CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 50-754

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-754

Trade Name: AMOXIL TABLETS, 500 mg and 875 mg in strength

Generic Name:(amoxicillin)

Sponsor: SmithKline Beecham

Approval Date: July 10, 1998

Indication: Allows for a change in the dosing regimen of amoxicillin from thrice daily to twice daily in adults and to provide for the use of new swallow tablet formulations.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 50-754

APPROVAL LETTER

NDA 50-754

SmithKline Beecham
Attention: Sharon Shapowal, R.Ph.
Assistant Director
U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929 (FP 1005)
Philadelphia, PA 19101-7929

JUL 10 1998

Dear Ms. Shapowal:

Please refer to your new drug application dated July 11, 1997, received July 14, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amoxil® (amoxicillin) Tablets, 500 mg and 875 mg in strength.

We note that this product is subject to the exception provisions of section 125 (d)(2) of Title 1 of the Food and Drug Administration Modernization Act of 1997.

We acknowledge receipt of your submissions dated November 13, 1997; February 13, 1998, March 6, 1998, March 30, 1998, May 15, 1998 and June 4, 1998.

The User Fee goal date for this application is July 14, 1998.

This new drug application allows for a change in the dosing regimen of amoxicillin from thrice daily to twice daily in adults and to provide for the use of new swallow tablet formulations.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated July 9, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on July 9, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-754. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mr. Stephen T. Trostle, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-754
HFD-002/ORM (with labeling)
HFD-104/Office Director
HFD-104/THassall
HFD-101/L.Carter
HFD-520/Div. Files
HFD-520/PMS/STrostle
HFD-520/MO/Mmakhene 7/10/98
HFD-520/PharmTox TL/ROsterberg
HFD-520/PharmTox/Kseethaler
HFD-520/Chemistry TL/DKatague 7/10/98
HFD-520/Chemistry/Ayu 7/10/98
HFD-520/Microbiology TL/ASheldon
HFD-520/Microbiology/Saltaie
HFD-520/Biopharmaceutics TL/FPelsor
HFD-520/Biopharmaceutics/Hsun
HFD-830/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)

Concurrence Only:
HFD-520/CPMS/JBona 7/9/98
HFD-520/MedicalTL/MAlbuerne 7/9/98

Drafted by: jrc/July 9, 1998/
Initialed by:
final:

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-754

MEDICAL REVIEW(S)

MEDICAL REVIEW OF NEW DRUG APPLICATION 50-754, AMOXIL SWALLOW TABLETS FOR Q12 HOURLY DOSING

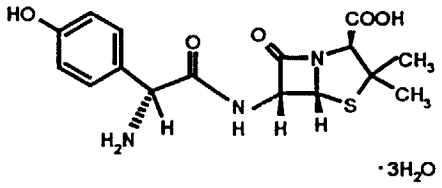
Applicant name: SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101
Sharon Shapowal, R. Ph.
215-751-3468

Date received: July 11, 1997
Date received by reviewer: August 7, 1997
Date review begun: May 6, 1998
Date draft completed: June 23, 1998
Date review completed: June 30, 1998

DRUG IDENTIFICATION

Generic Name:	amoxicillin
Trade Name:	Amoxil
Pharmacologic Class:	a semisynthetic penicillin-class antibiotic as a trihydrate

Chemical structure:
Chemically it is D-(-)-alpha-amino-p-hydroxybenzyl penicillin trihydrate.



Molecular formula and weight:
The amoxicillin molecular formula is $C_{16}H_{19}NO_5S.3H_2O$ and the molecular weight is 419.45.

Dosage Form:	swallow tablets
Route of Administration:	oral

CURRENT LABELLING

CLINICAL PHARMACOLOGY

Amoxicillin is stable in the presence of gastric acid and may be given without regard to meals. It is rapidly absorbed after oral administration.

INDICATIONS AND USAGE

Amoxil (amoxicillin) is indicated in the treatment of infections due to susceptible (ONLY beta-lactamase-negative) strains of the designated microorganisms in the conditions listed below:
Infections of the ear, nose, and throat due to *Streptococcus* spp. (alpha- and beta-hemolytic strains only), *S. pneumoniae, Staphylococcus* spp., or *H. influenzae*
Infections of the genitourinary tract due to *E. coli, Proteus mirabilis* and *E. faecalis*
Infections of the skin and skin structure due to *Streptococcus* spp. (alpha- and beta-hemolytic strains only), *S. pneumoniae, Staphylococcus* spp., or *E. coli*
Infections of the lower respiratory tract due to *Streptococcus* spp. (alpha- and beta-hemolytic strains only), *S. pneumoniae, Staphylococcus* spp., or *H. influenzae*
Gonorrhea, acute uncomplicated (ano-genital and urethral infections) due to *N. gonorrhoeae* (males and females)
Therapy may be instituted prior to obtaining results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to amoxicillin.
Indicated surgical procedures should be performed.
H. pylori eradication to reduce the risk of duodenal ulcer recurrence
Triple therapy: Amoxil/clarithromycin /lansoprazole
Amoxil, in combination with clarithromycin plus lansoprazole as triple therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See **CLINICAL STUDIES** and **DOSAGE ADMINISTRATION.**)
Dual Therapy: Amoxil/lansoprazole
Amoxil (amoxicillin), in combination with lansoprazole delayed-release capsules as dual therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.** Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See **CLINICAL STUDIES** and **DOSAGE ADMINISTRATION.**)

DOSAGE AND ADMINISTRATION

Infection	Usual Adult Dose
Ear/nose/throat	250 mg every 8 hours
Lower respiratory tract	500 mg every 8 hours
Skin/skin structure	250 mg every 8 hours
Genitourinary tract	250 mg every 8 hours
Gonorrhea; acute, uncomplicated ano-genital and urethral infections in males and females	3 grams as a single oral dose

In severe ear, nose, throat, genitourinary, skin and skin structure infections, or those caused by less susceptible organisms:
Adults: 500 mg every 8 hours.
All patients with gonorrhea should be evaluated for syphilis. (See **PRECAUTIONS**-Laboratory Tests.)
Larger doses may be required for stubborn or severe infections.
H pylori eradication to reduce the risks of duodenal ulcer recurrence
Triple therapy: Amoxil /clarithromycin/lansoprazole
The recommended adult oral dose is 1 gram Amoxil, 500 mg clarithromycin and 30 mg lansoprazole, each given three times daily (q8h) for 14 days. (See **INDICATIONS AND USAGE.**)
Dual therapy: Amoxil /lansoprazole
The recommended adult oral dose is 1 gram Amoxil and 30 mg lansoprazole, each given three times daily (q8h) for 14 days. (See **INDICATIONS AND USAGE.**)

PROPOSED LABELLING

Medical reviewer's comments:
The main purpose of the changes in the Amoxil label is to include the new swallow tablet formulations of 500-mg and 875-mg tablets for q12h dosing. There are no proposed changes to the list of indications or microorganisms for which Amoxil is currently approved.

The CLINICAL PHARMACOLOGY section of the current and proposed label indicates that Amoxil may be given without regard to meals; however, the applicant has not conducted a food effect study. Therefore, if approved, the label would have to reflect the conditions under which the drug was tested, and revisions in the label made accordingly. Additionally, the calculations of the mean pharmacokinetic parameters summarized in this section were based on results from 27 volunteers only, not 28 subjects as indicated in the proposed label.

Beginning in 1984 when an epidemic of gonorrhea with high level resistance to penicillin was reported in North Carolina, penicillin resistance of gonococci in the US has been increasing, from 8.4% in 1988 to 15.6% in 1994 . Since the mid -1980s, this high level resistance, experienced world-wide, has precluded the use of penicillins in the treatment of gonococcal infections (Fox et al, JID 1997; Eberling and Quinn, 1997). Indeed, amoxicillin is no longer among the CDC recommended or alternative regimens for the treatment of gonococcal infections. [CDC 1998 Guidelines of Treatment of Sexually Transmitted Diseases. MMWR 1998 Jan 23; 47: 1-116]. It is proposed that the label be revised to indicate this change in recommendations by adding the words

Related Drugs
Augmentin 500-mg and 875-mg tablets for q12 hour dosing.

Materials Reviewed
The applicant has submitted 3 volumes of the NDA to support this application. The materials contained in these volumes include the pharmacokinetic/pharmacodynamic justification and risk benefit analysis for the proposed change in dosing.
The single clinical study contained in this application is a bioequivalence study which compares the new Amoxil 875-mg swallow tablet to the Augmentin 875-mg tablet. Microbiologic efficacy data from NDA 50-720 have also been submitted to support this application. Lastly, the applicant has provided approximately 35 literature references cited in the submission.

Literature references

CDC 1998 Guidelines of Treatment of Sexually Transmitted Diseases. MMWR 1998 Jan 23;47: 1-116.

Craig WA. Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men. Clin Infect Dis 1998:26:1-12.

Craig, WA and Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J. 1996: 15:255-9.

Fox KK, Knapp JS, Holmes KK, Hook III EW, Judson FN, Thompson SE, Washington JA, and Whittington WL. Antimicrobial Resistance in *Neisseria gonorrhoeae* in the United States, 1988-1994: The Emergence of Decreased Susceptibility to the Fluoroquinolones. JID 1997; 175:1396-403.

Erbelding E, and Quinn TC. The Impact of Antimicrobial Resistance on the Treatment of STDs. Infect Dis Clin North Am 1997;11:889-903.

Hyatt JM, McKinnon PS, Zimmer GS, and Schentag JJ. The Importance of Pharmacokinetic/ Pharmacodynamic Surrogate Markers to Outcome. Focus on Antibacterial Agents. Clin Pharmacokinetics 1995:28:143-160.

Historical and Regulatory Background

February 13, 1996
Approval of Augmentin 875-mg and 500-mg tablets for q12 dosing in adults

June 14, 1996
Initial proposal for Amoxil b.i.d.submitted in a letter to FDA; a single bioequivalence study, in healthy adult volunteers, to compare the new formulation of Amoxil 875-mg swallow tablets to the marketed Augmentin 875-mg tablets, was proposed by the sponsor.

July 17, 1996
Teleconference with FDA during which the acceptability of the rationale and the proposed development program was communicated to SB.

October 10, 1996
Pivotal bioequivalence protocol (number 2333/058) was submitted for review

March 21, 1997
FDA requested inclusion of scientific rationale in the NDA to support the change in dosing schedule.

April 29, 1997
Teleconference with FDA, during which it was agreed that supportive clinical data specific for beta-lactamase-negative strains, from the Augmentin NDA 50-720, would be summarized and included in NDA 50-754. Additionally, it was agreed to that the draft labelling of NDA 50-754 would contain changes to the label submitted under NDA 50-542 supplements S-005 and S-010.

August 28, 1997
Teleconference with SB to discuss recommendation for submission of a food effect study. Since the current labelling contains a statement stating that amoxicillin may be given without regard to meals, and the applicant has submitted a new dose and new formulation, the Division strongly recommended a food effect study.
The SB representatives indicated that it would be difficult to justify a food effect study; Divisional representatives replied that if a food effect study was not submitted, then if approved, the label would have to be revised to reflect the conditions under which the drug was studied and dosed. SB then agreed to have the FDA Biopharmaceutists give guidance regarding a food effect study; a copy of the biopharmaceutist's study design comments for the food effect study was faxed to the applicant.

March 6, 1998
Amendment to pending NDA filed to provide for physician sample package (non-child-resistant aluminum/aluminum single unit blister pack) for the Amoxil 500-mg and 875-mg tablets.

April 21, 1998
Dissolution testing methods information faxed to Biopharmaceutics reviewer

May 29, 1998
Medical reviewer made request to Bob Pietrusko, Regulatory Affairs, SB for tables from NDA 50-720 referenced in NDA 50-754.

June 1, 1998
Requested tables received (faxed on May 29, 1998); desk copy received 6/3/98.

BACKGROUND
Amoxil (amoxicillin) is a semisynthetic antibiotic, an analog of ampicillin, with broad spectrum activity against many Gram-positive and Gram-negative bacteria. Amoxil has been approved since the 1970s and continues to be used to treat many common infections. Originally developed as an alternative to ampicillin, with the same desirable efficacy, its better safety and bioavailability profiles have resulted in fewer episodes of gastrointestinal disturbance and higher serum and tissue concentrations. These higher serum and tissue concentrations correspond with less frequent dosing for amoxicillin, and are the basis for the applicant's requested change in dosing regimen from q8 to q12 hours.

