

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

Approval Package for:

APPLICATION NUMBER:

65-117

Generic Name: Amoxicillin and Clavulanate Potassium
Tablets USP, 500mg/125mg (base)

Sponsor: LEK Services, Inc.

Approval date: November 27, 2002

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**APPLICATION NUMBER:
65-117**

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APPLICATION NUMBER:

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APPROVAL LETTER

ANDA 65-117

NOV 27 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 December 21, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Amoxicillin and Clavulanate Potassium Tablets USP, 500 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 27, October 28, and November 4, 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, 500 mg/125 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Augmentin[®] Tablets, 500 mg, of GlaxoSmithKline). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

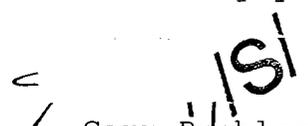
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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,


Gary Buehler 11/27/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-117

Final Printed Labeling

Amoxicillin and Clavulanate Potassium Tablets, USP

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

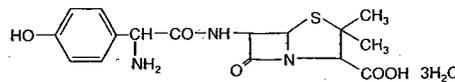
AMOXICILLIN, 875 mg, as the trihydrate and CLAVULANIC ACID, 125 mg, as clavulanate potassium

Rx only

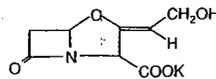
PRESCRIBING INFORMATION

DESCRIPTION

Amoxicillin and Clavulanate Potassium Tablet USP is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β -lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ and the molecular weight is 419.46. Chemically, amoxicillin is (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 β -lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β -lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid mediated β -lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$ 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 break-

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 (\pm S.D.)	clavulanate potassium (\pm S.D.)	amoxicillin (\pm S.D.)	clavulanate potassium (\pm S.D.)
250/125 mg q8h	26.7 \pm 4.56	12.6 \pm 3.25	3.3 \pm 1.12	1.5 \pm 0.70
500/125 mg q12h	33.4 \pm 6.76	8.6 \pm 1.95	6.5 \pm 1.41	1.8 \pm 0.61
500/125 mg q8h	53.4 \pm 8.87	15.7 \pm 3.86	7.2 \pm 2.26	2.4 \pm 0.83
875/125 mg q12h	53.5 \pm 12.31	10.2 \pm 3.04	11.6 \pm 2.78	2.2 \pm 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 spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

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

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

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

GRAM-POSITIVE AEROBES

Staphylococcus aureus (β -lactamase and non- β -lactamase producing).[†]

[†]Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

GRAM-NEGATIVE AEROBES

Enterobacter species (Although most strains of *Enterobacter* species are resistant *in vitro*, clinical

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Potassium Tablets, USP

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

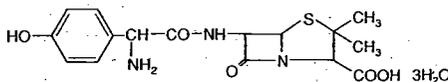
AMOXICILLIN, 875 mg, as the trihydrate and CLAVULANIC ACID, 125 mg, as clavulanate potassium

Rx only

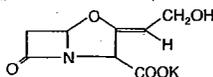
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DESCRIPTION

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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. The safety and efficacy of amoxicillin/clavulanate potassium have been established in clinical trials where amoxicillin/clavulanate potassium was taken without regard to meals.

below:

Dose ¹ and regimen	AUC ₀₋₂₄ (mcg·hr/mL)		C _{max} (mcg/mL)	
	amoxicillin (± S.D.)	clavulanate potassium (± S.D.)	amoxicillin (± S.D.)	clavulanate potassium (± S.D.)
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875/125 mg q12h	53.5 ± 12.31	10.2 ± 3.04	11.6 ± 2.78	2.2 ± 0.99

¹Mean 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.

²Administered 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 spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

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

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

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

GRAM-POSITIVE AEROBES

Staphylococcus aureus (β -lactamase and non- β -lactamase producing).¹

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

GRAM-NEGATIVE AEROBES

Enterobacter species (Although most strains of *Enterobacter* species are resistant *in vitro*, clinical efficacy has been demonstrated with amoxicillin/clavulanate potassium in urinary tract infections caused by these organisms.)
Escherichia coli (β -lactamase and non- β -lactamase producing).

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mase producing)

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

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

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

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

Amoxicillin/clavulanic acid exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.5 mcg/mL or less against most ($\geq 90\%$) strains of *Streptococcus pneumoniae*⁸; MICs of 0.06 mcg/mL or less against most ($\geq 90\%$) strains of *Neisseria gonorrhoeae*; MICs of 4 mcg/mL or less against most ($\geq 90\%$) strains of staphylococci and anaerobic bacteria; and MICs of 8 mcg/mL or less against most ($\geq 90\%$) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

⁸Because 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*¹¹

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

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

*Streptococcus pneumoniae*¹⁰

*Streptococcus pyogenes*¹⁰

viridans group *Streptococcus*¹⁰

GRAM-NEGATIVE AEROBES

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

*Neisseria gonorrhoeae*¹² (β -lactamase and non- β -lactamase producing)

*Proteus mirabilis*¹³ (β -lactamase and non- β -lactamase producing)

ANAEROBIC BACTERIA

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

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

Peptostreptococcus species⁹

⁹Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to these organisms.

¹⁰These are non- β -lactamase-producing organisms and, therefore, are susceptible to amoxicillin alone.

SUSCEPTIBILITY TESTING

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

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

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For gram-negative enteric aerobes:

MIC (mcg/mL)	Interpretation
$\leq 8/4$	Susceptible (S)
16/8	Intermediate (I)
$\geq 32/16$	Resistant (R)

For *Staphylococcus*¹⁴ and *Haemophilus* species:

MIC (mcg/mL)	Interpretation
$\leq 4/2$	Susceptible (S)
$\geq 8/4$	Resistant (R)

¹⁴Staphylococci which are susceptible to amoxicillin/clavulanic acid

lowing criteria s

MIC (mcg/mL)

$\leq 0.5/0.25$

1/0.5

$\geq 2/1$

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) ¹⁵
<i>Escherichia coli</i> ATCC 25922	2 to 8
<i>Escherichia coli</i> ATCC 35218	4 to 16
<i>Enterococcus faecalis</i> ATCC 29212	0.25 to 1.0
<i>Haemophilus influenzae</i> ATCC 49247	2 to 16
<i>Staphylococcus aureus</i> ATCC 29213	0.12 to 0.5
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03 to 0.12

¹⁵Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

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

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For *Staphylococcus*¹⁴ species and *H. influenzae*²:

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

For other organisms except *S. pneumoniae*³ and *N. gonorrhoeae*¹²:

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

¹⁴Staphylococci which are resistant to methicillin/oxacillin must be considered as resistant to amoxicillin/clavulanic acid.

²A broth microdilution method should be used for testing *H. influenzae*. Beta-lactamase negative, ampicillin-resistant strains must be considered resistant to amoxicillin/clavulanic acid.

³Susceptibility 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.

¹²A 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.

used:

Interpretation

Susceptible

Intermediate (I)

Resistant (R)

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)
<i>Escherichia coli</i> ATCC 25922	19 to 25
<i>Escherichia coli</i> ATCC 35218	18 to 22
<i>Staphylococcus aureus</i> 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 β -lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

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

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

Amoxicillin/clavulanic acid exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.5 mcg/mL or less against most ($\geq 90\%$) strains of *Streptococcus pneumoniae*⁶; MICs of 0.06 mcg/mL or less against most ($\geq 90\%$) strains of *Neisseria gonorrhoeae*; MICs of 4 mcg/mL or less against most ($\geq 90\%$) strains of staphylococci and anaerobic bacteria; and MICs of 8 mcg/mL or less against most ($\geq 90\%$) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

⁶Because 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*¹¹

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

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

*Streptococcus pneumoniae*¹¹

*Streptococcus pyogenes*¹¹

viridans group *Streptococcus*¹¹

GRAM-NEGATIVE AEROBES

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

*Neisseria gonorrhoeae*¹¹ (β -lactamase and non- β -lactamase producing)

*Proteus mirabilis*¹¹ (β -lactamase and non- β -lactamase producing)

ANAEROBIC BACTERIA

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

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

Peptostreptococcus species¹¹

¹¹Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to these organisms.
¹²These are non- β -lactamase-producing organisms and, therefore, are susceptible to amoxicillin alone.

SUSCEPTIBILITY TESTING

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method¹³ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanic acid.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanic acid 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
$\leq 8/4$	Susceptible (S)
16/8	Intermediate (I)
$\geq 32/16$	Resistant (R)

For *Staphylococcus*¹⁴ and *Haemophilus* species:

MIC (mcg/mL)	Interpretation
$\leq 4/2$	Susceptible (S)
$\geq 8/4$	Resistant (R)

¹⁴Staphylococci 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 fol-

MIC	Interpretation
$\leq 1/0.5$	Intermediate (I)
$\geq 2/1$	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/clavulanic acid powder should provide the following MIC values:

Microorganism	MIC Range (mcg/mL) ¹¹
<i>Escherichia coli</i> ATCC 25922	2 to 8
<i>Escherichia coli</i> ATCC 35218	4 to 16
<i>Enterococcus faecalis</i> ATCC 29212	0.25 to 1.0
<i>Haemophilus influenzae</i> ATCC 49247	2 to 16
<i>Staphylococcus aureus</i> ATCC 29213	0.12 to 0.5
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03 to 0.12

¹¹Expressed 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 procedure¹⁵ requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of amoxicillin/clavulanic acid (20 mcg amoxicillin plus 10 mcg clavulanic acid) 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/clavulanic acid (20 mcg amoxicillin plus 10 mcg clavulanic acid) disk should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For *Staphylococcus*¹⁶ species and *H. influenzae*¹⁶:

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

For other organisms except *S. pneumoniae*¹⁶ and *N. gonorrhoeae*¹⁶:

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

¹⁶Staphylococci which are resistant to methicillin/oxacillin must be considered as resistant to amoxicillin/clavulanic acid.

¹⁶A broth microdilution method should be used for testing *H. influenzae*. Beta-lactamase negative, ampicillin-resistant strains must be considered resistant to amoxicillin/clavulanic acid.

¹⁶Susceptibility 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.

¹⁶A 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-

anate potassium (20 mcg amoxicillin plus 10 mcg clavulanic acid) disk should provide the following zone diameters in these laboratory quality control strains.

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

INDICATIONS AND USAGE

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

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

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

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

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

While amoxicillin/clavulanic acid potassium is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to amoxicillin/clavulanic acid potassium treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β -lactamase-producing organisms susceptible to amoxicillin/clavulanic acid 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/clavulanic acid potassium. (See Microbiology subsection.)

Bacteriological studies, to determine the causative organisms and their susceptibility to amoxicillin/clavulanic acid 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/clavulanic acid potassium when there is reason to believe the infection may involve any of the β -lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

CONTRAINDICATIONS

Amoxicillin/clavulanic acid 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/clavulanic acid 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 combination of drugs

admits concurrently 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 Clinistix®, 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/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Teratogenic effects. Pregnancy (Category B):

Reproduction studies performed in pregnant rats and mice given amoxicillin/clavulanate potassium at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to amoxicillin/clavulanate potassium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

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

Nursing Mothers:

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

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 fre-

particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

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

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

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

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with amoxicillin/clavulanate potassium and, when reported, has been 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 con-

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.**

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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

amoxicillin. Concomitant use of oral contraceptives 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/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Teratogenic effects. Pregnancy (Category B):

Reproduction studies performed in pregnant rats and mice given amoxicillin/clavulanate potassium at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to amoxicillin/clavulanate potassium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

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

Nursing Mothers:

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

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

reactions include: abdominal discomfort, flatulence and headache.

