CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-564/S-022, NDA 50-575/S-016, NDA 50-579/S-020

Trade Name: AUGMENTIN

Generic Name:(amoxicillin/clavulanate postassium)

Sponsor: SmithKline Beecham

Approval Date: February 16, 1996

INDICATION: These supplemental applications contain revised wording for the WARNINGS section of the labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA50-564/S-022,NDA50-575/S-016,NDA50-597/S-020

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter	X			
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)				
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)				
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA50-564/S-022,NDA50-575/S-016,NDA50-597/S-020

APPROVAL LETTER

FEB 16 1996

NDA 50-564/S-022
NDA 50-575/S-016
NDA 50-597/S-020

Sharon W. Shapowal, R.Ph.
Assistant Director
U.S. Regulatory Affairs
SmithKline Beecham
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA. 19101

Dear Ms. Shapowal:

Reference is made to your supplemental new drug applications (NDA's) dated January 20, 1993 for Augmentin® (amoxicillin/clavulanate potassium) Tablets, NDA 50-564/S-022, Augmentin® (amoxicillin/clavulanate potassium) Powder for Oral Suspension, NDA 50-575/S-016, and Augmentin® (amoxicillin/clavulanate potassium) Chewable Tablets, NDA 50-597/S-020, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act.

We also refer to your amendment dated January 13, 1995, in response to the Agency approvable letter dated January 5, 1995, and to Augmentin labeling AG:L8B issued February, 1995.

These supplemental applications contain revised wording for the **WARNINGS** section of the labeling.

We have completed our review of these supplemental applications and have concluded that adequate data have been submitted to support this labeling change. Therefore, the applications are approved as of the date of this letter.

These approvals affect only those changes specifically submitted in these applications. Other changes which may have been approved or are pending are not affected.

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

If you have any questions concerning these supplemental NDA's, please contact Mr. Jose Cintron, Project Manager, at 301-827-2125.

Sincerely yours,

Mary Fanning, M.D., Ph.D., FACP
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

CC: Orig NDA
50-564
50-575
50-597
HF-2
HFD-80
HFD-240
HFD-500
HFD-638
HFD-730
HFD-100
HFD-230
HFD-520/SMO/Roberts
HFD-520/MO/Hamilton
HFD-520/CSO/Cintron
APPROVAL

Concurrence:

HFD-520/SCSO/Bona 1/30/96
HFD-520/Dir/Fanning 2/12/96

2/1/96

1/29/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA50-564/S-022,NDA50-575/S-016,NDA50-597/S-020

APPROVABLE LETTER

NDA 50-564/S-022
NDA 50-575/S-016
NDA 50-597/S-020

JAN 5 1995

Edward M. Yuhas, Ph.D.
Associate Director
U.S. Regulatory Affairs
SmithKline Beecham Pharmaceuticals
1500 Spring Garden Street
P.O. Box 7929
Philadelphia, PA 19101

Dear Dr. Yuhas:

Reference is made to your supplemental new drug applications (NDA's) submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for Augmentin® (amoxicillin /clavulanate potassium) Tablets, NDA 50-564/S-022; Augmentin® (amoxicillin/clavulanate potassium) Powder for Oral Suspension, NDA 50-575/s-016; and Augmentin® (amoxicillin/clavulanate potassium) Chewable Tablets, NDA 50-597/S-020.

These supplemental applications provide for revisions to the **WARNINGS** section of the labeling.

We have completed our review of these submissions and they are approvable. However, before these applications can be approved the last paragraph of the **WARNINGS** section should be revised to read as follows:

Within 10 days of the date of this letter, you are required to amend these applications, or notify us of your intent to file an amendment to each application, or follow one of the other alternatives under 21 CFR 314.110. In the absence of such action on your part, the FDA may proceed to withdraw these applications.

If you have any questions regarding these NDA's, please contact Mr. Carmen DeBellas, Project Manager, at 301-443-6797.

Sincerely,

1/4/95

Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CC: Orig NDA
50-564
50-575
50-597
HFC-130
HFD-82
HFD-473
HFD-520
HFD-735
HFD-730
HFD-500
HFD-638
HFD-520/SMO/Albuerne
HFD-520/MO/Roberts 1/4/95
HFD-520/CSO/DeBellas 1/3/95
HFD-520/Labelfile/
APPROVABLE

Concurrence

HFD-520/SCSO/Bona 11/28/94
HFD-520/ActDivDir/Gavrilovich

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA50-564/S-022,NDA50-575/S-016,NDA50-597/S-020

MEDICAL REVIEW(S)

NOV 1 1 1994

NDA 50-564/S-022
NDA 50-575/S-016
NDA 50-597/S-020

REVIEW OF FINAL PRINTED LABELING (FPL)

APPLICANT:	SmithKline Beecham Pharmaceuticals One Franklin Plaza P.O. Box 7929 (FP 1005) Philadelphia, PA 19101
DATE OF SUBMISSIONS:	January 20, 1993
DATE OF REVIEW:	September 21, 1994
NAME OF DRUGS:	NDA 50-564 Augmentin^{R} (amoxicillin/clavulanate potassium) Tablets NDA 50-575 Augmentin^{R} (amoxicillin/clavulanate potassium) Powder for Oral Suspension NDA 50-597 Augmentin^{R} (amoxicillin/ clavulanate potassium) Chewable Tablets
GENERIC NAME:	See above

