CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-542/S-005,010,011

MICROBIOLOGY REVIEW(S)

CONSULT FOR DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUTS (HFD-590)

NDA# 50-542/S-011

REVIEWER: Linda J. Utrup, Ph.D.
CORRESPONDENCE DATE: October 3, 1997
CDER RECEIPT DATE: October 6, 1997
REVIEW ASSIGN DATE: October 14, 1997
REVIEW COMPLETE DATE: October 29, 1997

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

Phone # 215-751-4000

SUBMISSIONS REVIEWED: Supplement 011

DRUG CATEGORY: Beta-lactam antimicrobial

INDICATION: Anti *Helicobacter pylori* therapy

DOSAGE FORM: Chewable tablets, capsules
PRODUCT NAMES:

a. PROPRIETARY: Amoxil

b. NONPROPRIETARY: Amoxicillin trihydrate

c. CHEMICAL: D-(-)-alpha-amino-para-hydroxybenzyl penicillin trihydrate

SUPPORTING DOCUMENTS: NDA 20-876, NDA 20-877

BACKGROUND:

Lansoprazole, amoxicillin, and clarithromycin triple therapy (NDA 20-876) and lansoprazole and amoxicillin dual therapy (NDA 20-877) have been approved previously by the Agency. The sponsor has submitted a labeling supplement to revise the labeling of Amoxil in accord with the approved labeling of lansoprazole. The supplement adds a new therapeutic regimen to the Amoxil label and provides for the use of amoxicillin in combination with lansoprazole (with or without clarithromycin) in patients with duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) to eradicate *H. pylori* and reduce the risk of duodenal ulcer recurrence.

CONCLUSIONS: The sponsor is recommending the following wording for the microbiology section of the label in accordance with the lansoprazole labeling:

Microbiology Reviewer's comments:

The title "Susceptibility testing for *Helicobacter pylori*:" should be italicized and the colon should be omitted.

The entire microbiology section needs to be updated, but this is being addressed in supplement 10 (which is being handled by HFD-520) and will not be readdressed here. However, the sponsor should be informed that there will be more changes in the microbiology section.

RECOMMENDATIONS:

From a microbiology perspective, the recommended action for the supplemental application is approval. It is suggested that the sponsor make the following changes in the label.

1) The sponsor should italicize the title "Susceptibility testing for *Helicobacter pylori*:" and omit the colon.

The microbiology section of the package insert should read as follows:

Additionally, the sponsor should be informed that the remaining changes in the microbiology section of the package insert will be addressed separately.

/S/

Linda J. Utrup, Ph.D.

CONCURRENCES:

HFD-590/Dep Div Dir _____ Signature rec'd rev 11/24/97 Date

CC:
HFD-590/NDA #50-542
HFD-520/NDA #50-542
HFD-590/Division files
HFD-590/SMicro/LUtrup
HFD-520/Smicro/ASheldon
HFD-520/MO/LGirardi
HFD-520/PM/STrostle
HFD-590/Dep. Div. Dir./RAlbrecht
HFD-590/Div.Dir./MGoldberger
HFD-520/Div. Dir./GChikami

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:

	Less severe infections	Severe / respiratory tract infections
adult dose	500 mg q 12h	875 mg q 12h
pediatric dose	25 mg/kg/d q 12h	45 mg/kg/d q 12h

Sponsor states that, these regimens match, and serve to bring Amoxil dosing into accord with the dosing for Augmentin q 12h. The sponsor believes that appropriate q 12h dose selection for amoxicillin has been proven in large clinical studies of Augmentin (NDA 50-720). Given that the kinetics of amoxicillin are linear and independent of the kinetics of clavulanate, the sponsor's clinical program, which involves formulation of a new swallow tablet form of Amoxil (currently available only as capsule, suspension and chewable tablets) consists of the following:

- One bioequivalence study in healthy adult volunteers (male and female) comparing a new swallow tablet formulation of Amoxil to the marketed tablet formulation of Augmentin. Specifically:
  875 mg Amoxil tablet q 12h vs. 875/125 mg Augmentin tablet q 12h (high-dose)

- One pharmacokinetic study in healthy adult volunteers (male and female) comparing only the high-dose chewable and high-dose suspension formulations (i.e. 400 mg strength, not 200 mg strength) of 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:

Microbiology
Amoxicillin is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin has been shown to be active against most strains of

the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms
Enterococcus faecalis
Staphylococcus spp.[§] (β-lactamase-negative strains only)
Streptococcus pneumoniae
Streptococcus spp. (alpha- and beta-hemolytic strains only)

[§] Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

Aerobic gram-negative microorganisms
Escherichia coli (β-lactamase-negative strains only)
Haemophilus influenzae (β-lactamase-negative strains only)
Neisseria gonorrhoeae (β-lactamase-negative strains only)
Proteus mirabilis (β-lactamase-negative strains only)

Susceptibility tests

Dilution techniques. Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of **ampicillin** powder.