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

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

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

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with amoxicillin/clavulanate potassium and, when reported, has been 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 q12h	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

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

and do not require gastric emptying. 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 intolerance, Amoxicillin and Clavulanate Potassium Tablet should be taken at the start of a meal.

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 q12h	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

- 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.
- National Committee for Clinical Laboratory Standards. Performance Standards for

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

NDC 48866-1002-0

Amoxicillin and Clavulanate Potassium Tablets, USP

Rx only
AMOXICILLIN, 500 mg,
as the trihydrate
CLAVULANIC ACID, 125 mg,
as clavulanate potassium

 **lek** 20 tablets
Manufactured by
Lek Pharmaceuticals d.d.
Verovškova 57, Ljubljana, Slovenia

Each film coated tablet contains 500 mg amoxicillin as the trihydrate and 125 mg clavulanate as the potassium salt. Each tablet contains 0.63 mEq potassium. 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.



676535

Exp. date:

NDC 48866-1002-1

Amoxicillin and Clavulanate Potassium Tablets, USP

Rx only
AMOXICILLIN, 500 mg,
as the trihydrate
CLAVULANIC ACID, 125 mg,
as clavulanate potassium

 **lek** 30 tablets
Manufactured by
Lek Pharmaceuticals d.d.
Verovškova 57, Ljubljana, Slovenia

Each film coated tablet contains 500 mg amoxicillin as the trihydrate and 125 mg clavulanate as the potassium salt. Each tablet contains 0.63 mEq potassium. 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.



676543

Exp. date:

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-117

CHEMISTRY REVIEW(S)

ANDA 65-117

Amoxicillin and Clavulanate Potassium Tablets USP, 500 mg/125 mg

**LEK Pharmaceutical and Chemical
Company d.d.**

**M. Scott Furness
Division of Chemistry II, Office of Generic Drugs**

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**APPEARS THIS WAY
ON ORIGINAL**

Chemistry Review Data Sheet

1. ANDA: 65-117
2. REVIEW #1
3. REVIEW DATE: 19-APR-2002
4. REVIEWER: M. Scott Furness
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	21-DEC-2001
Bioequivalence Electronic Submission	17-JAN-2002
Acceptable for Filing Notice	20-FEB-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	21-DEC-2001

7. NAME & ADDRESS OF APPLICANT:

Name: LEK Pharmaceutical and Chemical Company d.d.
Verovskova 57
Address: 1526 Ljubljana
SLOVENIA
LEK Services, Inc.
Representative: Attention: Paul Kleutghen
115 N. Third Street
Wilmington, NC 28401
Telephone: Phone: (910)-362-0760
Fax: (910)-362-0051

CHEMISTRY REVIEW

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name: Amoxicillin and Clavulanate Potassium Tablets USP, 500 mg/125 mg

9. 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.

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg Amoxicillin/125 mg Clavulanate Potassium

13. ROUTE OF ADMINISTRATION: Oral

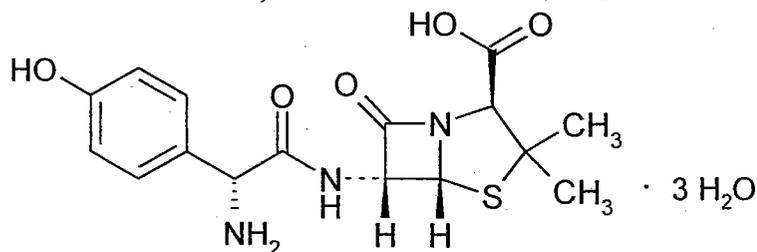
14. Rx/OTC DISPENSED: Rx OTC

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

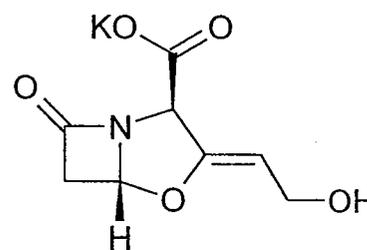
SPOTS product – Form Completed

Not a SPOTS product

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



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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Molecular Formula (Amoxicillin): $C_{16}H_{19}N_3O_5S \cdot 3H_2O$

Molecular Weight (Amoxicillin): 419.45

Molecular Formula (Clavulanate Potassium): $C_8H_8KNO_5$

Molecular Weight (Clavulanate Potassium): 237.25

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			3		2/27/02	-
	II			3		3/27/02	-
	III			3		9/26/00	
	III			4		-	-
	III			3,4		12/29/00	-
	III			3,4		2/13/02	-

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 –

4 –

5 –

6 –

7 –

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

B. Other Documents: N/A

CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS:

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

19. ORDER OF REVIEW

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

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA 65-117

The Executive Summary

I. Recommendations

A. **Recommendation and Conclusion on Approvability**
Not Recommended for Approval (MINOR)

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

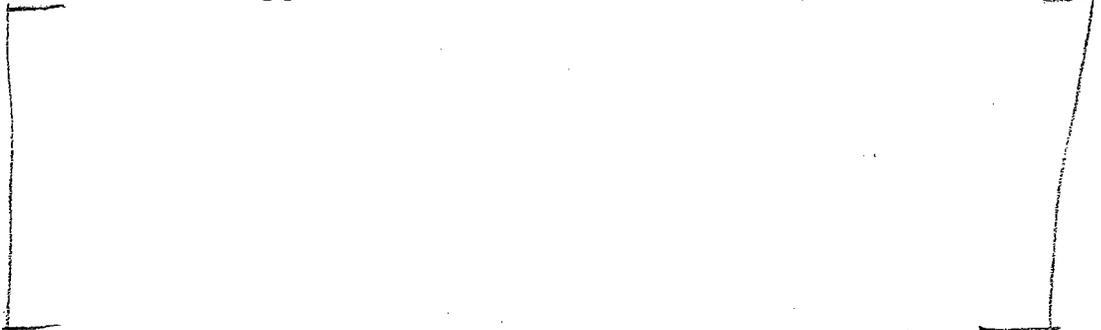
II. Summary of Chemistry Assessments

A. **Description of the Drug Product(s) and Drug Substance(s)**
The reference listed drug for this application is Augmentin[®] Tablets, manufactured by SmithKline Beecham, approved in NDA #50-720.

The drug substances are Amoxicillin USP and Clavulanate Potassium USP. The Amoxicillin USP drug substance has a 3 year expiration date, whereas the Clavulanate Potassium USP drug substance has a two year expiration date.

The drug product is Amoxicillin and Clavulanate Potassium Tablets USP, 500 mg/125 mg. The tablets are being marketed in 75 mL Bottles with counts of 20's and 30's. The formulation

The manufacturing process involves



In-process controls included:

CHEMISTRY REVIEW

Executive Summary Section

[]
B. Description of How the Drug Product is Intended to be Used
N/A

C. Basis for Approvability or Not-Approval Recommendation
[]

III. Administrative

cc: ANDA 65-117
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SFurness/4/19/02

HFD-643/RAdams/

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F/T by:

IS!

4/24/02

TYPE OF LETTER: NOT APPROVABLE - MINOR

Redacted

17

pages of trade

secret and /or

confidential

commercial

information

ANDA 65-117

Amoxicillin and Clavulanate Potassium Tablets USP, 500 mg/125 mg

**LEK Pharmaceutical and Chemical
Company d.d.**

**M. Scott Furness
Division of Chemistry II, Office of Generic Drugs**

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**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA 65-117

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Not Recommended for Approval (MINOR)

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

II. Summary of Chemistry Assessments

- A. **Description of the Drug Product(s) and Drug Substance(s)**
The reference listed drug for this application is Augmentin[®] Tablets, manufactured by SmithKline Beecham, approved in NDA #50-720.

The drug substances are Amoxicillin USP and Clavulanate Potassium USP. The Amoxicillin USP drug substance has a 3 year expiration date, whereas the Clavulanate Potassium USP drug substance has a two year expiration date.

The drug product is Amoxicillin and Clavulanate Potassium Tablets USP, 500 mg/125 mg. The tablets are being marketed in 75 mL Bottles with counts of 20's and 30's. The formulation

The manufacturing process involves



In-process controls included

- []
- B. Description of How the Drug Product is Intended to be Used**
N/A
- C. Basis for Approvability or Not-Approval Recommendation**
- []

III. Administrative

cc: ANDA 65-117
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SFurness/7/12/02

HFD-643/RAdams/7/14/02

V:\firmsam\LEK\ltrs&rev\65117na2.doc

F/T by: rad9/3/02

TYPE OF LETTER: NOT APPROVABLE - MINOR

Chemistry Review Data Sheet

1. ANDA: 65-117
2. REVIEW #2
3. REVIEW DATE: 12-JUL-2002
4. REVIEWER: M. Scott Furness
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	21-DEC-2001
Bioequivalence Electronic Submission	17-JAN-2002
Acceptable for Filing Notice	20-FEB-2002
CMC Deficiency #1	15-MAY-2002
Bioequivalence Acceptance	15-MAY-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
CMC Minor Amendment	12-JUN-2002
CMC Gratuitous Amendment	11-JUN-2002

7. NAME & ADDRESS OF APPLICANT:

Name: LEK Pharmaceutical and Chemical Company d.d.
Address: Verovskova 57
1526 Ljubljana
SLOVENIA
LEK Services, Inc.
Representative: Attention: Paul Kleutghen
115 N. Third Street
Wilmington, NC 28401
Telephone: Phone: (910)-362-0760
Fax: (910)-362-0051

CHEMISTRY REVIEW

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
 b) Non-Proprietary Name: Amoxicillin and Clavulanate Potassium Tablets USP, 500 mg/125 mg

9. 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.

