CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

65-093

Generic Name: Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/ 125 mg

Sponsor: LEK Services, Inc.

Approval Date: November 21, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
65-093

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-093

APPROVAL LETTER

ANDA 65-093

NOV 21 2002

LEK SERVICES, Inc.
Attention: Paul Kleutghen
U.S. Agent for: Lek Pharmaceuticals d.d.
115 North Third Street - Suite 301
Wilmington, NC 28401

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 14, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base). We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated September 2, September 24, October 28, November 4, and November 7, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Augmentin® Tablets, 875 mg, of GlaxoSmithKline). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

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

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

Sincerely yours,

/S/

Gary Buehler 11/24/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-093

Final Printed Labeling

AP

11/21/02

NDC 48866-1001-0

Amoxicillin and Clavulanate Potassium Tablets, USP

875/125 mg

Rx only

AMOXICILLIN, 875 mg
as the trihydrate
CLAVULANIC ACID, 125 mg,
as clavulanate potassium

lek
Manufactured by
Lek Pharmaceuticals d.d.
Verovškova 57, Ljubljana, Slovenia

20 tablets

APPROVED
NOV 1 2002

Each film coated tablet contains 875 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt. Each tablet contains [illegible] mg sodium.
Use only if inner seal is intact.
Store at or below 25°C (77°F).
Dispense in a tight moisture-proof container.
Advise patient to keep in closed container.
Usual Dosage: One tablet every 12 hours.
See prescribing information.

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8 06412 10010 8

Lot No:

Exp. date:

Amoxicillin and Clavulanate Potassium Tablets, USP

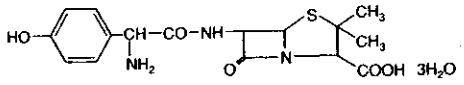
AMOXICILLIN, 500 mg, as the trihydrate and CLAVULANIC ACID, 125 mg, as clavulanate potassium;
AMOXICILLIN, 875 mg, as the trihydrate and CLAVULANIC ACID, 125 mg, as clavulanate potassium

Rx only

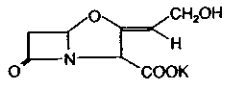
PRESCRIBING INFORMATION

DESCRIPTION

Amoxicillin and Clavulanate Potassium Tablet USP is 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 (*2S, 5R, 6R*)-6-[(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate and may be represented structurally as:



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*)-(*2R,5R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate, and may be represented structurally as:



Each film coated tablet contains 500 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt or 875 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.
In addition, each 500 mg/125 mg and 875 mg/125 mg amoxicillin and clavulanate potassium tablet contains 0.63 mEq potassium.
Inactive Ingredients: Colloidal silicon dioxide, croscarmellose sodium dried, crospovidone dried, ethylcellulose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose dried, polysorbate 80, talc, titanium dioxide, triethyl citrat.

CLINICAL PHARMACOLOGY

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of amoxicillin/clavulanate potassium. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin/clavulanate potassium can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In one study, the relative bioavailability of clavulanate was reduced when amoxicillin/clavulanate potassium was dosed at 30 and 150 minutes after the start of a high fat breakfast. 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.)
250/125 mg q8h	26.7 ± 4.56	12.6 ± 3.25	3.3 ± 1.12	1.5 ± 0.70
500/125 mg q12h	33.4 ± 6.76	8.6 ± 1.95	6.5 ± 1.41	1.8 ± 0.61
500/125 mg q8h	53.4 ± 8.87	15.7 ± 3.86	7.2 ± 2.26	2.4 ± 0.83
875/125 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/clavulanate potassium are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half-life of amoxicillin after the oral administration of amoxicillin/clavulanate potassium is 1.3 hours and that of clavulanic acid is 1.0 hour.
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/clavulanate potassium 250 mg or 500 mg tablet.
Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.
Neither component in amoxicillin/clavulanate potassium is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.
Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and [illegible] 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/clavulanate potassium protects amoxicillin from degradation by ß-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other ß-lactam antibiotics. Thus, amoxicillin/clavulanate potassium possesses 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 the INDICATIONS AND USAGE section.

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

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Amoxicillin and Clavulanate Potassium Tablets, USP
Rx only

676519

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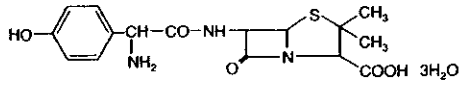
Amoxicillin and Clavulanate Potassium Tablets, USP

Rx only

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 (*2S, 5R, 6R*)-6-[(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate and may be represented structurally as:



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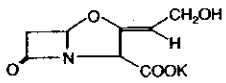

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Inactive Ingredients: Colloidal silicon dioxide, croscarmellose sodium dried, crospovidone dried, ethylcellulose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose dried, polysorbate 80, talc, titanium dioxide, triethyl citrat.

CLINICAL PHARMACOLOGY

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

approximately 1.5 hours after the dose.
[†] Administered at the start of a light meal.

Amoxicillin serum concentrations achieved with amoxicillin/clavulanate potassium are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half-life of amoxicillin after the oral administration of amoxicillin/clavulanate potassium is 1.3 hours and that of clavulanic acid is 1.0 hour.

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The formulation of amoxicillin and clavulanic acid in amoxicillin/clavulanate potassium protects amoxicillin from degradation by ß-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other ß-lactam antibiotics. Thus, amoxicillin/clavulanate potassium possesses 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 the INDICATIONS AND USAGE section.

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/clavulanate potassium in urinary tract infections caused by these organisms.)

Escherichia coli (ß-lactamase and non-ß-lacta-

mase 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 0.5 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 *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin.

GRAM-POSITIVE AEROBES
Enterococcus faecalis[¶]
Staphylococcus epidermidis (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 minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[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.
lowing criteria should be used:

MIC (mcg/mL)	Interpretation
≤ 0.5/0.25	Susceptible (S)
1/0.5	Intermediate (I)
≥ 2/1	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone 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 1.0
Haemophilus influenzae ATCC 49247	2 to 16
Staphylococcus aureus ATCC 29213	0.12 to 0.5
Streptococcus pneumoniae ATCC 49619	0.03 to 0.12

[††]Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.
Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.
Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) disk should be interpreted according to the following criteria:
RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING
For *Staphylococcus*[‡‡] species and *H. influenzae*[#]:

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

For other organisms except *S. pneumoniae*[§] and *N. gonorrhoeae*[^]:

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 broth microdilution method should be used for testing *H. influenzae*. Beta-lactamase negative, ampicillin-resistant strains must be considered resistant to amoxicillin/clavulanic acid.
[§]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.
[^]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 [illegible]
cal 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/clavulanate potassium is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:
Lower Respiratory Tract Infections-caused by ß-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis.*
Otitis Media-caused by ß-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis.*
Sinusitis-caused by ß-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis.*
Skin and Skin Structure Infections-caused by ß-lactamase-producing strains of *Staphylococcus aureus, Escherichia coli* and *Klebsiella* spp.
Urinary Tract Infections-caused by ß-lactamase-producing strains of *Escherichia coli, Klebsiella* spp. and *Enterobacter* spp.
While amoxicillin/clavulanate potassium is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to amoxicillin/clavulanate potassium treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and ß-lactamase-producing organisms susceptible to amoxicillin/clavulanate potassium should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and amoxicillin/clavulanate potassium. (See Microbiology subsection.)
Bacteriological studies, to determine the causative organisms and their susceptibility to amoxicillin/clavulanate potassium, should be performed together with any indicated surgical procedures.
Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to amoxicillin/clavulanate potassium when there is reason to believe the infection may involve any of the ß-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

CONTRAINDICATIONS

Amoxicillin/clavulanate potassium is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of amoxicillin/clavulanate potassium-associated cholestatic jaundice/hepatic dysfunction.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTI-

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.

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

GRAM-POSITIVE AEROBES
Enterococcus faecalis[a]
Staphylococcus epidermidis (ß-lactamase and non-ß-lactamase producing)
Staphylococcus saprophyticus (ß-lactamase and non-ß-lactamase producing)
Streptococcus pneumoniae[a][1]
Streptococcus pyogenes[a][1]
viridans group *Streptococcus*[a][1]
GRAM-NEGATIVE AEROBES
Eikenella corrodens (ß-lactamase and non-ß-lactamase producing)
Neisseria gonorrhoeae[a] (ß-lactamase and non-ß-lactamase producing)
Proteus mirabilis[a] (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[a]

[a]Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to these organisms.
[1]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 minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[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*[a][*] and *Haemophilus* species:

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

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

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

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)[1]
Escherichia coli ATCC 25922	2 to 8
Escherichia coli ATCC 35218	4 to 16
Enterococcus faecalis ATCC 29212	0.25 to 1.0
Haemophilus influenzae ATCC 49247	2 to 16
Staphylococcus aureus ATCC 29213	0.12 to 0.5
Streptococcus pneumoniae ATCC 49619	0.03 to 0.12

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

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

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

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

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

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

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

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

[a]Staphylococci which are resistant to methicillin/ oxacillin must be considered as resistant to amoxicillin/clavulanic acid.
[b] 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.
[c] 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.
[d] 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 techni-

INDICATIONS AND USAGE

Amoxicillin/clavulanate potassium is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections-caused by ß-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis.*

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

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

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

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

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

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

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

CONTRAINDICATIONS

Amoxicillin/clavulanate potassium is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of amoxicillin/clavulanate potassium-associated cholestatic jaundice/hepatic dysfunction.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENI-

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

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

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

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

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

PRECAUTIONS

General:

While amoxicillin/clavulanate potassium possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

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

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

Drug Interactions:

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

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the

administered concurrently.

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

Drug/Laboratory Test Interactions:

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

Mutagenesis:

The mutagenic potential of amoxicillin/clavulanate potassium was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in 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/clavulanate potassium at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 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/clavulanate potassium at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 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/clavulanate potassium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of amoxicillin/clavulanate potassium in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers:

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

ADVERSE REACTIONS

Amoxicillin/clavulanate potassium is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were

particular diarrhea, increased with the higher re ommended dose. Other less frequently reporte reactions include: abdominal discomfort, flat lence and headache.

The following adverse reactions have been repor ed for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, inc gestion, gastritis, stomatitis, glossitis, black "hair tongue, mucocutaneous candidiasis, enterocoliti and hemorrhagic/pseudomembranous colit Onset of pseudomembranous colitis symptom may occur during or after antibiotic treatment. (Se WARNINGS.)

Hypersensitivity Reactions: Skin rashes, pruritu urticaria, angioedema, serum sickness-like rea tions (urticaria or skin rash accompanied by arth tis, arthralgia, myalgia and frequently fever), er thema multiforme (rarely Stevens-Johnso Syndrome) and an occasional case of exfoliativ dermatitis (including toxic epidermal necrolysis have been reported. These reactions may be cor trolled with antihistamines and, if necessary, sys temic corticosteroids. Whenever such reaction occur, the drug should be discontinued, unless th opinion of the physician dictates otherwise. Seriou and occasional fatal hypersensitivity (anaphylac tic) reactions can occur with oral penicillin. (Se WARNINGS.)

Liver: A moderate rise in AST (SGOT) and/or AL (SGPT) has been noted in patients treated wit ampicillin class antibiotics but the significance c these findings is unknown. Hepatic dysfunctior including increases in serum transaminases (AS and/or ALT), serum bilirubin and/or alkaline phos phatase, has been infrequently reported witl amoxicillin/clavulanate potassium and, whe reported, has been reported more commonly i elderly and/or males, and/or in patients on pro longed treatment. The histologic findings on live biopsy have consisted of predominantly cholestat ic, hepatocellular, or mixed cholestatic-hepatocel lular changes. The onset of signs/symptoms o hepatic dysfunction may occur during or severa weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usu ally reversible. On rare occasions, deaths have been reported (less than 1 death reported per esti mated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocy topenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during thera py 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% o the patients treated with amoxicillin/clavulanate potassium. There have been rare reports o increased prothrombin time in patients receiving amoxicillin/clavulanate potassium and anticoagu lant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behav ioral changes, confusion, convulsions, dizziness insomnia, and reversible hyperactivity have bee reported rarely.

OVERDOSAGE

Most patients have been asymptomatic followin overdosage or have experienced primarily gas trointestinal symptoms including stomach an abdominal pain, vomiting, and diarrhea. Rash hyperactivity, or drowsiness have also bee observed in a small number of patients.

In the case of overdosage, discontinue amox cillin/clavulanate potassium, treat symptomatically and institute supportive measures as required. the overdosage is very recent and there is no con traindication, an attempt at emesis or other mean

sis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

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

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

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

PRECAUTIONS

General:

While amoxicillin/clavulanate potassium possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

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

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

Drug Interactions:

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

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

Fertility:

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

Mutagenesis:

The mutagenic potential of amoxicillin/clavulanate potassium was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in 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:

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Labor and Delivery:

Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of amoxicillin/clavulanate potassium in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers:

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

ADVERSE REACTIONS

Amoxicillin/clavulanate potassium is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. 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

occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.)

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

Renal: Interstitial nephritis and hematuria have been reported rarely.

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

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

OVERDOSAGE

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

In the case of overdosage, discontinue amoxicillin/clavulanate potassium, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison center suggested that over-

dosages 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. 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 Tablets 250 mg and 500 mg contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 Amoxicillin and Clavulanate Potassium Tablets 250 mg are not equivalent to 1 Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium). Therefore, 2 Amoxicillin and Clavulanate Potassium Tablets 250 mg should not be substituted for 1 Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium).
Dosage:
Adults: The usual adult dose is 1 Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium) every 12 hours or 1 Amoxicillin and Clavulanate Potassium Tablet 250 mg every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 875 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium) every 12 hours or 1 Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium) 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/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.
Hemodialysis patients should receive 500 mg or 250 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 Tablet 250 mg (250/125) versus the Amoxicillin and Clavulanate Potassium Chewable Tablet 250 mg (250/62.5), the Amoxicillin and Clavulanate Potassium Tablet 250 mg should not be used until the pediatric patient weighs at least 40 kg or more.
Administration: Amoxicillin and Clavulanate Potassium Tablet may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when Amoxicillin and Clavulanate Potassium Tablet is administered at the start of a meal. To minimize the potential for gastrointestinal

HOW SUPPLIED

Amoxicillin and Clavulanate Potassium Tablets, USP 500/125 mg are white to off-white, oblong film coated tablets with beveled edges, debossed with 500/125 on one side and AMC on the other side. They are supplied in plastic bottles of 20 and 30 (with desiccant).

Amoxicillin and Clavulanate Potassium Tablets, USP 875/125 mg are white to off-white, oblong film coated tablets with beveled edges, scored and debossed with 875/125 on one side and AMC on the other side.
They are supplied in plastic bottles of 20 (with desiccant).

Store tablets at or below 25°C (77°F). 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 amoxicillin/clavulanate potassium tablets q12h to 500 mg amoxicillin/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 q12h and 500 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: 1.0% for 875 mg q12h dosing versus 2.5% for the 500 mg q8h dosing.
In one 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 amoxicillin/clavulanate potassium tablets q12h or 500 mg amoxicillin/clavulanate potassium tablets q8h in the following distribution:

	875 mg q12 h	500 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/clavulanate potassium produced comparable bacteriological success rates in patients assessed 2 to 4 days immediately following end of therapy. The bacteriologic 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 q12h	500 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 significant 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.

Manufactured by
Lek Pharmaceuticals d.d.
Verovškova 57, Ljubljana, Slovenia

October 2002

clavulanic acid, 125 mg, as clavulanate potassium). Therefore, 2 Amoxicillin and Clavulanate Potassium Tablets 250 mg should not be substituted for 1 Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium).