Ampicillin is sometimes used to predict susceptibility of *Streptococcus pneumoniae* to amoxicillin; however, some intermediate strains have been shown to be susceptible to amoxicillin. Therefore, ***Streptococcus pneumoniae* susceptibility should be tested using amoxicillin powder.** The MIC values should be interpreted according to the following criteria:

For gram-positive aerobes:

Enterococcus

MIC (µg/mL)	Interpretation
≤ 8	Susceptible (S)
≥ 16	Resistant (R)

Staphylococcus[a]

MIC (µg/mL)	Interpretation
≤ 0.25	Susceptible (S)
≥ 0.5	Resistant (R)

Streptococcus (except *Streptococcus pneumoniae*)

MIC (µg/mL)	Interpretation
≤ 0.25	Susceptible (S)
0.5 - 4	Intermediate (I)
≥ 8	Resistant (R)

Streptococcus pneumoniae[b]
(**Amoxicillin** powder should be used to determine susceptibility)

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

For gram-negative aerobes:

Enterobacteriaceae

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

Haemophilus influenzae[c]

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

[a] Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.
[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 - 5 % lysed horse blood.

[c] These interpretive standards are applicable only to broth microdilution test with *Haemophilus influenzae* using *Haemophilus* Test Medium (HTM).[1]

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

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard **ampicillin** powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
E. coli ATCC 25922	2 - 8
E. faecalis ATCC 29212	0.5 - 2
H. influenzae ATCC 49247[d]	2 - 8
S. aureus ATCC 29213	0.25 - 1

Using **amoxicillin** to determine susceptibility:

Microorganism	MIC Range (µg/mL)
S. pneumoniae ATCC 49619[e]	0.03 - 0.12

[d] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM[1].

[e] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by the broth microdilution procedure using cation-adjusted Mueller-Hinton with 2-5% lysed horse blood.

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 µg ampicillin to test the susceptibility of microorganisms, **except** *S. pneumoniae,* to amoxicillin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for **ampicillin**.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-µg ampicillin disk should be interpreted according to the following criteria:

For gram-positive aerobes:

Enterococcus

Zone Diameter (mm)	Interpretation
≥17	Susceptible (S)
≤16	Resistant (R)

Staphylococcus[f]

Zone Diameter (mm)	Interpretation
≥29	Susceptible (S)
≤28	Resistant (R)

β-hemolytic streptococci

Zone Diameter (mm)	Interpretation
≥26	Susceptible (S)
19 - 25	Intermediate (I)
≤18	Resistant (R)

NOTE: For streptococci other than β-hemolytic streptococci an ampicillin MIC Should be determined

S. pneumoniae

S. pneumoniae should be tested using a 1-µg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin. An amoxicillin MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

For gram-negative aerobes:

Enterobacteriaceae

Zone Diameter (mm)	Interpretation
≥17	Susceptible (S)
14 - 16	Intermediate (I)

≤13	Resistant (R)

H. influenzae[g]

Zone Diameter (mm)	Interpretation
≥22	Susceptible (S)
19 - 21	Intermediate (I)
≤18	Resistant (R)

[f] Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

[g] These interpretive standards are applicable only to disk diffusion susceptibility tests with *H. influenza* using HTM[2].

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, disk diffusion susceptibility test procedures require the use of laboratory control microorganisms. The 10-µg **ampicillin** disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone diameter (mm)
E. coli ATCC 25922	16 - 22
H. influenzae ATCC 49247[h]	13 - 21
S. aureus ATCC 25923	27 - 35

Using 1-µg **oxacillin** disk:

Microorganism	Zone diameter (mm)
S. pneumoniae ATCC 49619[i]	8 - 12

[h] This quality control range is applicable to only *H. influenza* ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM)[2].

[i] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

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.