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11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg Amoxicillin/125 mg Clavulanate Potassium

13. ROUTE OF ADMINISTRATION: Oral

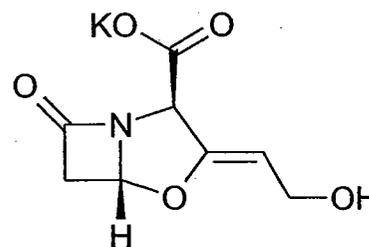
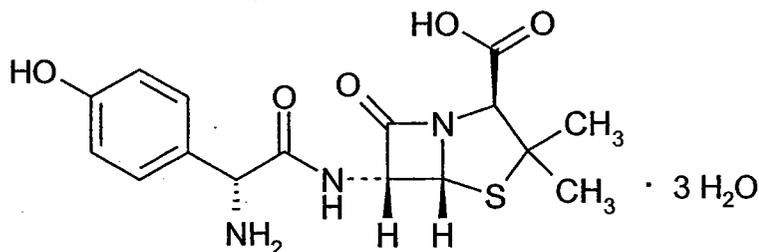
14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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



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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Molecular Formula (Amoxicillin): $C_{16}H_{19}N_3O_5S \cdot 3H_2O$

Molecular Weight (Amoxicillin): 419.45

Molecular Formula (Clavulanate Potassium): $C_8H_8KNO_5$

Molecular Weight (Clavulanate Potassium): 237.25

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
	II			3		2/27/02	-
	II			1		6/24/02	-
	III			3		9/26/00	
	III			4		-	
	III			3,4		12/29/00	-
	III			3,4		2/13/02	-

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 –

4 –

5 –

6 –

7 –

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

B. Other Documents: N/A

CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	N/A	N/A
EES	Pending	-	-
Methods Validation	N/A	N/A	N/A
Labeling	Pending	-	-
Bioequivalence	Acceptable	5/15/02	-
EA	N/A	N/A	N/A
Radiopharmaceutical	N/A	N/A	N/A

19. ORDER OF REVIEW

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

**APPEARS THIS WAY
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ANDA 65-117

Amoxicillin and Clavulanate Potassium Tablets USP, 500 mg/125 mg

**LEK Pharmaceutical and Chemical
Company d.d.**

**M. Scott Furness
Division of Chemistry II, Office of Generic Drugs**



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Chemistry Assessment 9

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Chemistry Review Data Sheet

1. ANDA: 65-117
2. REVIEW #3
3. REVIEW DATE: 22-OCT-2002
4. REVIEWER: M. Scott Furness
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Original Submission	21-DEC-2001
Bioequivalence Electronic Submission	17-JAN-2002
Acceptable for Filing Notice	20-FEB-2002
CMC Deficiency #1	15-MAY-2002
Bioequivalence Acceptance	15-MAY-2002
CMC Minor Amendment	12-JUN-2002
CMC Gratuitous Amendment	11-JUN-2002
CMC Deficiency #2	12-JUL-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

CMC Minor Amendment	27-SEP-2002
---------------------	-------------



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: LEK Pharmaceutical and Chemical Company d.d.
Address: Verovskova 57
1526 Ljubljana
SLOVENIA
LEK Services, Inc.
Representative: Attention: Paul Kleutghen
115 N. Third Street
Wilmington, NC 28401
Telephone: Phone: (910)-362-0760
Fax: (910)-362-0051

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name: Amoxicillin and Clavulanate Potassium Tablets USP, 500 mg/125 mg

9. 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.

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg Amoxicillin/125 mg Clavulanate Potassium

13. ROUTE OF ADMINISTRATION: Oral

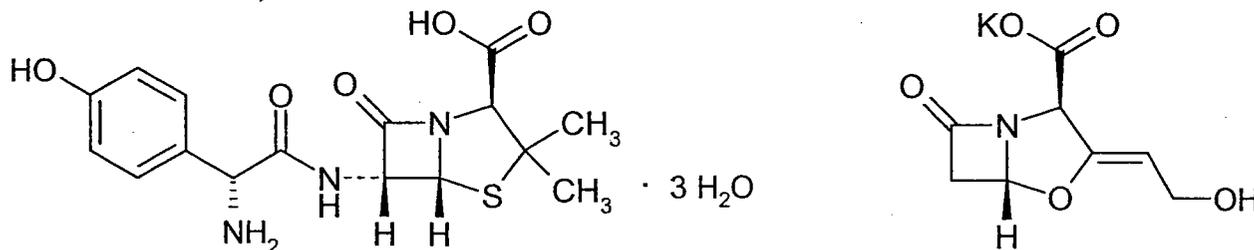
14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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


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): $C_{16}H_{19}N_3O_5S \cdot 3H_2O$

Molecular Weight (Amoxicillin): 419.45

Molecular Formula (Clavulanate Potassium): $C_8H_8KNO_5$

Molecular Weight (Clavulanate Potassium): 237.25

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
_____	II	_____	_____	1	_____	10/23/02	-
_____	II	_____	_____	1	_____	10/11/02	-
_____	III	_____	_____	3,4	_____	4/29/02	-
_____	III	_____	_____	3,4	_____	4/25/02	-
_____	III	_____	_____	3,4	_____	4/29/02	-
_____	III	_____	_____	3,4	_____	8/5/02	-

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – ~~_____~~

4 – ~~_____~~

5 – ~~_____~~

6 – ~~_____~~

7 – ~~_____~~

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	N/A	N/A
EES	Pending	-	-
Methods Validation	N/A	N/A	N/A
Labeling	Acceptable	11/26/02	J.Council
Bioequivalence	Acceptable	5/15/02	H.Nguyen
EA	N/A	N/A	N/A
Radiopharmaceutical	N/A	N/A	N/A

19. ORDER OF REVIEW

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

**APPEARS THIS WAY
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The Chemistry Review for ANDA 65-117

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Approval is recommended.
- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
N/A

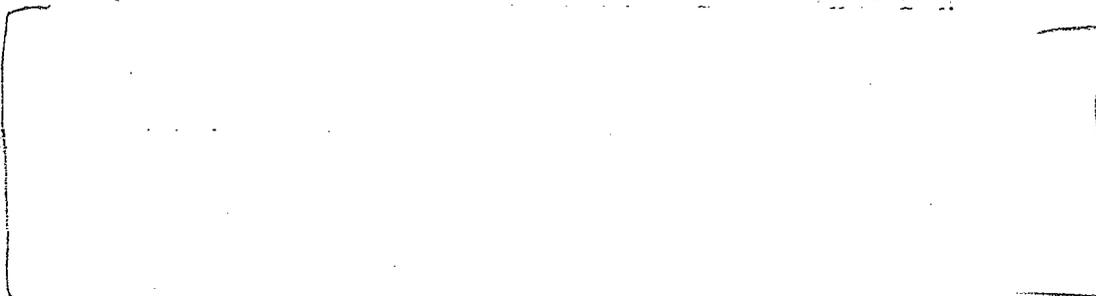
II. Summary of Chemistry Assessments

- A. **Description of the Drug Product(s) and Drug Substance(s)**
The reference listed drug for this application is Augmentin[®] Tablets, manufactured by SmithKline Beecham, approved in NDA #50-720.

The drug substances are Amoxicillin USP and Clavulanate Potassium USP. The Amoxicillin USP drug substance has a 3 year expiration date, whereas the Clavulanate Potassium USP drug substance has a two year expiration date.

The drug product is Amoxicillin and Clavulanate Potassium Tablets USP, 500 mg/125 mg. The tablets are being marketed in 75 mL ~~_____~~ Bottles with counts of 20's and 30's. The formulation ~~_____~~ ;

The manufacturing process involves ~~_____~~



In-process controls included ~~_____~~

CHEMISTRY REVIEW

Executive Summary Section

[]

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

C. Basis for Approvability or Not-Approval Recommendation

[]

III. Administrative

cc: ANDA 65-117
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/SFurness/10/22/02

HFD-643/RAdams/10/22/02

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F/T by: mda/11/26/02

TYPE OF LETTER: APPROVAL

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commercial

information

CHEMISTRY REVIEW

Chemistry Assessment Section

ANDA APPROVAL SUMMARY

ANDA: 65-117

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium Tablets USP

FIRM: LEK Pharmaceuticals d.d.

DOSAGE FORM: Tablets

STRENGTH(s): 500 mg Amoxicillin/125 mg Potassium Clavulanate

CGMP STATEMENT/EER UPDATE STATUS: Signed cGMP certification was provided on p. 4405 of the original submission. EER found acceptable on 9/23/02.

BIO STUDY: The Bioequivalency studies were found acceptable on 5/15/02.

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 exceptions: The firm has developed their own _____ method for Related Substances of the _____ substance and of the _____ drug product. An in-house GC method was also developed for _____ of the drug substance. Also, the firm has developed a NIR method for identification and _____ quantification in the Amoxicillin drug substance. Appropriate validation data were provided for each of these 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 11/25/02.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM’S SOURCE OF NDS OK?): The exhibit batch records were included for lot A01428105B on pp. 4592-4773 for _____ tablets. 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 6/11/02 gratuitous amendment, the firm provided executed batch records (lot #1379707C. _____ tablets) on pp. 139-322. The _____ 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

CHEMISTRY REVIEW

Chemistry Assessment Section

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

CHEMIST: SCOTT FURNESS
SUPERVISOR: RICHARD ADAMS

DATE: 10/22/02

DATE: 11/26/02

IS
11/25/02
IS
11/25/02

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-117

BIOEQUIVALENCE REVIEW

Q - Adams 12-26-01 1.1

AMOXICILLIN & CLAVULANATE
POTASSIUM TABLETS USP
500 mg + 125 mg
ANDA 65-117
Reviewer: Hoainhon Nguyen
65117N1201.doc

Lek. d.d.
Ljubljana, Slovenia
Submission Date: 12/26/01

Review of Bioequivalence Studies and Dissolution Data

I. Introduction

Indication: for the treatment of infections caused by susceptible (beta)-lactamase-producing strains of organisms in the following conditions: lower respiratory tract infections, otitis media and sinusitis (caused by *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*, skin and skin structure infections (caused by *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella* spp.) and urinary tract infections (caused by *Escherichia coli*, *Klebsiella* spp. And *Enterobacter* spp.)

Contents of Submission: a fasting bio study, a non-fasting bio study and dissolution data

RLD: The reference product used in the bio studies was Augmentin '500' Tablets, 500 mg + 125 mg, manufactured by SmithKline Beecham. The designated RLD drug product is Augmentin '875' Tablets, 875 mg +125 mg, manufactured by SmithKline Beecham.

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

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

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

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

Dose† and regimen	AUC ₀₋₂₄ (µg.hr/mL)		C _{max} (µg/mL)	
	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 the combination drug product are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half-life of amoxicillin after the oral administration of the drug product is 1.3 hours and that of clavulanic acid is 1.0 hour. Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of 10 mL of Augmentin 250 mg/5 mL suspension. One Augmentin 250 mg chewable tablet or 2 Augmentin 125 mg chewable tablets are equivalent to 5 mL of Augmentin 250 mg/5 mL suspension and provide similar serum levels of amoxicillin and clavulanic acid.

Neither component of the drug product is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound. Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. Experiments in animals suggest clavulanic acid is also well distributed in body tissues.

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

Financial Disclosure: pp. 106-113, Vol. C1.1

III. Protocol No.: 993614 Comparative, Randomized, 2-way Crossover Bioavailability Study of Lek and SmithKline Beecham (Augmentin) 500 mg Tablets Containing 500 mg Amoxicillin (as the Trihydrate)/125 mg Clavulanic Acid (as the Potassium Salt) in Healthy Adult Males Under Fasting Conditions

1) Study Information

STUDY FACILITY INFORMATION

Clinical Facility: _____
Medical Director: _____
Clinical Study Dates: 07/09/00 to 07/16/00
Analytical Facility: _____
Principal Investigator: _____
Analytical Study Dates: 07/19/00 to 08/25/00
Storage Period: 47 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Amoxicillin & Clavulanate Potassium (Co-Amoxiclav)	Amoxicillin & Clavulanate Potassium (Augmentin)
Manufacturer:	Lek, Ljubljana, Slovenia	SmithKline Beecham Pharmaceuticals, Philadelphia, USA
Manufacture Date:	N/A	N/A
Expiration Date:	05/02	05/01
ANDA Batch Size:		
Batch/Lot Number:	1428105B	MT2899
Potency:	99.7% + 97.5%	102.8% + 97.9%
Strength:	500 mg + 125 mg	500 mg + 125 mg
Dosage Form:	Tablets	Tablets
Dose Administered:	500 mg + 125 mg	500 mg + 125 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION

DESIGN

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

DOSING

SUBJECTS*

Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	50 males
Route of Administration:	oral	No. of Subjects Completing:	49

No. of Subjects Plasma Analyzed:	48 (per protocol)
No. of Dropouts:	1
Sex(es) Included:	Male
Healthy, Non-Smoking Volunteers Only:	Y
Mean age:	31 yrs (18-45)
Mean height:	174 cm (159-189)
Mean weight:	70 kg (58-84)
Race:	Black (4), Caucasian (46)

Exclusion/Inclusion Criteria: p. 158, Vol. C1.1.