Dosage:

Adults: The usual adult dose is 1 Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium) every 12 hours or 1 Amoxicillin and Clavulanate Potassium Tablet 250 mg every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 875 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium) every 12 hours or 1 Amoxicillin and Clavulanate Potassium Tablet, USP (amoxicillin, 500 mg, as the trihydrate and clavulanic acid, 125 mg, as clavulanate potassium) 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/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 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 Tablet 250 mg (250/125) versus the Amoxicillin and Clavulanate Potassium Chewable Tablet 250 mg (250/62.5), the Amoxicillin and Clavulanate Potassium Tablet 250 mg should not be used until the pediatric patient weighs at least 40 kg or more.

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

[illegible] complicated urinary tract infections compared a regimen of 875 mg amoxicillin/clavulanate potassium tablets q12h to 500 mg amoxicillin/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 q12h and 500 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: 1.0% for 875 mg q12h dosing versus 2.5% for the 500 mg q8h dosing.

In one 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 amoxicillin/clavulanate potassium tablets q12h or 500 mg amoxicillin/clavulanate potassium tablets q8h in the following distribution:

	875 mg q12 h	500 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/clavulanate potassium produced comparable bacteriological success rates in patients assessed 2 to 4 days immediately following end of therapy. The bacteriologic 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 q12h	500 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 significant 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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-093

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 65-093

3. NAME AND ADDRESS OF APPLICANT

LEK Pharmaceutical and Chemical Company d.d.
Verovskova 57
1526 Ljubljana
SLOVENIA

U.S. Agent:
LEK USA
Attention: Branko Huc
333 Sylvan Avenue, 2nd Floor
Englewood Cliffs, NJ 07632
Phone: (201)-541-9310

4. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product: Augmentin® Tablets, manufactured by SmithKline Beecham, approved in NDA #50-720. The firm states that this is an "old antibiotic" as defined under FDAMA; therefore patent certification or exclusivity provisions are NOT required. The proposed drug product contains the same active ingredients and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Amoxicillin and Clavulanate Potassium Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm	Original Submission:	14-MAY-2001
	Amendment:	13-JUN-2001
FDA	Acceptable for Filing:	29-JUN-2001
	Labeling Deficiency:	10-AUG-2001
	Bioequivalence Acceptance:	21-AUG-2001

10. PHARMACOLOGICAL CATEGORY
Antibacterial

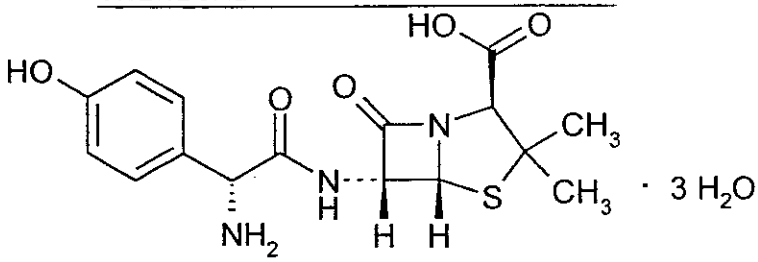
11. Rx or OTC
Rx

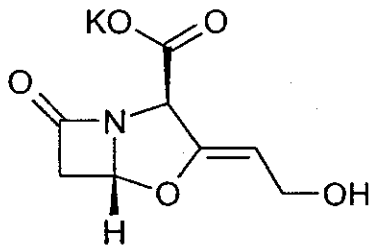
12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
875 mg Amoxicillin/125 mg Potassium Clavulanate

15. CHEMICAL NAME AND STRUCTURE





Name(Amoxicillin): (2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

Name(Clavulanate Potassium): Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate

Molecular Formula (Amoxicillin): $C_{16}H_{19}N_3O_5S \bullet 3H_2O$
Molecular Weight (Amoxicillin): 419.4
Molecular Formula (Clavulanate Potassium): $C_8H_8KNO_5$
Molecular Weight (Clavulanate Potassium): 237.25

16. RECORDS AND REPORTS
N/A

17. COMMENTS

[redacted]

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MINOR)

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 9/10/01

APPEARS THIS WAY ON ORIGINAL

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1. CHEMISTRY REVIEW NO. 2

2. ANDA # 65-093

3. NAME AND ADDRESS OF APPLICANT

LEK Pharmaceutical and Chemical Company d.d.
Verovskova 57
1526 Ljubljana
SLOVENIA

U.S. Agent:
LEK Services, Inc.
Attention: Donald Spiegel
115 N. Third Street
Wilmington, NC 28401
Phone: (910)-362-0760
Fax: (910)-362-0790

4. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product: Augmentin® Tablets, manufactured by SmithKline Beecham, approved in NDA #50-720. The firm states that this is an "old antibiotic" as defined under FDAMA; therefore patent certification or exclusivity provisions are NOT required. The proposed drug product contains the same active ingredients and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Amoxicillin and Clavulanate Potassium Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm		
	Original Submission:	14-MAY-2001
	Amendment:	13-JUN-2001
	Change of US Agent:	16-AUG-2001
	CMC/Labeling Amendment:	08-FEB-2002

FDA	Acceptable for Filing:	29-JUN-2001
	Labeling Acceptance:	08-MAR-2002
	Bioequivalence Acceptance:	21-AUG-2001
	CMC/Labeling Deficiency:	20-SEP-2002

10. PHARMACOLOGICAL CATEGORY
Antibacterial

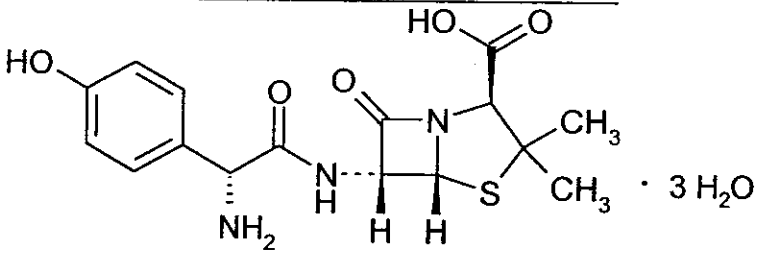
11. Rx or OTC
Rx

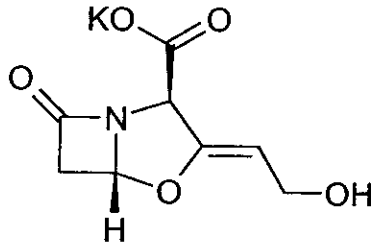
12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
875 mg Amoxicillin/125 mg Potassium Clavulanate

15. CHEMICAL NAME AND STRUCTURE





Name(Amoxicillin): (2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

Name(Clavulanate Potassium): Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate

Molecular Formula (Amoxicillin): $C_{16}H_{19}N_3O_5S \bullet 3H_2O$
Molecular Weight (Amoxicillin): 419.4
Molecular Formula (Clavulanate Potassium): $C_8H_8KNO_5$
Molecular Weight (Clavulanate Potassium): 237.25

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MINOR)

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 3/7/02

APPEARS THIS WAY
ON ORIGINAL

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1. CHEMISTRY REVIEW NO. 3

2. ANDA # 65-093

3. NAME AND ADDRESS OF APPLICANT

LEK Pharmaceutical and Chemical Company d.d.
Verovskova 57
1526 Ljubljana
SLOVENIA

U.S. Agent:
LEK Services, Inc.
Attention: Paul Kleutghen
115 N. Third Street
Wilmington, NC 28401
Phone: (910)-362-0760
Fax: (910)-362-0790

4. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product: Augmentin® Tablets, manufactured by SmithKline Beecham, approved in NDA #50-720. The firm states that this is an "old antibiotic" as defined under FDAMA; therefore patent certification or exclusivity provisions are NOT required. The proposed drug product contains the same active ingredients and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Amoxicillin and Clavulanate Potassium Tablets USP

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

9. AMENDMENTS AND OTHER DATES:

Firm Original Submission:	14-MAY-2001
Amendment:	13-JUN-2001
Change of US Agent:	16-AUG-2001
CMC/Labeling Amendment:	08-FEB-2002
CMC Amendment:	11-JUN-2002
Gratuitous CMC Amendment:	12-JUN-2002

FDA	Acceptable for Filing:	29-JUN-2001
	Labeling Deficiency:	10-AUG-2001
	Bioequivalence Acceptance:	21-AUG-2001
	CMC/Labeling Deficiency:	20-SEP-2002
	Labeling Approval:	08-MAR-2002

10. PHARMACOLOGICAL CATEGORY
Antibacterial

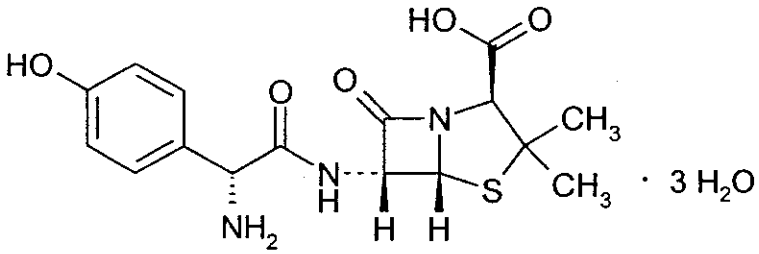
11. Rx or OTC
Rx

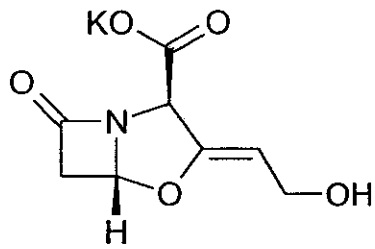
12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
875 mg Amoxicillin/125 mg Potassium Clavulanate

15. CHEMICAL NAME AND STRUCTURE





Name(Amoxicillin): (2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

Name(Clavulanate Potassium): Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate

Molecular Formula (Amoxicillin): $C_{16}H_{19}N_3O_5S \bullet 3H_2O$
Molecular Weight (Amoxicillin): 419.4
Molecular Formula (Clavulanate Potassium): $C_8H_8KNO_5$
Molecular Weight (Clavulanate Potassium): 237.25

16. RECORDS AND REPORTS
N/A

17. COMMENTS

[

]

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MINOR)

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 6/28/02

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ON ORIGINAL

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1. CHEMISTRY REVIEW NO. 4

2. ANDA # 65-093

3. NAME AND ADDRESS OF APPLICANT

LEK Pharmaceuticals d.d.
Verovskova 57
1526 Ljubljana
SLOVENIA

U.S. Agent:
LEK Services, Inc.
Attention: Donald Spiegel
115 N. Third Street
Wilmington, NC 28401
Phone: (910)-362-0760
Fax: (910)-362-0790

4. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product: Augmentin® Tablets, manufactured by SmithKline Beecham, approved in NDA #50-720. The firm states that this is an "old antibiotic" as defined under FDAMA; therefore patent certification or exclusivity provisions are NOT required. The proposed drug product contains the same active ingredients and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Amoxicillin and Clavulanate Potassium Tablets USP

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

9. AMENDMENTS AND OTHER DATES:

Firm		
	Original Submission:	14-MAY-2001
	Amendment:	13-JUN-2001
	Change of US Agent:	16-AUG-2001
	CMC/Labeling Amendment:	08-FEB-2002
	CMC Amendment:	11-JUN-2002
	Gratuitous CMC Amendment:	12-JUN-2002
	CMC Amendment:	24-SEP-2002

FDA	Acceptable for Filing:	29-JUN-2001
	Labeling Deficiency:	10-AUG-2001
	Bioequivalence Acceptance:	21-AUG-2001
	CMC/Labeling Deficiency:	20-SEP-2001
	Labeling Approval:	08-NOV-2002
	CMC Deficiency II:	28-MAR-2002
	CMC Deficiency III:	06-SEP-2002

10. PHARMACOLOGICAL CATEGORY
Antibacterial

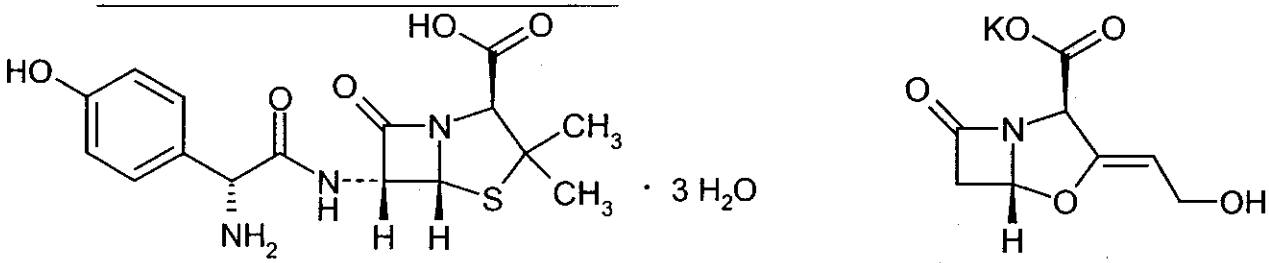
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Tablets

14. POTENCY
875 mg Amoxicillin/125 mg Potassium Clavulanate

15. CHEMICAL NAME AND STRUCTURE



Name(Amoxicillin): (2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

Name(Clavulanate Potassium): Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate

Molecular Formula (Amoxicillin): $C_{16}H_{19}N_3O_5S \bullet 3H_2O$
Molecular Weight (Amoxicillin): 419.4
Molecular Formula (Clavulanate Potassium): $C_8H_8KNO_5$

Molecular Weight (Clavulanate Potassium): 237.25

16. RECORDS AND REPORTS
N/A

17. COMMENTS

[redacted]

18. CONCLUSIONS AND RECOMMENDATIONS
Approval is recommended.

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 10/21/02

APPEARS THIS WAY
ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-093

BIOEQUIVALENCE REVIEW

BIOEQUIVALENCY COMMENTS

ANDA: 65-093

APPLICANT: LEK Pharmaceutical and Chemical Company d.d.

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

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

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

Sincerely yours,

/S/

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

6

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 65-093 SPONSOR: LEK Pharmaceutical and Chemical Company d.d.

DRUG AND DOSAGE FORM: Amoxicillin; Clavulanate Potassium Tablets, USP

STRENGTH(S): 875 mg; 125 mg

TYPES OF STUDIES: Fasting, postprandial and dissolution

CLINICAL STUDY SITE: [redacted]

ANALYTICAL SITE: [redacted]

STUDY SUMMARY: Fasting and postprandial studies are acceptable

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

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

PRIMARY REVIEWER: James Chaney BRANCH: I
INITIAL: JC DATE: 8/9/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I
INITIAL: /S/ DATE: 8/9/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL: /S/ DATE: 8/21/2001

Furness, Sc

Amoxicillin; Clavulanate Potassium Tablets, USP
875 mg; 125 mg
ANDA 65-093
Reviewer: James Chaney
V:\FIRMSAM\LEK\L.TRS&REV\65093sd.501

LEK Pharmaceutical and Chemical Company d.d.
Verovskova 57, 1526 Ljubljana, Slovenia
Submission Date:
May 14, 2001

Review of Two Bioequivalence Studies and Dissolution Data (Electronic Submission)

I. Introduction

Indication: It is indicated in the treatment of lower respiratory tract infections, otitis media, sinusitis, skin and skin structure infections, and urinary tract infections.
Type of Submission: Original ANDA
First Generic: No
Contents of Submission: Fasting and non-fasting studies and dissolution data
RLD: Augmentin® 875 (SmithKline Beecham). SmithKline Beecham also markets Augmentin® 500 (500/125) and Augmentin® 250 (250/125) tablets.
Recommended Dose: The usual adult dose is one Augmentin® 500 mg tablet every 12 hours or one Augmentin® 250 mg tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one Augmentin® 875 tablet every 12 hours or one Augmentin® 500 tablet every 8 hours.
Financial Disclosure: Form FDA 3454 was submitted. The firm has no conflict of interest with the investigators.