SUBMISSION HISTORY:

April 23, 1992:	The Applicant submitted supplemental applications for NDA 50-564/S-021, NDA 50-575/S-015 and NDA 50-597/S-019, providing for revisions to the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS,** and **ADVERSE REACTIONS** sections of the labeling.
July 21, 1992:	The Agency issued an approval letter and requested a change be made to the **WARNINGS** section of the labeling at the next printing.
January 20, 1993:	The Applicant submitted supplemental applications NDA 50-564/S-022, NDA 50-575/ S-016, 50-597/S-020 containing the revision to the **WARNINGS** section requested in the approval of July 21, 1992.

COMMENTS:

The labeling submitted January 20, 1993, contains the following sentence in the last paragraph:

The last paragraph should read:

RECOMMENDATIONS:

An approvable letter should be issued stating the change mentioned above.

Carmen L. DeBellas, PMS

Rosemary Roberts, M.D.

CC:
Orig NDA
50-564
50-575
50-597
HF-2
HFD-80
HFD-100
HFD-230
HFD-240
HFD-500
HFD-638
HFD-730
HFD-520
HFD-520/SMO/Albuerne 10/6/94 1/4/95
HFD-520/MO/Roberts
HFD-520/CSO/DeBellas 9/27/94
HFD-520/LabelFile/
FPL REVIEW

Concurrence:

HFD-520/SCSO/Bona 9/29/94
HFD-520/ActDivDir/Gavrilovich
11/21/94

FEB 16 1996

NDA 50-564/S-022
NDA 50-575/S-016
NDA 50-597/S-020

REVIEW OF A RESPONSE TO AN APPROVABLE LETTER

APPLICANT: SmithKline Beecham
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA. 19101

DATE OF SUBMISSIONS: January 13, 1995

DATE OF REVIEW: December 27, 1995

NAME OF DRUGS: NDA 50-564 Augmentin^{R} (amoxicillin/clavulanate) Tablets
NDA 50-575 Augmentin^{R} (amoxicillin/clavulanate) Oral Suspension
NDA 50-597 Augmentin^{R} (amoxicillin/clavulanate) Chewable Tablets

GENERIC NAME: See above

SUBMISSION HISTORY:

January 20, 1993: The Applicant submitted supplemental applications NDA 50-564/S-022, NDA 50-575/S-016, and NDA 50-597/S-020 providing a response to an approvable letter issued July 21, 1992, and updating the **WARNINGS** section of the labeling.

March 24, 1993: An updated copy of the wording for the **WARNINGS** section was negotiated by facsimile.

July 20, 1994: The Applicant submitted supplemental applications NDA 50-564/S-026, NDA 50-575/S-019, and NDA 50-597/S-024 (containing labeling) providing for changes to the **ADVERSE REACTIONS** and **WARNINGS** sections of the labeling. The changes to the **WARNINGS** section were in accordance with the negotiated wording of March 24, 1993.

January 5, 1995: The Agency issued an approvable letter for the supplemental applications submitted on January 20, 1993.

January 13, 1995: The Applicant submitted an amendment to these supplemental applications in response to the approvable letter mentioned above in the form of correspondence informing the Division that labeling containing changes to the **WARNINGS** section had been submitted in the supplemental applications dated July 20, 1994. The Applicant further noted that the additional editorial changes contained in the approvable letter of January 5, 1995, would be made at a later printing of the label.

COMMENTS:

The amendment submitted January 13, 1995 and the labeling in the supplemental applications submitted July 20, 1994, and the Augmentin labeling AG:L8B issued February 1995 contain the appropriate wording for this section.

RECOMMENDATIONS:

An approval letter should be issued.

Carmen L. DeBellas, PMS

Rosemary Roberts, M.D.

CC:
Orig NDA
50-564
50-575
50-597
HFD-80
HFD-100
HFD-230
HFD-240
HFD-104
HFD-638
HFD-730
HFD-520
HFD-520/SMO/Roberts
HFD-520/MO/Hamilton
HFD-520/CSO/Citron
FPL REVIEW

Concurrence:

HFD-520/SCSO/Bona
HFD-520/DivDir/Fanning
2/12/96

2/1/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA50-564/S-022,NDA-575/S-016,NDA50-597/S-020

ADMINISTRATIVE DOCUMENTS

Food and Drug Administration
Rockville MD 20857

Date FEB 5 1993

NDA No. 50-597

Edward M. Yuhas,Ph.D
SmithKline Beecham
One Franklin Plaza
P.O.Box 7929
Philadelphia, PA 19101
Attention:Edward M.Yuhas, Ph.D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Augmentin (amoxicillin/clavulanate potassium)
Chewable Tablets
NDA Number: 50-597

Supplement Number: S-026

Date of Supplement: January 30, 1993

Date of Receipt: January 15, 1993

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA50-564/S-022,NDA50-575/S-016,NDA50-597/S-020