Dietary Restrictions: Subjects were instructed to abstain from food or beverages containing xanthine (e.g. coffee, tea, caffeine-containing sodas, colas and chocolate, etc.) and alcohol starting 48 hours prior to dosing and throughout the study period. Grapefruit products were not allowed starting 7 days prior to dosing and throughout the study.

Activity Restrictions: Subjects were not permitted to lie down for the first 4 hours after dosing, unless medically necessary, in which case, it was documented. No vigorous physical activity was allowed during confinement.

Drug Restrictions: No concomitant drug therapy was allowed during the study except one to counteract an adverse event (e.g. occasional use of acetaminophen for headache). No prescription medication (including OTC medications) was allowed for 14 days prior to the study and throughout the study.

Confinement: At least 10 hours pre-dose to 12 hours post-dose

Blood Sampling: Pre-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 hours post-dose

2) Study Results

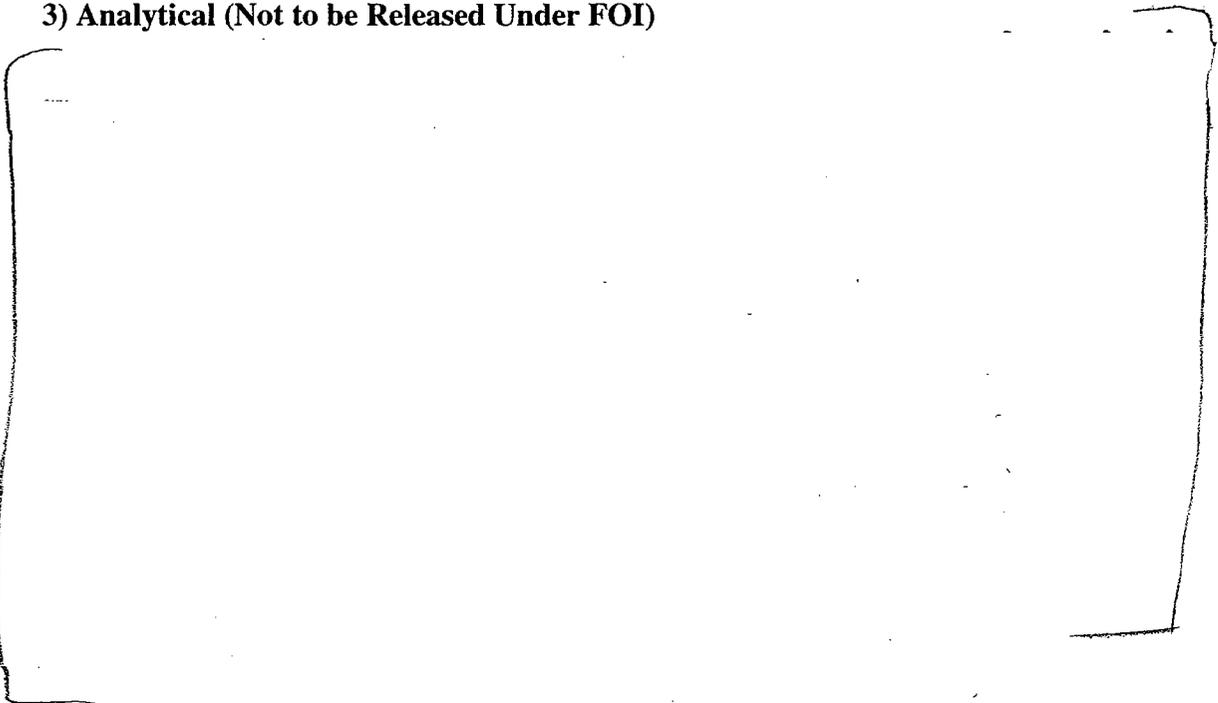
Clinical Adverse Events: There was no serious adverse event reported. None and one mild drug-related adverse reaction was reported during the Test and Referent treatments, respectively. The reaction was nausea.

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

Dropouts:

SUBJECT NO.: 20
REASON: Personal reasons
PERIOD: 1
REPLACEMENT Y(with alternate #49)

3) Analytical (Not to be Released Under FOI)



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Verification of Firm's Calculations and Analyses:

(a) Amoxicillin (based on reassayed concentration values only): Firm's values AUC(0-T) and AUC(0-Infinity) of amoxicillin, based on **reassayed** amoxicillin concentration values, were verified by the reviewer for all subjects. For Subjects # 1(Treatment A), 10 (Treatment A) and 42(Treatment A), the ratios for firm-calculated AUC's to reviewer-calculated AUC's were 1.09, 1.05 and 1.12, respectively, for both AUC(0-T) and AUC(0-Infinity). For all other subjects, these ratios were 1.0. The 90% confidence intervals based on reviewer-calculated AUC's were [0.92;0.99] and [0.92;0.99] for AUC(0-T) and AUC(0-Infinity), respectively. The 90% confidence interval based on firm-submitted CMAX's was also verified to be the same as the firm's.

(b) Amoxicillin (based on the originally assayed concentration values): The reviewer recalculated AUC's and re-determined CMAX based on the original assay values. The reviewer also reanalyzed the study results based on the original assay values. The results of the reanalyses are given in the amoxicillin PK parameter table below, in italic.

(c) Clavulanic Acid (based on reassayed concentration values only): Firm's values AUC(0-T) and AUC(0-Infinity) of clavulanic acid, based on **reassayed** clavulanic acid concentration values, were verified by the reviewer for all subjects. For Subject # 29(Treatment A), the ratio for firm-calculated AUC(0-Infinity)'s to reviewer-calculated AUC(0-Infinity)'s was 0.94. For all other subjects, these ratios were 1.0. The 90% confidence intervals based on reviewer-calculated AUC's and firm-submitted CMAX's were identical to the firm's.

(d) Clavulanic Acid (based on the originally assayed concentration values): The reviewer recalculated AUC's and re-determined CMAX based on the original assay values. The reviewer also reanalyzed the study results based on the original assay values. The results of the reanalyses are given in the clavulanic acid PK parameter table below, in italic.

**APPEARS THIS WAY
ON ORIGINAL**

Results:

TABLE I

**FASTING IN VIVO BIOEQUIVALENCE STUDY #993614
LEAST-SQUARES MEANS AND 90% GEOMETRIC CONFIDENCE INTERVALS
FOR PHARMACOKINETIC PARAMETERS**

Dose=500 mg; N=48

a) Amoxicillin

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)	90% C.I.
AUC(T) [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	23.69	24.63	0.96	0.93-1.00
(Geometric mean)	23.82*	24.73*	0.96*	0.93-1.00*
AUC(I) [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	24.04	24.95	0.96	0.93-1.00
(Geometric mean)	24.10*	24.98*	0.96*	0.93-1.00*
Cmax [$\mu\text{g}/\text{mL}$]	8.43	8.85	0.95	0.90-1.01
(Geometric mean)	8.59*	8.85*	0.97*	0.91-1.03*

*Re-analysis results based on original assay values.

**APPEARS THIS WAY
ON ORIGINAL**

TABLE II

Dose=125 mg; N=48
b) Clavulanic acid

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)	90% C.I.
AUC(T) [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	7.77	7.21	1.08	0.97-1.20
(Geometric mean)	7.81*	7.26*	1.08*	0.97-1.19*
AUC(I) [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	7.94	7.36	1.08	0.97-1.19
(Geometric mean)	7.93*	7.38*	1.07*	0.96-1.20*
Cmax [$\mu\text{g}/\text{mL}$]	3.71	3.51	1.06	0.94-1.19
(Geometric mean)	3.72*	3.51*	1.06*	0.94-1.19*

*Re-analysis results based on original assay values.

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TABLE III

**FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #993614
ARITHMETIC MEAN PLASMA CONCENTRATIONS ($\mu\text{G/ML}$)
VERSUS TIME (CV%) IN 48 SUBJECTS**

**Dose=500 mg
a) Amoxicillin**

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B
Pre-dose	0	0
0.25	0.267(186)	0.163(234)
0.50	2.73(72)	2.17(82)
0.75	5.45(49)	5.17(58)
1.00	7.25(40)	7.05(47)
1.25	7.70(35)	7.73(41)
1.50	7.54(32)	7.96(36)
1.75	7.18(29)	7.71(34)
2.00	6.80(28)	7.37(28)
2.50	5.75(27)	6.15(25)
3.00	4.58(32)	4.98(32)
4.00	2.77(51)	2.86(45)
5.00	1.41(49)	1.50(57)
6.00	0.759(48)	0.783(51)
7.00	0.407(41)	0.416(46)
8.00	0.243(43)	0.258(43)
10.0	0.0758(99)	0.0865(84)
12.0	0.0045(486)	0.0119(294)

**APPEARS THIS WAY
ON ORIGINAL**

TABLE IV
Dose=125 mg; N=48
b) Clavulanic acid (µG/ML)

TIME (HR)	TEST TREATMENT A(CV %)	REFERENCE TREATMENT B(CV %)
Pre-dose	0	0
0.25	0.178(203)	0.123(177)
0.50	1.68(76)	1.32(73)
0.75	3.26(52)	2.93(51)
1.00	3.82(40)	3.62(43)
1.25	3.68(36)	3.51(39)
1.50	3.34(36)	3.18(37)
1.75	2.81(33)	2.68(36)
2.00	2.39(34)	2.22(36)
2.50	1.63(41)	1.52(38)
3.00	1.14(45)	1.07(52)
4.00	0.558(44)	0.534(69)
5.00	0.285(43)	0.273(62)
6.00	0.168(42)	0.163(54)
7.00	0.101(41)	0.0964(46)
8.00	0.0610(64)	0.0522(78)
10.0	0.00964(229)	0.00703(268)
12.0	0	0

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ON ORIGINAL

FIGURE 1

**PLASMA CONCENTRATION ($\mu\text{g}/\text{mL}$) VERSUS TIME
SINGLE-DOSE FASTING STUDY #993614**

Project No. 993614
Mean Plasma Amoxicillin Concentrations
(Linear Plot)

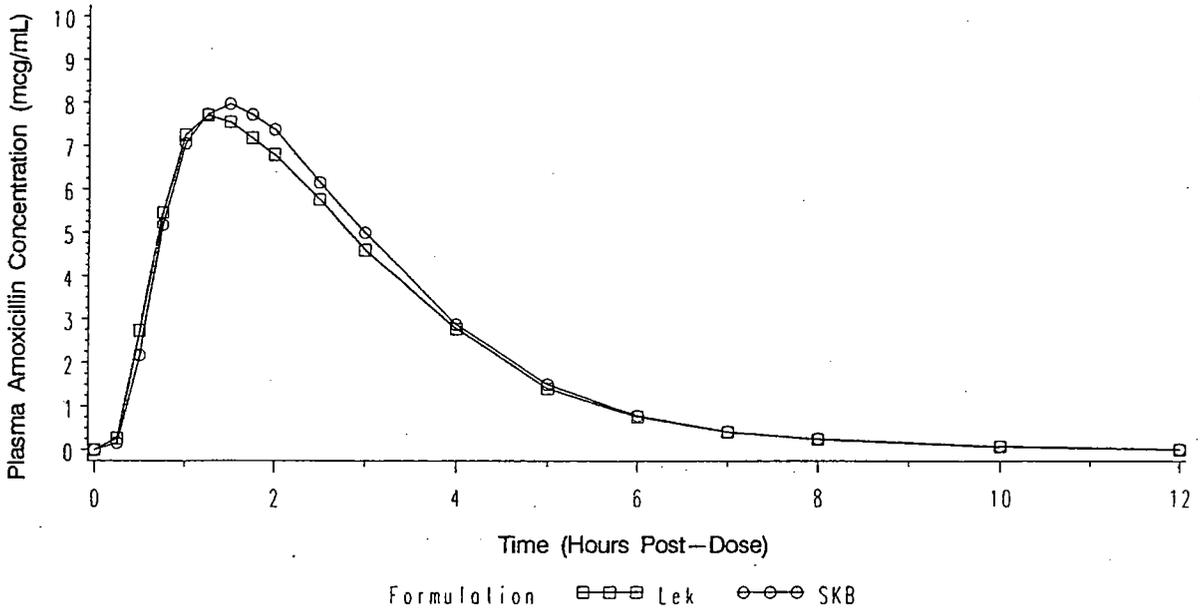


FIGURE 2

**PLASMA CONCENTRATION ($\mu\text{g/mL}$) VERSUS TIME
SINGLE-DOSE FASTING STUDY #993614**

Project No. 993614
Mean Plasma Clavulanic acid Concentrations
(Linear Plot)