II. Background

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

III. Protocol No.: 992128, Comparative, Randomized, 2-Way Crossover Bioavailability Study of Lek and SmithKline Beecham (Augmentin® (R)) 875 mg Tablets Containing 875 mg Amoxicillin/125 mg Clavulanic Acid in Healthy Adult Males Under Fasting Conditions

Study Information

STUDY FACILITY INFORMATION	
Clinical Facility:	[redacted]
Medical Director:	[redacted]
Scientific Director:	[redacted]
Clinical Study Dates:	02/13/00 to 02/20/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	02/24/00 to 04/08/00
Storage Period (Study Samples)	55 Days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Amoxicillin (as the trihydrate)/Clavulanic Acid (as the potassium salt)	Augmentin®
Manufacturer:	Lek, Pharmaceutical and Chemical Company d.d.	SmithKline Beecham Pharmaceuticals
Manufacture Date:	5/1/00	N/A
Expiration Date:	N/A	October 2000
ANDA Batch Size:	[redacted]	---
Full Batch Size:	[redacted]	---
Batch/Lot Number:	1400501B	MH2464
Potency:	Amoxicillin, 98.8% Clavulanic Acid, 97.4	Amoxicillin, 98.3% Clavulanic Acid, 95.5
Content Uniformity:	Amoxicillin; 99.4% (98.6-100), 0.4%CV Clavulanic acid; 98.6% (97.4-100.7), 1.0%CV	Amoxicillin: 98.3% (97.4-99.4), 0.7%CV Clavulanic acid: 95.1% (93.8-96.0), 0.7%CV
Strength:	875 mg/125 mg	875 mg/125 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	875 mg/125 mg	875 mg/125 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

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

Randomization scheme:
AB: 2, 4, 6, 7, 9, 11, 12, 15, 16, 18, 21, 24, 26, 28, 30, 32, 33, 36, 37, 39, 41, 43, 44, 45, 49
BA: 1, 3, 5, 8, 10, 13, 14, 17, 19, 20, 22, 23, 25, 27, 29, 31, 34, 35, 38, 40, 42, 46, 47, 48, 50

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	50
Route of Administration:	oral	**No. of Subjects Completing:**	50
Dosing Interval:	NA	**No. of Subjects Plasma Analyzed:**	48
Number of Doses:	N/A	**No. of Dropouts:**	0
Loading Dose:	N/A	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	15

Demographics of the 50 Dosed Subjects

Age (yrs): 29.2±7.4(19-45)

	Age Group	
	< 18 yrs	0
	18-40 yrs	43 (86%)
	40-64 yrs	7 (14%)
	65-75 yrs	0
	> 75 yrs	0
Sex	Female	0
	Male	50 (100%)
Race	Asian	0
	Black	2 (4%)
	Caucasian	47 (94%)
	Hispanic	0
	Other	1 (2%)

Weight (lbs): 157.2±14.4 (128.3-183.6)

Height (in): 69.3±2.3(63.4-73.2)

Dietary Restrictions: No alcohol- or xanthine-containing drinks/ foods for 48 hours pre-dose and throughout the period of sample collection. No grapefruit-containing drinks/ foods for 7 days pre-study and throughout the entire study.

Activity Restrictions: Subjects remained ambulatory or seated upright for the first 4 hours post-dose except when prevented by adverse events. No strenuous activity at any time during the housing period.

Drug Restrictions: No medication (including OTC products, except for vitamins taken as nutritional supplements for non-therapeutic indications) for 14 days pre-study and throughout the duration of the study.

Blood Sampling: Pre-dose and at the following times post-dose: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12 and 14 hours

Study Results

1) Clinical

Adverse Events:

A total of 15 adverse events were experienced by 7 subjects during the study. Of these events, 1 was judged to have a probable association with the study drug, 6 were judged to have a possible association with the study drug, 4 were judged to have a remote association with the study drug and 4 were judged to be unrelated to the study drug. These events were mild or moderate in severity at onset.

Protocol Deviations:

The Principal Investigator judged the deviations unlikely to have affected the bioavailability comparison.

Dropouts: None

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Comments:

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3) Pharmacokinetics:

Amoxicillin:		
Mean Plasma Concentrations:	Table 1, Figure 1	
Pharmacokinetic Parameters:	Tables 2 and 3	
90% Confidence Intervals:	LAUC0-t	91.4-105.4%
	LAUC0-inf	91.4-105.3%
	LCmax	92.1-109.2%
Arith. Mean AUCT/AUCI Ratios:	Test	0.99 (0.98-1.00)
	Ref	0.98 (0.91-0.99)
Arith. MeanT/R Ratios:	AUC0-t	1.03 (0.28-2.87), 35%CV
	AUC0-inf	1.02 (0.29-1.78), 34%CV
	Cmax	1.08 (0.33-4.16), 51%CV
Root MSE:	LAUC0-t	0.208643
	LAUC0-inf	0.205310
	LCmax	0.248139
Clavulanic acid:		
Mean Plasma Concentrations:	Table 4, Figure 2	
Pharmacokinetic Parameters:	Tables 5 and 6	
90% Confidence Intervals:	LAUC0-t	87.3-114.5%
	LAUC0-inf	87.8-114.1%
	LCmax	84.0-110.6%
Arith. Mean AUCT/AUCI Ratios:	Test	0.98 (0.95-0.99)
	Ref	0.98 (0.91-0.99)

Arith. MeanT/R Ratios:	AUC0-t	1.20 (0.33-5.89), 83.9%CV
	AUC0-inf	1.18 (0.34-5.43), 78%CV
	Cmax	1.14 (0.26-5.21), 74%CV
Root MSE:	LAUC0-t	0.395925
	LAUC0-inf	0.382181
	LCmax	0.401666

Comments:

- There were no measurable drug concentrations at 0 hr for amoxicillin or clavulanic acid under fasting conditions. There was no observation of first measurable drug concentration as Cmax for amoxicillin or clavulanic acid under fasting conditions.
- The reviewer recalculated pharmacokinetic parametes and 90% confidence intervals. The reported values are in agreement with those obtained by the reviewer.
- The 90% confidence intervals for log transformed AUC0-t, AUC0-inf, and Cmax are within acceptable limits of 80-125%.

Conclusion: The fasting study is acceptable.

IV. Protocol No.: 992129, Comparative, Randomized, 3-Way Crossover Bioavailability Study of Lek and SmithKline Beecham (Augmentin®) 875 mg Tablets Containing 875 mg Amoxicillin/125 mg Clavulanic Acid in Healthy Adult Males Under Fed/Fasting Conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	[redacted]
Scientific Director:	[redacted]
Clinical Study Dates:	02/15/00 to 02/29/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	03/14/00 to 04/10/00
Storage Period (Study Samples)	55 Days

TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	Test - Fasted	Test - Fed	Reference – Fed
Product Name:	Amoxicillin (as trihydrate)/ Clavulanic Acid (as potassium salt)	Amoxicillin (as trihydrate)/ Clavulanic Acid (as potassium salt)	Augmentin®
Manufacturer:	Lek Pharmaceutical and Chemical Company d.d.	Lek Pharmaceutical and Chemical Company d.d.	SmithKline Beecham Pharmaceuticals
Manufacture Date:	5/1/00	5/1/00	N/A
Expiration Date:	N/A	N/A	N/A
ANDA Batch Size:	[redacted]	[redacted]	---
Full Batch Size:	[redacted]	[redacted]	---
Batch/Lot Number:	1400501B	1400501B	MH2464

Potency:	Amoxicillin, 98.8% Clavulanic Acid, 97.4	Amoxicillin, 98.8% Clavulanic Acid, 97.4	Amoxicillin, 98.3% Clavulanic Acid, 95.5
Content Uniformity:	Amoxicillin; 99.4% (98.6-100), 0.4%CV Clavulanic acid; 98.6% (97.4-100.7), 1.0%CV	Amoxicillin; 99.4% (98.6-100), 0.4%CV Clavulanic acid; 98.6% (97.4-100.7), 1.0%CV	Amoxicillin: 98.3% (97.4-99.4), 0.7%CV Clavulanic acid: 95.1% (93.8-96.0), 0.7%CV
Strength:	875 mg/125 mg	875 mg/125 mg	875 mg/125 mg
Dosage Form:	Tablet	Tablet	Tablet
Dose Administered:	875 mg/125 mg	875 mg/125 mg	875 mg/125 mg
Study Condition:	Fasting	Fed	Fed
Length of Fasting:	Overnight	Overnight	Overnight
Standard Breakfast:	N	Y	Y
Breakfast Specifics:	N/A	Std. FDA high-fat meal	Std. FDA high-fat meal
Standardized Lunch:	Y	Y	Y

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

Randomization Scheme:
ABC: 10,11,15
ACB: 3,6,14
BAC: 1,5,18,
BCA: 2,13,16
CAB: 8,9,12
CBA: 4,7,17

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	18
Route of Administration:	Oral	**No. of Subjects Completing:**	18
Dosing Interval:	NA	**No. of Subjects Plasma Analyzed:**	18
Number of Doses:	N/A	**No. of Dropouts:**	0
Loading Dose:	N/A	**Sex(es) Included:**	Male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	3

Demographics of the 18 Dosed Subjects

Age (yrs): 30.8±6.8(19-41)

	Age Group	
	< 18 yrs	0
	18-40 yrs	17 (94%)
	40-64 yrs	1 (6%)
	65-75 yrs	0
	> 75 yrs	0
Sex	Female	0
	Male	18 (100%)
Race	Asian	0
	Black	2 (11%)
	Caucasian	16 (89%)
	Hispanic	0
	Other	0

Weight (lbs): 158.9±17.6 (128.3-184.5)

Height (in): 68.6±2.8(63.8-72.8)

Dietary Restrictions:	No alcohol- or xanthine-containing drinks/ foods for 48 hours pre-dose and throughout the period of sample collection. No grapefruit-containing drinks/foods for 7 days pre-study and throughout the entire study.
Activity Restrictions:	Subjects remained ambulatory or seated upright for the first 4 hours post-dose except when prevented by adverse events. No strenuous activity at any time during the housing period.
Drug Restrictions:	No medication (including OTC products, except for vitamins taken as nutritional supplements for non-therapeutic indications) for 14 days pre-study and throughout the duration of the study.
Blood Sampling:	Pre-dose and at the following times post-dose: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12 and 14 hours

Study Results

1) Clinical

Adverse Events:

A total of three adverse events were experienced by two subjects during the study. Of these events, one (headache following ref-fed) was judged to be remote associated with the study drug and two were judged to be unrelated to the study drug. These events were mild in severity at onset..

Protocol Deviations:

The Principal Investigator judged the deviations unlikely to have affected the bioavailability comparison.

Dropouts: None

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3) Pharmacokinetics:

Amoxicillin:		
Mean Plasma Concentrations:	Table 7, Figure 3	
Pharmacokinetic Parameters:	Tables 8 and 9	
Arith. Mean AUCT/AUCI Ratios:	Test fasting	0.99 (0.98-1.00)
	Test non-fasting	0.99 (0.99-0.99)
	Ref non-fasting	0.99 (0.98-1.00)
Arith. MeanT-Fed/R-Fed Ratios:	AUC0-t	1.03 (0.83-1.18), 11%CV
	AUC0-inf	1.03 (0.83-1.18), 11%CV
	Cmax	1.02 (0.61-1.73), 26%CV
Clavulanic Acid:		
Mean Plasma Concentrations:	Table 10, Figure 4	
Pharmacokinetic Parameters:	Tables 11 and 12	
Arith. Mean AUCT/AUCI Ratios:	Test fasting	0.98 (0.95-0.99)
	Test non-fasting	0.97 (0.94-0.99)
	Ref non-fasting	0.97 (0.94-0.99)
Arith. MeanT-Fed/R-Fed Ratios:	AUC0-t	1.18 (0.34-5.52), 97%CV
	AUC0-inf	0.97 (0.38-1.62), 34%CV
	Cmax	1.12 (0.20-4.08), 76%CV

Comments:

- There were no measurable drug concentrations at 0 hr for amoxicillin or clavulanic acid in the food study. There was no observation of first measurable drug concentration as Cmax for amoxicillin or clavulanic acid in the food study.
- The reviewer recalculated pharmacokinetic parameters and ratios of means. The reported values are in agreement with those obtained by the reviewer.
- The non-fasting study is acceptable.

V. Formulation

- Formulation information is provided in Table 13.
- All inactive ingredients in the formulation found to be present at or below the levels cited in the FDA Inactive Ingredient Guide (1996) except for croscarmellose sodium. Although croscarmellose sodium is not listed in the 1996 IIG at a concentration at or above that in the test formulation, this ingredient has been used in a higher amount than in the test product. For example, Biaxin tablet 500 mg (NDA 50-662) contains 65.6 mg of croscarmellose sodium.

VI. Dissolution

A. Dissolution Method Used by Firm

The dissolution method is the USP method.
No. Units Tested: 12 tablets
USP XXIV apparatus: 2 (paddle)
Medium: Water
Temperature: 37°C
Volume: 900 mL
Rpm: 75
Sampling Times: 10, 20, 30 and 40 minutes
Tolerance: Not less than 85% (Q) of the labeled amount of amoxicillin and 80% (Q) of the labeled amount of clavulanate potassium are dissolved in 30 minutes.

B. Results

Dissolution data are presented in Table 14.

C. Comment:

The dissolution testing is acceptable.

VII. Recommendations

1. The single-dose, fasting bioequivalence study and the single-dose postprandial bioequivalence study conducted by LEK Pharmaceutical and Chemical Company d.d. on its amoxicillin/clavulanate potassium 875/125 mg tablet, lot # 1400501B, comparing it with Augmentin® 875 tablet, lot #MH2464, manufactured by SmithKline Beecham have been found acceptable to the Division of Bioequivalence. The studies demonstrate that the test product, LEK Pharmaceutical and Chemical Company d.d.'s amoxicillin/clavulanate potassium 875 mg/125 mg tablet, is bioequivalent to the reference product, Augmentin® 875 tablet manufactured by SmithKline Beecham.

2. The dissolution testing conducted by the firm on its test product is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water at 37° C using apparatus 2 (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than 85% (Q) of the labeled amount of amoxicillin and 80% (Q) of the labeled amount of clavulanic acid are dissolved in 30 minutes

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang /S/ Date 8/9/2001
FT INITIALED YCHuang

Concur: /S/ Date 8/21/2001
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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TABLE 1. FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992128. ARITHMETIC MEAN AMOXICILLIN PLASMA CONCENTRATIONS [µg/mL] (CV%) VERSUS TIME IN 48 SUBJECTS

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B		RATIO (A/B)%
0	0.0000	(0.0)	0.0000	(0.0)	N/A
0.25	0.1231	(187.3)	0.2204	(172.5)	55.9
0.5	2.2817	(61.5)	2.6547	(69.3)	85.9
0.75	5.9402	(46.5)	6.3503	(51.4)	93.5
1	8.9849	(39.7)	8.6222	(44.7)	104.2
1.25	10.7440	(34.4)	10.0743	(43.3)	106.6
1.5	11.0234	(32.3)	10.5287	(38.8)	104.7
1.75	11.0474	(27.4)	10.5516	(32.2)	104.7
2	10.5230	(26.5)	10.2437	(28.7)	102.7
2.5	8.8174	(26.8)	8.8796	(26.4)	99.3
3	6.9849	(28.7)	7.1520	(29.3)	97.7
4	4.1418	(43.3)	4.1515	(40.9)	99.8
5	2.1645	(52.3)	2.4955	(73.1)	86.7
6	1.1831	(56.1)	1.3079	(67.2)	90.5
7	0.6525	(50.2)	0.7316	(57.4)	89.2
8	0.3875	(48.3)	0.4346	(58.4)	89.2
10	0.1236	(71.4)	0.1491	(67.0)	82.9
12	0.0136	(267.6)	0.0272	(200.2)	50.0
14	0.0000	(0.0)	0.0000	(0.0)	N/A

TABLE 2. FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992128 ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR AMOXICILLIN IN 48 SUBJECTS

PK PARAMETER	N	TEST TREATMENT A		N	REFERENCE TREATMENT B		RATIO (A/B)%
AUCT [µg•hr/mL]	48	34.97	(23.5)	48	35.42	(20.4)	98.7
AUCI [µg•hr/mL]	48	35.29	(23.3)	48	35.75	(20.2)	98.7
Cmax [µg/mL]	48	12.0788	(28.9)	48	12.0843	(28.9)	100.0
tmax [hr]	48	1.587	(22.6)	48	1.767	(47.1)	89.8
kel [1/hr]	48	0.5092	(19.9)	48	0.4900	(20.5)	103.9
t½ [hr]	48	1.4149	(19.8)	48	1.4743	(21.1)	96.0