CORRESPONDENCE

ORIGINAL

SB

SmithKline Beecham

Response to "Approvable" Action Letter

Augmentin® (amoxicillin/clavulanate potassium)
ADA 50-564/S-022 Tablets
ADA 50-575/S-016 Powder for Oral Suspension
ADA 50-597S-020 Chewable Tablets

January 13, 1995

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gavrilovich:

We are writing with regard to our labeling supplements for Augmentin® (amoxicillin/clavulanate potassium): 50-564/S-022 (tablets), 50-575/S-016 (powder for oral suspension), and 50-597/S-020 (chewable tablets), all deemed "approvable" by the FDA in an action letter dated January 5, 1995. The action letter was received by the sponsor on January 9, 1995.

The supplements, submitted simultaneously on January 20, 1993, provided for revision of the pseudomembranous colitis warning. The labeling code on the final printed labeling submitted was AG:L5 (9417100). Subsequently, in labeling supplements submitted on July 20, 1994 ("Changes Being Effected"), the warning was again revised. The labeling code was then changed to AG:L6 (9417100). The approval of these supplements is outstanding. The supplements include: 50-564/S-026, 50-575/S-019, and 50-597/S-024. The language of the warning was taken, at that time, from a FAX sent to the sponsor by the FDA in regards to several SB products (ref. FAX of March 24, 1993).

The warning paragraph in question according to the recent January 5, 1995 letter, which addressed the January 20, 1993 supplements, reads as follows:

The bracketed words, considered by the sponsor to be editorial changes to the paragraph, are the only differences between the language of the January 5, 1995 approvable letter and the labeling submitted July 20, 1994 (label code AG:L6), which is currently in use.

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

Because the sponsor revised and superceded in 1994 the *Augmentin* labeling submitted in 1993, using text that was in accord with a version of the warning paragraph used by the Division of Anti-Infective Drug Products, the sponsor believes that the editorial changes above can be made at a later printing of labeling, and reported in the annual report for the product. Mr. Carmen DeBellas and I discussed this issue and believed that this approach would be acceptable to the Division (ref. telephone conversation of January 10, 1995). No further amendment of supplements 50-564/S-022, 50-575/S-016, and 50-597/S-020 will, therefore, be made.

If you have any questions regarding this application, please write or call us at (215) 751-3868.

Sincerely yours,

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

ORIGINAL

SmithKline Beecham

January 20, 1993

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

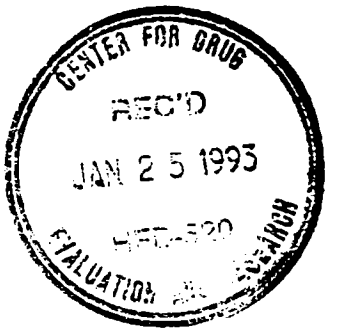
ADA 50-564 S-022
Augmentin® (amoxicillin/clavulanate potassium)
Tablets

NDA [illegible]

ADA 50-575 S-016
Augmentin® (amoxicillin/clavulanate potassium)
Powder for Oral Suspension

NDA [illegible]

ADA 50-597 S-020
Augmentin® (amoxicillin/clavulanate potassium)
Chewable Tablets



Murray Lumpkin, M.D., Director
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products (HFN-520)
Document Control Room 12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Doctor Lumpkin:

Reference is made to our approved New Drug Applications for Augmentin® Tablets (ADA 50-564), Augmentin® Powder for Oral Suspension (ADA 50-575) and Augmentin® Chewable Tablets (ADA 50-597).

Reference is also made to the Agency's letter of July 21, 1992 (see attached) wherein the Agency recommended that at the time of next printing of the labeling, the last sentence of the last paragraph of the **WARNINGS** section be deleted and replaced with the following:

Pursuant to 21 CFR § 314.70 (c)(2)(i) we hereby submit applications to provide for the above mentioned change in labeling. Submitted herewith, are 12 copies of final printed labeling for Augmentin®, AG:L5, which replaces AG:L4. We are planning to implement the new labeling during January 1993.

If you have any questions regarding this submission, please do not hesitate to contact me at (215) 751-3868.

Sincerely yours,

Edward M. Yuhas, Ph.D.
Associate Director
U.S. Regulatory Affairs

EMY/jg

000001

[illegible] Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400

NDAs

50-564/S-026

50-575/S-019

50-597/S-024

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA50-564/S-026,NDA50-575/S-019,NDA50-597/024

Trade Name:AUGMENTIN

Generic Name:(Amoxicillin/Clavulanate Potassium)

Sponsor: SmithKline Beecham

Approval Date: March 4, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA50-564/S-026,NDA50-575/S-019,NDA50-597/S-024

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling				
Medical Review(s)	X			
Chemistry Review(s)				
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)				
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA50-564/S-026,NDA50-575/S-019,NDA50-597/S-024

APPROVAL LETTER

NDA 50-564/S-026
NDA 50-575/S-019
NDA 50-597/S-024

MAR - - 1996

Smith Kline 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

Dear Ms. Shapowal:

Reference is made to your supplemental new drug applications (NDA's) dated July 20, 1994, submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for Augmentin® (amoxicillin/clavulanate potassium) Tablets, NDA 50-564/S-026; Augmentin® (amoxicillin/clavulanate potassium) Powder for Oral Suspension, NDA 50-575/S-019; and Augmentin®(amoxicillin/clavulanate potassium) Chewable Tablets, NDA 50-597/S-024.