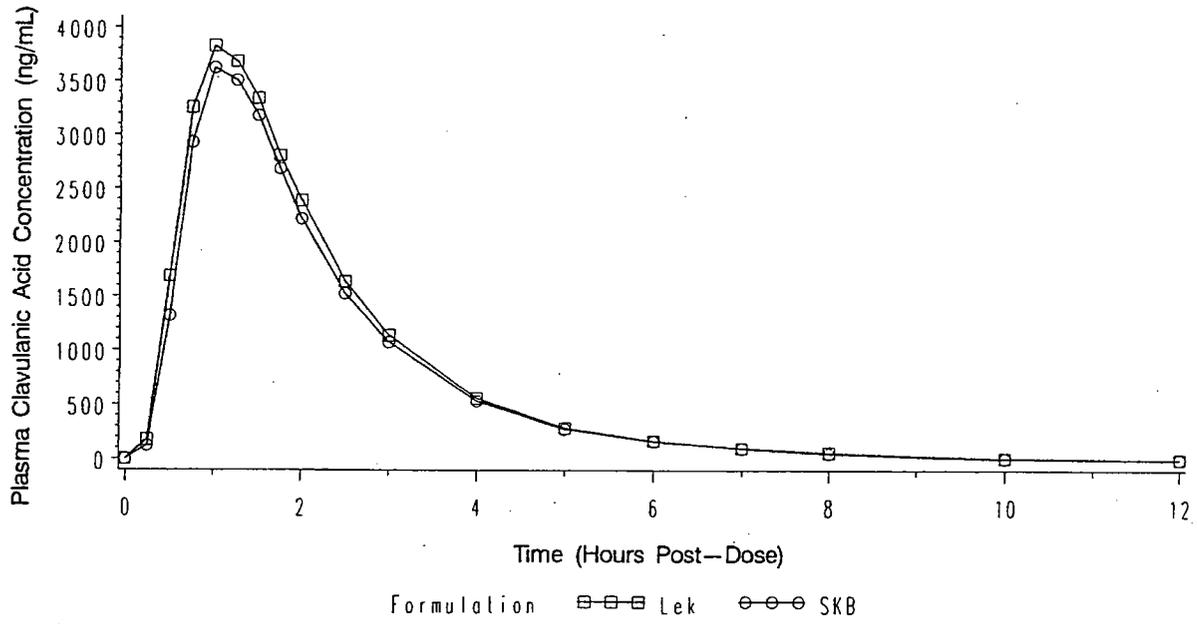


TABLE V
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #993614
ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS IN
48 SUBJECTS

a) Amoxicillin

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B
AUCT [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	24.12(20)	25.07(19)
AUCI [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	24.47(20)	25.38(19)
C _{max} [$\mu\text{g}/\text{mL}$]	8.69(24)	9.17(26)
T _{max} [hr]	1.62(44)	1.73(41)
Kel [1/hr]	0.489(26)	0.470(22)
T _{1/2} [hr]	1.52(30)	1.55(23)

TABLE VI

b) Clavulanic acid

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B
AUCT [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	8.43(34)	7.84(36)
AUCI [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	8.58(34)	7.98(35)
C _{max} [$\mu\text{g}/\text{mL}$]	4.10(36)	3.87(38)
T _{max} [hr]	1.14(25)	1.18(31)
Kel [1/hr]	0.461(19)	0.468(16)
T _{1/2} [hr]	1.57(25)	1.53(22)

5) Statistical Analysis: Fifty subjects entered the study. With the dropout of Subject #20, there were 49 subjects that completed the clinical portion of the study and, per protocol, a total of 48 sets of data used in the statistical analysis for this study (See Dropout, p.4).

There was no statistically significant difference ($\alpha=0.05$) between treatments for LAUC(0-T), LAUC(0-Infinity) or LCMAX of clavulanic acid or amoxicillin.

Conclusion: The 90% C.I.'s for lnAUC(0-T), lnAUC(0-Infinity) and lnCMAX were within the acceptable limit of [0.80; 1.25]. The study is acceptable.

IV. Protocol No.: 993615, Comparative, Randomized, 3-Way Crossover Bioavailability Study of Lek and SmithKline Beecham (Augmentin) 500 mg Tablets Containing 500 mg Amoxicillin (As the Trihydrate)/125 mg Clavulanic Acid (As the Potassium Salt) in Healthy Adult Males Under Fed and Fasting Conditions

1) Study Information

STUDY FACILITY INFORMATION

Clinical Facility: _____
Medical Director: _____
Clinical Study Dates: 06/29/00 to 07/13/00
Analytical Facility: _____
Principal Investigator: _____
Analytical Study Dates: 07/14/00 to 08/04/00
Storage Period: 36 days

TREATMENT INFORMATION

Treatment ID:	B	C	A
Test or Reference:	T	R	T
Product Name:	Amoxicillin & Clavulanate Potassium (Co-Amoxiclav)	Amoxicillin & Clavulanate Potassium (Augmentin)	Amoxicillin & Clavulanate Potassium (Co-Amoxiclav)
Manufacturer:	Lek, Ljubljana, Slovenia	SmithKline Beecham Pharmaceuticals, Philadelphia, USA	Lek, Ljubljana, Slovenia
Manufacture Date:	N/A	N/A	N/A
Expiration Date:	05/02	05/01	05/02
ANDA Batch Size:	_____	_____	_____
Batch/Lot Number:	1428105B	MT2899	1428105B
Potency:	99.7% + 97.5%	102.8% + 97.9%	99.7% + 97.5%
Strength:	500 mg + 125 mg	500 mg + 125 mg	500 mg + 125 mg
Dosage Form:	Tablets	Tablets	Tablets
Dose Administered:	500 mg + 125 mg	500 mg + 125 mg	500 mg + 125 mg
Study Condition:	fed	Fed	fasting
Length of Fasting:	At least 10 hours predose	At least 10 hours predose	at least 10 hours predose & 4 hours postdose
Breakfast Specifics:	1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 240 mL of whole milk, 180 mL of orange juice.	1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 240 mL of whole milk, 180 mL of orange juice.	N/A

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

DOSING		SUBJECTS	
Single or Multiple Dose:	single	IRB Approval:	Y
Volume of Liquid Intake:	180 mL	Informed Consent :	Y
Route of Administration:	oral	No. of Subjects Enrolled:	18
		No. of Subjects Completing:	18
		No. of Subjects Plasma Analyzed (per protocol):	18
		No. of Dropouts:	0
		Sex(es) Included:	Male only
		Healthy Non-Smoking Volunteers Only:	Y
		Mean age:	32 yrs (21-40)
		Mean height:	174 cm (165-182)
		Mean weight:	72 kg (60-81)
		Race:	Black (3), Caucasian (15)

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

Blood Sampling: See the Fasting Study above.

2)Study Results

Clinical Adverse Events: There was no serious adverse event reported. Two, two and none mild to moderate, drug-related adverse reactions were reported during the Test (Fasted), Test (Fed) and Reference (Fed) treatments, respectively. These reactions included headache, dizziness and nausea.

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

Dropouts: None

Redacted _____

(B)

pages of trade

secret and /or

confidential

commercial

information

Verification of Firm's Calculations and Analyses:

(a) **Amoxicillin** : Firm's values AUC(0-T) and AUC(0-Infinity) of amoxicillin were verified by the reviewer for all subjects. For all subjects, the ratios for firm-calculated AUC's to reviewer-calculated AUC's were 1.0 for both AUC(0-T) and AUC(0-Infinity).

(b) **Clavulanic Acid (based on reassayed concentration values only)**: Firm's values AUC(0-T) and AUC(0-Infinity) of clavulanic acid, based on **reassayed** clavulanic acid concentration values, were verified by the reviewer for all subjects. For all subjects, the ratio for firm-calculated AUC's to reviewer-calculated AUC's was 1.0 for both AUC(0-T) and AUC(0-Infinity).

(c) **Clavulanic Acid (based on the originally assayed concentration values)**: The reviewer recalculated AUC's and re-determined CMAX based on the original assay values. The reviewer also reanalyzed the study results based on the original assay values. The results of the reanalyses are given in the clavulanic acid PK parameter table below, in italic.

TABLE VII
FOOD EFFECTS IN VIVO BIOEQUIVALENCE STUDY # 993615
LEAST-SQUARES MEANS (n= 18) FOR PHARMACOKINETIC PARAMETERS
a) Amoxicillin

PK PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REFERENCE TREATMENT C	RATIO (B/C)
AUC(T) [µg.hr/mL] (Geometric mean)	21.39	20.63	21.24	0.97
AUC(I) [µg.hr/mL] (Geometric mean)	21.71	21.03	21.57	0.98
Cmax [µg/mL] (Geometric mean)	7.22	8.02	8.25	0.97

TABLE VIII
b) Clavulanic acid

PK PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REFERENCE TREATMENT C	RATIO (B/C)
AUC(T) [µg.hr/mL] (Geometric mean)	6.04	5.16 5.25*	5.56	0.93 0.94*
AUC(l) [µg.hr/mL] (Geometric mean)	6.16	5.29 5.60*	5.68	0.93 0.99*
Cmax [µg/mL] (Geometric mean)	2.72	2.45 2.54*	2.57	0.95 0.99*

*Reanalysis results based on original assay values.