TABLE 3. FASTING IN VIVO BIOEQUIVALENCE STUDY, GEOMETRIC LSMEANS AND 90% CONFIDENCE INTERVALS FOR PHARMACOKINETIC PARAMETERS FOR AMOXICILLIN

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)	90% C.I.
AUCT [µg.hr/mL]	33.877	34.525	98.1	91.4-105.4
AUCI [µg.hr/mL]	34.214	34.872	98.1	91.4-105.3
Cmax [µg /mL]	11.56883	11.53537	100.3	92.1-109.2

TABLE 4. FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992128. ARITHMETIC MEAN CLAVULANIC ACID PLASMA CONCENTRATIONS [NG/ML] (CV%) VERSUS TIME IN 48 SUBJECTS

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B		RATIO (A/B)%
0	0.00	(0.0)	0.00	(0.0)	N/A
0.25	27.07	(219.9)	75.62	(231.9)	35.8
0.5	493.19	(83.4)	989.47	(89.8)	49.8
0.75	1542.74	(60.2)	2241.13	(61.0)	68.8
1	2386.85	(49.1)	2758.40	(49.4)	86.5
1.25	2623.16	(41.5)	2784.50	(41.4)	94.2
1.5	2567.55	(40.1)	2493.49	(36.0)	103.0
1.75	2331.79	(36.9)	2140.87	(31.4)	108.9
2	2013.16	(33.9)	1833.54	(30.7)	109.8
2.5	1386.28	(33.4)	1252.88	(31.4)	110.6
3	975.66	(37.6)	855.49	(35.8)	114.0
4	471.25	(48.8)	421.88	(52.0)	111.7
5	243.45	(53.9)	221.40	(63.1)	110.0
6	136.26	(54.7)	125.74	(72.4)	108.4
7	67.33	(81.9)	60.47	(96.8)	111.3
8	21.10	(174.0)	19.02	(185.0)	110.9
10	0.00	(0.0)	1.22	(692.8)	0.0
12	0.00	(0.0)	0.00	(0.0)	N/A
14	0.00	(0.0)	0.00	(0.0)	N/A

TABLE 5. FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992128 ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR CLAVULANIC ACID IN 48 SUBJECTS

PK PARAMETER	N	TEST TREATMENT A		N	REFERENCE TREATMENT B		RATIO (A/B)%
AUCT [ng•hr/mL]	48	6075.2	(34.1)	48	6142.7	(33.7)	98.9
AUCI [ng•hr/mL]	48	6210.6	(33.6)	48	6259.8	(33.1)	99.2
Cmax [ng/mL]	48	2845.27	(37.8)	48	3032.99	(40.1)	93.8
tmax [hr]	48	1.398	(25.9)	48	1.286	(28.3)	108.7
kel [1/hr]	48	0.5858	(18.6)	48	0.6086	(13.8)	96.3
t½ [hr]	48	1.2286	(20.9)	48	1.1616	(14.6)	105.8

TABLE 6. FASTING IN VIVO BIOEQUIVALENCE STUDY. GEOMETRIC LSMEANS AND 90% CONFIDENCE INTERVALS FOR PHARMACOKINETIC PARAMETERS FOR CLAVULANIC ACID

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)	90% C.I.
AUCT [µg.hr/mL]	5683.29	5685.3	100	87.3-114.5
AUCI [µg.hr/mL]	5824.48	5818	100.1	87.8-114.1
Cmax [µg /mL]	2622.563	2720.324	96.4	84.0-110.6

TABLE 7. POSTPRANDIAL SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992129. ARITHMETIC MEAN PLASMA AMOXICILLIN CONCENTRATIONS [µg/mL] (CV%) VERSUS TIME IN 18 SUBJECTS

TIME (HR)	TEST FASTED (A)		TEST FED (B)		TEST FED (C)		RATIO (B/A)%	RATIO (B/C)%
0	0.0000	(0.0)	0.0000	(0.0)	0.0000	(0.0)	N/A	N/A
0.25	0.2043	(112.7)	0.0000	(0.0)	0.0099	(424.3)	0.0	0.0
0.5	2.9550	(62.7)	0.4186	(123.0)	0.4681	(181.5)	14.2	89.4
0.75	6.3427	(49.0)	1.6749	(90.5)	1.6466	(118.7)	26.4	101.7
1	8.6610	(46.0)	4.0066	(82.8)	3.8682	(93.3)	46.3	103.6
1.25	9.6516	(39.6)	6.2667	(59.8)	6.4259	(69.1)	64.9	97.5
1.5	10.1203	(38.0)	8.5876	(52.0)	9.2679	(49.6)	84.9	92.7
1.75	10.1497	(35.7)	10.1861	(44.6)	10.5114	(35.8)	100.4	96.9
2	9.8058	(35.1)	10.1703	(39.7)	10.7646	(26.2)	103.7	94.5
2.5	7.9534	(29.3)	8.9058	(25.7)	9.2386	(20.4)	112.0	96.4
3	6.2193	(24.8)	7.1884	(24.0)	7.3629	(24.4)	115.6	97.6
4	3.9117	(34.8)	4.7254	(41.7)	4.1678	(30.9)	120.8	113.4
5	1.9833	(53.9)	2.7437	(61.8)	2.2498	(37.9)	138.3	122.0
6	1.1019	(68.4)	1.6111	(73.4)	1.2914	(44.9)	146.2	124.8
7	0.6357	(74.4)	0.9100	(71.6)	0.7340	(51.3)	143.1	124.0
8	0.3723	(75.5)	0.5322	(83.2)	0.4281	(56.5)	142.9	124.3
10	0.1220	(111.9)	0.1693	(94.7)	0.1263	(90.3)	138.8	134.0
12	0.0209	(317.3)	0.0261	(254.3)	0.0248	(192.7)	124.9	105.2
14	0.0000	(0.0)	0.0065	(424.3)	0.0000	(0.0)	N/A	N/A

TABLE 8. POSTPRANDIAL SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992129. ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR AMOXICILLIN IN 18 SUBJECTS

PK PARAM	N	TEST FASTED (A)	N	TEST FED (B)	N	REFERENCE FED (C)	B/A %	B/C %
AUCT [µg•hr/mL]	18	32.64 (21.0)	18	32.46 (18.5)	18	31.50 (16.9)	99.4	103.0
AUCI [µg•hr/mL]	18	32.98 (20.9)	18	32.78 (18.4)	18	31.85 (16.8)	99.4	102.9
Cmax [µg/mL]	18	11.2449 (31.3)	18	11.9585 (27.6)	18	12.0119 (25.3)	106.3	99.6
Tmax [hr]	18	1.753 (37.6)	18	2.208 (34.6)	18	2.087 (24.2)	126.0	105.8
Kel [1/hr]	18	0.5117 (22.0)	18	0.5393 (19.1)	18	0.5507 (23.2)	105.4	97.9
T½ [hr]	18	1.4202 (22.6)	18	1.3330 (20.2)	18	1.3210 (22.7)	93.9	100.9

TABLE 9. POSTPRANDIAL IN VIVO BIOEQUIVALENCE STUDY. GEOMETRIC MEAN LEAST-SQUARES MEAN PK VALUES FOR AMOXICILLIN IN 18 SUBJECTS

PK PARAMETER	N	TEST FASTED (A)	N	TEST FED (B)	N	REFERENCE FED (C)	RATIO (A/B)	RATIO (B/C)
AUCT [µg.hr/mL]	18	32.074	18	31.834	18	30.933	0.993	1.029
AUCI [µg.hr/mL]	18	32.427	18	32.127	18	31.294	0.990	1.027
Cmax [µg/mL]	18	10.982	18	11.925	18	11.385	1.046	1.009

TABLE 10. POSTPRANDIAL SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992129. ARITHMETIC MEAN CLAVULANIC ACID PLASMA CONCENTRATIONS [NG/ML] (CV%) VERSUS TIME IN 18 SUBJECTS

TIME (HR)	TEST FASTED (A)		TEST FED (B)		TEST FED (C)		RATIO (B/A)%	RATIO (B/C)%
0	0.00	0.0	0.00	0.0	0.00	0.0	N/A	N/A
0.25	32.50	210.2	0.00	0.0	4.40	424.3	0.0	0.0
0.5	674.12	99.9	34.77	181.1	113.39	256.1	5.2	30.7
0.75	1633.22	79.1	144.94	136.4	330.69	175.5	8.9	43.8
1	2373.14	63.6	418.06	109.9	852.59	139.6	17.6	49.0
1.25	2674.86	57.2	913.09	106	1352.73	109.5	34.1	67.5
1.5	2575.56	48	1483.32	82.3	1830.89	80.8	57.6	81.0
1.75	2343.74	42.7	1773.06	64.8	1915.69	70.2	75.7	92.6
2	2041.48	41	1715.02	56.7	1796.70	64.2	84.0	95.5
2.5	1458.34	44.7	1331.64	48.5	1327.36	52.5	91.3	100.3
3	1104.17	49.8	960.68	50.1	929.01	55.1	87.0	103.4
4	603.20	61.1	479.61	60.7	461.16	64.5	79.5	104.0
5	295.87	70.6	231.75	69.6	222.01	78.9	78.3	104.4
6	154.38	78.6	119.80	91.9	114.07	93.5	77.6	105.0
7	71.38	109.6	58.70	129.3	63.08	106.9	82.2	93.1
8	24.27	188.5	22.53	230.7	23.86	179.6	92.8	94.4
10	0.00	0.0	4.45	424.3	0.00	0.0	N/A	N/A
12	0.00	0.0	0.00	0.0	0.00	0.0	N/A	N/A
14	0.00	0.0	0.00	0.0	0.00	0.0	N/A	N/A

TABLE 11. POSTPRANDIAL SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992129. ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR CLAVULANIC ACID IN 18 SUBJECTS

PK PARAMETER	N	TEST FASTED (A)	N	TEST FED (B)	N	REFERENCE FED (C)	RATIO (B/A)%	RATIO (B/C)%
AUCT [ng•hr/mL]	18	6513.8 (40.7)	18	4113.9 (52.9)	18	4493.0 (61.0)	63.2	91.6
AUCI [ng•hr/mL]	18	6621.9 (40.3)	17	4454.5 (45.2)	17	4837.6 (54.7)	67.3	92.1
Cmax [ng/mL]	18	3033.7 (45.7)	18	1949.9 (59.0)	18	2210.8 (65.8)	64.3	88.2
Tmax [hr]	18	1.375 (23.5)	18	2.056 (29.4)	18	1.875 (27.9)	149.5	109.7
kel [1/hr]	18	0.6880 (14.0)	17	0.6851 (18.2)	17	0.6543 (20.1)	99.6	104.7
t½ [hr]	18	1.0274 (14.7)	17	1.0472 (20.4)	17	1.0979 (19.0)	101.9	95.4

TABLE 12. POSTPRANDIAL IN VIVO BIOEQUIVALENCE STUDY, GEOMETRIC MEAN LEAST-SQUARES MEAN PK VALUES FOR CLAVULANIC ACID IN 18 SUBJECTS

PK PARAMETER	N	TEST FASTED (A)	N	TEST FED (B)	N	REFERENCE FED (C)	RATIO (A/B)	RATIO (B/C)
AUCT [µg.hr/mL]	18	6048	18	3087	18	3499	0.993	1.029
AUCI [µg.hr/mL]	18	5746	17	3665	17	4197	0.990	1.027
Cmax [µg/mL]	18	2743	18	1458	18	1720	1.046	1.009

TABLE 13. FORMULATION OF AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP, 875/125 MG

INGREDIENT	AMOUNT (mg) PER DOSAGE UNIT
[redacted]	
Amoxicillin	875.000
Clavulanic acid (as the potassium salt)	125.000
Colloidal silicon dioxide	[redacted]
Crospovidone dried	[redacted]
Croscarmellose sodium dried	[redacted]
Magnesium stearate	[redacted]
Microcrystalline cellulose dried	[redacted]
[redacted]	
Hydroxypropyl cellulose	[redacted]
Ethylcellulose	[redacted]
Polysorbate 80	[redacted]
Triethyl citrate	[redacted]
Titanium dioxide	[redacted]
Talc	[redacted]
TOTAL TABLET WEIGHT (MG)	1473.000

TABLE 14.. RESULTS OF IN VITRO DISSOLUTION/RELEASE TESTING:						
AMOXICILLIN						
Sampling Times (Min)	Test Product: Amoxicillin and Clavulanate Potassium Tablets USP Lot No.: 1400501B Strength: 875/125 mg			Reference Product: Augmentin® Lot No.: MH2464 Strength: 875/125 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	45.9	[redacted]	11.0	58.2	[redacted]	24.8
20	93.5	[redacted]	2.8	94.5	[redacted]	4.9
30	100.2	[redacted]	0.7	99.0	[redacted]	1.1
40	100.7	[redacted]	0.7	99.4	[redacted]	0.9
CLAVULANIC ACID						
Sampling Times (Min)	Test Product: Amoxicillin and Clavulanate Potassium Tablets USP Lot No.: 1400501B Strength: 875/125 mg			Reference Product: Augmentin® Lot No.: MH2464 Strength: 875 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	30.2	[redacted]	17.1	59.6	[redacted]	19.9
20	88.2	[redacted]	6.3	92.8	[redacted]	3.2
30	97.7	[redacted]	1.0	96.3	[redacted]	1.2
40	97.8	[redacted]	1.2	96.0	[redacted]	1.2

APPEARS THIS WAY
ON ORIGINAL

FIGURE 1
AMOXICILLIN PLASMA CONCENTRATIONS (MCG/ML) VERSUS TIME
SINGLE-DOSE FASTING STUDY #992128

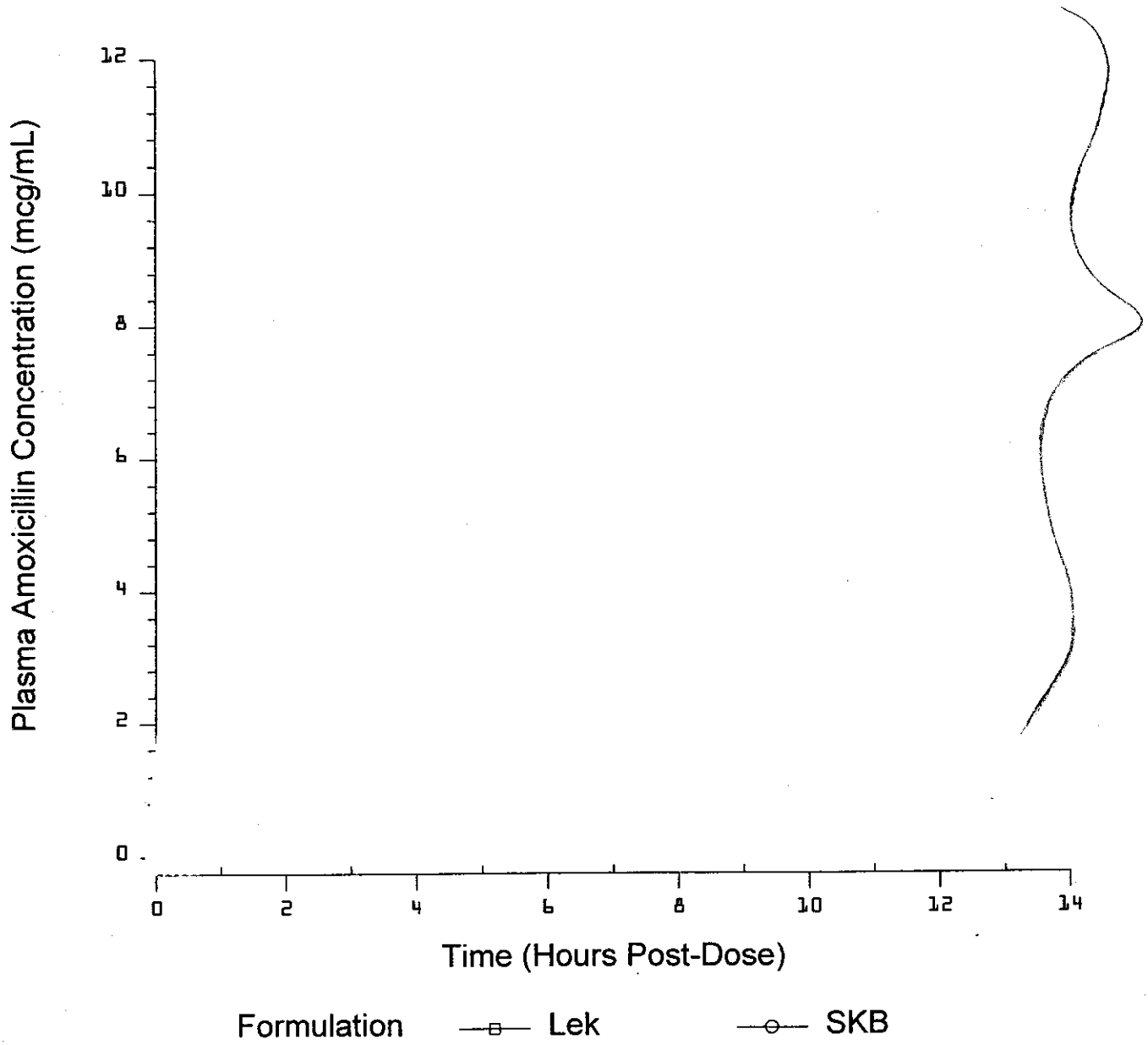


FIGURE 2
CLAVULANIC ACID PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME
SINGLE-DOSE FASTING STUDY #992128
(LINEAR PLOT)