These supplemental applications provide for additions to the **ADVERSE REACTIONS** section of the labeling. These include:

We have completed the review of these applications and have concluded that adequate information has been presented to demonstrate that the drugs are safe and effective for use as recommended in the draft final printed labeling submitted on July 20, 1994. Accordingly, the applications are approved effective on the date of this letter.

This approval affects only those changes specifically submitted in these supplemental applications. Other changes that may have been approved or are pending evaluation are not affected.

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

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

NDA 50-564/S-026
NDA 50-575/S-019
NDA 50-597/S-024

Should you have any questions concerning these supplemental NDA's, please call Mr. Jose R. Cintron, Project Manager, at 301-827-2125.

Sincerely.

Mary Fanning, M.D., Ph.D., FACP
Director
Division of Anti-Infective Drug Products
Officer of Drug Evaluation IV
Center for Drug Evaluation and Research

NDA 50-564/S-026
NDA 50-575/S-019
NDA 50-597/S-024

cc: Original. NDA
HFD-82
HFD-473
HFD-104
HFD-635
HFD-520
HFD-520/DivDir/MFanning
HFD-520/SRT/JBlank
HFD-520/PM/JRCintron
jrc/Jan 22, 1996
TYPE OF LETTER-APPROVAL

Concurrence Only:
HFD-520/SCSO/JBona
HFD-520/SMO/RRoberts

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA50-564/S-026,NDA50-575/S-019,NDA50-597/S-024

MEDICAL REVIEW(S)

Clinical Review of Supplement

OCT 19 1995

NDA 50-597/S-024

Date of Supplement: July 20, 1994
July 18, 1995

Date of Review: September 20, 1995

Applicant: SmithKline Beecham

Drug - Generic: Amoxicillin/clavulanate potassium
Trade: Augmentin® Chewable Tablets
Pharmacologic Class: Penicillin/β-lactamase inhibitor

Route of Administration: Oral

Purpose of Submission

The applicant has filed this submission in accordance with provisions found under 21 CFR 314.70 (c)(2)(i),i.e., changes to add or strengthen a contraindication, warning, precaution, or adverse reaction. These changes can be made before FDA approval with the submission marked: "Special Supplement - Changes Being Effected."

The applicant has made the following additions to the ADVERSE REACTIONS section:

In support of these additions, the applicant has submitted a line listing and, upon request, copies of CIOMS I reports (Council for International Organisations of Medical Sciences), which are equivalent to Form FDA 1639/MedWatch 3500 reports, of all patients who experienced those adverse reactions while receiving either amoxicillin or amoxicillin/clavulanate. The following information was submitted for each of the adverse reactions.

Mucocutaneous candidiasis

There were 89 reports of patients who developed a fungal infection, yeast infection, or candidiasis after taking amoxicillin/clavulanate. There were not many details given in many of the reports (n = 63) concerning the dosage, duration of therapy or even a good description of the symptoms/conditions of the patients. In many cases, the adverse reaction was simply described as candidiasis or yeast infection.

Of the 89 cases reported, 27 were from the U.S. and 62 were foreign reports. There were 56 females, 22 males, and 11 patients whose gender was not specified. The majority of the patients recovered or the outcome was unknown. However, there were five deaths that occurred among the 89 patients who experienced this adverse reaction. Four of the deaths were listed as possibly related to adverse reactions due to amoxicillin/clavulanate therapy.

The first patient who died while receiving the drug was a 56-year-old man from France who was treated with amoxicillin/clavulanate (3 g/day) for 11 days for purulent pleurisy due to *Peptostreptococcus, Fusobacterium* and *Staphylococcus aureus*. He recovered from the bacterial infection, but developed a septicemia due to *C. albicans*. He expired as a result of multivisceral failure and acute respiratory distress syndrome.

The second patient was also from France. She was a 38-year-old woman who received amoxicillin/clavulanate (500 mg X 2) for seven days for the treatment of a breast abscess. She was diagnosed as having systemic lupus erythematosus and developed digestive candidiasis. She died as a result of the candidiasis and cardiac arrest.

The third patient was a 69-year-old woman from France who was treated with amoxicillin/clavulanate (3 g/day IV) and Tiberal for 31 days for a purulent pleurisy. She recovered from the pleurisy but subsequently expired due to agranulocytosis and *C. albicans* septicemia.

The fourth patient was a 52-year-old man from Thailand who was treated with amoxicillin/clavulanate (7.2 g/day IV) for four days for septicemic melioidosis. Three days after beginning therapy, he developed a fungal infection of the knee and left foot. The amoxicillin/clavulanate was discontinued. He was given Itraconazole and ceftazidime. He died due to septic shock.