**APPEARS THIS WAY
ON ORIGINAL**

TABLE IX
LIMITED FOOD EFFECTS SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY
#993615
ARITHMETIC MEAN PLASMA CONCENTRATIONS ($\mu\text{g/mL}$) VERSUS TIME (CV%)
IN 18 SUBJECTS

a) Amoxicillin

TIME (HR)	FASTING TEST TREATMENT A	NON-FASTING TEST TREATMENT B	NON-FASTING REFERENCE TREATMENT C
Pre-dose	0	0	0
0.25	0.149(144)	0.0176(310)	0.0191(314)
0.50	1.68(57)	0.484(155)	0.612(126)
0.75	3.67(44)	1.68(115)	1.90(93)
1.00	5.46(36)	3.48(79)	3.42(79)
1.25	6.43(45)	5.64(57)	5.46(62)
1.50	6.66(36)	6.52(41)	6.76(45)
1.75	6.50(33)	6.86(34)	7.36(35)
2.00	5.96(29)	6.56(26)	7.11(32)
2.50	5.31(26)	5.55(29)	5.75(31)
3.00	4.53(27)	4.19(40)	4.61(29)
4.00	2.91(31)	2.66(43)	2.86(40)
5.00	1.52(43)	1.61(74)	1.56(52)
6.00	0.820(39)	1.05(111)	0.923(63)
7.00	0.464(37)	0.568(88)	0.534(58)
8.00	0.257(37)	0.327(88)	0.286(58)
10.0	0.0688(106)	0.0781(142)	0.0759(113)
12.0	0	0	0

TABLE X
b) Clavulanic acid

TIME (HR)	FASTING TEST TREATMENT A	NON-FASTING TEST TREATMENT B	NON-FASTING REFERENCE TREATMENT C
Pre-dose	0	0	0
0.25	0.0989(182)	0.00314(424)	0.00312(424)
0.50	0.945(81)	0.0944(161)	0.162(97)
0.75	2.03(59)	0.370(138)	0.559(94)
1.00	2.61(50)	1.13(89)	1.11(80)
1.25	2.67(41)	1.88(72)	1.66(62)
1.50	2.52(42)	2.38(49)	2.25(45)
1.75	2.26(38)	2.36(39)	2.49(31)
2.00	1.97(38)	2.22(34)	2.33(27)
2.50	1.39(38)	1.64(35)	1.71(31)
3.00	1.01(39)	1.12(40)	1.20(31)
4.00	0.508(44)	0.553(50)	0.555(35)
5.00	0.253(50)	0.251(47)	0.275(36)
6.00	0.148(51)	0.143(51)	0.153(39)
7.00	0.0794(54)	0.0733(60)	0.0803(61)
8.00	0.0305(120)	0.0228(152)	0.0271(132)
10.0	0	0	0
12.0	0	0	0

FIGURE 3

**PLASMA CONCENTRATION ($\mu\text{g/mL}$) VERSUS TIME
SINGLE-DOSE LIMITED FOOD EFFECTS STUDY #993615**

Project No. 993615
Mean Plasma Amoxicillin Concentrations
(Linear Plot)

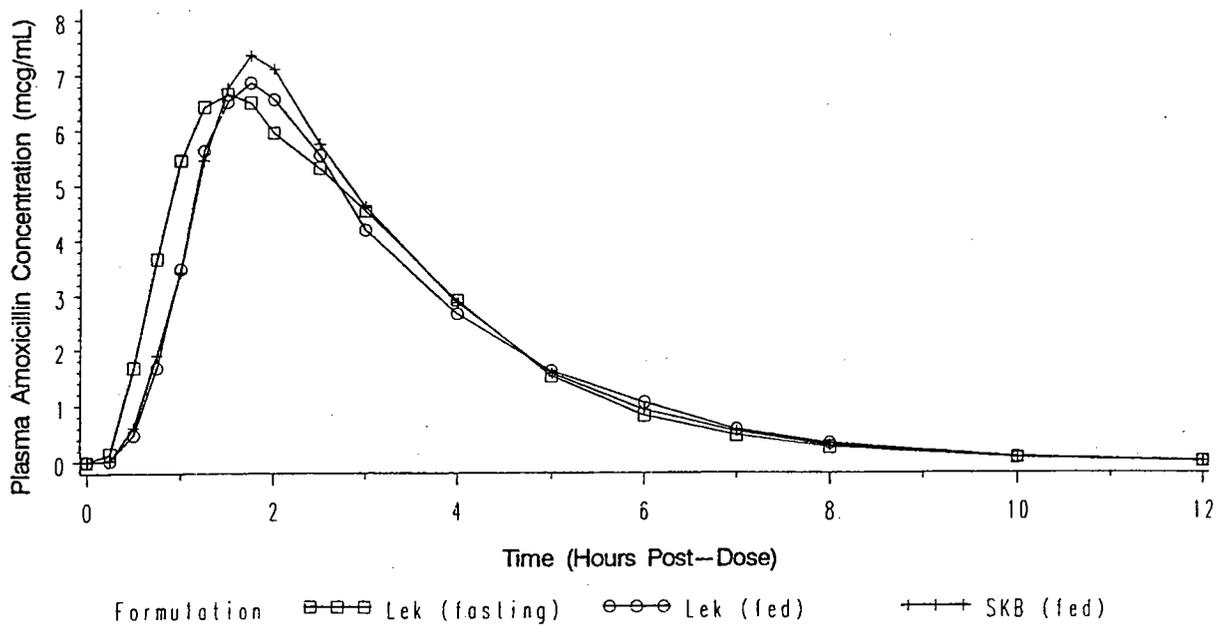


FIGURE 4

**PLASMA CONCENTRATION ($\mu\text{g/mL}$) VERSUS TIME
SINGLE-DOSE LIMITED FOOD EFFECTS STUDY #993615**

Project No. 993615

Mean Plasma Clavulanic Acid Concentrations
(Linear Plot)

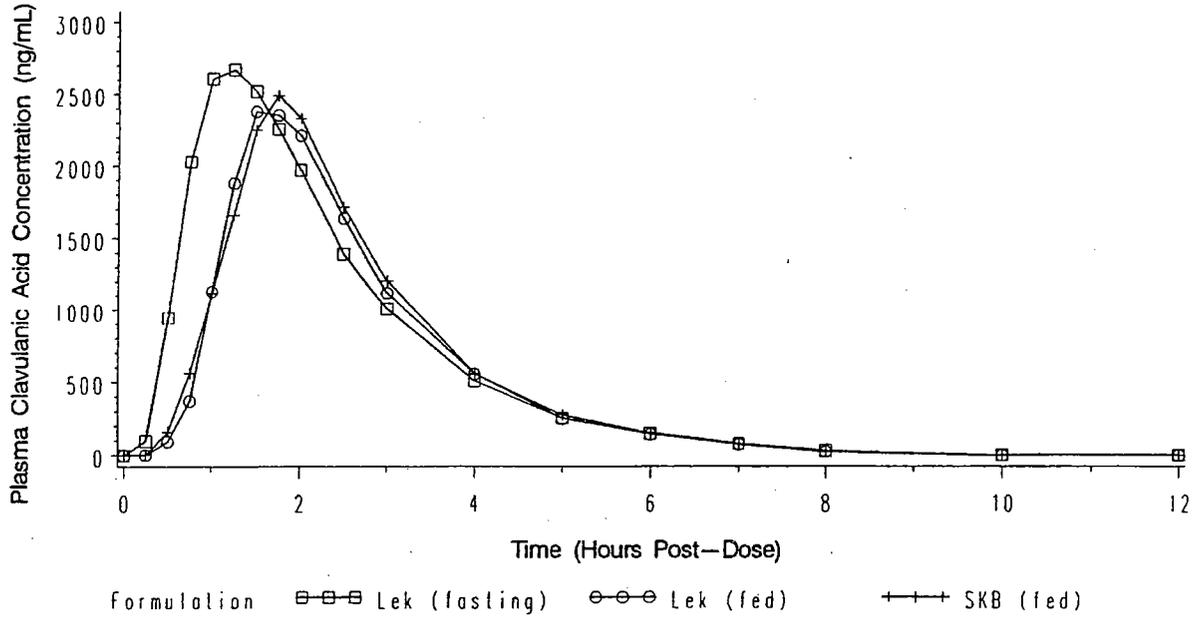


TABLE XI

**LIMITED FOOD EFFECTS SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY
#993615
ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS IN
18 SUBJECTS**

c) Amoxicillin

PK PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REFERENCE TREATMENT C
AUCT [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	21.97(22)	20.92(17)	21.68(19)
AUCI [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	22.29(22)	21.32(16)	22.01(19)
Cmax [$\mu\text{g}/\text{mL}$]	7.62(33)	8.26(25)	8.56(27)
Tmax [hr]	1.54(30)	2.04(44)	1.90(34)
Kel [1/hr]	0.546(20)	0.508(20)	0.557(18)
T $\frac{1}{2}$ [hr]	1.31(17)	1.42(24)	1.28(17)

TABLE XII

d) Clavulanic acid

PK PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REFERENCE TREATMENT C
AUCT [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	6.45(36)	5.55(35)	5.75(28)
AUCI [$\mu\text{g}\cdot\text{hr}/\text{mL}$]	6.57(36)	5.67(34)	5.87(28)
Cmax [$\mu\text{g}/\text{mL}$]	2.96(40)	2.70(37)	2.72(30)
Tmax [hr]	1.28(35)	1.76(23)	1.71(20)
Kel [1/hr]	0.587(18)	0.600(14)	0.606(15)
T $\frac{1}{2}$ [hr]	1.22(18)	1.18(14)	1.17(18)

5) Statistical Analysis: All eighteen enrolled subjects completed the study. Samples from all 18 completing subjects were analyzed and used for the pharmacokinetic and statistical analyses. Standard three-way crossover ANOVA models were used.

There was no statistically significant difference ($\alpha=0.05$) between treatments for LAUC(0-T), LAUC(0-Inf) and LCMAX of clavulanic acid or amoxicillin.

Conclusion: The ratios of lnAUC(0-T), lnAUC(0-Infinity) and lnC_{MAX} were within the limit of [0.80; 1.25]. The study is acceptable.

V. Dissolution(Not to be released under FOI)

Dissolution Method: USP

Dissolution Medium: Water, 900mL @ 37°C ± 0.5°C
 Apparatus: 2 (Paddles)
 Speed: 75 rpm
 Sample Times: @ 2, 6, 10, 15 and 30 minutes
 Limits: NLT — (Q) of amoxicillin in 30 minutes
 NLT — (Q) of clavulanic acid in 30 minutes

Results:

Amoxicillin Mean Dissolution Data

TEST: Lek's Co-AMOXICLAV Tablets

REFERENCE: SmithKline Beecham's Augmentin 500 mg Tablets

Lot No.: 1428105B
 Strength: 500 + 125 mg
 No. of Units: 12

Lot No.: MT2899
 Strength: 500 + 125 mg
 No. of Units: 12

Time(min.)	Mean	Range	%CV	Mean	Range	%CV
10	74.5	————	12	65.1	————	17
20	95.7	————	1.7	100.5	————	2.9
30	97.8	————	1.5	102.0	————	1.1
40	98.4	————	1.4	102.1	————	1.2

Clavulanic Acid Mean Dissolution Data

TEST: Lek's Co-AMOXICLAV Tablets

REFERENCE: SmithKline Beecham's Augmentin 500 mg Tablets

Lot No.: 1428105B
 Strength: 500 + 125 mg
 No. of Units: 12

Lot No.: MT2899
 Strength: 500 + 125 mg
 No. of Units: 12

Time(min.)	Mean	Range	%CV	Mean	Range	%CV
10	72.8	————	16	64.8	————	14
20	96.2	————	1.8	97.0	————	2.5
30	97.6	————	1.1	98.2	————	0.8
40	97.7	————	0.9	98.2	————	0.8

Comments: The dissolution data are acceptable. Both the test and reference products meet the specification of NLT — % dissolved in 30 minutes for amoxicillin and NLT — dissolved in 30 minutes for clavulanic acid. The similarity factor f₂ can not be calculated due to the fact that

both the test and reference products are fast dissolving with means dissolved being greater than at the second time point.

VII. Formulation: See Review Attachment . As shown in the third column of the formulation table, all inactive ingredients in the formulations of all strengths were reviewed and found to be present at or below levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products.