Currently, Augmentin (amoxicillin-clavulanate) 875-mg and 500-mg formulations are approved for q12 hour dosing for the treatment of specific infections caused by beta-lactamase producing organisms.

NON-CLINICAL STUDIES
CHEMISTRY/MANUFACTURING CONTROLS
See full review by Chemist, Andrew Yu, PhD.

ANIMAL PHARMACOLOGY/TOXICOLOGY
K Seethaler, PhD. recommended amending the wording regarding mutagenic potential based on data from Augmentin NDA 50-720. See full review.

MICROBIOLOGY
See full Microbiology review by S. Altaie, PhD., for the recommended revisions to the Microbiology section of the label. These recommendations were part of the review of NDA 50-542, S-005 and S-010.

HUMAN PHARMACOKINETICS/PHARMACODYNAMICS
See full review by Biopharmaceutist, He Sun, Ph.D. and discussion below which summarizes the bioequivalence study. The Biopharmaceutics reviewer has recommended approval of the requested change in dosing.

INTRODUCTION TO CLINICAL TRIALS

General Overview

As noted previously, the applicant has provided bioequivalence and supportive microbiologic data as the basis for approval of the q8 hours to q12 hours dosing change. There were no clinical efficacy trials conducted in support of this application.

RATIONALE

The purpose of this application is to seek approval for the b.i.d. regimen of Amoxil which was designed to achieve enhanced dosing convenience and preserve the efficacy relative to already established t.i.d. regimen.

The sponsor has proposed 2 regimens as alternatives to the currently approved doses for adults. Both formulations represent an increase in the dose that is administered currently; when compared with the 500 mg q8 hours dosing regimen, the 875 mg q12 regimen is a 75% increase in the unit dose of amoxicillin over the previous highest dose of 500 mg, and a 16.7% increase in the total daily dose. The 500 mg q12 hour regimen represents a 100% greater unit dose and 33.3% increase in the total daily dose when compared with the 250 mg q8 hourly dose. However, the highest dose of each of the new strengths is still within the maximum 3g labelled amoxicillin dose which can be given as a single dose. In addition, these new doses match those currently approved for Augmentin 500-mg and 875-mg tablets q12 hours.

The major benefit expected from the proposed q12 hour dosing regimen is the possibility of improved patient compliance while providing efficacy equivalent to the Amoxil regimens dosed q8 hours.

It is expected that the safety and efficacy profile of the twice daily regimen should be comparable to that of the thrice daily regimen for the following reasons:

1. A determinant of the efficacy of beta-lactam antibiotics is the time over MIC (T>MIC) of the pathogen. The Amoxil 875 mg and 500 mg q12 regimens are designed to approximate the T>MIC of amoxicillin observed in the Amoxil 500 mg and 250 mg q8 hour regimens.
2. The recently approved Augmentin 875/125mg and 500/125 mg formulations were demonstrated to be safe and effective in three pivotal studies in community-acquired pneumonia and acute exacerbations of chronic bronchitis, complicated urinary tract infections and pyelonephritis, and skin and soft tissue infections.

Thus the Amoxil q12 hourly regimen is expected to exhibit efficacy similar to that of the Augmentin q12 hourly regimen against non beta-lactamase producing pathogens.

The applicant believes that the benefits of improved compliance outweigh the risk of a potential diminished efficacy from the slightly lower T>MIC for Amoxil q12 hour dosing regimens for pathogens of low MIC. An overall improvement in the risk-benefit ratio between the q12-hour and q8-hour Amoxil regimens is expected.

Medical Reviewer's comments:

As was noted in the review of NDA 50-720, the terms b.i.d. and q12 hours, and tid and q8 hours are not interchangeable; when dosing is based on a b.i.d. or t.i.d. schedule, in general, the requisite doses are administered during the waking hours, whereas when dosing on a q8h or q12h schedule, an attempt is made to stay as close to the prescribed schedule as possible. This allows for a more even drug distribution throughout the 24 hour period, which is important in the maintenance of adequate drug levels above the MIC during the dosing interval.

Primary Objective

The purpose of this supplement is to seek marketing approval for two new q12 hour dosing regimens for Amoxil; the first regimen is Amoxil 875 mg q12 hours, an alternative to the currently approved dose of 500 mg q 8 hours, and the second is Amoxil 500 mg q12 hours, an

alternative to the currently approved dose of 250 mg q 8 hours. In addition, a new formulation, the swallow tablet, is being introduced for use in adults.

Study Design

HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

The applicant submitted one study, an open-label, randomized, 2 part single-dose, crossover bioequivalence study in healthy adult volunteers, which compared the new Amoxil 875-mg swallow tablet formulation with the currently approved Augmentin 875/125 mg tablet. Patients received dosing in the morning, concurrent with a light breakfast after an overnight fast. Though recommended to support a new formulation or new strength, no food effect study was conducted.

	Study BRL-2333/058
Primary Objective	to demonstrate bioequivalence of Amoxil 875-mg swallow tablet to Augmentin 875/125mg tablet
Study design	randomized, open-label, crossover study
Patient Population	males and females;18-60 years of age
Number of subjects enrolled	28
Number of evaluable subjects	27
Study drug	Amoxicillin 875 mg; then Augmentin 875-mg 3 days later
Duration of therapy	single dose
Study visits	pre treatment screening and enrollment within 21 days before administration of study drug treatment phase follow-up within 15 days of final dose
Pharmacokinetic Labs	blood specimen collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 12 hours after dosing
Safety parameters	hematology, chemistry, urinalysis, and pregnancy tests done pre treatment and at the follow-up visit
Adverse events	assessments made pre-dose, 12 hours post dose, and at follow-up
primary outcome measures	AUC (0-inf) and C_{max}
secondary endpoint	T_{max}

Medical reviewer's comments:
The design of the study appears consistent with that outlined in the CFR 320.26 for single dose in vivo bioavailability studies.

Results

Study 23333/058

Of the 28 volunteers enrolled in the trial, the mean age was 35 years (20-57) and the mean weight was 70.2 kg (55.0-103.0); there were 13 males and 15 females. All the patients were white. One subject was withdrawn after completing the first arm of the trial (sufficient number of subjects had completed the study to meet the protocol objectives). This patient received Amoxil 875 mg dose but not the Augmentin 875 mg dose. The results in the following tables are based on 27 subjects who completed both study periods.

Table Pharmacokinetic Parameters Estimates for Amoxil

Parameter	Amoxil	Augmentin
AUC (0-infinity) (mcg.h/mL)	35.4 (8.1)	35.8 (10.0)

C_{max} (mcg/mL)	13.8 (4.1)	12.8 (3.9)
T_{max} [a] (hours)	1.50 (1.00-2.00)	1.50 (1.00-3.00)
T_{MIC} [b] (hours)	5.69 (4.77-6.95)	5.96 (3.98-7.40)
$T_{½}$ (hours)	1.180.90-1.56)	1.26 (0.87-1.81)

[a] Data presented as median (range)
[b] Data presented as mean (range)

Statistical analysis
Statistical analysis for the two primary efficacy parameters, AUC and C_{max}, showed the two drugs to be bioequivalent.

Table Point Estimates and Confidence Intervals

Parameter	Amoxil	Augmentin	Point Estimate	90% CI
AUC (mcg.h/mL)	35.4	35.8	1.00	(0.91, 1.11)
C_{max} (mcg/mL)	13.8	12.8 (3.9)	1.07	(0.97, 1.19)

Medical reviewer's comments:
Based on all these results, the Biopharmaceutics reviewer has concluded that the results from study 23333/058 have shown that the new Amoxil 875-mg swallow tablet is bioequivalent to the amoxicillin component of the marketed Augmentin 875/125mg tablet. Also according to the Biopharmaceutics reviewer, since the bioequivalence of Amoxil to Augmentin was demonstrated at the higher dose, based on the linear kinetics of amoxicillin, bioequivalence is inferred at the lower dose of Amoxil 500 mg q 12 hours.

Safety Overview of Pharmacokinetic study
There were no deaths or serious adverse events. Thirty six treatment emergent adverse events were reported during the study, none of which was severe. There were no withdrawals due to adverse events.
Fifteen subjects and 12 subjects reported adverse experiences, following administration of Amoxil 875 mg and Augmentin 875/125 mg, respectively. The most frequently reported adverse event was diarrhea. The adverse events are summarized in the table below.

Table Treatment emergent adverse experiences

Adverse event	Amoxil 875 mg	Augmentin 875/125 mg
Number exposed to study drug	28	27
Diarrhea	7	3
Headache	5	4
URI	3	1
Dyspepsia	1	0
Pharyngitis	1	1
Fatigue	1	0
Increased Sweating	0	1
Tremor	0	1
Somnolence	0	1
Vomiting	0	1
Abdominal Pain	0	1
Nausea	0	1

Micturition Frequency	0	1
Number with Adverse events	15	12

Two subjects experienced diarrhea in each of the treatment arms, and one subject reported headache in each treatment arm. None of the headaches was considered by the investigator to be likely related or related to the study treatment. Of the 4 cases with URI, all were judged unrelated to the study treatment. Of the remaining adverse events, only the mild dyspepsia was considered related to the study treatment.

Laboratory Tests
There were no clinically important changes in the hematology, chemistry, or urinalysis parameters for any of the subjects.
One subject had a post creatinine level of 170 umol/L with a baseline of 100 umol/L. However, in the absence of any associated changes in the plasma urea, electrolytes, or urinalysis, and in the absence of symptoms, the increased value was not considered to be clinically significant.

Medical reviewer's comments:
The adverse events were similar between groups except for diarrhea, which was noted twice as often in the Amoxil group when compared with Augmentin. It is not clear why this would be the case, since the clavulanate is implicated more often in the higher incidence of diarrhea than amoxicillin.

Pharmacokinetics data

Table Comparative PD relationship between Amoxil 500 mg q8h and Amoxil 875 mg q12h

MIC (mcg/mL)	Time (% of dosing interval) above MIC		Representative Pathogen
	Amoxil 500 mg q 8h	Amoxil 875 mg q 12h	
0.25	99	74	*Staphylococcus* spp.
0.5	82	63	*S. pneumoniae*
1.0	66	52	*H. influenzae*
2	49	42	*E. coli* ATCC 25922*
4	32	31	*E. coli* ATCC 25922
8	16	19	*Enterobacteriaceae*

*Reference strain used to perform test

Medical reviewer's comments:
For beta-lactams in general, bacterial killing has been observed with amoxicillin and amoxicillin-clavulanate even when the serum concentrations were above the MIC for only 30% of the dosing interval (Craig, Ped Infect Dis J1996;15:255-9). A Time above MIC > 40% is associated with a bacteriologic cure rate between 85-100% (Craig J. Infect Dis 1998; 26:1-12). At MICs of 1mcg/mL and 2mcg/mL, T>MIC for both formulations exceed this level.

Table Comparative PD relationship between Amoxil 500 mg q12h and Amoxil 250 mg q8h

MIC (mcg/mL)	Time (% of dosing interval) above MIC		Representative Pathogen
	Amoxil 250 mg q 8h	Amoxil 500 mg q 12h	
0.25	97	67	*Staphylococcus* spp.
0.5	88	52	*S. pneumoniae*
1.0	63	40	*H. influenzae*
2	38	29	*E. coli* ATCC 25922

4	—	23	*E. coli* ATCC 25922
8	—	—	*Enterobacteriaceae*

Medical reviewer's comments:
At an MIC of 2mcg/mL, the T>MIC values are 38% and 29% for Amoxil 250-mg q8h and Amoxil 500-mg q12h, respectively. Because the total and unit doses of drug being delivered by the q12h regimen are increased over the q8 hour dosing regimen, and T>MIC is dose dependent, these values are acceptable. The several years of clinical experience with Augmentin 500-mg q12h is reassuring regarding the adequacy of this dosing interval.

EFFICACY STUDIES
No clinical efficacy studies were submitted to support this application; however, the applicant referenced bacteriologic efficacy data from clinical studies submitted for the approval of NDA 50-720, for Augmentin q 12 hourly dosing; these data were reviewed.