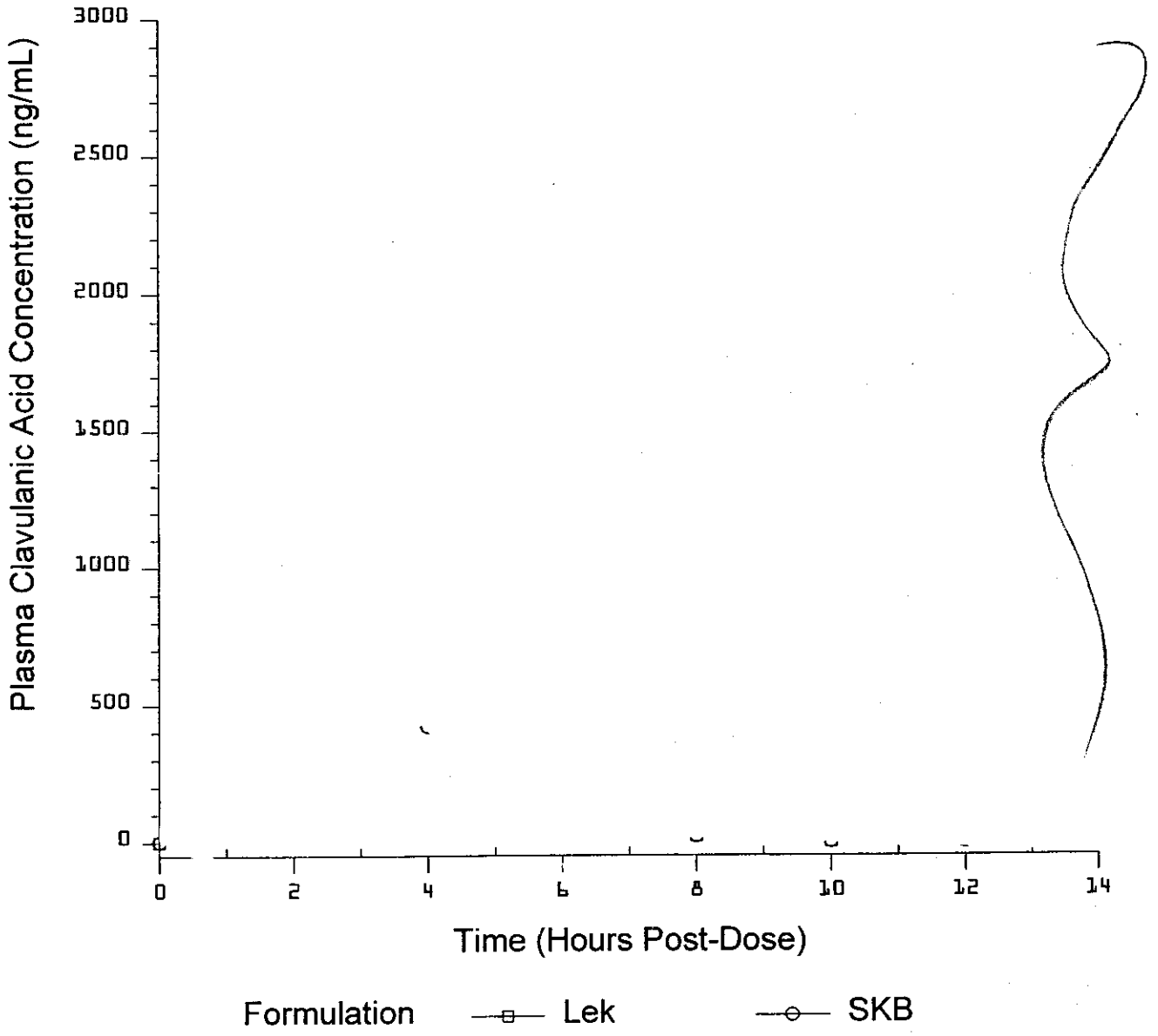


FIGURE 3
AMOXICILLIN PLASMA CONCENTRATIONS (MCG/ML) VERSUS TIME
FED/FASTING SINGLE-DOSE STUDY #992129

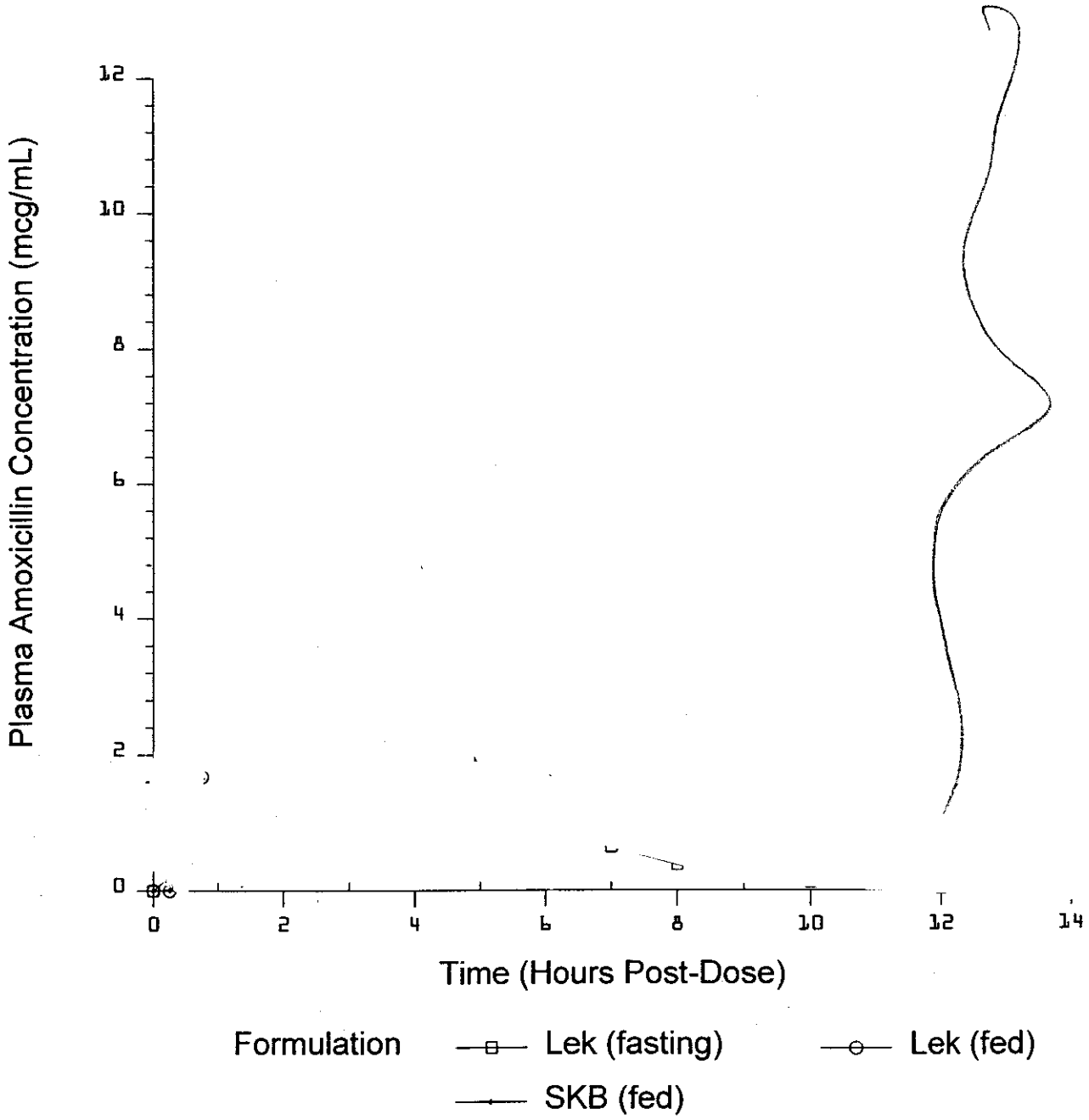
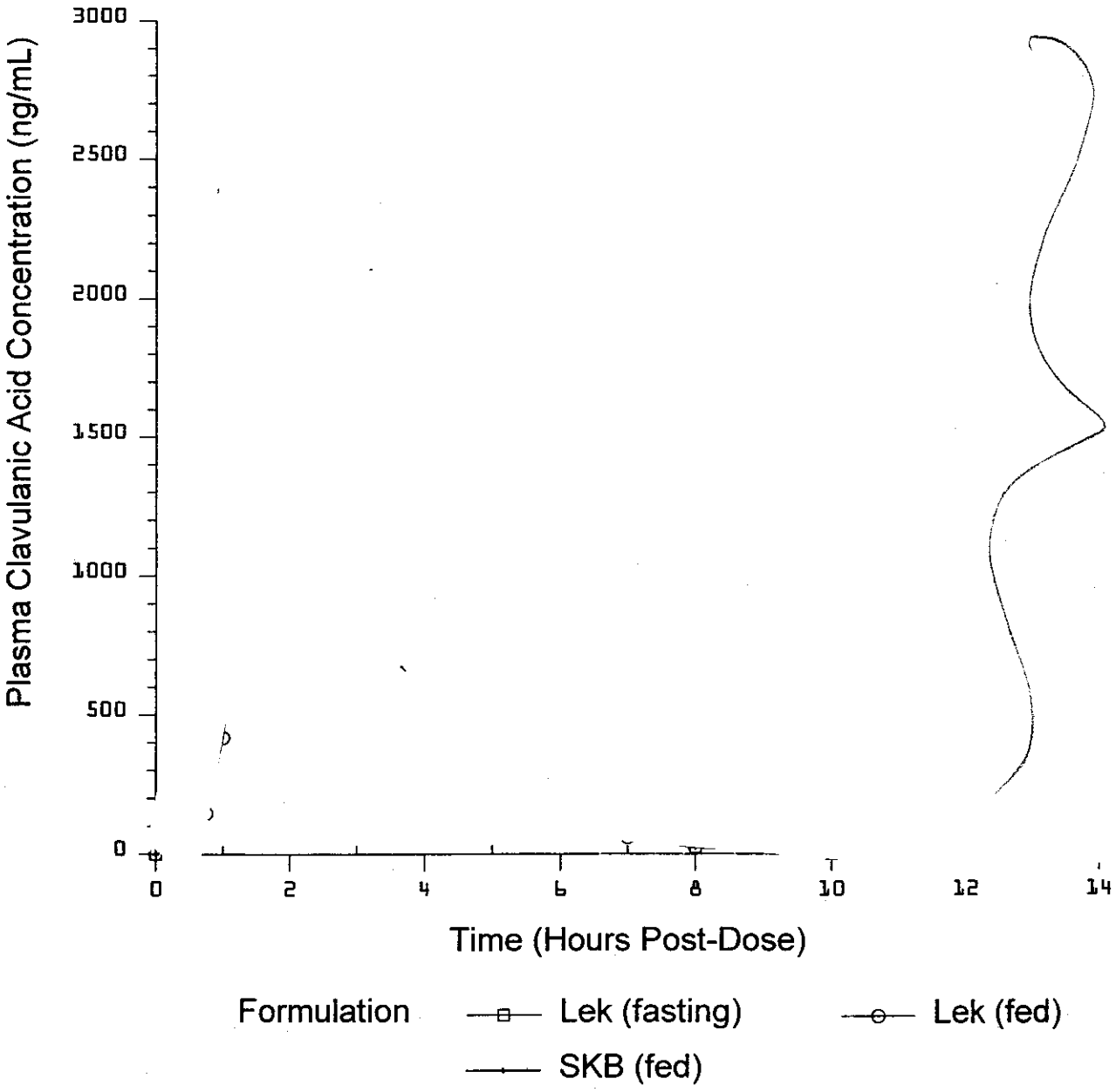


FIGURE 4
CLAVULANIC ACID PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME

FED/FASTING SINGLE-DOSE STUDY #992129



BIOEQUIVALENCY COMMENTS

ANDA: 65-093

APPLICANT: LEK Pharmaceutical and Chemical Company d.d.

DRUG PRODUCT: Amoxicillin; Clavulanate Potassium Tablets, USP 875 mg; 125 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

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

Sincerely yours,

/S/

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

CC: ANDA 65-093
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chanev /S/ /S/ 8/9/2001
HFD-652/ Y. Huang /S/ 8/9/2001
HFD-617/ K. Scardin
HFD-650/ D. Conn for IWJ 8/21/2001

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BIOEQUIVALENCY - ACCEPTABLE Submission date: 05/14/01

1. **FASTING STUDY** (STF) o/c
Clinical:
Analytical:
Strength: 875 mg/125 mg
Outcome: AC

2. **FOOD STUDY** (STP) o/c
Clinical:
Analytical:
Strengths: 875 mg/125 mg
Outcome: AC

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:
The biostudies and dissolution data were found acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 65-093 SPONSOR: LEK Pharmaceutical and Chemical Company d.d.

DRUG AND DOSAGE FORM: Amoxicillin; Clavulanate Potassium Tablets, USP
STRENGTH(S): 875 mg; 125 mg
TYPES OF STUDIES: Fasting, postprandial and dissolution
CLINICAL STUDY SITE: [redacted]

ANALYTICAL SITE: [redacted]

STUDY SUMMARY: Fasting and postprandial studies are acceptable

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

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

PRIMAR[illegible] /S/ .R: James Chaney BRANCH: I
INITIA[illegible] _____ DATE: 8/9/2001

TEAM LEADER: Yih-Chain Huang BRANCH: I
INITIAL: _____ /S/ DATE: 8/9/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL : ___ /S/ ___ DATE : 8/21/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-093

ADMINISTRATIVE DOCUMENTS

Furness, Scott

	Council, Jacqueline
cc:	Adams, Richard C; Anderson, Mark D
Subject:	Chemist's Response To Questions from the Lablening Division

Hi Jackie,

We just finished the first cycle CMC review of LEK's Amoxicillin/Clavulanate Tablet application. I have answered each of your questions below (my comments in italics):

NOTES/QUESTIONS TO THE CHEMIST:

1. The firm indicates that their drug product is produced by fermentation of Streptomyces clavuligerus. Is this statement accurate?