VIII. Recommendations:

1. The single-dose, fasting bioequivalence study and the single-dose post-prandial bioequivalence study conducted by Lek on the test product, Amoxicillin and Clavulanate Potassium Tablets USP, 500 + 125 mg, lot # 1428105B, comparing it with the reference product, SmithKline Beecham's Augmentin 500 mg Tablets, amoxicillin and clavulanate potassium 500 + 125 mg, lot # MT2899, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Lek's Amoxicillin and Clavulanate Potassium Chewable Tablets USP, 500 + 125 mg, is bioequivalent to the reference product, SmithKline Beecham's Augmentin 500 + 125 mg amoxicillin and clavulanate potassium tablets, under fasting and non-fasting conditions.
2. The in-vitro dissolution testing conducted by Lek on its Amoxicillin and Clavulanate Potassium Tablets USP, 500 + 125 mg, has been found acceptable.

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

Not less than 80% of the labeled amount of amoxicillin and 80% of the labeled amount of clavulanic acid in the dosage form are dissolved in 30 minutes.

ISI
Hoangdon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

ISI 3/22/2002

Concur: *ISI* Date: 4/15/2002
fx Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS

ANDA: 65-117

APPLICANT: Lek d.d.

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium Tablets USP,
500 + 125 mg

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

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

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

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

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

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

Sincerely yours,

^

Jr Dale P. ~~Conner~~^{Sl}, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

formulation

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secret and /or

confidential

commercial

information

CC:ANDA 65-117
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen *HN*
HFD-652/ YHuang *Wti 3/22/2002*
HFD-617/ K. Scardina
HFD-650/ D. Conner *for [Signature] 4/15/2002*

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 12-²¹26-01

1. FASTING STUDY (STF) *oic*
Clinical: _____
Analytical: _____

Strength: 500 + 125 MG
Outcome: AC

2. NON-FASTING STUDY (STP) *oic*
Clinical: _____
Analytical: _____

Strength: 500 + 125 MG
Outcome: AC

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

WINBIO COMMENTS:

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA #: 65-117

SPONSOR : Lek d.d.

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

STRENGTH(S) : 500 + 125 mg

TYPES OF STUDIES : Fasting Study & Non-Fasting Study

CINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : Acceptable

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
 INITIAL : hm DATE : 3/15/02

TEAM LEADER : Yih-Chait Huang BRANCH : I
 INITIAL : IS DATE : 3/22/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
 INITIAL : fr DATE : 4/15/2002

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-117

**ADMINISTRATIVE
DOCUMENTS**

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

ANDA Number: 65-117

Date of Submission: December 21, 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, 500 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.
- b. Include the amount of potassium per tablet.
- c. Revise " _____" read "Usual Dosage".

2. INSERT

a. DESCRIPTION

Revise to read as follows:

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.

b. DOSAGE AND ADMINISTRATION

Throughout this section revise " _____" to read "Amoxicillin and Clavulanate Potassium Tablet".

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

**APPEARS THIS WAY
ON ORIGINAL**

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 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)			
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, [croscarmellose sodium dried, crospovidone dried, ethylcellulose, hydroxypropyl cellulose, dried polysorbate 80, talc and triethyl citrat]	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:

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

Chemist response: Although a new strain has been developed in the Lek DMF, it still is a strain of *Streptomyces clavuligerus*. So this is an accurate statement.
[S.F.]

- 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.

Chemist response: Yes...all containers pass the USP <671> moisture permeation requirements.

FOR THE RECORD:

- Augmentin® (Amoxicillin and Clavulanate Potassium Tablets, USP)/50-564/S-032, approved on 2/11/98.
NOTE: The most recent approved labeling for NDA 50-564/S-034/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-032 as the labeling model for this drug product.
- The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
[B1.1, p. 4242, 4243]
- Manufacturing Processing Facility:

Lek Pharmaceutical and Chemical Company d.d.
Ljubljana, Slovenia
[B1.1, p.4400]

4. Container/Closure:
Plastic bottle with CRC
[Vol. B1.3, p.4828]

5. Physical Description:
The firm's physical description of the tablet in the HOW SUPPLIED section is consistent with the finished dosage form statement.
[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: 8/13/02

4/5/01

Primary Reviewer:
Jacqueline Council, Pharm.D.

Date: 8-24-02

Acting Team Leader:
Captain Lillie Golsch

Date: 8/29/02

cc: ANDA: 65-117
DUP/DIVISION FILE
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Review

... 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.

JSI

01
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

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

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:

Has this been verified by the MIS system for the NDA? Yes No

Was this approval based upon an OGD labeling guidance? Yes No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels:

Basis of Approval for the Carton Labeling:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 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)			
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, [croscarmellose sodium dried, crospovidone dried, ethylcellulose, hydroxypropyl cellulose, dried polysorbate 80, talc and triethyl citrat]	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:

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

Chemist response: Although a new strain has been developed in the Lek DMF, it still is a strain of *Streptomyces clavuligerus*. So this is an accurate statement.
[S.F.]

- 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.

Chemist response: Yes...all containers pass the USP <671> moisture permeation requirements.

FOR THE RECORD:

- Augmentin® (Amoxicillin and Clavulanate Potassium Tablets, USP)/50-564/S-032, approved on 2/11/98.
NOTE: The most recent approved labeling for NDA 50-564/S-034/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-032 as the labeling model for this drug product.

- The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
[B1.1, p. 4242, 4243]

- Manufacturing Processing Facility:

Lek Pharmaceutical and Chemical Company d.d.
Ljubljana, Solvenia
[B1.1, p.4400]

4. Container/Closure:

Plastic bottle with CRC
[Vol. B1.3, p.4828]

5. Physical Description:

The firm's physical description of the tablet in the HOW SUPPLIED section is consistent with the finished dosage form statement.
[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: 10/22/02

Date of Submission: - September 2, 2002
September 27, 2002

Primary Reviewer: *ISI*
Jacqueline Council, Pharm.D.

Date: *10-23-02*

Acting Team Leader:
Captain Lillie Golso *ISI*

Date: *10/24/02*

cc: ANDA: 65-117
DUP/DIVISION FILE
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Review

APPROVAL SUMMARY

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

ANDA Number: 65-117

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

Applicant's Name: Lek Pharmaceuticals d.d.

Established Name: Amoxicillin and Clavulanate Potassium Tablets USP, 500 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 [See FTR#1]

NDA Drug Name: Amoxicillin/clavulanate 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, [croscarmellose sodium dried, crospovidone dried, ethylcellulose, hydroxypropyl cellulose, dried polysorbate 80, talc and triethyl citrat]	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?

Chemist response: Although a new strain has been developed in the Lek DMF, it still is a strain of *Streptomyces clavuligerus*. So this is an accurate statement.
[S.F.]

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.

Chemist response: Yes...all containers pass the USP <671> moisture permeation requirements.

FOR THE RECORD:

1. Augmentin® (Amoxicillin and Clavulanate Potassium Tablets, USP)50-720/S-003-50-564/S-032, approved on 2/11/98.
NOTE: The most recent approved labeling for NDA 50-720/S-006/50-564/S-034/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-032 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. 4242, 4243]
3. Manufacturing Processing Facility:

Lek Pharmaceutical and Chemical Company d.d.
Ljubljana, Solvenia
[B1.1, p.4400]

4. Container/Closure:

Plastic bottle with CRC
[Vol. B1.3, p.4828]

5. Physical Description:

The firm's physical description of the tablet in the HOW SUPPLIED section is consistent with the finished dosage form statement.
[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

**APPEARS THIS WAY
ON ORIGINAL**

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: 500 mg/125 mg tablet (base)

Amoxicillin

Parameter	ANDA	NDA	Insert
ACUI (mcg.hr/mL)	24.47	25.38	33.4±6.76
ACUT (mcg.hr/mL)	24.12	25.07	[500 mg q12h]
Cmax (mcg/mL)			
T ½ (hr)	1.52	1.55	1.3
Tmax (hr)	1.62	1.73	1.5

CLAVULANIC ACID

Parameter	ANDA	NDA	Insert [clavulanate potassium]
ACUI (mcg.hr/mL)	8.58	7.98	10.2±3.04 [only value]
ACUT (mcg.hr/mL)	8.43	7.94	
Cmax (mcg/mL)			
T ½ (hr)	1.2	1.1	1

Non-Fasting Bioequivalence study: 500 mg/125 mg(base) tablet

Amoxicillin

Parameter	ANDA	NDA	Insert
ACUI (mcg.hr/mL)	21.32	22.01	Dosing in the fasted or fed state has minimal effect on the pharmacokinetic of amoxicillin
ACUT (mcg.hr/mL)	20.92	21.68	
Cmax (mcg/mL)			
T ½ (hr)	1.42	1.28	
Tmax (hr)	2.04	1.90	

CLAVULANIC ACID

Parameter	ANDA	NDA	Insert [clavulanate potassium]
ACUI (mcg.hr/mL)	5.67	5.87	Dosing in the fasted or fed state has minimal effect on the pharmacokinetic of amoxicillin
ACUT (mcg.hr/mL)	5.55	5.75	
Cmax (mcg/mL)			
T ½ (hr)	1.18(14)	1.17	

Date of Review: 11/21/02

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

Primary Reviewer: *ms*
Jacqueline Council, Pharm.D.

Date: 11/25/02

Acting Team Leader: *ms*
Captain Lillie Golson

Date: 11/28/02

cc: ANDA: 65-117
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Review

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-117

CORRESPONDENCE



LEK Services, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760
Fax: 910 362 0790

*N/A J. P. Lewis Ph.D.
12/12/02*

November 7, 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

NEW CORRESP

NC to labeling

Re: Correction to 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 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 500 mg/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 08 2002

OGD / CDER



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

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Food and Drug Administration

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Facsimile: + 386 1 568 13 66

No.: 1779/02
Date: November 4, 2002

ORG AMENDMENT

N/AF

FPL

SUBJECT: ANDA 65-117
Final prints to the Telephone Amendment to ANDA 65-117 for Amoxicillin and Clavulanate Potassium Tablets, USP 500/125 mg (dated October 28, 2002)

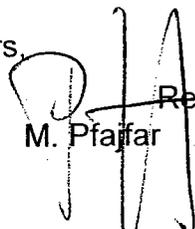
Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) no. 65-117 for Amoxicillin and Clavulanate Potassium Tablets, USP 500/125 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 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,


M. Pfajfar

Regulatory Affairs

A. Vukadin-Škulj
Director



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

RECEIVED

NOV 07 2002

OGD / CDER



LEK Services, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760

Fax: 910 362 0790

October 29, 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
Fax #: 301-443-3839

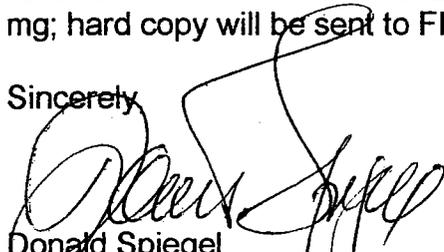
Re: Telephone Amendment to ANDA # 65-117
Product : Amoxicillin and Clavulanate Potassium Tablets, USP
500 mg/125 mg
Manufacturer: LEK Pharmaceuticals d.d.
Ljubljana, Slovenia
U.S. Agent : LEK Services, Inc.
Donald Spiegel, Director, Scientific Affairs

Re: October 24, 2002 FDA Correspondence from Division of
Labeling and Program Support - Labeling Review Branch

To whom it may concern;

On behalf of LEK Pharmaceuticals d.d. enclosed is a fax copy of a Telephone
Amendment for Amoxicillin and Clavulanate Potassium Tablets, USP 500 mg/125
mg; hard copy will be sent to FDA.