Pruritus

There were 68 reports submitted concerning patients who developed pruritus while on amoxicillin or amoxicillin/clavulanate therapy. As was the case with candidiasis, many of the reports for pruritus did not contain many details. There were 35 reports with some details regarding the dosage, duration of therapy, patient's symptoms/conditions and concomitant medications. Many of the reports listed pruritus or itching as an adverse reaction.

Twenty of the reports were from the U.S. and the other reports were foreign. Of the 68 patients, there were 27 males, 33 females and eight patients whose gender was not listed. Most of the patients recovered or the outcome was not stated. There was one death among the reports. The patient was an 83-year-old woman from the United Kingdom. She had been treated with amoxicillin (dosage and duration of therapy were not specified) for a lower respiratory tract infection. She expired due to heart failure.

Toxic Epidermal Necrolysis (TEN)

There were 31 cases of patients who developed toxic epidermal necrolysis while on amoxicillin/clavulanate therapy. Of the 31 reports, 15 contained details regarding dosage, symptoms and/or concomitant medications. Six of the cases were from the U.S.; the other 25 were foreign reports. Among the patients, there were 12 males, 17 females and two patients whose gender was not specified.

Among the reports with details, patients were described as developing a diffuse, macular, erythematous rash on the face and upper trunk shortly (1-2 days) after receiving amoxicillin/clavulanate. The rash spread rapidly and progressed to sloughing of the skin. For some patients, as much as 80% of the total body surface was involved, with oral and vaginal ulceration among females. Some patients developed photophobia and conjunctivitis. Most of the patients were treated with fluid therapy and corticoids, along with a variety of other medications. The results were not very successful.

Of the 31 patients with toxic epidermal necrolysis, 14 died. For nine of the patients, death was listed as either related or possibly related to an adverse reaction associated with amoxicillin/clavulanate therapy. A brief summary of each of the nine patients follows.

The first patient was a 45-year-old Japanese woman who was treated with amoxicillin/clavulanate tablets (750 mg/day), sulpyrine and three other drugs (aldioxa, carbetapentane citrate and methylcysteine HCl) for fever. She developed eruptions on

the skin, itching and finally toxic epidermal necrolysis. She was treated at a hospital with 10 different drugs for this adverse reaction. She was admitted to a second hospital with the following symptoms: high fever (39.3 ^{0}C), generalized eruption, epidermolysis, strong itching, eruption and mucomembrane detachment in the eye conjunctiva and the oral cavity membrane. She was given an antidote, vitamin and fluid therapy. She left the hospital at her own will and later died in a third hospital.

The second patient was a 38-year-old Japanese woman who had taken two doses of amoxicillin/clavulanate (375 mg), aspirin-dialuminate and two other drugs (ambroxal HCl and axaprozin). She developed palpebral and conjunctival congestion, and erythema on the face and neck. She was admitted to a hospital with an initial diagnosis of "drug eruption", later changed to toxic epidermal necrolysis. She was treated with methylprednisolone sodium succinate therapy. Her X-rays showed pneumonia and fosfomycin (4 g/day) was started. Twelve days later, she died from toxic epidermal necrolysis, secondary infections and multiple organ failure.

The third patient who died of TEN possibly related to amoxicillin/clavulanate therapy was a 27-year-old French woman who was discharged from a hospital on Augmentin (500 mg), prednisolone, oxatamide, clobutinol, cetirizine and local treatment on her skin. The next day she experienced a purpuric rash and was admitted to the hospital with a diagnosis of Lyell's syndrome. She was treated with rehydration, albumin, perfloxacin and amikacin. She developed acute respiratory distress syndrome with pulmonary edema, was intubated and ventilated. Vancomycin was administered after a methicillin-resistant *Staphylococcus aureus* was found in blood cultures. She was transferred to an ICU in another hospital and expired the next day.

The fourth patient was a 69-year-old man from Spain who was prescribed Augmentin (500 mg q8h) for a common cold. Twenty-four hours after starting therapy, he experienced skin rash, maculopapular erythema and mucous involvement. Forty-eight hours after beginning therapy, he developed exfoliative lesions (2-4 cm). On day 3 of his therapy, he was hospitalized with generalized skin exfoliation (81% of body surface affected). He also had conjunctive ecchymosis, involvement of buccal mucosa, fever (38 ^{0}C) and blood pressure of 16/10. He was treated with fluid therapy, corticoids and erythromycin, but died 10 days later.

The fifth patient was a 69-year-old woman from Germany who developed Stevens-Johnson syndrome after taking Augmentin (dosage not specified) for six days. She died with the cause of death listed as toxic epidermal necrolysis. No other details were given.

The sixth patient was a 52-year-old woman from the U.S. She was treated with Augmentin (500 mg TID) and developed a rash and itch the next day. The Augmentin was discontinued but the rash continued to worsen. She was taking seven concomitant medications (Atarax, depakote, ibuprofen, phenobarbital, Seldane and valproic acid) at the time. Her rash and fever worsened and her skin began to exfoliate. She was admitted to a hospital with a diagnosis of toxic epidermal necrolysis involving 100% of her body surface. Thirteen days later, she died from sepsis due to the toxic epidermal necrolysis.