Bacteriologic Efficacy data from Augmentin Clinical studies, NDA 50-720.
The data extracted from NDA 50-720, and summarized in the tables which follow for each of the indications, represent bacteriologic efficacy results in patients with beta-lactamase-negative organisms, where clavulanate would not be expected to make a difference in the bacteriologic outcome.

Definitions
Bacteriological per protocol definition of Bacteriologically evaluable patients
The end of therapy visit was considered the tests of cure visit for bacteriologic evaluations by the sponsor. To be included in the per protocol population for analysis of the bacteriologic response at the end of therapy, patients were required to:

- be clinically evaluable per protocol at the end of therapy
- have a pre-therapy organism as defined previously
- have an end of therapy bacteriologic assessment as defined below.

Eradication
Elimination of original pathogen from the original site is documented by culture.

Presumed Eradication
Symptomatic response was cure or improvement but no original pathogen or culture from the original site of infection was available.

Colonization
An organism other than original pathogen which appears after treatment and is not associated with the initial signs and symptoms of infection.

Superinfection
The emergence of new pathogen during therapy at the site of infection or at a distant site that is different for the pre-treatment pathogen, such that its contribution to the symptoms and signs led to a requirement for additional antibacterial therapy.

Failure
Non eradication of the original pathogen, continued infection

Unable to evaluate
Evaluation cannot be made secondary to no pretreatment pathogen, concomitant drug to which the pathogen is susceptible was used, inadequate treatment, isolation of a baseline organism not considered to be the etiologic pathogen.

Protocol 25000/231
Comparison of the safety and efficacy of Augmentin 500/125mg po q 12 hours vs. Augmentin 250/125 mg po q 8 hours in the treatment of uncomplicated skin and skin structure infections

Sponsor's results
Table Bacteriologic successes at the End of Therapy by Beta-lactamase-negative Pre-therapy Organism (Per Protocol bacteriologically evaluable population)

Pre-therapy organisms	Augmentin 250 mg q 8h		Augmentin 500 mg q 12h	
	n/N	%	n/N	%
S. aureus	10/11	90.9	8/9	88.9
Streptococcus Group A	7/7	100	3/3	100
S. viridans	2/2	100	4/4	100
Enterococcus	6/6	100	2/3	66.7
S. haemolyticus	2/2	100	3/3	100
E. coli	1/1	100	4/4	100

n= bacteriologic successes N= bacteriologic successes and failures

Medical reviewer's comments:
The organisms in the proposed label for the skin and skin structure infections indication are *Streptococcus* spp. (alpha- and beta-hemolytic strains only), *S. pneumoniae, Staphylococci* spp., or *E. coli*. The two most common pathogens associated with skin and skin structure infections are *S. aureus* and Group A streptococci. The results indicate that there is some support for the claim of bacteriologic efficacy of Augmentin 500 mg for the treatment of skin and skin structure infections due to beta-lactamase-negative organisms; however, the numbers are small for Group A streptococci.
Results of the medical officer's review of NDA 50-720 in 1996 were extracted from the review and are summarized below. In the review of NDA 50-720, the medical officer defined the follow-up visit as the test of cure visit for the bacteriologic response and included patients in foreign studies who had confirmation of pre-therapy organisms at a local lab in the evaluable population. Therefore, there were differences in the numbers of pathogens considered for efficacy when compared with the sponsor's results.

Medical Reviewer's data from review of NDA 50-720

Table Bacteriologic Efficacy by specific organism at the follow-up visit

Pre-therapy organisms	Augmentin 250 mg q 8h		Augmentin 500 mg q 12h	
	n/N	%	n/N	%
S. aureus	8/14	57.1	12/17	70.6
Streptococcus Group A	4/8	50	5/5	100
S. viridans	2/3	66.7	2/3	66.7
Enterococcus	1/2	50	2/4	50
E. coli	2/3	66.7	4/5	80

Medical reviewer's comments:
At a dose of Amoxil 500 mg q12 hours, the results from the medical officer's review show lower success rates when compared with the sponsor's results, however, other than for *S. aureus*, the numbers of pathogens are small.

Protocol 25000/233
Comparison of the safety and efficacy of Augmentin 875/125mg po q 12 hours vs. Augmentin 500/125 mg po q 8 hours in the treatment of complicated urinary tract infections and pyelonephritis

Sponsor's results
Table Pre-therapy ampicillin-susceptible uropathogens, 48-96 hours post-Therapy by Beta-lactamase-negative (bacteriologically evaluable population at the end of therapy)

Pre-therapy organisms	Augmentin 500 mg q 8h		Augmentin 875 mg q 12h	
	n/N	%	n/N	%
E. coli	5/6	83.3	10/11	90.9
P. mirabilis	1/1	100	3/ 4	75
Enterococcus spp.	3/3	100	3/ 4	75

Medical reviewer's comments:
These results and those in the following tables reflect bacteriologic efficacy rates for complicated urinary tract infections and pyelonephritis. The results in this table are end of therapy results and do not represent efficacy at the test of cure.

Table Bacteriologic response by pathogen at 2-4 weeks post therapy

Pre-therapy organisms	Augmentin 500 mg q 8h		Augmentin 875 mg q 12h	
	n/N	%	n/N	%
E. coli	7/15	46.7	10/14	71.4
P. mirabilis	1/1	100	4/5	80
Enterococcus spp.	2/3	66.7	3/ 4	75

Medical reviewer's comments:
The results for Augmentin 875 mg q 12 hours are better than those for the Augmentin 500-mg q 8 hourly dosing. The numbers for *P. mirabilis* and *Enterococcus* spp. are small, but efficacy rates range from 66.7% to 100% at this visit.
Results of the medical officer's review of NDA 50-720 are summarized below. The medical reviewer accepted any visit greater than 4 days after the completion of study therapy as the first follow-up visit, and the test of cure visit. Therefore, depending on the protocol, the results in the table below represent those from patients who had the first follow-up visit at 5-9 days post-therapy and 2-4 weeks after the completion of therapy.

Medical officer's results of review of NDA 50-720

Table Pre-therapy ampicillin-susceptible uropathogens at first follow-up

Pre-therapy organisms	Augmentin 500 mg q 8h		Augmentin 875 mg q 12h	
	n/N	%	n/N	%
E. coli	31/57	54.4	30/58	51.7
P. mirabilis	2/4	50	2/2	100
Enterococcus spp.	5/8	62.5	4/7	57.1

Medical reviewer's comments:
In general, the bacteriologic efficacy rates of Augmentin 875 mg from the medical officer's review were lower than those from the sponsor's analysis, especially for *E. coli*. Again, as in the sponsor's analysis, the numbers of *P. mirabilis* and *Enterococcus* spp. are small.

Protocol 25000/234
Comparison of the safety and efficacy of Augmentin 875/125mg po q 12 hours vs. Augmentin 500/125 mg po q 8 hours in the treatment of lower bacterial respiratory infections.

Sponsor's Results

Table Bacteriologic successes at the End of Therapy by Beta-lactamase negative Pre-therapy Organism (Per Protocol bacteriologically evaluable population)

Pre-therapy organisms	Augmentin 500 mg q 8h		Augmentin 875 mg q 12h	
	n/N	%	n/N	%
S. pneumoniae	20/22	91	19/19	100
H. influenzae	10/13	76.9	12/13	92.3
M. catarrhalis	1/1	100	4/4	100
S. aureus	3/3	100	2/2	100

Data generated from combined infections of community acquired pneumonia and acute exacerbation of chronic bronchitis.

Medical reviewer's comments:
The organisms in the proposed label for the lower respiratory infection indication are *Streptococcus* spp. (alpha- and beta-hemolytic strains only), *S. pneumoniae, Staphylococci* spp., or *H. influenzae.*
The data presented in the table above indicate that, although the numbers are for *M. catarrhalis and S. aureus* small, in general, the bacteriologic efficacy rates for Augmentin 875 mg q 12 hours for the treatment of lower respiratory tract infections are high. Results of the medical officer's review of NDA 50-720 are summarized below.

Medical officer's results from review of NDA 50-720

Tables Bacteriologic successes at the End of Therapy by Beta-lactamase-negative Pre-therapy Organism (Per Protocol bacteriologically evaluable population)

Community Acquired Pneumonia

Pre-therapy organisms	Augmentin 500-mg q 8h		Augmentin 875-mg q 12h	
	n/N	%	n/N	%
S. pneumoniae	23/25	92	22/23	95.6
H. influenzae	14/15	93.3	13/20	70
M. catarrhalis	1/1	100	3/3	100
S. aureus	1/1	100	1/1	100

Acute Exacerbation of Chronic Bronchitis

Pre-therapy organisms	Augmentin 500-mg q 8h		Augmentin 875-mg q 12h	
	n/N	%	n/N	%
S. pneumoniae	10/13	76.9	6/7	85.7
H. influenzae	7/12	58.3	11/14	78.6
M. catarrhalis	1/1	100	3/3	100
S. aureus	0/1	0	2/2	100

Medical reviewer's comments:
When compared to those of the sponsor, the combined bacteriologic efficacy rates of the reviewer for Augmentin 875 mg q 12h were lower for *S. pneumoniae* and *H. influenzae*.
No data are included for infections of the upper respiratory tract, but the pathogens are the same as those seen in lower respiratory tract infections.

CONCLUSIONS

1. The results of study 23333/058, the bioequivalence study, have shown that the new Amoxil 875-mg swallow tablet is bioequivalent to the amoxicillin component of the marketed Augmentin 875/125mg tablet.

2. The adverse events were similar between groups except for diarrhea, which was noted twice as often in the Amoxil group when compared with Augmentin.

3. The **CLINICAL PHARMACOLOGY** section must be revised to reflect that a food effect study was not conducted, and that the analysis of the bioequivalence study was based on results from 27 volunteers only, not 28 subjects.

4. Amoxicilin is no longer part of the recommended or alternative regimens for treatment of gonococcal infections. This change in recommendations, and in clinical practice, should be reflected in the INDICATIONS AND USAGE section of the label, such that it reads

5. Overall, the results for the treatment of beta-lactamase-negative organisms with Augmentin tablets, from NDA 50-720, are consistent with acceptable bacteriologic efficacy.

RECOMMENDATIONS

It is recommended that NDA 50-754, which seeks a marketing claim for the new Amoxil 500-mg and 875-mg swallow tablets for q12 hourly dosing be approved, with the labelling revisions as outlined above.

/S/

Mamodikoe Makhene, M.D.
Medical Officer/HFD-520

cc:
original IND, NDA
NDA 50-754
HFD-520/Office Director/Murphy
HFD-520/ Div Director/Chikami
HFD-520/Medical TL/Albueme
HFD-344/DSI/Thomas
HFD-520/PharmTox TL/Osterberg
HFD-520/PharmTox/Seethaler
HFD-520/Chemistry TL/Katague
HFD-520/Chemistry/Yu
HFD-520/Microbiology TL/Sheldon
HFD-520/Microbiology/Altaie
HFD-520/Biopharm TL/Pelsor
HFD-520/Biopharm/Sun
HFD-520/CSO Supervisor/Bona
HFD-520/CSO/Trostle
mkm/6/30/98

7/6/98
6/26/98 (draft)
7/1/98 (final)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-754

CHEMISTRY REVIEW(S)

JUN 16 1998

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-754 CHEM.REVIEW #: 2 REVIEW DATE: 15-JUN-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11-JUL-97	14-JUL-97	21-JUL-97
AMENDMENT (Stability update)	13-NOV-97	14-NOV-97	20-NOV-97
AMENDMENT (Environment Assessment)	13-FEB-98	17-FEB-98	20-FEB-98
AMENDMENT (Stability update)	06-MAR-98	07-MAR-98	10-MAR-98
AMENDMENT (Facility Amendment)	30-MAR-98	31-MAR-98	07-APR-98
AMENDMENT (Response to Review #1)	15-MAY-98	18-MAY-98	27-MAY-98
AMENDMENT (Stability Update)	04-JUN-98	15-JUN-98	15-JUN-98

NAME & ADDRESS OF APPLICANT: SMITHKLINE BEECHAM PHARMACEUTICALS
One Franklin Plaza P.O. Box 7929 Philadelphia,
PA 19101-7929

DRUG PRODUCT NAME

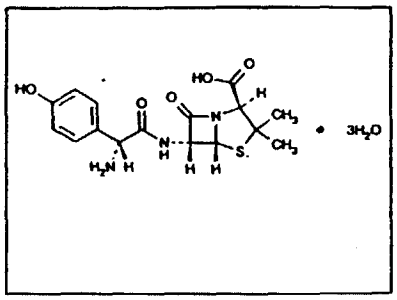
Proprietary:	Amoxil Tablets
Nonproprietary/USAN:	Amoxicillin tablets
Code Names/#'s:	
Chemical Type/ Therapeutic Class:	3 S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION:
Anti-infective

DOSAGE FORM:	Tablet
STRENGTHS:	500 & 875 mg
ROUTE OF ADMINISTRATION:	oral
DISPENSED:	_X_ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



Ampicillin Trihydrate $C_{15}H_{19}N_3O_5S.3H_2O$

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.
CAS-61-336-70-7
M.W. 419.46

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable)
USP 23 Page 100
USP 23 Page 102
Other related Amoxil NDAs
NDA 50542
Amoxil capsule
Amoxil chewable tablet
Amoxil powder for oral suspension
Pediatric drop for oral suspension
For HDPE bottles, No DMF authorization needed, the DMF's are held by the sponsor.