Sincerely,



Donald Spiegel
Director, Scientific Affairs

cc.: Mateja Pfajfar, Head of FP Registrations



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.:
Date: October 28, 2002

SUBJECT: ANDA 65-117
Telephone Amendment to ANDA 65-117 for Amoxicillin and Clavulanate Potassium Tablets USP, 500/125 mg

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

ORIG AMENDMENT

N/AE

FPL

Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) no. 65-117 for Amoxicillin and Clavulanate Potassium Tablets USP, 500/125 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. 65-117. 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. Pfajfar
M. Pfajfar

Regulatory Affairs

A. Vukadin-Škulj
Director

RECEIVED

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

NOV 07 2002

OGD / CDER



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/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

To Whom It May Concern:

Please note that the enclosed documentation is to be treated as a Telephone Amendment to ANDA #65-117 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,

A handwritten signature in cursive script, appearing to read 'Branko Huc'.

Branko Huc, Ph.D.
Executive Vice President

BH/kwf

RECEIVED

OCT 30 2002

OGD / CDER



LEK Services, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760
Fax: 910 362 0790

September 27, 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

ORIG AMENDMENT

N/AM

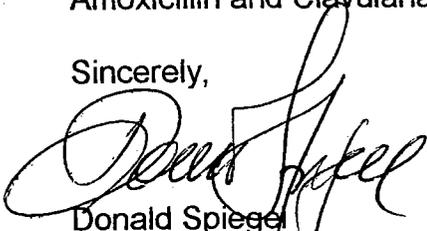
FPL

Product : Minor Amendment to ANDA # 65-117
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: FDA's Deficiency Letter of September 6, 2002

To whom it may concern;

On behalf of LEK Pharmaceuticals d.d. enclosed is a Minor Amendment for Amoxicillin and Clavulanate Potassium Tablets, USP 500 mg/125 mg.

Sincerely,



Donald Spiegel
Director, Scientific Affairs

cc.: Mateja Pfajfar, Head of FP Registrations

RECEIVED

SEP 30 2002

OGD / CDER

Handwritten note: *new 10/1/02*

65-117 (5.1)



LEK Pharmaceuticals, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0021
Fax: 910 362 0051

NAT
[Signature]
9/19/2002
NEW CORRESP
NC

September 11, 2002

Food and Drug Administration, CDER
Office of Generic Drugs
MPN II, HFD-600
7500 Standish Place
Rockville, Maryland 20855

Subject: Change of Corporate Name

Corporation:

Former Name: LEK Pharmaceutical and Chemical Company d.d.

New Name: LEK Pharmaceuticals d.d.

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

To whom it may concern:

On behalf of LEK Pharmaceuticals d.d. enclosed is their correspondence indicating the new name of the Corporation along with eleven specifically referenced ANDA's/Amendments/Supplements.

Sincerely,

[Signature of Donald Spiegel]

Donald Spiegel
Director, Scientific Affairs

Enclosures

RECEIVED

SEP 16 2002

OGD / CDER

[Handwritten signature]



Lek Pharmaceuticals d.d.

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

NEW CORRESP

NC

Verovškova 57
SI - 1526 Ljubljana
Slovenia

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

MPN II, HFD-600
7500 Standish Place
Rockville, MD20855
USA
No.: 1187/02

ORIG AMENDMENT

N/AE

Regulatory Affairs

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

Date: 2 September 2002

Subject: **AMENDMENT to ANDA 65-117, CHANGE OF THE CORPORATE NAME**
Amoxicillin and Clavulanate Potassium Tablets USP, 500/125 mg

Dear Sirs

Reference is made to our Abbreviated New Drug Application (ANDA) #65-117 for Amoxicillin and Clavulanate Potassium Tablets USP, 500/125 mg submitted on December 26, 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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SEP 16 2002

OGD / CDER



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

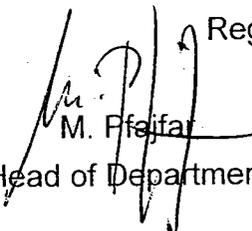
Headquarters in Ljubljana:

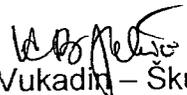
Regulatory Affairs,
Mrs. A. Vukadin - Škulj, Director
Phone: + 386 1 580 3 332, + 386 1 580 2 338
Fax: + 386 1 568 1366

Sincerely yours

Lek Pharmaceuticals d.d.

Regulatory Affairs


M. P. P. P.
Head of Department


A. Vukadin - Škulj
Director

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



*DA To Scott
M Anderson*

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

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

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

Regulatory Affairs
Tel: + 386 1 580 33 32

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

Facsimile: + 386 1 568 13 66

N/A
ORIG AMENDMENT

June 12, 2002 *1/68/OK*

**SUBJECT: ANDA 65-117
Minor Amendment to ANDA for Amoxicillin and Clavulanate Potassium
Tablets USP, 500/125 mg**

Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) no. 65-117 for Amoxicillin and Clavulanate Potassium Tablets USP, 500/125 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 Chemistry II "Minor Amendment" letter and Division of Bioequivalence comments dated May 15, 2002.

This Minor Amendment is being submitted in order to respond all the questions raised in the above mentioned deficiency letter dated May 15, 2002 for ANDA no. 65-117.

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

Sincerely yours,

M Pfajfar
M. Pfajfar

Regulatory Affairs

A. Vukadin-Škulj
A. Vukadin-Škulj
Director

**RECEIVED
JUN 18 2002
OGD / CDER**

MW



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

N/AC

DRUG AMENDMENT

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

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

*To Scott
M Anderson
& 6/2/02*

June 11, 2002/752/02

**SUBJECT: Amendment to ANDA 65-117 for Amoxicillin and Clavulanate Potassium
Tablets USP, 500/125 mg**

Dear Sirs,

Reference is made to our Abbreviated New Drug Application (ANDA) no. 65-117 for Amoxicillin and Clavulanate Potassium Tablets USP, 500/125 mg dated December 26, 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. 65-117 to support the following changes:

- []
- []
- []

requirements.

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

- Copy of the transmittal letter for the annual update of DMF _____ The annual update was submitted to the FDA on March 26, 2002.

- []

JUN 14 2002



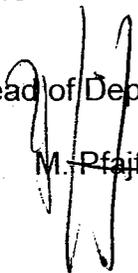
- Revised specifications for tablets (revision to USP 25 and FDA requirements)
- Specification and DMF letter for _____
- Revised (proposed) blank batch record for manufacture of _____ and proposed blank batch record for packaging of 20 tablets _____ . Differences between the old and proposed batch records are explained.
- Executed batch records (exhibit batch no. 0379707C, manufactured according to the revised manufacturing procedure with the clavulanate potassium obtained with _____)
- Analytical certificates for active ingredients used in the production of tablets batch no. 0379707C
- Analytical certificates for inactive ingredients used in the production of tablets batch no. 0379707C
- Analytical certificates for packaging materials used in the packaging of tablets batch no. 0379707C
- Analytical certificate for tablets batch no. 0379707C
- Dissolution profiles (comparative dissolution profiles between Augmentin® 500 mg tablets, Lek's biobatch (pre-change product) and Lek's tablets batch no. 0379707C (post-change product))
- Stability data (comparative accelerated and long-term stability testing on tablets batch no. 1379707C)

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).

Sincerely yours

Head of Department


~~M. Pifajfar~~


Regulatory Affairs
Director
A. Vukadin-Škulj



65-117

LEK Services, Inc.

NEW CORRESP
NC

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760
Fax: 910 362 0790

January 17, 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 : **Amendment to ANDA**
Amoxicillin and Clavulanate Potassium Tablets, USP
500 mg/125 mg

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

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

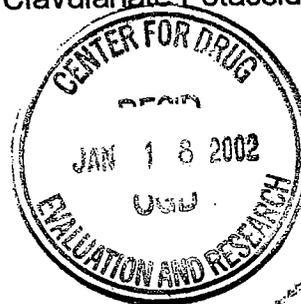
Re: December 21, 2001 ANDA submission

To whom it may concern;

On behalf of LEK Pharmaceutical and Chemical Company d.d., enclosed is a BE ESD electronic submission Amendment for Amoxicillin and Clavulanate Potassium Tablets, USP 500 mg/125 mg

Sincerely,

Donald Spiegel
Director, Scientific Affairs



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



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

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 1 580 33 11

Facsimile:

65-117

NEW CORRESP
NC/Bio

Ljubljana, January 14, 2002

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

Subject:

**ANDA
Amoxicillin and Clavulanate Potassium Tablets USP, 500/125 mg
Amendment**

Dear Sirs,

Reference is made to our ANDA for Amoxicillin and Clavulanate Potassium Tablets 500/125 mg of December 21, 2001.

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

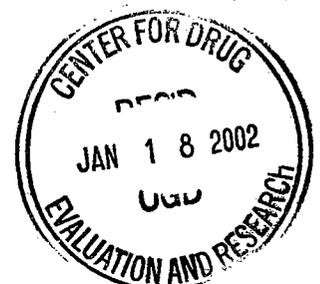
Declaration

The information contained in the electronic submission of January 14, 2002 is not different from the information contained in the hard copy submission of December 21, 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 3.5 inch double sided floppy disks are provided, with identical information on each.





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

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

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 SERVICES, INC.

A handwritten signature in black ink, appearing to be 'M. Žorž', written over the printed name and title.

20 A handwritten signature in black ink, appearing to be 'M. Šopar-Urleb', written over the printed name and title.

Enclosures:

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



LEK Services, Inc.

115 N. Third Street
Suite 301
Wilmington, NC 28401

Phone: 910 362 0760

Fax: 910 362 0790

December 26, 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

505(d)(2)(A) OK
19-FEB-2002
ISI

NEW CORRESP

nc

Product : ANDA for Amoxicillin and Clavulanate Potassium Tablets, USP,
500/125 mg
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 the ANDA application for Amoxicillin and Clavulanate Potassium Tablets, USP, 500/125 mg in three copies (Archival, Review and Third copy).

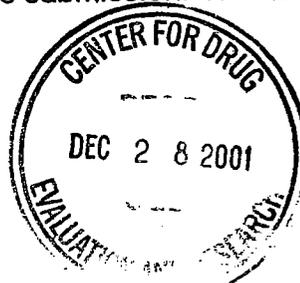
The shipment is composed of 11 carton boxes with 37 volumes submitted:

Archival copy : 14 volumes
Review copy : 16 volumes
Third copy : 5 volumes
Two additional copies of the analytical methods : 2 volumes each

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

Sincerely,

Donald Spiegel
Director, Scientific Affairs



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



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

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

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

+ 386 1 5053 150

Facsimile: + 386 1 5057 881

December 21, 2001

SUBJECT: ANDA for Amoxicillin and Clavulanate Potassium Tablets USP, 500/125 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, 500/125 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.

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)

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

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

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, 500/125 mg

Number of volumes submitted:

- Archival copy (14 volumes); two 3.5 inch diskettes with BE data provided (bound in the first volume of the archival copy)
- Review copy (16 volumes)
- Third copy (5 volumes)
- Two additional copies of analytical methods (2 volumes each)

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

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. 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 SERVICES, INC.