   Yes, that is an accurate statement.

2. The firm recommends dispensing their drug product in tightly closed, moisture-proof containers. Has the firm submitted data to support this statement for their package size of 20s.

   The firm has submitted acceptable USP <661> and <671> tests results. Hence, these appear to be tightly closed, moisture proof containers.

3. Can you inform me if the firm's container closure is child-resistant or non-child-resistant. [I saw both listed].

   Actually, the only supporting data I observed was for the child-resistant closure. No non-child resistant closures were indicated.

Thanks!

Scott

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

ANDA Number: 65-093

Date of Submission: - September 2, 2002
- September 24, 2002

Applicant's Name: Lek Pharmaceuticals d.d.

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base)

Labeling Deficiencies:

1. CONTAINER: 20s

   a. On the front and side panels revise " [redacted] to read "as clavulanate potassium".

   b. On the side panel prior to the "Usual Dosage: ..." statement add the text, "Advise patient to keep in closed container".

2. INSERT

   a. TITLE

      Following the established name, either delete the strengths of your drug products or include the strength of each active ingredient, amoxicillin ___ mg as the trihydrate and clavulanic acid ___ mg as clavulanate potassium.

   b. CLINICAL PHARMACOLOGY

      i. We encourage you to print the second footnote on same column as the table.

      ii. Microbiology/Susceptibility Testing

      Dilution Techniques

      We acknowledge that you revised this subsection in your September 24, 2002, submission. However, at this time we request that this subsection remain the same as your insert labeling submitted on February 8, 2002.

   c. PRECAUTIONS/Labor and Delivery

      We note that you added the text, [redacted] subsection in this amendment. Delete this text.

   d. DOSAGE AND ADMINISTRATION

      i. Use the official USP established name when referring to your drug product as follows:

... amoxicillin ___ mg as the trihydrate and clavulanic acid
___ mg as clavulanate potassium.

If you prefer, you may use the official USP established name followed by the strength of each active ingredient.

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

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

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

/S/

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 [red jackets, need to check blue or with Mark]

Container Labels: 20's

Satisfactory in final print as of the, 2002, submission.

Professional Package Insert Labeling:

Satisfactory in final print as of the---- Feb.8, 2002, submission.

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/clavulante potassium tablets

NDA Firm: GlaxoSmithKline

Date of Approval of NDA Insert and supplement #: S-32, approved 2/11/98.

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

Was this approval based upon an OGD labeling guidance? No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels: RLD

Basis of Approval for the Carton Labeling: RLD

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	NA
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 25		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?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	X*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the 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 indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus.* Is this statement accurate?

2. The firm recommends dispensing their drug product in tightly closed, moisture-proof containers. Has the firm submitted data to support this statement for their package size of 20s.

3. Can you inform me if the firm's container closure is child-resistant or non-child-resistant. [I saw both listed].

-----Original Message-----
From: Furness, Scott
Sent: Tuesday, October 22, 2002 9:45 AM
To: Anderson, Mark D; Council, Jacqueline
Subject: RE: 65093/65117 NOTES TO THE CHEMIST

Jackie,

My answers follow your questions in blue type.

Thanks,
Scott

-----Original Message-----
From: Anderson, Mark D
Sent: Tuesday, October 22, 2002 8:53 AM
To: Furness, Scott
Cc: Council, Jacqueline
Subject: FW: 65093/65117 NOTES TO THE CHEMIST

Scott,

Here are 2 more applications for comment.

thanks, Mark

-----Original Message-----
From: Council, Jacqueline
Sent: Monday, October 21, 2002 7:18 PM
To: Anderson, Mark D
Subject: 65093/65117 NOTES TO THE CHEMIST

Mark,

Below are my NOTES TO THE CHEMIST for 65093 and 65117.

Jacqueline

ANDA Number: 65-093

Date of Submission: - September 2, 2002

- September 24, 2002

Applicant's Name: Lek Pharmaceuticals d.d.

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base)

NOTES/QUESTIONS TO THE CHEMIST:

1. The firm indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus*. Is this statement accurate?

   Yes, this is an accurate statement.

2. The firm recommends dispensing their drug product in tightly closed, moisture-proof containers.

   Has the firm submitted data to support this statement for their package size of 20s.

Data have been submitted which support that statement.

3. Can you inform me if the firm's container closure is child-resistant or non-child-resistant. [I saw both listed].

The information I have show child-resistant closures only.

FOR THE RECORD:

1. Reference Listed drug: Augmentin® (amoxicillin/clavulante potassium)/NDA 50-564
   Current insert approved 2/11/98.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
   [B1.1, p. 4311, 4312]

3. Manufacturing Processing Facility:

   Lek Pharmaceutical and Chemical Company d.d.
   Ljublana, Solvenia
   [B1.2, p.4507]

4. Container/Closure:

plastic bottle with CRC
[Vol. B1.3, p.4805]

The chemist review indicates that the firm's caps are CRC.
[V:drive]

5. Physical Description:

The firm's physical description of their tablet found in the HOW SUPPLIED section is consistent with their finished dosage statements.
[Vol. B1.3, p.4848]

6. Package Size:

NDA – 20s and 100s unit dose
ANDA – 20s

7. Patent/Exclusivity: None

8. Storage/Dispense:

NDA – Store tablets at or below 25°C (77°F). Dispense in tightly closed, moisture-proof containers.
ANDA- same

9. Scoring: NDA – unscored
ANDA – unscored

Date of Review: 10/21/02

Date of Submission: 9/2/02 and 9/24/02

Primary Reviewer: |S| 10-23-02
Jacqueline Council, Pharm.D. Date:

Acting Team Leader: |S| Date: 10/24/02
Captain Lillie Golson

---

cc: ANDA: 65-093
DUP/DIVISION FILE
V:\FIRMSAM\LEK\LTRS&REV\65093.na3.l.doc
Review

Mark,

Below are my NOTES TO THE CHEMIST for 65093 and 65117.

Jacqueline

ANDA Number: 65-093

Date of Submission: - September 2, 2002
- September 24, 2002

Applicant's Name: Lek Pharmaceuticals d.d.

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base)

NOTES/QUESTIONS TO THE CHEMIST:

1. The firm indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus.* Is this statement accurate?

   Yes, this is an accurate statement.

2. The firm recommends dispensing their drug product in tightly closed, moisture-proof containers.
Has the firm submitted data to support this statement for their package size of 20s.

Data have been submitted which support that statement.

3. Can you inform me if the firm's container closure is child-resistant or non-child-resistant. [I saw both listed].

The information I have show child-resistant closures only.

FOR THE RECORD:

1. Reference Listed drug: Augmentin® (amoxicillin/clavulante potassium)/NDA 50-720
   Current insert approved 2/11/98/S-3.
   NOTE: The most recent approved labeling for NDA 50-720/S-6/approved 4/10/02 is not currently available. After numerous attempts to obtain a hard copy and/or electronic copy from the Division of Anti-Infective Drug Products, we were informed that neither is available. Therefore, an Office decision was made to continue to use the approved insert labeling from S-3 as the labeling model for this drug product.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
   [B1.1, p. 4311, 4312]

3. Manufacturing Processing Facility:

   Lek Pharmaceutical and Chemical Company d.d.
   Ljublana, Solvenia
   [B1.2, p.4507]

4. Container/Closure:

   [redacted] plastic bottle with CRC
   [Vol. B1.3, p.4805]

   The chemist review indicates that the firm's caps are CRC.
   [V:drive]

5. Physical Description:

   The firm's physical description of their tablet found in the HOW SUPPLIED section is consistent with their finished dosage statements.
   [Vol. B1.3, p.4848]

6. Package Size:

   NDA – 20s and 100s unit dose
   ANDA – 20s

7. Patent/Exclusivity: None

8. Storage/Dispense:

   NDA – Store tablets at or below 25°C (77°F). Dispense in tightly closed, moisture-proof containers.
   ANDA- same

9. Scoring: NDA – unscored
   ANDA – unscored

10. Bioavailability/Bioequivalence:

- The firm's pharmacokinetic parameters from the fasting and non-fasting bioequivalence studies were comparable to the reference listed drug.
- The firm's pharmacokinetic parameters listed in the insert labeling are comparable to the bioequivalence study results.
- The bioequivalence fasting and fed studies are acceptable from a labeling point of view.
- The reported pharmacokinetic parameters from the fasting and fed bioequivalence studies were found to be within acceptable limits by the Division of Bioequivalence.

Fasting Bioequivalence study: 875 mg/125 mg tablet (base)
Amoxicillin

Parameter	ANDA	NDA	Insert
ACUI (mcg.hr/mL) ACUT (mcg.hr/mL)	35.29 34.97	35.75 35.42	53.5 ±12.31 [875 mg q12h]
Cmax (mcg/mL)	—	—	—
T ½ (hr)	1.41	1.47	1.3
Tmax (hr)	1.58	1.76	1.5

CLAVULANIC ACID

Parameter	ANDA	NDA	Insert [clavulanate potassium]
ACUI (mcg.hr/mL ACUT (mcg.hr/mL)	6.2 6.	6.2 6.1	10.2±3.04 [only value]
Cmax (mcg/mL)	—	—	—
T ½ (hr)	1.2	1.1	1

Non-Fasting Bioequivalence study: 875 mg/125 mg(base) tablet
Amoxicillin

Parameter	ANDA	NDA	Insert
ACUI (mcg.hr/mL ACUT (mcg.hr/mL)	32.78 32.46	31.85 31.50	Dosing in the fasted or fed state has minimal effect on the pharmacokinetic of amoxicillin
Cmax (mcg/mL)	—	—	
T ½ (hr)	1.33	1.32	
Tmax (hr)	2.2	2.08	

CLAVULANIC ACID

Parameter	ANDA	NDA	Insert [clavulanate potassium]
ACUI (mcg.hr/mL ACUT (mcg.hr/mL)	4.4 4.1	4.8 4.4	Dosing in the fasted or fed state has minimal effect on the pharmacokinetic of amoxicillin
Cmax (mcg/mL)	—	—	
T ½ (hr)	1		

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 11/13/02

Da[illegible] /S/ .8/02 and 11/04/02

Primary Reviewer: [illegible]
Jacqueline Council, Pharm.D. Date: 11-18-02

Acting Team Leader: [illegible] /S/
Captain Lillie Golso[illegible] Date: 11/18/02

cc: ANDA: 65-093
DUP/DIVISION FILE
V:\FIRMSAM\LEK\LTRS&REV\65093..ap.l...doc
Review

APPROVAL SUMMARY

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

ANDA Number: 65-093

Date of Submission: - October 28, 2002
- November 4, 2002

Applicant's Name: Lek Pharmaceuticals d.d.

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base)

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: 20's
  Satisfactory in final print as of the November 4, 2002, submission. [Vol. 5.1]
- Professional Package Insert Labeling:
  Satisfactory in final print as of the November 4, 2002, submission.
  [Insert code: 676519][Revised October 2002] – Vol. 5.1

-Future revisions:

1. CONTAINER: 20s - Side panel
   As previously requested, revise ' _____ .' to read "as clavulanate potassium",
2. INSERT
   a. TITLE
      Add "or" between your drug product strengths.
   b. DOSAGE AND ADMINISTRATION
      As previously requested, use the official USP established name when referring to your drug product and include the strength of both active ingredients. For example:
      - Amoxicillin and Clavulanate Potassium Tablet USP, amoxicillin ___ mg as the trihydrate and clavulanic acid ___ mg as clavulanate potassium
        or
      - Amoxicillin and Clavulanate Potassium Tablet USP, ___mg amoxicillin as the trihydrate and ___mg clavulanic acid as the potassium salt
        or
      - Amoxicillin and Clavulanate Potassium Tablet USP, ___ mg/___ mg (base)

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Augmentin®
NDA Number: 50-720
NDA Drug Name: Amoxicillin/clavulante potassium tablets
NDA Firm: GlaxoSmithKline
Date of Approval of NDA Insert and supplement #: S-3, approved 2/11/98.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: RLD
Basis of Approval for the Carton Labeling: RLD

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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 25		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?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration? *Some of the inactives differ from the RLD.	X*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the 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 indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus*. Is this statement accurate?

2. The firm recommends dispensing their drug product in tightly closed, moisture-proof containers. Has the firm submitted data to support this statement for their package size of 20s.

3. Can you inform me if the firm's container closure is child-resistant or non-child-resistant. [I saw both listed].

-----Original Message-----
From: Furness, Scott
Sent: Tuesday, October 22, 2002 9:45 AM
To: Anderson, Mark D; Council, Jacqueline
Subject: RE: 65093/65117 NOTES TO THE CHEMIST

Jackie,

My answers follow your questions in blue type.

Thanks,
Scott

-----Original Message-----
From: Anderson, Mark D
Sent: Tuesday, October 22, 2002 8:53 AM
To: Furness, Scott
Cc: Council, Jacqueline
Subject: FW: 65093/65117 NOTES TO THE CHEMIST

Scott,

Here are 2 more applications for comment.

thanks, Mark

-----Original Message-----
From: Council, Jacqueline
Sent: Monday, October 21, 2002 7:18 PM
To: Anderson, Mark D
Subject: 65093/65117 NOTES TO THE CHEMIST

ANDA APPROVAL SUMMARY

ANDA: 65-093

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium Tablets USP

FIRM: LEK Pharmaceuticals d.d.

DOSAGE FORM: Tablets

STRENGTH(s): 875 mg Amoxicillin/125 mg Potassium Clavulanate

CGMP STATEMENT/EER UPDATE STATUS: Signed cGMP certification was provided on p. 4512 of the original submission. EER found acceptable on 9/23/02.

BIO STUDY: The Bioequivalency studies were found acceptable on 21-AUG-2001.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substances and drug product are USP. The firm is using the USP testing methods with the following

[redacted]

exceptions: [redacted] in house methods.

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

LABELING: Acceptable on November 18, 2002.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): The exhibit batch records were included for lot A01400501B on pp. 4659-4793. Master batch records were also provided (same batch sizes as in the exhibit batches). The manufacturing process described in the executed batch records is essentially the same as that provided in the master batch records. In support of the drug product formulation changes proposed in the 6/12/02 gratuitous amendment, the firm provided executed batch records (lot #2409102D, ~~~~ tablets) on pp. 179-371. The Amoxicillin

drug substance was obtained from ——— and the Clavulanate Potassium drug substance was obtained from Lek's own in-house facility.

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

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): See Above.

CHEMIST: SCOTT FURNESS **DATE:** 11/19/02 /S/ 11/19/02

SUPERVISOR: RICHARD ADAMS **DATE:** 11/19/02 /S/ 11/19/02

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 65-093

Date of Submission: May 14, 2001

Applicant's Name: Lek Pharmaceutical and Chemical Company d.d. [U.S. Agent: Lek USA, Inc.]

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base)

Labeling Deficiencies:

1. CONTAINER: 20s

   a. Relocate your "Each tablet contains ..." statement to appear as the first statement on the side panel. In addition, revise this statement to read, "Each film coated tablet contains ___ mg amoxicillin as the trihydrate and ___ mg clavulanic acid as the potassium salt".

   b. To be consistent with your HOW SUPPLIED section of your insert labeling revise your "Dispense in..." statement to read, "Dispense in a tight moisture-proof...".

2. INSERT

   a. General Comment

      Use the abbreviation "mcg" for micrograms instead of '

   b. DESCRIPTION

      Prior to your list of inactive ingredients print the following text:

      > Each film coated tablet contains ___ mg amoxicillin as the trihydrate and ___ mg clavulanic acid as the potassium salt. Each... 0.63 mEq potassium.

   c. PRECAUTIONS (Drug/Laboratory Test)

      Revise the last sentence of the first paragraph to read, "... Clinistix®) or be used".
      [Delete "

   d. We note that you only included the dosage and administration text for Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base). Revise this section to be consistent with the reference listed drug insert labeling by referencing all strengths. See attachment.