Other DMFs:
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
The firm has provided DMF authorization letters.

CONSULTS
Consult to CDER Labeling and Nomenclature committee was submitted for Amoxil tablets.

REMARKS/COMMENTS :

In addition to the 3 facilities listed, was added through an amendment on 30-MAR-98. All four facilities were approved based on either profile or actual inspection.

CONCLUSIONS & RECOMMENDATIONS:
Recommend approval from the manufacturing and controls standpoint. All pending issues have been satisfactory resolved.

/S/ 6/15/98

Andrew Yu, Review Chemist

cc: Orig. NDA 50-754 (other NDA's may be included if appropriate)
HFD-520/Division File
HFD-520/AYu
HFD-520/MMakhene
HFD-520/MAlbuerne
HFD-520/ROsterberg
HFD-520/Micro/SAltaire
HFD-520/STrostle
HFD-520/DKatague R/D Init by: DKatague DBK 6/16/98

520 Trosille

MAY 1 1998

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-754 CHEM.REVIEW #: 1 REVIEW DATE: 20-Apr-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11-JUL-97	14-JUL-97	21-JUL-97
AMENDMENT (Stability update)	13-NOV-97	14-NOV-97	20-NOV-97
AMENDMENT (Environment Assessment)	13-FEB-98	17-FEB-98	20-FEB-98
AMENDMENT (Stability update)	06-MAR-98	07-MAR-98	10-MAR-98
AMENDMENT (Facility Amendment)	30-MAR-98	31-MAR-98	07-APR-98

NAME & ADDRESS OF APPLICANT: SMITHKLINE BEECHAM PHARMACEUTICALS
One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101-7929

DRUG PRODUCT NAME
Proprietary: Amoxil Tablets
Nonproprietary/USAN: Amoxicillin tablets
Code Names/#'s:
Chemical Type/
Therapeutic Class: 3 S

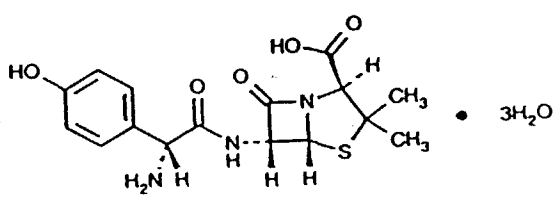
ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION:
Anti-infective

DOSAGE FORM: Tablet
STRENGTHS: 500 & 875 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: _X_ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Ampicillin Trihydrate $C_{15}H_{19}N_3O_5S.3H_2O$



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.
CAS-61-336-70-7
M.W. 419.46

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable)
USP 23 Page 100
USP 23 Page 102
Other related Amoxil NDAs
NDA 50542
Amoxil capsule
Amoxil chewable tablet
Amoxil powder for oral suspension
Pediatric drop for oral suspension
For HDPE bottles, No DMF authorization needed, the DMF's are held by the sponsor.

Other DMFs:
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
The firm has provided DMF authorization letters.

CONSULTS
Consult to CDER Labeling and Nomenclature committee was submitted for Amoxil tablets.

REMARKS/COMMENTS :

In addition to the 3 facilities listed, was added through an amendment on 30-MAR-98. All four facilities were approved based on either profile or actual inspection.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505(b) of the Act. Specific items which are not approvable are identified under the following headings:

All manufacturing facilities are currently in acceptable GMP compliance as of 01-APR-1988

/S/ 4/30/98

Andrew Yu, Review Chemist

cc: Orig. NDA 50-754 (other NDA's may be included if appropriate)
HFD-520/Division File
HFD-520/AYu/12/16/97
HFD-520/MMakhene
HFD-520/MAlbuerne
HFD-520/ROsterberg
HFD-520/Micro/SAltaire
HFD-520/STrostle
HFD-520/DKatague R/D Init by: DKatague DBK 5/1/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-754

MICROBIOLOGY REVIEW(S)

NDA 50720/ TRoStic Susp.

FEB 27 1998

Division of Anti-Infective Drug Products
Clinical Microbiological Review #2

NDA NUMBER:	REVIEW DATE:	SUBMISSION/TYPE:
50542 SLR-005 & 010 50754	2-26-98	Labeling Supplements Original NDA

DOCUMENT DATE	CDER DATE	ASSIGNED DATE
4-23-97 & 7-30-97 7-11-97	4-28-97 & 7-31-97 7-14-97	5-29-97 & 5-27-97 7-31-97

NAME & ADDRESS OF APPLICANT:
SmithKline Beecham Pharmaceuticals
One Franklin Plaza
P. O. Box 7929
Philadelphia, PA 19101-7929

CONTACT PERSON:
Sharon W. Shapowal, R. Ph.
Assistant Director, U.S. Reg. Affairs
One Franklin Plaza
P. O. Box 7929
Philadelphia, PA 19101-7929
Phone Number: (215) 751-3868

DRUG PRODUCT NAME

Proprietary:	Amoxil®
Nonproprietary/USAN:	Amoxicillin trihydrate
Code Names/#'s:	
Therapeutic Class:	Antibiotic

PHARMACOLOGICAL CATEGORY: β-Lactam

DOSAGE FORM: Tablets (chewable)
Tablets (swallow)

STRENGTHS: 125 and 250 mg/tablet
500 and 875 mg/tablet

ROUTE OF ADMINISTRATION: Oral
Intravenous infusion

DISPENSED: _X_ Rx ___ OTC

RELATED DOCUMENTS (if applicable):
NDA 50720

REMARKS/COMMENTS:

Pursuant to the provision of 21 CFR 314.70 (b) and the letter of January 26, 1993 from Dr. M. M. Lumpkin, concerning labeling supplements for anti-infective products, the sponsor have revised the labeling for the Amoxil® capsule, oral suspension, and chewable tablets and have submitted the revisions under NDA 50542 supplements 005 and 010. They have also submitted the Amoxil® NDA 50754 to change the dosing interval for adult and pediatric patients based on the data in a related NDA 50720 for Augmentin® tablets.

Historical perspective: In the early 1970's, the sponsor received approval for the use of Amoxil® (amoxicillin) in the treatment of gram positive and gram negative infections due to certain susceptible organisms. Clinical studies across a number of indications demonstrated that the following general dosing guidelines were appropriate:

	Usual dose	**Severe infections or less susceptible organisms**
adult dose	250 mg q 8h	500 mg q 8h
pediatric dose	20 mg/kg/d q 8h	40 mg/kg/d q 8h

In the mid-1980's when Augmentin was approved for the treatment of infections caused by amoxicillin-resistant, beta-lactamase producing strains of indicated organisms, clinical studies confirmed that it was possible to maintain the Amoxil dosing scheme and simply add clavulanate potassium. While expanding the microbiologic activity of amoxicillin, clavulanate produced no effect on amoxicillin pharmacokinetics and the general dosing guidelines for Augmentin remained in line with Amoxil:

	Usual dose (amoxicillin/clavulanate)	**More severe infections (amoxicillin/clavulanate)**
adult dose	250/125 mg q 8h	500/125 mg q 8h
pediatric dose	20/10 mg/kg/d q 8h	40/10 mg/kg/d q 8h

SmithKline Beecham recently received approval of every 12 hourly dosing regimens for Augmentin. Efficacy of the new dosing regimens was confirmed in large clinical trials involving adult and pediatric patients. The sponsor states that as a second-line therapy, Augmentin is designed to follow Amoxil therapy, and it is both desirable and appropriate that the dosing schemes for the two agents be in accord. Thus, the sponsor proposes the following to transition Amoxil to a q 12h product, like Augmentin, and to bring the labeling back into agreement.

Sponsor Proposal: Amoxil for Q 12H Dosing:

The labeling and indications sought by the sponsor for Amoxil as a q 12h product is identical to the labeling and indications presently approved for Amoxil as a q 8h product. As a result the medical officer had requested the efficacy data for Amoxil as a q 12h to be extracted from the data for Augmentin (NDA 50-720) as a q 12h product. The extracted efficacy data will include only the data from patients with an infection caused by beta-lactamase-negative organisms.

If the other involved reviewers would approve the new proposed dosing, the microbiology section of the product insert should be revised to read as follows:

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fourth Edition; Approved Standard. NCCLS Document M7-A4, Vol. 17, No. 2. NCCLS, Wayne, PA, January 1997.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition; Approved Standard. NCCLS Document M2-A6, Vol. 17, No. 1. NCCLS, Wayne, PA, January 1997.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY section of the package insert. The changes needed should be sent to the sponsor. These revisions are listed on pages 3-8 of this review.

/S/

Sousan S. Altaie, Ph.D.
Clinical Microbiology Review Officer

cc: Orig. NDA 50-754
Orig. NDA 50-542 SLR-005
Orig. NDA 50-542 SLR-010
HFD-520/Division File
HFD-520/MO/M. Makhene
HFD-520/Biopharm/H. Sun
HFD-520/Chem/A. Yu
HFD-520/Micro/S. Altaie
HFD-520/CSO/S. Trostle
HFD-520/Pharm/K. Seethaler

2/27/98
Concurrence Only: Gary K Chikami
HFD-520/Dep. Dir./L. Gavrilovich
HFD-520/TL Micro/A. Sheldon
R.D. Init. 9/10/97 Final 10/17/97 11/14/97
TB 3/26/98

4/1997

Division of Anti-Infective Drug Products
Clinical Microbiological Review

NDA NUMBER:	REVIEW DATE:	SUBMISSION/TYPE:
50542 SLR-005 & 010	8-27-97	Labeling Supplements
50754		Original NDA

DOCUMENT DATE	CDER DATE	ASSIGNED DATE
4-23-97 & 7-30-97	4-28-97 & 7-31-97	5-29-97 & 5-27-97
7-11-97	7-14-97	7-31-97

NAME & ADDRESS OF APPLICANT:
SmithKline Beecham Pharmaceuticals
One Franklin Plaza
P. O. Box 7929
Philadelphia, PA 19101-7929

CONTACT PERSON:
Sharon W. Shapowal, R. Ph.
Assistant Director, U.S. Reg. Affairs
One Franklin Plaza
P. O. Box 7929
Philadelphia, PA 19101-7929
Phone Number: (215) 751-3868

DRUG PRODUCT NAME

Proprietary:	Amoxil®
Nonproprietary/USAN:	Amoxicillin trihydrate
Code Names/#'s:	
Therapeutic Class:	Antibiotic

PHARMACOLOGICAL CATEGORY: β-Lactam

DOSAGE FORM: Tablets (chewable)
Tablets (swallow)

STRENGTHS: 125 and 250 mg/tablet
500 and 875 mg/tablet

ROUTE OF ADMINISTRATION: Oral
Intravenous infusion

DISPENSED: _X_ Rx ___ OTC

RELATED DOCUMENTS (if applicable):
NDA 50720

REMARKS/COMMENTS:

Pursuant to the provision of 21 CFR 314.70 (b) and the letter of January 26, 1993 from Dr. M. M. Lumpkin, concerning labeling supplements for anti-infective products, the sponsor have revised the labeling for the Amoxil® capsule, oral suspension, and chewable tablets and have submitted the revisions under NDA 50542 supplements 005 and 010. They have also submitted the Amoxil® NDA 50754 to change the dosing interval for adult and pediatric patients based on the data in a related NDA 50720 for Augmentin® tablets.