The seventh patient was a 73-year-old German woman who was admitted to a dermatology department of a hospital because of epidermolysis and exanthema. Her condition was listed as life threatening. She died three days later from decompensation of "Cor pulmonale". A probable relationship between Augmentin and/or Foligan (allopurinol) was suggested. She was also taking Decortin, Digimerck, heparin, ISMO and Lasix.

The eighth patient who died of TEN possibly related to Augmentin therapy was a 30-year-old man from France. He was admitted to a hospital for the treatment of an abscess on his hand. He was given Bristopen, Prodafalgan and Flagyl, followed by Rinothiol, Rohypnol, Apranax and Augmentin (1 g TID). Two days later, he experienced pruriginous erythema and fever. All medications were discontinued except Prodafalgan. The next day bullous exanthema, fever, and epidermal detachment occurred and he was transferred to an intensive care unit with a diagnosis of Lyell's syndrome. The patient died eight days later.

Very few details were given concerning the ninth patient, who was an 81-year-old woman from Italy. She had taken Augmentin (2 g/day) for four days for bronchitis. No other details were available.

Comment

Toxic epidermal necrolysis is listed as an adverse reaction in the labeling for Amoxil. See SRT review dated October 11, 1994.

Interstitial nephritis

There were 17 reports submitted regarding patients who developed interstitial nephritis while taking amoxicillin or amoxicillin/clavulanate. Three of the reports were domestic and 14 concerned foreign patients. Nine of the reports contained details, while eight listed interstitial nephritis as an adverse event experienced by the patient. As stated in one report, drug induced interstitial nephritis "clinically involves acute kidney failure with extrarenal symptoms which suggest a hypersensitivity process (fever, arthralgia and exanthema - although one or all

may be absent)." Eosinophilia is usually present in most cases. The diagnosis is usually made after eliminating other causes of acute kidney failure and discontinuing the drug.

Among the 17 cases reported, there were five males, nine females and three patients whose gender was not listed. There were no deaths. Most of the patients recovered without sequelae or their outcome was unknown.

Hematuria

Twenty-nine reports were submitted regarding patients who experienced hematuria while on therapy with amoxicillin or amoxicillin/clavulanate. Nine of the reports were from the U.S., while 20 were foreign reports. Seventeen reports contained details concerning dosage, duration of therapy and symptoms/conditions for the patient. Twelve of the reports listed hematuria along with other adverse events experienced by the patient.

Among the 29 patients, there were 14 males, 12 females and three patients whose gender was not identified. There was one death. The other patients either recovered or the outcome was unknown.

The patient who died was a 29-year-old woman from Thailand who was treated for septicemic melioidosis from a urinary tract infection. She received Augmentin (7.2 g/day) for nine days. Her condition improved initially after two days of therapy, but then she developed gross hematuria, hypotension, and disseminated intravascular coagulation with a low platelet count. Her condition did not improve and four days later she died after having a cardiac arrest.

Comments

The adverse reaction reports submitted by the applicant support the addition of the requested adverse events to the labeling.

Consultation from the Division of Epidemiology and Surveillance

On June 7, 1995, the reviewers submitted a consultation request to the Division of Epidemiology and Surveillance for information regarding all reports of mucocutaneous candidiasis, pruritus, toxic epidermal necrolysis, interstitial nephritis, and hematuria associated with Augmentin therapy that have been reported to the agency. On June 20, 1995, we received a memorandum and a line listing of reports from the computerized Spontaneous Reporting System (SRS) from Ms. Joslyn Swann. The following information was received.

The SRS database contained 227 adverse reaction reports for Augmentin using the costart terminology to identify the adverse events in question. There were 99 reports listed as serious with 16 deaths, 88 hospitalizations, and 10 disabilities. All five adverse events were grouped together, and it was necessary to separate the data to determine the numbers of serious events and deaths reported for each event. The following table shows this information that was reported for the events during the years 1985-1995.

Costart Term	Number of Reports	Number of Serious Reports	Number of Deaths
Epiderm Necro	30	29	15
Hematuria	18	9	0
Infect Fung	0	0	0
Nephritis	15	12	0
Pruritus	170	50	1

Six of the patients had two of the adverse reactions reported. There were four deaths due to toxic epidermal necrolysis with pruritus reported as a secondary event.

Recommendation

The CIOMS I reports submitted by the applicant and the information provided by the Division of Epidemiology and Surveillance support the proposed additions to the labeling.

It is recommended that the supplement be approved.