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

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

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

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

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

Attachment: DOSAGE AND ADMINISTRATION section of 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 24	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		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?			
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 indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus.* Is this statement accurate?

2. The firm recommends dispensing their drug product in tightly closed, moisture-proof containers. Has the firm submitted data to support this statement for their package size of 20s.

3. Can you inform me if the firm's container closure is child-resistant or non-child-resistant. [I saw both listed].

FOR THE RECORD:

1. Reference Listed drug: Augmentin® (amoxicillin/clavulante potassium)/NDA 50-564
   Current insert approved 2/11/98.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
   [B1.1, p. 4311, 4312]

3. Manufacturing Processing Facility:

   Lek Pharmaceutical and Chemical Company d.d.
   Ljublana, Solvenia
   [B1.2, p.4507]

4. Container/Closure:

   _____ plastic bottle with CRC or non-CRC???
   [Vol. B1.3, p.4805]

5. Physical Description:

   The firm's physical description of their tablet found in the HOW SUPPLIED section is consistent

with their finished dosage statements.
[Vol. B1.3, p.4848]

6. Package Size:

NDA – 20s and 100s unit dose
ANDA – 20s

7. Patent/Exclusivity: None

8. Storage/Dispense:

NDA – Store tablets at or below 25°C (77°F). Dispense in tightly closed, moisture-proof containers.
ANDA- same

9. Scoring: NDA – unscored
ANDA – unscored

Date of Review: 7/23/01

D[illegible] /01

8-9-01

Primary Review[illegible]
Jacqueline Co[illegible] arm.D. Date:

Team Lead[illegible] Date: 8/10/01

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cc: ANDA: 65-093
DUP/DIVISION FILE
V:\FIRMSAM\LEK\LTRS&REV\65093NA1.L.doc
Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY

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

ANDA Number: 65-093

Date of Submission: February 8, 2002

Applicant's Name: Lek Pharmaceutical and Chemical Company d.d. [U.S. Agent: Lek USA, Inc.]

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base)

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

Do you have 12 Final Printed Labels and Labeling? Yes [red jackets, need to check blue or with Mark]

Container Labels: 20's

Satisfactory in final print as of the February 8, 2002, submission.

Professional Package Insert Labeling:

Satisfactory in final print as of the February 8, 2002, submission.

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/clavulante potassium tabets

NDA Firm: GlaxoSmithKline

Date of Approval of NDA Insert and supplement #: S-32, approved 2/11/98.

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

Was this approval based upon an OGD labeling guidance? No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels: RLD

Basis of Approval for the Carton Labeling: RLD

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		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?			
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 indicates that their drug product is produced by fermentation of *Streptomyces clavuligerus*. Is this statement accurate?

2. The firm recommends dispensing their drug product in tightly closed, moisture-proof containers. Has the firm submitted data to support this statement for their package size of 20s.

3. Can you inform me if the firm's container closure is child-resistant or non-child-resistant. [I saw both listed].

FOR THE RECORD:

1. Reference Listed drug: Augmentin® (amoxicillin/clavulante potassium)/NDA 50-564
   Current insert approved 2/11/98.

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
   [B1.1, p. 4311, 4312]

3. Manufacturing Processing Facility:

   Lek Pharmaceutical and Chemical Company d.d.
   Ljublana, Solvenia
   [B1.2, p.4507]

4. Container/Closure:

   [redacted] plastic bottle with CRC or non-CRC?
   [Vol. B1.3, p.4805]

   The chemist review indicates that the firm's caps are CRC.
   [V:drive]

5. Physical Description:

   The firm's physical description of their tablet found in the HOW SUPPLIED section is consistent with their finished dosage statements.
   [Vol. B1.3, p.4848]

6. Package Size:

NDA – 20s and 100s unit dose
ANDA – 20s

7. Patent/Exclusivity: None

8. Storage/Dispense:

NDA – Store tablets at or below 25°C (77°F). Dispense in tightly closed, moisture-proof containers.
ANDA- same

9. Scoring: NDA – unscored
ANDA – unscored

10. Bioavailability/Bioequivalence:

- The firm's pharmacokinetic parameters from the fasting and non-fasting bioequivalence studies were comparable to the reference listed drug.
- The firm's pharmacokinetic parameters listed in the insert labeling are comparable to the bioequivalence study results.
- The bioequivalence fasting and fed studies are acceptable from a labeling point of view.
- The reported pharmacokinetic parameters from the fasting and fed bioequivalence studies were found to be within acceptable limits by the Division of Bioequivalence.

Date of Review: 2/25/02

Date of S[illegible] 2/8/02

Primary Reviewer: /S/ 3-7-02
Jacqueline Council, Pharm.D. Date:

Charles Hoppes, Team Le[illegible] /S/ Date: 3/8/02

cc: ANDA: 65-093
DUP/DIVISION FILE
V:\FIRMSAM\LEK\LTRS&REV\65093ap.ldoc.doc
Review

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

ANDA Number: 65-093

Date of Submission: May 14, 2001

Applicant's Name: Lek Pharmaceutical and Chemical Company d.d. [U.S. Agent: Lek USA, Inc.]

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base)

Labeling Deficiencies:

1. CONTAINER: 20s

   a. Relocate your "Each tablet contains ..." statement to appear as the first statement on the side panel. In addition, revise this statement to read, "Each film coated tablet contains ___ mg amoxicillin as the trihydrate and ___ mg clavulanic acid as the potassium salt".

   b. To be consistent with your HOW SUPPLIED section of your insert labeling revise your "Dispense in..." statement to read, "Dispense in a tight moisture-proof...".

2. INSERT

   a. General Comment

      Use the abbreviation "mcg" for micrograms instead of .

   b. DESCRIPTION

      Prior to your list of inactive ingredients print the following text:

      > Each film coated tablet contains ___ mg amoxicillin as the trihydrate and ___ mg clavulanic acid as the potassium salt. Each... 0.63 mEq potassium.

   c. PRECAUTIONS (Drug/Laboratory Test)

      Revise the last sentence of the first paragraph to read, "... Clinistix®) or be used". [Delete

   d. We note that you only included the dosage and administration text for Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg (base). Revise this section to be consistent with the reference listed drug insert labeling by referencing all strengths. See attachment.

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

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

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

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

/S/

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

Attachment: DOSAGE AND ADMINISTRATION section of Augmentin® insert labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-093

CORRESPONDENCE

lek

LEK Services, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760
Fax: 910 362 0790

November 7, 2002

ORIG AMENDMENT
NIAF
DRAFT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

Re:	Correction to Telephone Amendment to ANDA # 65-093
Product :	Amoxicillin and Clavulanate Potassium Tablets, USP 875 mg/125 mg
Manufacturer:	LEK Pharmaceuticals d.d. Ljubljana, Slovenia
U.S. Agent :	LEK Services, Inc. Donald Spiegel, Director, Scientific Affairs
Re:	October 24, 2002 FDA Correspondence from Division of Labeling and Program Support - Labeling Review Branch My October 29, 2002 and November 6, 2002 letters to FDA

To whom it may concern;

On behalf of LEK Pharmaceuticals d.d. enclosed are three copies of a correction to the November 6, 2002 Telephone Amendment for Amoxicillin and Clavulanate Potassium Tablets, USP 875mg/125 mg.

The three-page correction involves a comparison of the 20-count label container regarding prior and proposed labeling.

Sincerely,

Donald Spiegel
Director, Scientific Affairs

cc.: Mateja Pfajfar, Head of FP Registrations

RECEIVED
NOV 0 8 2002
OGD / CDER

lek

Lek Pharmaceuticals d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

Tel: + 386 1 580 21 11
Facsimile: + 386 1 568 35 17
Cable: lek ljubljana si
Regulatory Affairs
Tel: + 386 1 580 33 32

Facsimile: + 386 1 568 13 66

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

MPN II, HFD-600
7500 Standish Place
Rockville, MD20855
USA

ORIG AMENDMENT
N/AF

FPL

No.: 1780/02
Date: November 4, 2002

SUBJECT: **ANDA 65-093**
Final prints to the Telephone Amendment to ANDA 65-093 for Amoxicillin and Clavulanate Potassium Tablets, USP 875/125 mg (dated October 28, 2002)

Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) no. 65-093 for Amoxicillin and Clavulanate Potassium Tablets, USP 875/125 mg dated May 14, 2001 and submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act.
Reference is also made to the Telephone Amendment submitted to the FDA on October 28, 2002. As stated in the cover letter of this Telephone Amendment Lek is submitting the final prints (12) for each pack size of container label and package insert.

The documentation is sent in three copies (review, archival and field copy). Lek hereby certifies that the field (third) copy provided is a true copy of the archival and review copies of the application.

Sincerely yours,

Regulatory Affairs
M. Pfajfar

A. Vukadin-Škulj
Director

CC: Mr. P. Kleutghen, Lek Services, Inc.; Mr. M. Žorž, Mr. M. Jesenko, Lek d.d.

lek

LEK Services, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760
Fax: 910 362 0790

November 6, 2002

ORIG AMENDMENT
N/AF

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

Re:	Telephone Amendment to ANDA # 65-117
Product :	Amoxicillin and Clavulanate Potassium Tablets, USP 500 mg/125 mg
Manufacturer:	LEK Pharmaceuticals d.d. Ljubljana, Slovenia
U.S. Agent :	LEK Services, Inc. Donald Spiegel, Director, Scientific Affairs
Re:	October 24, 2002 FDA Correspondence from Division of Labeling and Program Support - Labeling Review Branch My October 29, 2002 letter to FDA

To whom it may concern;

On behalf of LEK Pharmaceuticals d.d. enclosed are three hard copies {Archival, Review and Field} of a Telephone Amendment for Amoxicillin and Clavulanate Potassium Tablets, USP 500 mg/125 mg.

Also included are three hard copies {Archival, review and Field} of final printed labeling for the subject product.

Sincerely,

Donald Spiegel
Director, Scientific Affairs

cc.: Mateja Pfajfar, Head of FP Registrations

lek

Lek Pharmaceuticals d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

Tel: + 386 1 580 21 11
Facsimile: + 386 1 568 35 17
Cable: lek ljubljana si
Regulatory Affairs
Tel: + 386 1 580 33 32

Facsimile: + 386 1 568 13 66

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

MPN II, HFD-600
7500 Standish Place
Rockville, MD20855
USA

NEW CORRESP
NC

No.:
Date: October 28, 2002

SUBJECT: **ANDA 65-093**
Telephone Amendment to ANDA 65-093 for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg

Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) no. 65-093 for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg dated December 26, 2001 and submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act.
Reference is also made to the FDA, Office of Generic Drugs, Division of Labeling and Program Support deficiency letter dated October 24, 2002.

This Telephone Amendment is being submitted in order to respond the questions raised in the above mentioned deficiency letter dated October 24, 2002 for ANDA no. 65-093.
We acknowledge that the final prints of labels and package insert are requested, but due to the fact that final prints can not be available in due time and to facilitate the review of this Telephone Amendment, we are submitting computer generated labels and package insert. Please note that the computer generated labels and package insert are exactly the same as will be the final prints. Lek will submit the final prints as a separate correspondence as soon as they are available.

The amendment is submitted by fax followed by three hard copies (archival, review and field).

Sincerely yours,

M. Prajfar
Regulatory Affairs
A. Vukadin-Škulj
Director

CC: Mr. P. Kleutghen, Lek Services, Inc.; Mr. M. Žorž, Mr. M. Jesenko, Lek d.

RECEIVED
NOV 0 7 2002
OGD / CDER

lek

Lek Services, Inc.

115 North Third Street
Suite 301
Wilmington, NC 28401

Phone: (910) 362 0760
Fax: (910) 362 0790

October 28, 2002

ORIG AMENDMENT
N/A FT
DRFT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

To Whom It May Concern:

Please note that the enclosed documentation is to be treated as a Telephone Amendment to ANDA #65-093 as indicated in the cover letter.

Due to the high number of pages, less than optimal fax print quality, and the need to submit several pages in color, Lek Services, Inc. is sending the amendment by courier rather than by fax. A hard copy will follow.

Sincerely,

Branko Huc, Ph.D.
Executive Vice President

BH/kwf

lek

Lek Pharmaceuticals d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

Tel: + 386 1 580 21 11
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Cable: lek ljubljana si
Regulatory Affairs
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Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

MPN II, HFD-600
7500 Standish Place
Rockville, MD20855
USA

ORIG AMENDMENT
N/A m

FPL

September 24, 2002/139102

SUBJECT: **ANDA 65-093**
Minor Amendment to ANDA for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg

Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) no. 65-093 for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg dated May 14, 2001 and submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act.
Reference is also made to the FDA, Office of Generic Drugs, Division of Chemistry II "Minor Amendment" letter dated September 6, 2002.

This Minor Amendment is being submitted in order to respond all the questions raised in the above mentioned deficiency letter dated September 6, 2002 for ANDA no. 65-093. In addition please note that based on the labeling comments in the deficiency letter dated September 6, 2002 for Amoxicillin and Clavulanate Potassium Tablets USP, 500/125 mg (ANDA 65-117) we considered these comments also for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg. Simultaneously we introduce the combined package insert for both tablet strengths (875/125 mg and 500/125 mg) for marketing of Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg. Please note that the combined insert was made uniform to the RLD labeling Augmentin® (amoxicillin/clavulanate potassium) Tablets issued on May 2002. Final prints of container labels and package insert as well as side-by-side comparisons are enclosed in this Amendment.
The amendment is submitted in three copies (archival, review and field).

Sincerely yours,

Head of Department

M. Pfajfar

Regulatory Affairs
Director
A. Vukadin-Škulj

CC: Mr. P. Kleutghen, Lek Services, Inc.; Mr. M. Žorž, Mr. M. Jesenko, Lek d.d.

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SEP 30 2002
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10/4/02

Lek Pharmaceuticals d.d.

lek

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

MPN II, HFD-600
7500 Standish Place
Rockville, MD20855
USA
No.: 118181/02

NEW CORRESP
NC
ORIG AMENDMENT
N/AF
DOCKET

Verovškova 57
SI - 1526 Ljubljana
Slovenia

Phone: +386 1 580 21 11
Fax: +386 1 568 35 17

Regulatory Affairs

Phone: +386 1 580 33 32
Fax: + 386 1 568 13 66

Date: 2 September 2002

Subject: **AMENDMENT to ANDA 65-093, CHANGE OF THE CORPORATE NAME**
Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg

Dear Sirs

Reference is made to our Abbreviated New Drug Application (ANDA) #65-093 for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg submitted on May 14, 2001 pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act.

This amendment is being submitted to advise you that as of July 16, 2002, by an official registration at the District Court of Ljubljana, Department of Commercial Judicature, the name of the company changed from:

Lek Pharmaceutical and Chemical Company d.d., Verovškova 57, 1526 Ljubljana, Slovenia

to

Lek Pharmaceuticals d.d., Verovškova 57, 1526 Ljubljana, Slovenia.

Please note that the change of the name implements no change in ownership of the Lek's ANDA. From now on Lek will use and apply the new name in all future correspondence to the FDA.

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lek

The Amendment includes revised 356h Form, revised letter "Notification of Agent" and computer generated labeling including revised corporate name.
Since the ANDA is still under review the final prints of container labels and package insert will be submitted at the time of the next Amendment or prior to approval.

The documentation is sent in three copies (review, archival and field copy).

Should you have any questions concerning this ANDA, please contact:

Mr. Paul Kleutghen
President and CEO, LEK SERVICES, INC.
115 North Third Street - Suite 301
Wilmington NC 28401
Phone: (910) 362 - 0760
Fax: (910) 362 - 0051

or
Headquarters in Ljubljana:

Regulatory Affairs,
Mrs. A. Vukadin - Škulj, Director
Phone: + 386 1 580 3 332, + 386 1 580 2 338
Fax: + 386 1 568 1366

Sincerely yours

Lek Pharmaceuticals d.d.
Regulatory Affairs

M. Pfajfar
Head of Department

A. Vukadin - Škulj
Director

cc: Mr. Paul Kleutghen, LEK SERVICES, INC.; Mr. M. Žorž Lek d.d.

lek

Pharmaceutical and Chemical Company d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

Tel: + 386 1 580 21 11
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Cable: lek ljubljana si
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Facsimile: + 386 1 568 13 66

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

MPN II, HFD-600
7500 Standish Place
Rockville, MD20855
USA

N/Am

ORIG AMENDMENT

June 12, 2002/767/02

SUBJECT: **Amendment to ANDA 65-093 for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg**

Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) no. 65-093 for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg dated May 14, 2001 and submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act.

