these questions and/or comments is now provided.

A. DEFICIENCIES

1. **In response to FDA question #1, we state that the [redacted] FDA would like us to describe and justify how we come up with this number.**

RECEIVED
APR 22 2004
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Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

4/21/2004 SANDOZ LETTER

SANDOZ

Beth Brannan
Director, Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
Broomfield, CO 80038-0446

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

AM

UPS OVERNIGHT MAIL

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MINOR AMENDMENT – RESPONSE TO CHEMISTRY DEFICIENCIES

RECEIVED
DEC 2 3 2004
OGD / CDER

DEC 2 2 2004

RE: ANDA 65-189; Amoxicillin & Clavulanate Potassium Tablets, USP 250 mg/125 mg
Minor Amendment – Response to Chemistry Deficiencies
Response to FDA Letter dated June 30, 2004

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application 65-189 for Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg, as required by Secion 505 (j) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR Part 314.96.

Reference is made to your letter dated June 30, 2004. A response to the comments raised in this letter is provided below:

A. DEFICIENCIES

1. **In accordance with USP 27, please clarify that you have added a test and acceptance criteria for [redacted] to the release testing protocol for the [redacted].**

Sandoz Response:

[redacted]

ok

European Pharmacopeia, which is identical to the USP method.

ENCLOSURE 1

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

12/22/2004 SANDOZ LETTER

Please find enclosed the revised acceptance criteria and test methods as well as a COA of batch 118115.

ENCLOSURE 5
ENCLOSURE 6

The information is submitted for your review and approval.

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

Sincerely,

Sandoz Inc.

Beth Brannan/jep

Beth Brannan, Director
Regulatory Affairs

/jep

Enclosures

SANDOZ

Beth Brannan
Director, Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

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

ORIG AMENDMENT
N/AF

4UPS OVERNIGHT MAIL

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluataion and Research
Food and Drug Administration
Metro Park North II
Room 150, 7500 Standish Place
Rockeville, MD 20855

LABELING AMENDMENT

N
N

JAN 2 0 2005

RE: ANDA 65-189; Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg
Special Supplement – Changes Being Effected; Revised Labeling

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting a labeling amendment to its Abbreviated New Drug Application 65-189 for Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg in accord with Section 505 (j) of the Federal Food, Drug and Cosmetic Act and in accord with 21 CFR Part 314.96.

Reference is made to your facsimile of May 21, 2004. We have revised our labeling as requested. Please find enclosed a table of contents to locate the appropriate supporting response and documents.

This information is submitted for 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 yours,

Sandoz Inc.

Beth Brannan
Director,Regulatory Affairs

/jep
Enclosures

RECEIVED
JAN 2 1 2005
OGD / CDER

SANDOZ

Beth Brannan
Director, Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
Broomfield, CO 80038-0446

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

UPS OVERNIGHT MAIL

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

LABELING AMENDMENT

ORIG AMENDMENT
M/AF

MAR 2 9 2005

RE: ANDA 65-189, Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg
Labeling Amendment – Response to facsimile of March 14, 2005

Dear Sirs:

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application # 65-189 for **Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg**, as required by Secion 505 (j) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR Part 314.96.

Reference is made to your facsimile of March 14, 2005. A response to the commends raised in your letter is provided on page 3. As requested, however, we have revised our physician insert. Enclosed you will find four copies each of our draft physician insert. Also enclosed is a CD (in FDA's original copy only) containing the electronic labeling.