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	Usual dose	**Severe infections or less susceptible organisms**
adult dose	250 mg q 8h	500 mg q 8h
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In the mid-1980's when Augmentin was approved for the treatment of infections caused by amoxicillin-resistant, beta-lactamase producing strains of indicated organisms, clinical studies confirmed that it was possible to maintain the Amoxil dosing scheme and simply add clavulanate potassium. While expanding the microbiologic activity of amoxicillin, clavulanate produced no effect on amoxicillin pharmacokinetics and the general dosing guidelines for Augmentin remained in line with Amoxil:

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pediatric dose	20/10 mg/kg/d q 8h	40/10 mg/kg/d q 8h

SmithKline Beecham recently received approval of every 12 hourly dosing regimens for Augmentin. Efficacy of the new dosing regimens was confirmed in large clinical trials involving adult and pediatric patients. The sponsor states that as a second-line therapy, Augmentin is designed to follow Amoxil therapy, and it is both desirable and appropriate that the dosing schemes for the two agents be in accord. Thus, the sponsor proposes the following to transition Amoxil to a q 12h product, like Augmentin, and to bring the labeling back into agreement.

Sponsor Proposal: Amoxil for Q 12H Dosing:

The labeling and indications sought by the sponsor for Amoxil as a q 12h product is identical to the labeling and indications presently approved for Amoxil as a q 8h product. As a result the medical officer had requested the efficacy data for Amoxil as a q 12h to be extracted from the data for Augmentin (NDA 50-720) as a q 12h product. The extracted efficacy data will include only the data from patients with an infection caused by beta-lactamase-negative organisms.

If the other involved reviewers would approve the new proposed dosing, the microbiology section of the product insert should be revised to read as follows:

Redacted 4

pages of trade

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information

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fourth Edition; Approved Standard. NCCLS Document M7-A4, Vol. 17, No. 2. NCCLS, Wayne, PA, January 1997.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition; Approved Standard. NCCLS Document M2-A6, Vol. 17, No. 1. NCCLS, Wayne, PA, January 1997.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY section of the package insert. The changes needed should be sent to the sponsor. These revisions are listed on pages 3-8 of this review.

/S/

Sousan S. Altaie, Ph.D.
Clinical Microbiology Review Officer

cc: Orig. NDA 50-754
Orig. NDA 50-542 SLR-005
Orig. NDA 50-542 SLR-010
HFD-520/Division File
HFD-520/MO/M. Makhene
HFD-520/Biopharm/H. Sun
HFD-520/Chem/A. Yu
HFD-520/Micro/S. Altaie
HFD-520/CSO/S. Trostle
HFD-520/Pharm/K. Seethaler

Concurrence Only:
HFD-520/Dep. Dir./L. Gavrilovich
HFD-520/TL Micro/A. Sheldon
R.D.Init. 9/10/97 Final 10/17/97 11/14/97 ASS

11/14/97
11/14/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-754

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA 50,754
Amoxil (Amoxicillin) tablet,
500mg and 875mg

DATE of SUBMISSION
July 11, 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

SPONSOR: SmithKline Beecham
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101

REVIEWER: HE SUN, Ph.D.

I. BACKGROUND

The sponsor submitted this NDA to support Amoxil (amoxicillin) tablets, to allow for the change in the dosing regimen of amoxicillin from thrice daily to twice daily dosing in adults, and to provide support for the new swallow tablet formulation. These new Amoxil tablets (500 mg and 875 mg in strength) are matched to Augmentin (amoxicillin/clavulanate potassium) tablet antibiotic containing amoxicillin that was recently approved for twice daily dosing in adults (NDA 50-720, approved February 13, 1996).

One bioequivalence study in healthy adult volunteers (male and female) comparing the new 875-mg Amoxil film coated swallow tablet to the marketed *875/125 Augmentin* tablet is the only biopharmaceutic study included in the submission.

The sponsor provided the history of interactions between the sponsor and the Agency review staff. In those agreements, it is indicated that the comparative study of the 875 mg Amoxil tablet q12h vs. the marketed 875/125 mg Augmentin tablet q12h would suffice to form the "bridge" to the extensive pharmacokinetic, pharmacodynamic, microbiologic, and clinical trials data in approved Augmentin NDA 50-720.

Pharmacokinetic-pharmacodynamic data have shown that the anti-infective activity of amoxicillin is Time above MIC (T_{MIC}) dependent. T_{MIC} greater than 30-40% of dose interval is required to ensure clinical efficacy.

II. RECOMMENDATION

Study results show that the 90% CI of both AUC and C_{max} of the novel Amoxil tablet (875mg) fall in the 80-125% range of the amoxicillin component of the standard Augmentin tablet (875/125mg). In terms of the primary parameters AUC_{0-inf}, and C_{max}, the novel Amoxil tablet (875mg) is bioequivalent to the amoxicillin component of the standard Augmentin tablet (875/125mg).

Dissolution study is acceptable.

Food effect study is required for the new tablet formulation.

Based on the results of this bioequivalence study, the reviewer recommend marketing approval to be granted to both new tablet formulations (500 mg and 875 mg).

II. BIEQUIVALENCE STUDY #BRL-002333.

1. **Title:** A study to determine the bioequivalence of amoxicillin in a novel tablet formulation of Amoxil (875 mg) to the standard marketed formulation of Augmentin (875/125 mg).

2. **Investigator:**

3. **Assay:**

   Acceptable.

4. **Study Summary:**

The objective of the study is to demonstrate the bioequivalence of amoxicillin in a single dose of a novel 875 mg tablet formulation of Amoxil to amoxicillin in the standard Augmentin 875/125 mg tablet.

Study design: This was an open, randomized, 2-part, single dose crossover study. 28 male or female volunteers aged 18 to 60 years who were not allergic to penicillin antibiotics were recruited to ensure valuable data from at least 24 subjects.

Treatment and administration. Augmentin 875/125 mg tablet as standard formulation. Amoxil 875 mg novel tablets as test formulation. Each subject received two single oral doses: one

single tablet of Augmentin 875/125, Batch B96026 and one single tablet of Amoxil 875 mg Batch B96014, which were administered with approximately 200 ml water. Doses were administered at least 3 days apart. Dosing was at the start of a light meal following an overnight fast.

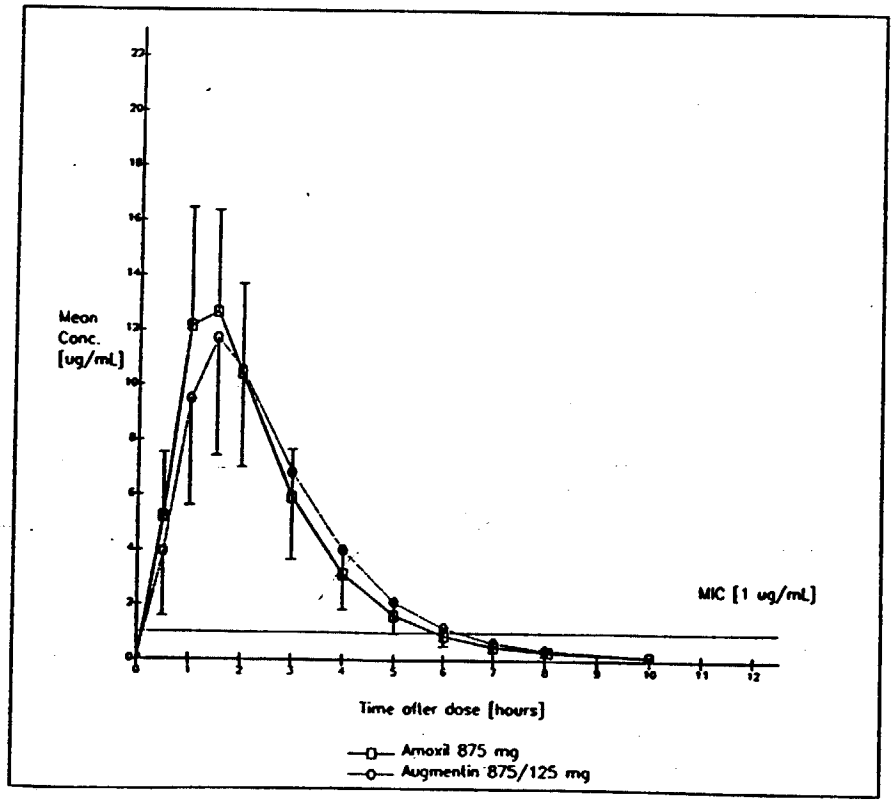
Pharmacokinetic parameters. AUC and Cmax were calculated. The 90% confidence intervals were calculated for bioequivalence assessment.

The pharmacokinetic study results are shown in Table 1 and Figure 1.

Table 1. Amoxicillin pharmacokinetics results

Parameter	Augmentin	Amoxil	Point Estimate	90% CI
C_{max} (ug/ml)	12.8	13.8	1.07	(0.97, 1.19)
AUC_{0-inf} (ug.h/ml)	35.8	35.4	1.00	(0.91, 1.11)

Figure 1 Mean [± SD] amoxicillin plasma concentrations (mcg/mL) following a single oral dose of either a novel Amoxil tablet (875 mg; test) or a standard Augmentin tablet (875/125 mg; reference) administered on separate dosing days



6. **Conclusions.**

In terms of the primary parameters AUC_{0-inf}, and C_{max}, the novel Amoxil tablet (875mg) is bioequivalent to the amoxicillin component of the standard Augmentin tablet (875/125mg).

IV. DISSOLUTION STUDY

The dissolution testing method used to generate the dissolution data was not included in the original NDA submission. The information was requested, and information was received via Fax on April 21, 1998.

Method: Using USP apparatus 2 (rotation paddle), at 75 rpm, with 900 ml deionized water at 37°C±0.5 °C. Results are listed in page 6-9.

Proposed specification: For Amoxil 500 mg and 875 mg film coated tablets, Q % of labeled amoxicillin dissolved in min.

V. SPECIFIC COMMENTS

Comments need not to be conveyed to the sponsor

1. It was found that the 500 mg and 875 mg formulations are proportional in composition (see formulation attachment on page 12). Therefore, *in vivo* bioavailability study with 500 mg Amoxil and Augmentin tablet formulations is not required. The comparative *in vitro* dissolution study is acceptable.

Comments to be conveyed to the sponsor

1. The Amoxil 875 mg to be marketed tablet is a new formulation. Food effect study is required for the new formulation. Therefore, the current study is acceptable while food effect study should be conducted and submitted to support the new tablet formulation. Below are recommended food effect study key design points:

   1000 calories with 50% derived from fat.
   240 ml water
   a.m. dosing (i.e., breakfast)
   meal within ½ hours and drug administration within 5 minutes of meals
   S.D. 2-way crossover food effect study.
   To claim "no effect," the average BE AUC fall in 80-125%, C_{max} falls in 70-143%.

The sponsor was advised to conduct this food effect study and to submit the results for review in the filing letter. Without the results of this study, Amoxil tablets (500 and 875mg) should be labeled to take with food.

2. The dissolution testing method as described in the Facsimile of April 21 was found to meet the requirement of Office of Clinical Pharmacology and Biopharmaceutics. The quality control specification for the tablet formulation should be changed to Q % in min.