James Blank, Ph.D.

for Rosemary Roberts, M.D. 10/19/95

Concurrence Only:
HFD-520/DivDir/MFanning 10/19/95
HFD-520/SMO/RRoberts

cc: Orig. NDA
HFD-638
HFD-520
HFD-520/MO/Roberts
SRT/Blank
CSO/DeBellas
Chem/Roy
Pharm/Osterberg
Micro/Sheldon
WP5.1; 50-597.024;9-27-95;10-11-95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA50-564/S-026,NDA50-575/S-019,NDA50-597/S-024

ADMINISTRATIVE DOCUMENTS

Food and Drug Administration
Rockville MD 20857

Date AUG 1 1994

NDA No. 50-597

Sharon Y. Shapowal, R.Ph.
SmithKline Beecham
One Franklin Plaza
P. O. Box 7929
Philadelphia, PA 19101

Attention: Sharon Y. Shapowal, R.Ph.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Augmentin Chewable Tablets

NDA Number: 50-597

Supplement Number: S-024

Date of Supplement: July 20, 1994

Date of Receipt: July 25, 1994

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA50-564/S-026,NDA50-575/S-019,NDA50-597/S-024

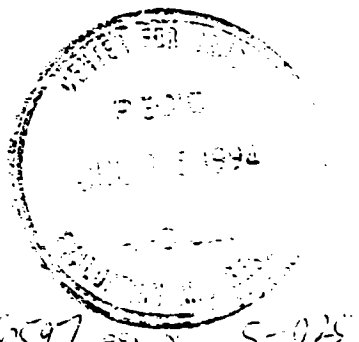
CORRESPONDENCE

ORIGINAL

SmithKline Beecham

July 20, 1994

NDA 50-564 (tablets) **
NDA 50-575 (powder for oral suspension)
NDA 50-597 (chewable tablets)
Augmentin® (amoxicillin/clavulanate potassium)



Lillian Gavrilovich, M.D., Acting Director
Center for Drug Evaluation and Research
Office of Drug Standards
Division of Anti-infective Drug Products (HFD-520)
Document Control Room 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA NO. 50597 REF. NO. 5-025
NDA SUPPL FOR 17

Re: Labeling supplement - "Changes Being Effected"

Dear Dr. Gavrilovich:

We are writing with regard to our approved applications for *Augmentin*® (amoxicillin/clavulanate potassium): NDA 50-564 (tablets), NDA 50-575 (powder for oral suspension), and NDA 50-597 (chewable tablets).

At this time we wish to submit a labeling supplement under 314.70(c)(2)(i) to add several adverse reactions to the labeling of the product. These include:

Documentation to support these changes is enclosed. SmithKline Beecham has already amended, and intends further to amend 'Amoxil' (amoxicillin) prescribing information for these events, as well.

In addition, you will note that the warnings for have been revised to reflect current class labeling statements.

This amendment is being made in duplicate, twelve copies of final printed labeling (code AG:L6, 9417100) enclosed for your inspection. Certain journal advertisements will begin to carry the new labeling in July, but the revised labeling is scheduled to be implemented fully in journal advertising in August 1994 issues. Implementation in packaging operations is scheduled for August 1, 1994.

If you have any questions regarding this application, please write or call us at (215) 751-3868.

Sincerely yours,

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

Desk copy: Ms. P. DeSantis (x1)

**** Twelve copies of final printed labeling submitted to this application, only.**

000001

SmithKline Beecham, PO Box 7929, Philadelphia, PA 19101 Telephone (215) 751-4000 Fax (215) 751-3400

ORIGINAL

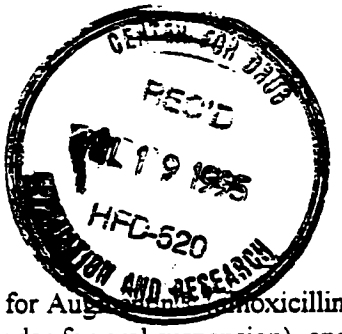
SmithKline Beecham

Amendment to a Pending Labeling Supplement

Augmentin® (amoxicillin/clavulanate potassium)
ADA 50-564/S-026 Tablets *
ADA 50-575/S-019 Powder for Oral Suspension
ADA 50-597S-024 Chewable Tablets

July 18, 1995

Mary Fanning, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Fanning:

We are writing with regard to our labeling supplements for Aug[illegible]moxicillin/clavulanate potassium): 50-564/S-026 (tablets), 50-575/S-019 (powder for oral suspension), and 50-597/S-024 (chewable tablets), submitted July 20, 1994. The supplements, submitted simultaneously, provide for addition of several adverse reactions to the labeling of the product.

At this time, in agreement with labeling review officer Dr. James Blank, and in response to his telephone request of June 7, 1995, we are amending the supplements with a different form of supporting data. Dr. Blank, requiring more complete information than was available on the submitted line listings, asked for a 'MEDWATCH' style of per patient summary. The 'MEDWATCH' form is only used by this sponsor when reporting U.S. cases to the FDA. Otherwise, the international CIOMS I style of per patient summary is submitted. Because many of the cases supporting addition of the new adverse reactions to *Augmentin* labeling are foreign cases, and for consistency, we are providing CIOMS I summaries for all cases which have formed the basis of support for adding

to labeling. Please note that this type of summary was submitted originally for interstitial nephritis, and therefore, is not required as part of the amendment.