Susan Altaie

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: 2/27/98 Gary K Clark for
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 ASP
TB 3/26/98

Division of Anti-Infective Drug Products
Clinical Microbiological Review

NDA NUMBER:	REVIEW DATE:	SUBMISSION/TYPE:
50542 SLR-005 & 010 50754	8-27-97	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 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)**
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Sponsor Proposal: Amoxil for Q 12H Dosing:

	Less severe infections	**Severe / respiratory tract infections**
adult dose	500 mg q 12h	875 mg q 12h
pediatric dose	25 mg/kg/d q 12h	45 mg/kg/d q 12h

Sponsor states that, these regimens match, and serve to bring Amoxil dosing into accord with the dosing for Augmentin q 12h. The sponsor believes that appropriate q 12h dose selection for amoxicillin has been proven in large clinical studies of Augmentin (NDA 50-720). Given that the kinetics of amoxicillin are linear and independent of the kinetics of clavulanate, the sponsor's clinical program, which involves formulation of a new swallow tablet form of Amoxil (currently available only as capsule, suspension and chewable tablets) consists of the following:

- One bioequivalence study in healthy adult volunteers (male and female) comparing a new swallow tablet formulation of Amoxil to the marketed tablet formulation of Augmentin. Specifically:
  875 mg Amoxil tablet q 12h vs. 875/125 mg Augmentin tablet q 12h (high-dose)

- One pharmacokinetic study in healthy adult volunteers (male and female) comparing only the high-dose chewable and high-dose suspension formulations (i.e. 400 mg strength, not 200 mg strength) of 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

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 ASP

11/14/97
11/14/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-542/S-005,010,011

ADMINISTRATIVE DOCUMENTS

Trosh 1g
S20

NDA 50-542/S-011

OCT 7 1997

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

Dear Ms. Shapowal:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Amoxil (amoxicillin) Chewable Tablets

NDA Number: NDA 50-542

Supplement Number: S-011

Therapeutic Classification: Standard

Date of Supplement: October 3, 1997

Date of Receipt: October 6, 1997

This supplement provides for adding the new indication of *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence to the Amoxil Chewable Tablets labeling. The labeling was revised in the following sections to provide for the new indication: **CLINICAL PHARMACOLOGY** (specifically, the **Microbiology** subsection), **INDICATIONS AND USAGE, ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION**. A **CLINICAL STUDIES** section, in which the clinical studies for the new indication were described, was also added to the labeling.

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 December 5, 1997, in accordance with 21 CFR 314.101(a).

Changes of the kind that you have proposed, in our opinion, are not the kind of changes permitted by regulation to be put into effect prior to approval of a supplement. An approved supplement is required for the proposed changes, therefore, the supplement is being reviewed under 21 CFR 314.70(b).

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely yours,

/S/

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 50-542
HFD-520/Div. Files
HFD-520/CSO/STrostle
HFD-520/TL/MO/MAlbuerne
HFD-520/MO/MMakhene
HFD-520/TL/Micro/ASheldon
HFD-520/Micro/SAltaie
DISTRICT OFFICE

Final typed: stt/10/07/97 ST 10/07/97

ACKNOWLEDGEMENT (AC)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 50-542 Supplement # 011 Circle one: (SE1) SE2 SE3 SE4 SE5
SE6

HFD-520 Trade and generic names/dosage form: Amoxil (amoxicillin) Chewable Tablets, Capsules, Oral Suspension Action: (AP) AE NA
Smith Kline

Applicant Beecham Pharmaceuticals Therapeutic Class 3S (penicillins)

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 Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence. (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 02.26.98
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 50-542 / SE1-011
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)

DEBARMENT CERTIFICATION NOT REQUIRED

CROSS-REFERENCE APPROVED PREVACID LABELING

See Irvin's letter dated 10/03/97 behind "Correspondence" tab.

SAFETY UPDATE REVIEW
NOT REQUIRED

BIOPHARMACEUTICS REVIEW
NOT REQUIRED

PHARMACOLOGY REVIEW
NOT REQUIRED

CHEMISTRY REVIEW
NOT REQUIRED

Environmental Assessment and FONSI
NOT REQUIRED

EER
NOT REQUIRED

DSI AUDIT OF PIVOTAL CLINICAL STUDIES NOT REQUIRED

NO MINUTES OF MEETINGS

NO MEMOS AND TELECON

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-542/S-005,010,011

CORRESPONDENCE

SmithKline Beecham
Pharmaceuticals

NDA 50-542
Amoxil® (amoxicillin) Chewable Tablets

October 3, 1997

Gary Chikami, M.D., Acting 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

Special Supplement - Changes Being Effected

Dear Dr. Chikami:

Reference is made to our approved antibiotic drug application for *Amoxil* (amoxicillin) Chewable Tablets, NDA 50-542. At this time, pursuant to 314.70 (c)(2), SmithKline Beecham is submitting a labeling supplement to revise the labeling of *Amoxil* in accord with the approved labeling of PREVACID® (lansoprazole) Delayed-Release Capsules*. The supplement adds a new therapeutic regimen to the *Amoxil* label and provides for the use of amoxicillin in combination with *Prevacid* (with or without clarithromycin) in patients with duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) to eradicate *Helicobacter pylori* and reduce the risk of duodenal ulcer recurrence.