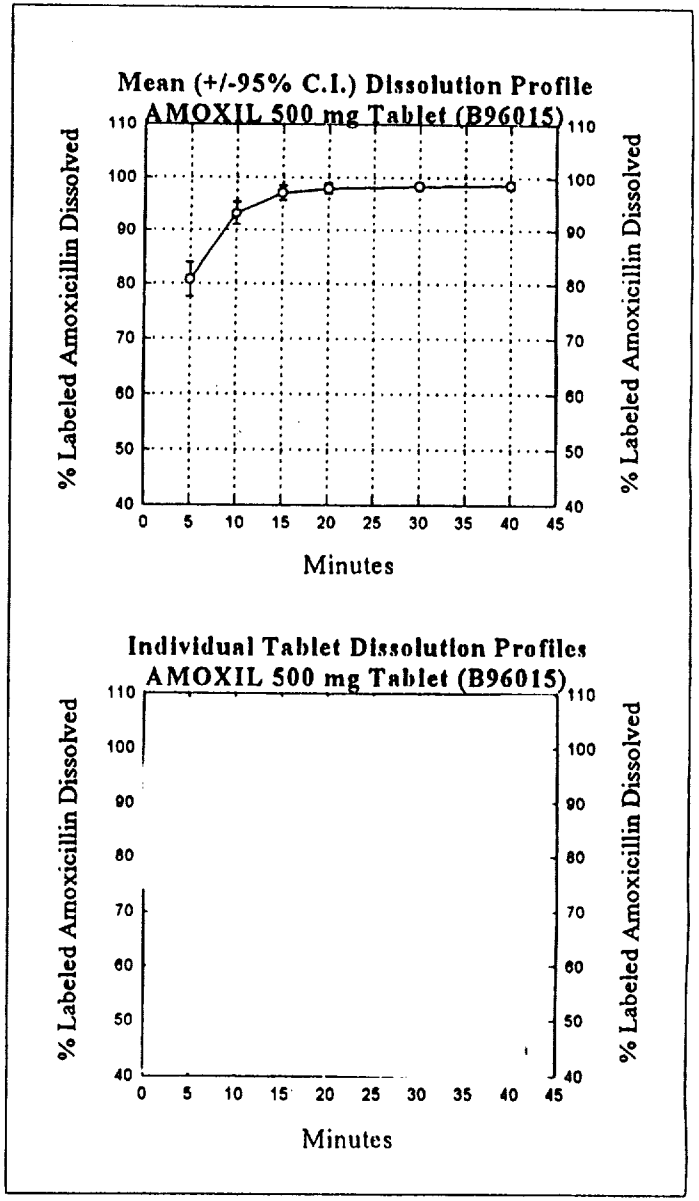
/S/ 6/26/98

He Sun, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D. /S/ 6/30/98

cc:
NDA 50,754,
HFD-520 (Clinical, CSO),
HFD-340 (Viswanathan),
HFD-880 (Pelsor, Sun)
HFD-880 Div. File NDA 50,754(Amoxicillin),
CDR (Attn.: Barbara Murphy)

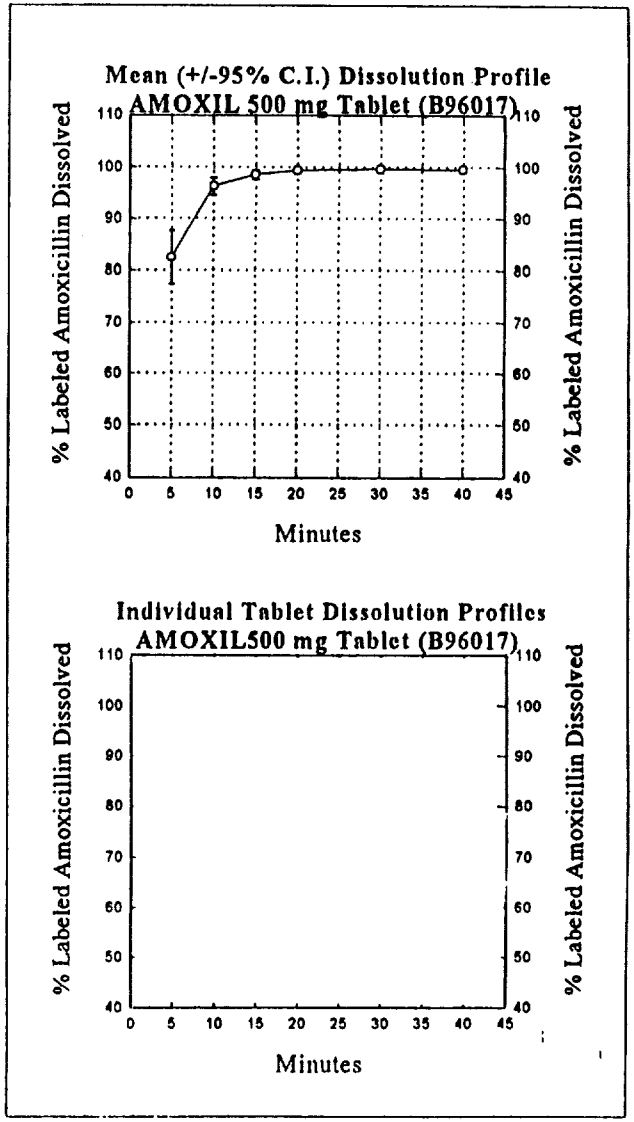
AMOXIL 500 mg Tablet Amoxicillin Dissolution Profile Batch B96015						
Tablet No.	% Labeled Amoxicillin Dissolved					
	Minutes	Minutes	Minutes	Minutes	Minutes	Minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	81	93	97	98	98	99
% CV	6.1	3.6	2.2	1.6	1.2	1.2
Min						
Max						



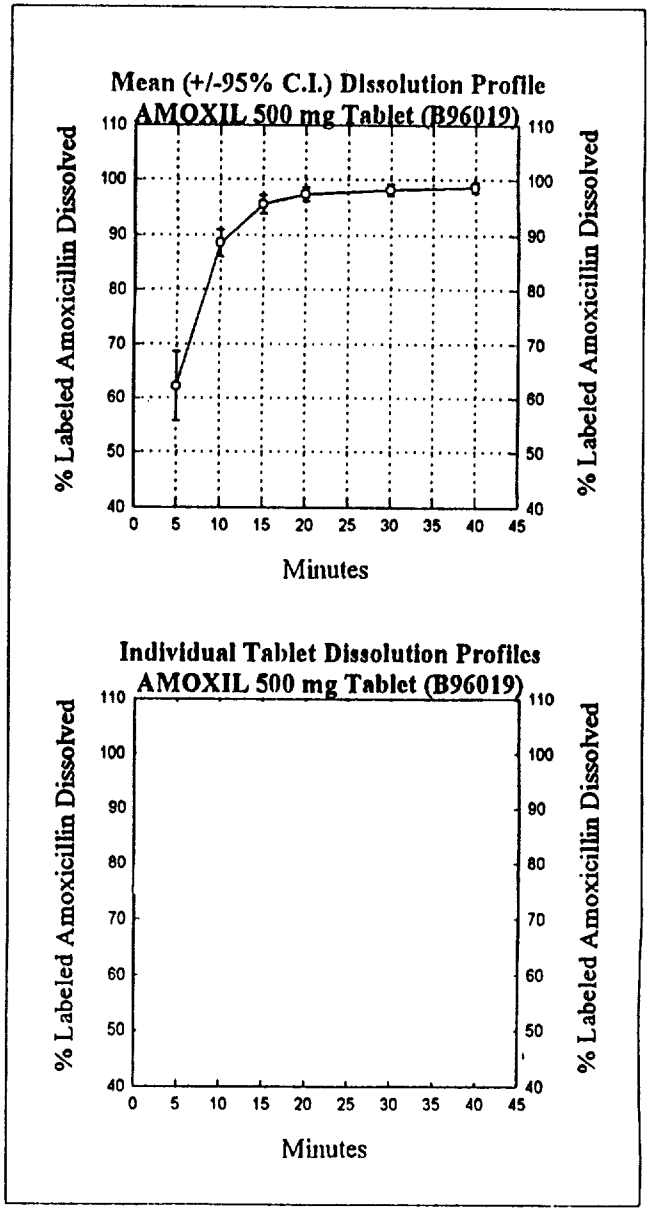
AMOXIL 500 mg Tablet
Amoxicillin Dissolution Profile
Batch B96017

Tablet No.	% Labeled Amoxicillin Dissolved					
	Minutes	Minutes	Minutes	Minutes	Minutes	Minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	83	96	99	99	100	100
% CV	9.6	2.9	1.4	1.1	1.1	1.0
Min						
Max						

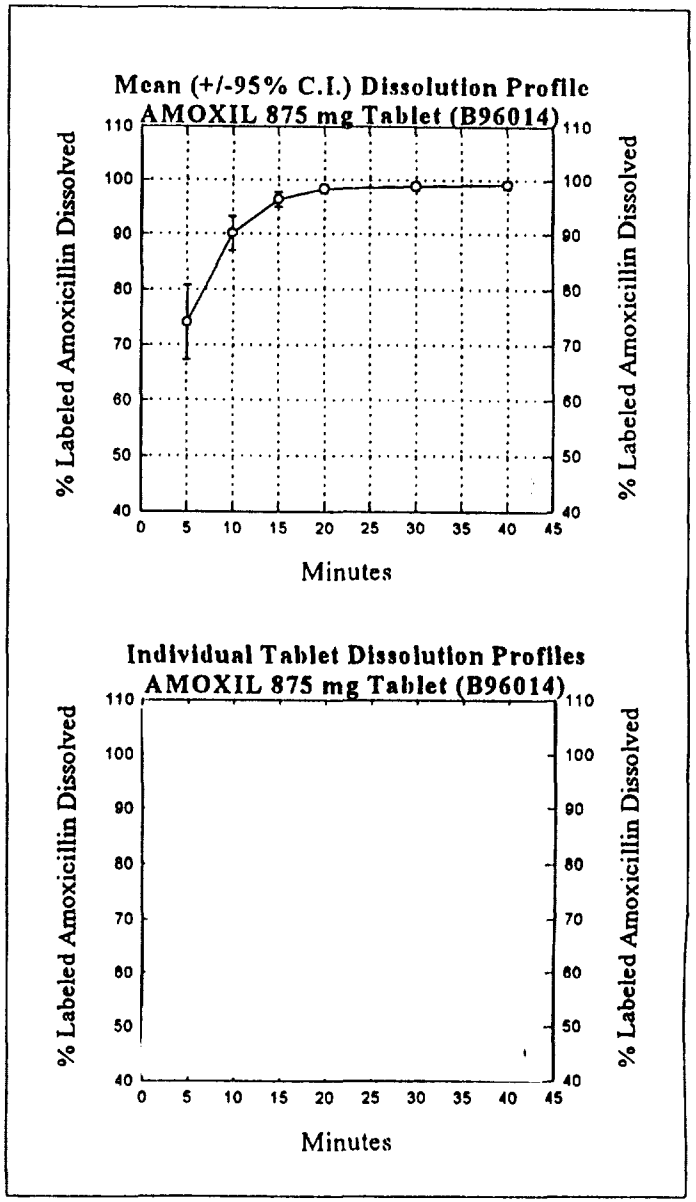
** No Result acquired from assay



AMOXIL 500 mg Tablet Amoxicillin Dissolution Profile Batch B96019						
Tablet No.	% Labeled Amoxicillin Dissolved					
	Minutes	Minutes	Minutes	Minutes	Minutes	Minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	62	89	96	97	98	99
% CV	16.2	4.4	2.7	2.0	1.7	1.4
Min						
Max						