Lek at this time is submitting the Amendment to the ANDA no. 65-093 to support the following changes:

[redacted]

Specifications for tablets were revised to assure compliance with USP 25 and FDA requirements.

To support the changes the following items are included in the Amendment:

- Copy of the transmittal letter for the annual update of DMF [redacted] for Clavulanate Potassium substance including [redacted]. The annual update was submitted to the FDA on March 26, 2002.
- Revised specifications for active ingredients (revision to USP 25 and additional FDA requirements for Clavulanate Potassium)
- Revised specifications for inactive ingredients (revision to USP 25/NF 20)

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lek

Pharmaceutical and Chemical Company d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

- Revised specification for screw cap (additional parameter)
- Revised specifications for tablets (revision to USP 25 and FDA requirements)
- Specification and DMF letter for [redacted] (Lek proposes packaging of 20 tablet bottle with [redacted]
- Revised (proposed) blank batch records for manufacturing and proposed blank batch record for packaging of 20 tablets with [redacted]. Differencies between the old and proposed batch records are explained.
- Executed batch records (exhibit batch no. 2409102D, manufactured according to the revised manufacturing procedure with the clavulanate potassium obtained with [redacted] and packaged partly with [redacted]
- Analytical certificates for active ingredients used in the production of tablets batch no. 2409102D
- Analytical certificates for inactive ingredients used in the production of tablets batch no. 2409102D
- Analytical certificates for packaging materials used in the packaging of tablets batch no. 2409102D
- Analytical certificate for tablets batch no. 2409102D
- Dissolution profiles (comparative dissolution profiles between Augmentin® 875 mg tablets, Lek's biobatch (pre-change product) and Lek's tablets batch no. 2409102D (post-change product))
- Stability data (comparative accelerated and long-term stability testing on tablets batch no. 2409102D packed with [redacted]

We believe the data demonstrates that the proposed changes do not have any impact on the quality of the drug product.

This Amendment is sent in three copies (archival, field and review).

Regulatory Affairs

M. Pfajfar

A. Vukadin-Škulj
Director

ANDA 65-093

LEK USA Inc.,
U.S. Agent for: Lek Pharmaceutical and Chemical Company d.d.
Attention: Paul Kleutghen
333 Sylvan Avenue
Englewood Cliffs, NJ 07632

JUN 29 2001

Dear Sir:

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

NAME OF DRUG: Amoxicillin and Clavulanate Potassium Tablets USP, 875 mg/125 mg(base)

DATE OF APPLICATION: May 14, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 16, 2001

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

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

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5848

Sincerely yours,

/S/

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

lek

Pharmaceutical and Chemical Company d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

Tel: + 386 1 580 21 11
Facsimile: + 386 1 568 35 17
Cable: lek ljubljana si
Regulatory Affairs
Tel: + 386 1 580 33 32

Facsimile: + 386 1 568 13 66

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

MPN II, HFD-600
7500 Standish Place
Rockville, MD20855
USA

ORIG AMENDMENT
N/AM

June 11, 2002/753/02

SUBJECT: **ANDA 65-093**
Minor Amendment to ANDA for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg

Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) no. 65-093 for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg dated May 14, 2001 and submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act.
Reference is also made to the FDA, Office of Generic Drugs, Division of Chemistry II "Minor Amendment" letter dated March 28, 2002.

This Minor Amendment is being submitted in order to respond all the questions raised in the above mentioned deficiency letter dated March 28, 2002 for ANDA no. 65-093.

The amendment is submitted in three copies (archival, review and field).

Sincerely yours,

Head of Department
M. Prajfar

Regulatory Affairs
Director
A. Vukadin-Škulj

RECEIVED
JUN 1 4 2002
OGD / CDER

lek

NEW CORRESP

NC

LEK Services, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760
Fax: 910 362 0790

June 13, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Product :	**Minor Amendment to ANDA # 65-093** **Amoxicillin and Clavulanate Potassium Tablets, USP** **875 mg/125 mg**
Manufacturer:	LEK Pharmaceutical and Chemical Company d.d. Ljubljana, Slovenia
U.S. Agent :	LEK Services, Inc. Donald Spiegel, Director, Scientific Affairs
Re:	May 14, 2001 ANDA submission and FDA's March 28, 2002 Deficiency Letter

To whom it may concern;

On behalf of LEK Pharmaceutical and Chemical Company d.d., enclosed is a Minor Amendment for Amoxicillin and Clavulanate Potassium Tablets, USP 875 mg/125 mg in response to the subject Deficiency letter.

Sincerely,

Donald Spiegel
Director, Scientific Affairs

RECEIVED

JUN 1 4 2002

OGD / CDER

cc.: Mateja Pfajfar, Head of FP Registrations

6/18/02

lek

LEK USA, Inc.

333 Sylvan Avenue
Englewood Cliffs
N.J. 07632

Phone: (201) 541 9310
Fax: (201) 541 9314

505(b)(2)(A) OK
8-JUN-2001
/S/
/S/

May 14, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855, U.S.A.

Product :	ANDA for Amoxicillin and Clavulanate Potassium Tablets, USP, 875/125 mg
Manufacturer:	LEK Pharmaceutical and Chemical Company d.d. Ljubljana, Slovenia
U.S. Agent :	LEK USA, Inc. Donald Spiegel, Director Scientific Affairs

Abbreviated New Drug Application Submission

To whom it may concern:

On behalf of LEK Pharmaceutical and Chemical Company d.d., enclosed is the ANDA application for Amoxicillin and Clavulanate Potassium Tablets, USP, 875/125 mg in three copies (Archival, Review and Third copy).

The shipment is composed of 12 carton boxes with 37 volumes submitted:

Archival copy :	16 volumes
Review copy :	16 volumes
Third copy :	5 volumes

This application will include a BE ESD electronic submission. The diskettes will be sent as new correspondence within 30 days

CENTER FOR DRUG
RECD
MAY 16 2001
EVALUATION AND RESEARCH

Sincerely,

Donald Spiegel
Director, Scientific Affairs

CC.: Ms. Mirjam Sopar- Urleb, Director of Product Registration

lek

LEK Services, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760
Fax: 910 362 0790

February 8, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

[illegible] AMENDMENT FPL

Product : Amoxicillin and Clavulanate Potassium Tablets, USP, 875/125 mg

Manufacturer: LEK Pharmaceutical and Chemical Company d.d. Ljubljana, Slovenia

U.S. Agent : LEK Services, Inc.
Donald Spiegel, Director, Scientific Affairs

MINOR AMENDMENT to ANDA #65-093
Deficiency Letter of September 20, 2001

To whom it may concern:

On behalf of LEK Pharmaceutical and Chemical Company d.d., enclosed is a Minor Amendment responding to the questions raised in FDA's September 20, 2001 deficiency letter.

Sincerely,

CENTER FOR DRUG [illegible] FEB 11 2002 EVALUATION [illegible]

Donald Spiegel
Director, Scientific Affairs

CC.: Alenka Vukadin-Skulj, Director of Product Registration

2/13/02

lek

Pharmaceutical and Chemical Company d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

Tel: + 386 1 580 21 11
Facsimile: + 386 1 568 35 17
Cable: lek ljubljana si
Regulatory Affairs
Tel: + 386 1 580 33 32

Facsimile: + 386 1 568 13 66

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

MPN II, HFD-600
7500 Standish Place
Rockville, MD20855
USA

February 4, 2002

SUBJECT: **ANDA 65-093**
Minor Amendment to ANDA for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg

Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) #65-093 for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg dated May 14, 2001 pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act. Reference is also made to the FDA, Office of Generic Drugs, Division of Chemistry II and Division of Labeling and Program Support "Minor Amendment" letter dated September 20, 2001.

This Minor Amendment is being submitted in order to respond all the questions raised in the above mentioned deficiency letter dated September 20, 2001 for ANDA #65-093.

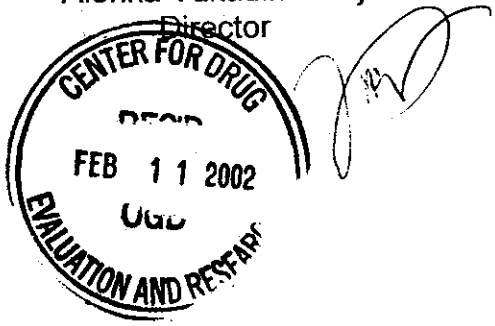
The amendment is submitted in three copies (archival, review and field).

Sincerely yours,

Lek Pharmaceutical and Chemical Company d.d.
Regulatory Affairs

Mirjan Žorž, Ph.D.
Head of Department

Alenka Vukadin-Škulj
Director



Enclosures:
- Minor Amendment in three copies (each in 1 volume)

cc: Mr. PAUL KLEUTGHEN, LEK SERVICES, INC.

lek

LEK Services, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760
Fax: 910 362 0790

August 16, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD. 20855

NEW CORRESP
NC

Subject: Change of Corporate Name and address for the U.S. Agent

Manufacturer: LEK Pharmaceutical and Chemical Company d.d.
Ljubljana, Slovenia

U.S. Agent : LEK Services, Inc.
Donald Spiegel, Director, Scientific Affairs

To whom it may concern:

On behalf of LEK Pharmaceutical and Chemical Company d.d., enclosed is correspondence in regard to a name change/address for the U.S. agent for nine described ANDA's.

Sincerely,

Donald Spiegel

Donald Spiegel
Director, Scientific Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 2 0 2001
DGD

Enclosures: Supplements for nine ANDA's

cc.: Mirjam Sopar-Urleb, Director of Product Registrations

lek

LEK USA, Inc.

333 Sylvan Avenue
Englewood Cliffs
N.J. 07632

Phone: (201) 541 9310
Fax: (201) 541 9314

June 13, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855, U.S.A.

NEW CORRESP
NC to Bio

Product :	Amendment to ANDA for Amoxicillin and Clavulanate Potassium Tablets, USP, 875/125 mg
Manufacturer:	LEK Pharmaceutical and Chemical Company d.d. Ljubljana, Slovenia
U.S. Agent :	LEK USA, Inc. Donald Spiegel, Director Scientific Affairs

Amendment to ANDA Submission of May 11, 2001

To whom it may concern:

On behalf of LEK Pharmaceutical and Chemical Company d.d., enclosed is a BE ESD electronic submission for Amoxicillin and Clavulanate Potassium Tablets, USP, 875/125 mg in one volume.

Sincerely,

Donald Spiegel
Director, Scientific Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECEIVED
JUN 18 2001
OGD

CC.: Mirjam Sopar- Urleb, Director of Product Registration

lek

Pharmaceutical and Chemical Company d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

Tel: + 386 1 580 21 11
Facsimile: + 386 1 568 35 17

Regulatory Affairs
Tel: + 386 1 581 41 11
+ 386 1 505 31 50
Facsimile: + 386 1 505 78 81

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD20855
USA

Ljubljana, June 12, 2001

This application includes a bioequivalence ESD electronic submission. The diskettes are enclosed.

Subject: **ANDA**
Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg
Amendment

Dear Sirs,

Reference is made to our ANDA for Amoxicillin and Clavulanate Potassium Tablets 875/125 mg of May 11, 2001.

This Amendment is being submitted in order to submit a BE ESD electronic submission.

Declaration

The information contained in the electronic submission of June 12, 2001 is not different from the information contained in the hard copy submission of May 11, 2001.

Number of volumes submitted:

1 volume of EVA supporting documentation containing 356 h form, Electronic Submission Document (ESD), Companion Document and Data Files.

Two sets of 3.5 inch double sided floppy disks (total four disks) are provided, with identical information on each set.

Should you have any questions concerning this ANDA, please contact:

Paul P. Kleutghen,
President of Lek USA, Inc.
333 Sylvan Avenue
Englewood Cliffs, New Jersey 07632
Phone: (201) 541-9310
Fax: (201) 541-9314

lek

Headquaters in Ljubljana:

Regulatory Affairs

Mrs Mirjam Šopar-Urleb, Director
Phone: + 386 1 581 41 11
+ 386 1 505 31 50
Fax: + 386 1 505 78 81

Yours faithfully,

Lek Pharmaceutical and Chemical Company d.d.
Regulatory Affairs

Mirjan Žorž, Ph.D.
Head of Department

Mirjam Šopar-Urleb
Director

cc: Paul P. Kleutghen, Lek USA Inc.

Enclosures:
1. A copy of the original application cover letter
2. EVA supporting documentation

APPEARS THIS WAY
ON ORIGINAL

lek

Pharmaceutical and Chemical Company d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

Tel: + 386 1 580 21 11
Facsimile: + 386 1 568 35 17
Cable: lek ljubljana si
Regulatory Affairs
Tel: + 386 1 581 41 11
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Facsimile: + 386 1 5057 881

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

MPN II, HFD-600
7500 Standish Place
Rockville, MD20855
USA

May 11, 2001

SUBJECT: **ANDA for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg**

This application will include a BE ESD electronic submission. The diskettes will be sent as new correspondence within 30 days.

Dear Sirs,

Enclosed please find original Abbreviated New Drug Application submission for Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg.

The ANDA is submitted pursuant to the Section 505(j) of the Food, Drug and Cosmetics Act and regulations implementing that Act (Title 21 of the Code of Federal Regulations), and contains in Lek's opinion and to the best of our knowledge all information required.

Please note that for simplicity the proposed product is referred to throughout the ANDA by the USAN recognized pharmacy equivalent name, " ————————Lek's proposed labeling reflects the established name "Amoxicillin and Clavulanate Potassium Tablets USP".

Lek hereby commits to resolve any issues identified in the methods validation process after approval.

Please note the following data:

Type of submission:

ANDA - original (paper version)

Additionally, this application includes a BE ESD electronic submission. The duplicate diskettes as well as the supporting documentation for EVA are enclosed in the separate volume of the archival copy. The declaration that the information in the electronic files is identical to the information provided in the paper (hard copy) submission, is enclosed in the Supporting documentation for EVA on pages 1-4.

Name, title, signature, and address of the applicant:

Lek Pharmaceutical and Chemical Company d.d.
Verovškova 57, 1526 Ljubljana, Slovenia

lek

Pharmaceutical and Chemical Company d.d.
Verovškova 57, 1526 Ljubljana, SLOVENIA

Responsible Official:
M. Šopar - Urleb, Director of Regulatory Affairs
Established name of the drug product:
Amoxicillin and Clavulanate Potassium Tablets USP, 875/125 mg
Number of volumes submitted:

- Archival copy (15 volumes)
- Review copy (16 volumes)
- Third copy (5 volumes)
- Two additional copies of analytical methods (3 volumes each)

Two 3.5 inch diskettes with BE data provided (bound in the separate volume of the archival copy),

Should you have any questions concerning this ANDA, please contact:
PAUL KLEUTGHEN,
President and CEO, LEK USA, Inc.
333 Sylvan Avenue
Englewood Cliffs, New Jersey 07632
Phone: (201) 541-9310
Fax: (201) 541-9314

or
Headquarters in Ljubljana:
Regulatory Affairs
Mrs. M. Šopar-Urleb, Director
Phone: + 386 1 5814111
+ 386 1 5053150
Fax: + 386 1 5057881

Sincerely yours

Lek Pharmaceutical and Chemical Company d.d.
Regulatory Affairs

Mirjan Žorž, Ph.D.
Head of Department

Mirjam Šopar-Urleb
Director

cc: Mr. PAUL KLEUTGHEN, LEK USA, Inc.