Reference is made to telephone conversations on August 22, 1997, separately involving Mr. José Cintron and Mr. Thomas Hassal, wherein this supplement was discussed. As agreed with these gentlemen, SB incorporates by cross-reference into this supplement the safety and efficacy information from two TAP Holdings Inc. New Drug Applications: 20-877 (dual therapy) and 20-876 (triple therapy), both approved on June 17, 1997, and now part of NDA 20-406, administered by the Division of Gastrointestinal and Coagulation Drug Products. We have enclosed a cross-reference letter of authorization from Ms. Linda J. Peters of TAP Holdings Inc. for this purpose. (See Attachment 1.) No prescription drug user fee is assessable for this application, as explained by Mr. Hassal, because clinical data is by reference to the applications for *Prevacid*.

Please note that approved language from the *Prevacid* label has been incorporated into the Microbiology, Indications, Adverse Reactions, and Dosage and Administration sections, and a Clinical Studies section was added. Only the most minor of editorial changes was made for the purpose of *Amoxil* labeling (e.g. reversal of product names).

**Prevacid* is a registered trademark of TAP Holdings Inc.

Please note that approved language from the *Prevacid* label has been incorporated into the Microbiology, Indications, Adverse Reactions, and Dosage and Administration sections, and a Clinical Studies section has been added. Only the most minor of editorial changes were made for the purpose of the *Amoxil* labeling (e.g. reversal of product names).

It should be noted that SB did not incorporate the contraindications of lansoprazole and clarithromycin into the *Amoxil* label, except through cross-reference to the other product labels. Further, the current market label of *Amoxil*, into which the lansoprazole text is incorporated, does not include a *Drug Interactions* subsection in Precautions or a *Laboratory Values* subsection in Adverse Reactions. For this cause, and because there was no new safety information to incorporate, SB did not include these two statements from the *Prevacid* prescribing information:

Draft annotated *Amoxil* labeling is provided for the purpose of illustrating the changes to the *Amoxil* prescribing information that is in use in the marketplace. (See Attachment 2.) Final printed labeling, copied to card stock paper, follows this and is coded AM:L13B (9416646). (See Attachment 3.) Given the number of pending labeling supplements for *Amoxil* that are currently held within the Division, we appreciate the agreement of Mr. Stephen Trostle (ref. conversation of August 25, 1997) to separate the subject matter of this supplement and not attempt a "merge" of everything pending.

This application is being submitted in duplicate. Simultaneously, or shortly hereafter, we will intend to submit corresponding supplements to AADAs 62-216 and 62-226, held by the Office of Generic Drugs. If you have any questions or requests regarding this amendment, 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

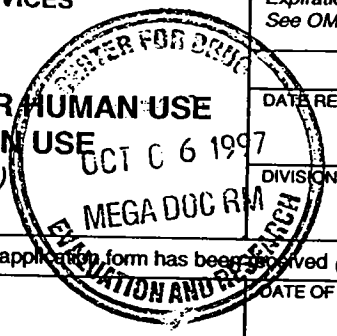
3oct97.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: November 30, 1990
See OMB Statement on Page 3.



FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASSIGNED**

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
SmithKline Beecham Pharmaceuticals	October 3, 1997
ADDRESS *(Number, Street, City, State and Zip Code)*	**TELEPHONE NO.** *(Include Area Code)*
One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101-7929	(215) 751-3868
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* NDA 50-542

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*	
amoxicillin trihydrate	Amoxil®	
CODE NAME *(If any)*	**CHEMICAL NAME**	
DOSAGE FORM	**ROUTE OF ADMINISTRATION**	**STRENGTH(S)**
chewable tablets	oral	'125' mg '250' mg

PROPOSED INDICATIONS FOR USE

Treatment of infections caused by susceptible strains of designated organisms in the ear, nose and throat, the genitourinary tract, the lower respiratory tract, the skin and soft tissues, and treatment of acute uncomplicated gonorrhea.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION.

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION
☐ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☒ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

FORM FDA 356h (7/90)

000003

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

X	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
X	ii. final printed labeling *(12 copies)*
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case report forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter, and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application on 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Sharon W. Shapowal, R.Ph. Associate Director, U.S. Regulatory Affairs	Sharon W. Shapowal	October 3, 1997

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
One Franklin Plaza, P.O. Box 7929 Philadelphia, PA 19101-7929	(215) 751-3868

WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)