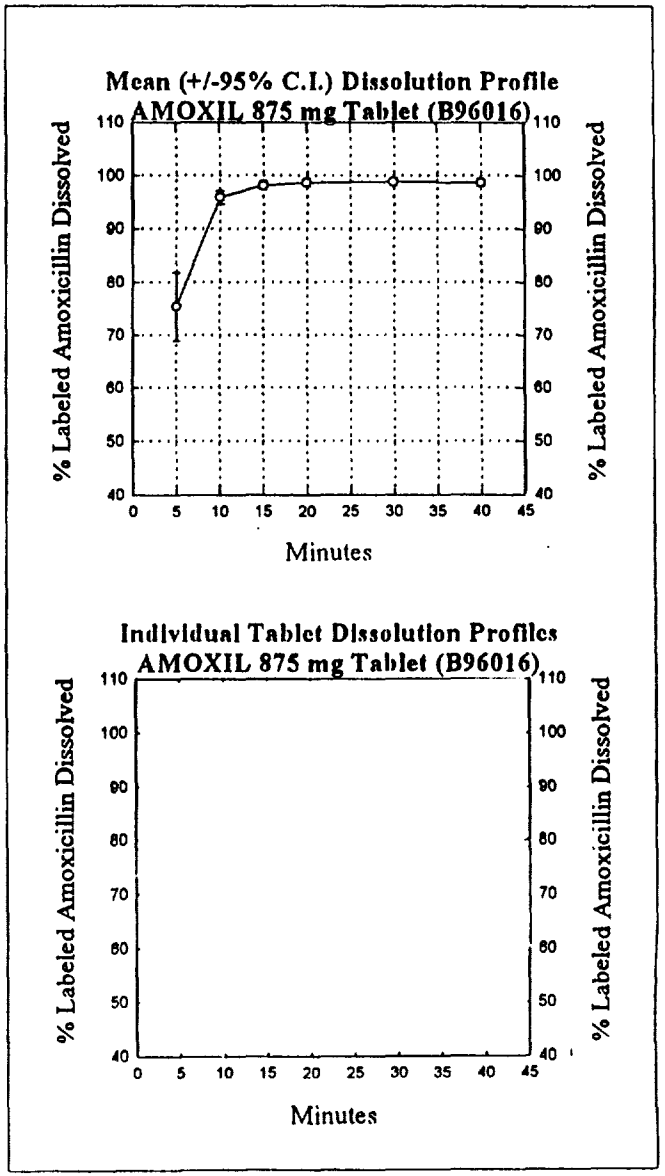


AMOXIL 875 mg Tablet Amoxicillin Dissolution Profile Batch B96014						
Tablet No.	% Labeled Amoxicillin Dissolved					
	Minutes	Minutes	Minutes	Minutes	Minutes	Minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	74	90	96	98	99	99
% CV	14.3	5.3	2.2	1.3	1.2	1.2
Min						
Max						

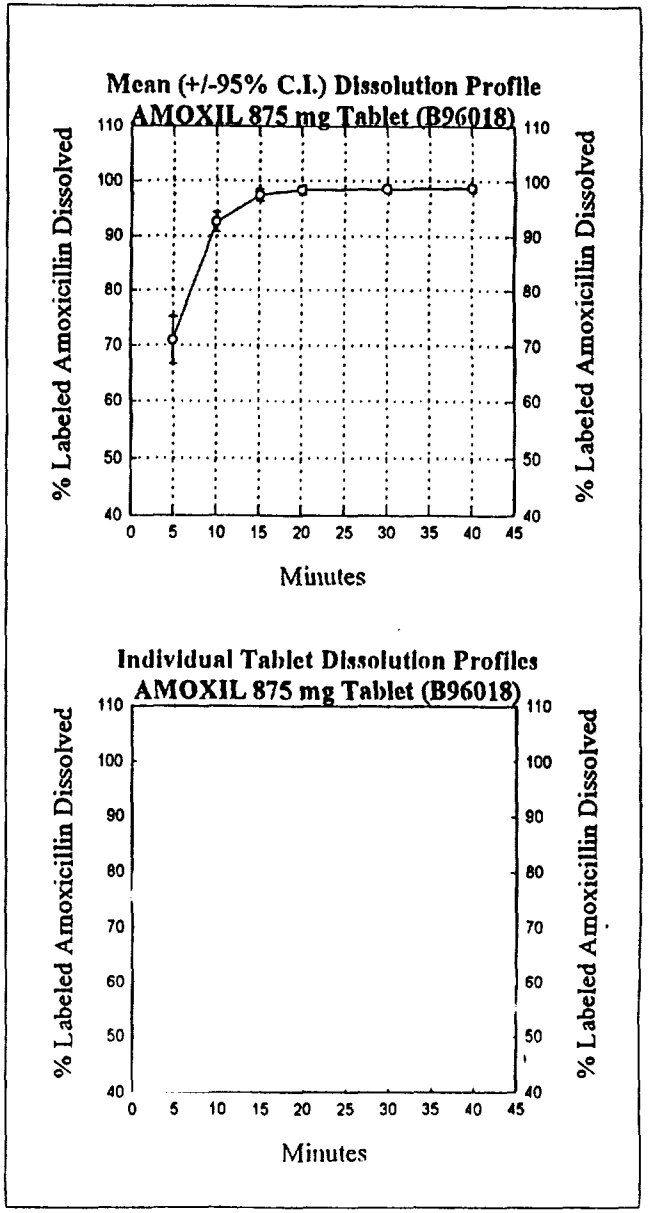


AMOXIL 875 mg Tablet
Amoxicillin Dissolution Profile
Batch B96016

Tablet No.	% Labeled Amoxicillin Dissolved					
	Minutes	Minutes	Minutes	Minutes	Minutes	Minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	75	96	98	99	99	99
% CV	13.5	2.0	1.3	1.2	1.1	1.2
Min						
Max						



AMOXIL 875 mg Tablet Amoxicillin Dissolution Profile Batch B96018						
Tablet No.	% Labeled Amoxicillin Dissolved					
	Minutes	Minutes	Minutes	Minutes	Minutes	Minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	71	93	97	98	99	99
% CV	9.4	3.0	1.8	1.4	1.2	1.1
Min						
Max						



INVESTIGATIONAL FORMULATIONS

c. Quantitative Composition of Investigational Formulations

Amoxil® (amoxicillin) 875mg Aqueous Film-Coated Tablet CT Batch Formula
Formula Code AD

Comparison of Amoxil® 875mg Tablet with Augmentin ® 875mg Tablet and corresponding 500mg Tablet strengths of Amoxil® and Augmentin ® .

Component	Tablet Components (mg)			
	500 mg Tablet		875 mg Tablet	
	Augmentin®	Amoxil®	Augmentin®	Amoxil®
Amoxicillin Trihydrate (86% as amoxicillin pfa)				
K Clavulanate:microcrystalline cellulose blend (41% as clavulanic acid)				
Microcrystalline Cellulose, 100 micron				
Polyplasdone XL (Crospovidone)				
Sodium Starch Glycolate				
Magnesium Stearate				
Colloidal Silicon Dioxide				
Core Tablet Weight				
Opadry White, YS-1-7700				
Opadry Pink, YS-1-14725				
Purified Water[3]				
Coated Tablet Weight				

[1] The Augmentin® 500 mg tablet, historically, has a % formula overage of amoxicillin free acid
[2] Weight is adjusted according to the potency of the amoxicillin trihydrate and K clavulanate:microcrystalline cellulose (Augmentin® tablets), in order to maintain a constant tablet weight
[3] Removed during the film-coating operation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-754

ADMINISTRATIVE DOCUMENTS

SmithKline Beecham
Pharmaceuticals

NDA 50-754
Amoxil® (amoxicillin) Tablets

Debarment Certification

Pursuant to Section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to Section 306(e) as debarred under subsections 306(a) or (b) of the Act.

EXCLUSIVITY SUMMARY for NDA # 50-754

Trade Name Amoxil Tablets Generic Name amoxicillin
Applicant Name SmithKline Beecham Pharmaceuticals HFD- 520

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_XX_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_XX_/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /___/ NO /_XX_/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   The study compared Amoxil 875 mg tabletes (unapproved formulation) to Augmentin 875 mg tablets (approved formulation).

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_XX_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_XX_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_XX_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_XX_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 50-542 Amoxil Capsules, Chewable Tablets, and Powder for Oral Suspension

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_XX_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /___/ NO /___/ Explain: ____

_____

Investigation #2

IND # ____ YES /___/ NO /___/ Explain: ____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/

_____ July 1, 1998

Signature Date

Title: Regulatory Health Project Manager

/S/

_____ 7/10/98

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/~~PLA/PMA~~ # 50-754 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Amoril (amoricillin) Tablets Action: (AP) AE NA

Applicant SmithKline Beecham Pharmaceuticals Therapeutic Class Penicillins 35

Indication(s) previously approved treatment of infections due to susceptible strains of organisms,
Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate ___

Indication in this application _____ (For supplements, answer the following questions in relation to the proposed indication.)

✓ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Regulatory Health Project Manager — July 1, 1998

Signature of Preparer and Title — Date

cc: Orig NDA/~~PLA/PMA~~ #50-754
HFD-520 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 9/30/96)

NOV 5 1997

New Drug Application - Label Review
Division of Anti-Infective Drug Products, HFD-520

NDA: 50-754 and NDA 50-542 (S-005)

DRUG: Amoxil

CATEGORY: Semisynthetic aminopenicillin

SPONSOR: SmithKline Beecham
One Franklin Plaza
Philadelphia, PA

CONTACT PERSON: S. W. Shapowal
Assistant Director, Regulatory Affairs
Phone 215-751-4000

INTRODUCTION

Amoxil (amoxicillin) is an approved product. This NDA seeks approval of two new tablet formulations (500 mg and 875 mg tablets intended for twice daily dosing).

The available pharmacology and toxicology data on amoxicillin was reviewed in 1973 . Acute, subchronic, and reproductive effects were evaluated; there was no mutagenicity or carcinogenicity data.

In 1983, an NDA for Augmentin was filed (NDA 50-564). Augmentin is a mixture of amoxicillin and the beta-lactamase inhibitor, potassium clavulanate, in a ratio of either 4:1 or 2:1. Results of genotoxicity testing were included in NDA 50-564.

AMOXIL LABEL

The current proposed labeling for Amoxil indicates that mutagenicity and carcinogenicity studies have not been conducted. It also provides information on reproductive effects, and proposes Pregnancy Category B.

The information on carcinogenicity, reproduction, and Category B should be left as is.

The Augmentin genotoxicity data has been used to develop the following proposed mutagenicity label for Amoxil.

The sentence

should be replaced with the following information:

/S/

Kenneth Seethaler, Ph.D., D.A.B.T.
Pharmacologist/Toxicologist HFD-520

cc: Original ~~IND~~ NDA 50-754
HFD-340
HFD-520
HFD-520/Pharm/K.Seethaler
HFD-520/MO/M.Albuerne
HFD-520/Micro/S.Altaie
HFD-520/Chem/A.Yu
HFD-520/CSO/S.Trostle
HFD-520/Biopharm/H.Sun
HFD-520/Biostat/D.Lin

Concurrence Only:
HFD-520/L.Gavrilovich
HFD-520/R.Osterberg 11/5/97

4/12/97

(Faxed 09/04/97)

MEMORANDUM OF TELECONFERENCE

NDA 50-754 August 28, 1997
Amoxil (amoxicillin) Tablets, 500 mg and 875 mg
SmithKline Beecham Pharmaceuticals

SmithKline Beecham Pharmaceuticals (SKB) Attendees:
Ms. Sharon Shapowal, U.S. Regulatory Affairs
Mr. George Moonsammy, Medical
Dr. Clive Kaye, U.K. Pharmacokinetics

FDA Attendees:
Dr. Mercedes Albuerne, Team Leader, Medical Officer
Dr. Mamodikoe Makhene, Medical Officer
Dr. Frank Pelsor, Team Leader, Biopharmaceutics (HFD-880)
Dr. He Sun, Biopharmaceutics (HFD-880)
Mr. Stephen Trostle, Consumer Safety Officer

Type of meeting:
Teleconference with the firm to convey our recommendation for a food effect study and the design for that study, and our alternative action of revising the labeling if the firm does not submit the recommended food effect study.

Discussion:
Current labeling for Amoxil contains the following statement in the CLINICAL PHARMACOLOGY section: "Amoxicillin is stable in the presence of gastric acid and may be given without regard to meals." In the application for Amoxil Tablets, the bioequivalence study compared Amoxil Tablets, b.i.d., to Augmentin Tablets, b.i.d. Both study drugs were taken with a light meal. No comparison was made in the fasting state.

The application for Amoxil Tablets is for a new dosing regimen and a new formulation. The Division recommends that applications that are for a new dosing regimen and a new formulation should contain a food effect study. The Division offered to give guidance to SKB for a proposed food effect study for this application.

Conclusion:
In the event that SKB does not provide the recommended food effect study, the Division's alternative is to revise the labeling to reflect the data submitted in the application. The labeling would be changed to reflect the data submitted with the application that a bioequivalence study comparing Amoxil Tablets, b.i.d., to Augmentin Tablets, b.i.d., was conducted in which the study drugs were taken with a light meal.

The Division will give guidance to SKB for a food effect study. (See Action item.)

Action item:
Mr. Trostle faxed a copy of the Division's details for the food effect study to SKB on August 28, 1997. (See attachment.)

Meeting chair: /S/
Mercedes Albuerne, M.D.