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,

Beth Brannan/gf

Beth Brannan
Director, Regulatory Affairs

Enclosures

RECEIVED
MAR 3 0 2005
OGD/CDER

SANDOZ

Beth Brannan
Director
Drug Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
Broomfield, CO 80038-0446

Tel: +1 303 438-4237
Fax: +1 303 438-4600
Internet: beth.brannan
@sandoz.com

ORIG AMENDMENT
N/AB

UPS OVERNIGHT MAIL

Mr. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

BIOEQUIVALENCY AMENDMENT

APR 1 3 2005

RE: ANDA 65-189; Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg, Bioequivalency Amendment

Response to Facsimile of February 07, 2005, concerning Amoxicillin Tablets USP, 500 mg and 875 mg (ANDA 65-228)

Dear Mr. Buehler,

Sandoz Inc. is hereby submitting an amendment to its unapproved Abbreviated New Drug Application #65-189 for Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg, 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 Facsimile of February 07, 2005, concerning Bioequivalence Deficiencies for Amoxicillin Tablets USP, 500 mg and 875 mg (ANDA 65-228). As requested in item 3 of this letter, the in-vivo study data, dissolution data and formulation data are provided also for the pending application for Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg (ANDA 65-189). The data are provided in the format specified in the attached template. Please find the respective completed tables enclosed. A separate CD containing the respective files is also enclosed.

RECEIVED
APR 1 5 2005
OGD / CDER

The information is submitted for your review and approval.

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

Sincerely,

Sandoz Inc.

Beth Brannan/gp

Beth Brannan
Director Drug Regulatory Affairs

Enclosures

Beth Brannan
Director

Sandoz Inc.
Drug Regulatory Affairs
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

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

SANDOZ

UPS OVERNIGHT 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

May 25, 2005

ORIG AMENDMENT
N/AM

RE: ANDA 65-189: Amoxicillin and Clavulanate Potassium Tablets USP, 250 mg/125 mg Telephone Amendment – Corrected Formula Composition Page

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting a Telephone Amendment to its Abbreviated New Drug Application 65-189, Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg 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 Jean Pederson (Sandoz) and Lisa Kim (FDA). Ms. Kim noted that a corrected formula composition page for Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg, was previously sent via telefax to Mark Anderson (FDA) on 6/02/04, and that it had not been officially filed to the application. We are, therefore, filing this corrected formula composition page to the application. A footnote (6) was added to the

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,

SANDOZ INC.

Beth Brannan/jep
Beth Brannan, Director
Drug Regulatory Affairs

Enclosures
BB/jep

RECEIVED
MAY 26 2005
OGD / CDER

SANDOZ

Beth Brannan
Director, Regulatory Affairs

Sandoz Inc.
2555 W. Midway Blvd.
Broomfield, CO 80038-0446

Tel: +1 303 438-4237
Fax: +1 303 438-4600
Internet: beth.brannan
@sandoz.com

ORIG AMENDMENT

N/AF

UPS OVERNIGHT MAIL

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

LABELING AMENDMENT

JUN 1 4 2005

RE: ANDA 65-189, Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg
Labeling Amendment – Response to Telephone Conversation of May 23, 2005

Dear Mr. Buehler,

Sandoz Inc., is hereby submitting an amendment to its unapproved Abbreviated New Drug Application # 65-189 for Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg, as required by Secion 505 (j) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR Part 314.96.

Reference is made to a telephone call made to Ms. Jean Pederson (Sandoz) by Jacqueline Council (FDA) on May 23, 2005. During her message, Ms. Council informed Ms. Pederson that a labeling change for Amoxicillin/Clavulanate Potassium Tablets 250 mg/125 mg would be required. A request to remove both the ——————————— from the PRECAUTIONS section was made. Ms. Council indicated the changes could be filed in a labeling amendment to the application.

The physician insert for Amoxicillin and Clavulanate Potassium Tablets, USP 250 mg/125 mg has been revised as instructed. Enclosed you will find a side-by-side comparison of Sandoz old vs. new insert. Also provided are 12 copies each of the final printed insert.

RECEIVED
JUN 1 5 2005
OGD / CDER

In addition to hard copies of our current labeling we have included in electronic format the content of our professional labeling. The electronic format (i.e. CD) containing the content of our professional labeling is provided.

This amendment 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,

Beth Brannan/gp

Beth Brannan
Director, Regulatory Affairs

Enclosures