Minutes preparer: /S/
Stephen T. Trostle, CSO
Division of Anti-Infective
Drug Products, HFD-520

Attachment:
Dr. Sun's comment on food effect study dated August 28, 1997.

NDA 50-754
Amoxil (Amoxicillin) tablet

DATE of SUBMISSION
July 11, 1997

Comment on food effect study:

The *Amoxil* 875 mg to be marketed tablet it is a new formulation. It is understood that although food effect studies are not a requirement with respect to filling NDA, sponsors are strongly recommended to conduct these studies. Therefore, the NDA is fileable while food effect study is recommended to be conducted and submitted to support the new *Amoxil* tablet formulation. Proposed food effect study key design points are:

A single dose, two-way crossover food effect study with about 12 subjects,
Meal contains 1000 calories with 50% derived from fat,
Drug to be administered with 240 ml water,
Prefer the a.m. dosing (i.e., drug to be given with breakfast),
The meal should be finished within ½ hour,
Drug should be administrated within 5 minutes after the start of meal,

/S/ 8/28/97

He Sun, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D. 8/28/97

cc: NDA Arch (50-754)
HFD-520
FDA attendees
HFD-520/TL/Chem/DKatague
HFD-520/Chem/AYu
HFD-520/TL/Pharm/ROsterberg
HFD-520/Pharm/KSeethaler
HFD-520/TL/Micro/ASheldon
HFD-520/Micro/SAltaie
HFD-520/STrostle/draft/stt/08/28/97
ft/stt/09/02/97

Concurrence:
HFD-520/C/PMS/JBona 9/3/97

\n50754tc.001

NDA 50-754

JUL 29 1997

SmithKline Beecham Pharmaceuticals
Attention: Ms. Sharon W. Shapowal
One Franklin Plaza
P.O. Box 7929
Philadelphia, Pennsylvania 19101-7929

Dear Ms. Shapowal:

We have received your new drug application (NDA) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Amoxil (amoxicillin) Tablets, 500 mg and 875 mg

Therapeutic Classification: Standard

Date of Application: July 11, 1997

Date of Receipt: July 14, 1997

Our Reference Number: 50-754

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 507 of the Act on September 12, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Mr. Stephen T. Trostle, Consumer Safety Officer, at (301) 827-2125.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

7/28/97

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: Original NDA 50-754
HFD-520/Div. Files
HFD-520/CSO/STrostle
HFD-520/TL/MO/MAlbuerne
HFD-520/TL/Chem/DKatague
HFD-520/Chem/AYu
HFD-520/TL/Biopharm/FPelsor
HFD-520/Biopharm/HSun
DISTRICT OFFICE

Final typed: stt/07/23/97 ST 07/23/97

ACKNOWLEDGEMENT (AC)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-754

CORRESPONDENCE

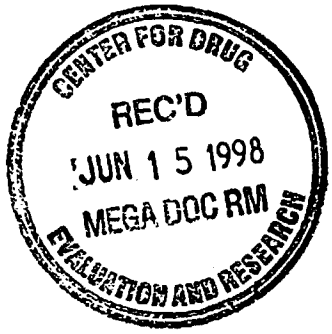
SmithKline Beecham
Pharmaceuticals

ORIGINAL

June 4, 1998

ORIG AMENDMENT

Amendment to Pending NDA
NDA 50-754
Amoxil® (amoxicillin) Tablets, q12h



Gary K. Chikami, M.D., Director
Division of Anti-Infective Drug Product (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Office of Drug Evaluation IV
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Chikami:

Reference is made to SmithKline Beecham's pending New Drug Application for Amoxil® (amoxicillin) Tablets q12h, NDA 50-754 submitted on July 11, 1997, and amendments of November 13, 1997, and March 6, 1998, which provided stability data for tablets packaged in HDPE bottles (12 months) and physician sample pack blisters (6 months), respectively.

Specific reference is made to our teleconference of June 2, 1998, requested by Jose R. Cintron R.Ph., M.A., FDA Division of Anti-Infective Drug Products, during which we advised the Agency that additional stability data were available and agreed to submit them as quickly as possible. This amendment provides the following data:

- Nine-month stability data for Amoxil 875 mg and 500 mg tablets packaged in non-child-resistant, aluminum/aluminum, single unit blisters (Physician Sample Packs)
- Eighteen-month stability data for Amoxil 875 mg and 500 mg tablets packaged in 20-, 100-, and 500-count HDPE bottles.

While statistical analysis of the data from tablets in blister packs easily predicts greater than the desired 18 months shelf life, we propose 12 month expiration dating based on the current 9 months of data, as agreed with the Agency during the above-referenced teleconference. Furthermore, we confirm that we will provide additional data as it becomes available in a *Supplement - Changes Being Effected*, which the Agency agreed to consider expeditiously for extension of the expiration period.

In addition, the 18-month, real-time data provided herein from all HDPE bottle presentations confirm that expiration dating of 18 months is appropriate, as agreed in the above-referenced teleconference with the Agency.

If you have any questions, please do not hesitate to contact the undersigned at (610) 917-6457.

Sincerely,

Sharon M Maglennon
Assistant Director
US Regulatory Affairs

Desk Copies: David B. Katague, Ph.D., Team Leader
Jose R. Cintron R.Ph., M.A., Project Manager
Andrew B. Yu, Ph.D., Review Chemist
Field Copy: Howard Lewis, Nashville District Office
Letter copy: Ms. Debra L. Pagano - Philadelphia District Office

SB
SmithKline Beecham
Pharmaceuticals

BC
ORIG AMENDMENT

March 30, 1998 ORIGINAL

Amendment to Pending NDA 50-754
Amoxil® (amoxicillin) Tablets, q12h

Gary K. Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Office of Drug Evaluation IV
Corporate Building
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Chikami:

Reference is made to the SmithKline Beecham's pending New Drug Application NDA 50-754 Amoxil® (amoxicillin) Tablets, q12h.

Specific reference is made to Item 1 on FDA Form 483 by George Flynn, CSO, Investigator from the Nashville District Office, oberved during the pre-approval inspection which took place at our Bristol facility March 9 - 13, 1998: *The application does not identify the contract micro lab which is*

At this time, we hereby request to amend the pending application to replace SmithKline Beecham Pharmaceuticals, Bristol, Tennessee, with as the facility to perform microbiological testing for inactive ingredients used in the manufacture of the drug product. The address is as follows:

000001

1250 S Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989 Telephone (610) 917 7000 Fax (610) 917 7707

For your information, we note that during the past month we have received approval from FDA Anti-Infectives Division for similar submissions: (7) supplements to our commercial Augmentin® and Amoxil® product NDAs submitted January 10, 1998.

procedures comply with USP and employ the same procedures currently reflected in the application. Please be advised that we were informed by that their last satisfactory FDA inspection was conducted

A list of inactive ingredients impacted as a result of the change in site for microbiological testing is provided as Attachment 1. A full description of the water testing and ingredient testing performed by is provided as Attachment 2. Certification from that they are in conformance with cGMPs is provided with the submission as Attachment 3.

If there are any questions regarding this amendment, please do not hesitate to contact me at (610) 917-6888.

Sincerely,

Ann C Dailey
Sr Regulatory Associate
U.S. Regulatory Affairs

Desk Copies: David B. Katague, Ph.D., Team Leader
Stephen T. Trostle, Project Manager
Field Copy: Howard Lewis, Nashville District Office
Letter copy: Ms. Debra L. Pagano - Philadelphia District Office

SmithKline Beecham
Pharmaceuticals

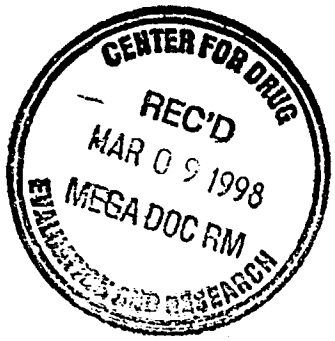
March 6, 1998

BL

ORIG AMENDMENT
ORIGINAL

Amendment of Pending NDA
NDA 50-754
Amoxil® (amoxicillin) Tablets, q12h

Gary K. Chikami, M.D., Director
Division of Anti-Infective Drug Product (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Office of Drug Evaluation IV
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850



Dear Dr. Chikami:

Reference is made to SmithKline Beecham's pending New Drug Application for Amoxil® (amoxicillin) Tablets q12h, NDA 50-754 submitted on July 11, 1997. Reference is also made to a conversation on March 3, 1998, between David B. Katague, Ph.D., FDA Division of Anti-Infective Drug Products, and Peter J. Kitz of SmithKline Beecham Pharmaceuticals, wherein Dr. Katague confirmed that this amendment may be filed at this time within the FDA's review time for said application.

Specifically, we wish to amend the aforementioned application in order to provide for a physician sample package presentation for the 500 mg and 875 mg strength tablets: a non-child-resistant, aluminum/aluminum, single unit blister pack. This blister material is identical to the blister packaging currently approved for certain other Amoxil® and Augmentin® formulations on the market. In support of this proposal, we are providing the following data:

- Six-month Stability Report for Amoxil 875 mg and 500 mg tablets packaged in non-child-resistant, aluminum/aluminum, single unit blisters (Appendix 1)
- Specifications and manufacturer's DMF for packaging materials (Appendix 2)

Current commercial packaging proposals in the NDA consist of HDPE bottles with induction seal plastic caps. Twelve month stability for the bottle presentations may be found in our amendment of November 13, 1997.

000001

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000 Fax (610) 917 7707

Based on the data within this amendment, as well as the data and the rationale provided within the pending NDA, we conclude that the tablets packaged in blisters retain stability comparable to those packaged in HDPE bottles. The available data suggest that expiration dating of tablets in blisters is easily 18 months when stored at or below 25°C (77°F).

As agreed in the above-referenced conversation between Dr. Katague and Mr. Kitz, nine-month stability data will be available by the end of May 1998.

The blister samples are controlled to the product specification limits and stability studies follow the qualification stability protocol as per the NDA. (The protocol and product specification are provided in Section 3.0 of the stability report provided in Appendix 1.) We confirm that the blister sample presentations will be included in the commercial validation protocol as proposed in the pending NDA.

Draft container labeling samples are provided in Appendix 3.

If you have any questions, please do not hesitate to contact the undersigned at (610) 917-6888.

Sincerely,

Ann C Dailey
Sr. Regulatory Associate
US Regulatory Affairs

Desk Copies: David B. Katague, Ph.D., Team Leader
Stephen T. Trostle, Project Manager
Field Copy: Howard Lewis, Nashville District Office
Letter copy: Ms. Debra L. Pagano - Philadelphia District Office

SB

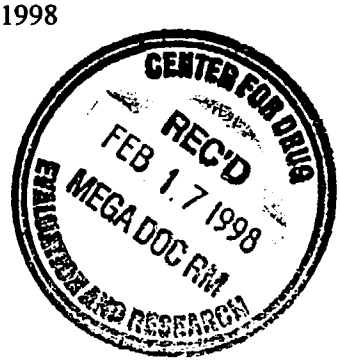
SmithKline Beecham

Pharmaceuticals

BC ORIGINAL

Amendment of Pending NDA
NDA 50-754
Amoxil® (amoxicillin) Tablets, q12h dosing

February 13, 1998



Gary Chikami, M.D., Director
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products (HFD-520)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Response to FDA Chemistry Reviewer

Dear Dr. Chikami:

We are writing with regard to our New Drug Application for Amoxil® (amoxicillin) Tablets, NDA 50-754, submitted July 11, 1997, which provides for a change in the dosing regimen of amoxicillin from thrice daily to twice daily dosing in adults, and provides for the use of new swallow tablet formulations.

At this time and as agreed and communicated to chemistry reviewer Dr. Andrew Yu (ref. telephone conversations on January 23, and February 11, 1998), SmithKline Beecham is submitting a categorical exclusion claim for the environmental assessment for the NDA. This documentation supercedes the environmental assessment data that was submitted with the NDA, prior to the change in the law.

If you have any questions regarding these data or have additional data requests regarding NDA 50-754, please do not hesitate to contact me at (215) 751-3468.

Sincerely,

Sharon W. Shapowal

Sharon W. Shapowal, R.Ph.
Associate Director
U.S. Regulatory Affairs

Desk copy: Mr. S. Trostle (project manager)

000001

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101 Telephone (215) 751 4000 Fax (215) 751 3400