As agreed with Dr. Blank, SB has not attempted to re-create the same data set as previously filed, but has included all cases to the present (i.e. there have been more reports since June 30, 1994). For this reason, the data set may be larger than originally submitted. In addition, the search strategy used to query our safety database for "fungal infection" was somewhat broader than last time, and several more cases were identified. Finally, upon further review of the cases and reconciliation of the data, the reviewer may note that certain cases have been deleted. These were identified as duplicate cases.

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

We appreciate the reviewer's patience during our preparation of this new data package. If you have any questions regarding this amendment, please write or call us at (215) 751-3868.

Sincerely yours,

Sharon W. Shapowal

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

* *Complete documentation submitted to this supplement only*

Desk copy: Dr. J. Blank

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA50-564/S-031,NDA50-575/S-022,NDA50-597/S-027,NDA50-720/S-002,NDA50-725/S-001,NDA50-726/S-001

Trade Name: AUGMENTIN

Generic Name:(Amoxicillin/Clavulanate Potassium)

Sponsor: SmithKline Beecham

Approval Date: March 19, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA50-564/S-031,NDA50-575/S-022,NDA50-597/S-027,NDA50-720/S-002,NDA50-725/S-001,NDA50-726/S-001

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling				
Medical Review(s)	X			
Chemistry Review(s)				
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)				
Administrative Document(s)				
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA50-564/S-031,NDA50-575/S-022,NDA50-597/S-027,NDA50-720/S-002,NDA50-725/S-001,NDA50-726/S-001

APPROVAL LETTER

NDA 50-564/S-031
NDA 50-575/S-022
NDA 50-597/S-027
NDA 50-720/S-002
NDA 50-725/S-001
NDA 50-726/S-001

MAR 19 1997

SmithKline Beecham Pharmaceuticals
Attention: Sharon W. Shapowal, R.Ph.
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Dear Ms. Shapowal:

We acknowledge your supplemental new drug applications dated August 21, 1996, received August 22, 1996, (NDA 50-564/S-031, NDA 50-720/S-002); August 22, 1996, received August 23, 1996, (NDA 50-575/S-022, NDA 50-597/S-027); and August 22, 1996, received August 26, 1996, (NDA 50-725/S-001, NDA 50-726/S-001), submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Augmentin (amoxicillin/clavulanate potassium) Tablets, NDA 50-564/S-031; Augmentin (125 mg and 250 mg/5mL formulations) for Oral Suspension, NDA 50-575/S-022; Augmentin (125 mg and 250 mg formulations) Chewable Tablets, NDA 50-597/S-027; Augmentin (875 mg) Tablets, NDA 50-720/S-002; Augmentin (200 mg and 400 mg/5mL formulations) for Oral Suspension, NDA 50-725/S-001; and Augmentin (200 mg and 400 mg formulations) Chewable Tablets, NDA 50-726/S-001.

These supplemental applications provide for an updated **OVERDOSAGE** section and additions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections of the labeling.

We have completed the review of these supplemental applications including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling in the submissions dated August 21, 1996, with the following revision. Accordingly, the supplemental applications are approved effective on the date of this letter.

The sentence proposed
which reads

should be placed as a third paragraph in this subsection.

These revisions are terms of the supplemental NDA approval.

Additionally, it is requested that a supplement for the following be submitted:

1. From the [redacted] should be deleted.

2. The [redacted] should be revised to either remove the following sentence discussing [redacted] label only.

The changes proposed in these supplements should also be applied to the Amoxil® label, where applicable.

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 supplemental NDAs 50-564/S-031, 50-575/S-022, 50-597/S-027, 50-720/S-002, 50-725/S-001, and 50-726/S-001. Approval of this submission by FDA is not required before the labeling is used.

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

Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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. Steve Trostle, Project Manager, at (301) 827-2125.

Sincerely yours,

3.15.97

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDAs 50-564, 50-575, 50-597, 50-720, 50-725, 50-726,
HFD-520/Div. files
HFD-520/CSO/M.Dillon-Parker
HFD-520/CTL/Roberts
HFD-520/MO/Rakowsky
HFD-520/CTL/Leissa
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/OTC (with labeling - for OTC Drug Products Only)
HFI-20/Press Office (with labeling)

Drafted by: mdp/February 3, 1997/N50720.S02
Initialed by: mdp
final: February 28, 1997

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA50-564/S-031,NDA50-575/S-022,NDA50-597/S-027,NDA50-720/S-002,NDA50-725/S-001,NDA50-726/S-001

MEDICAL REVIEW(S)

MEDICAL OFFICER'S REVIEW OF LABELING SUPPLEMENTS
Augmentin (Amoxicillin/Clavulanic Acid) Formulations

NDA's Affected:	1. #50-575, Supplement 022: Augmentin for Oral Suspension (125 mg and 250 mg/5mL formulations). 2. #50-597, S-027: Augmentin Chewable Tablets (125 mg and 250 mg formulations). 3. #50-564, S-031: Augmentin Tablets (250 mg and 500 mg formulations). 4. #50-725, S-001: Augmentin for Oral Suspension (200 mg and 400 mg/5mL formulations). 5. #50-726, S-001: Augmentin Chewable Tablets (200 mg and 400 mg formulations). 6. #50-720, S-002: Augmentin Tablets (875 mg formulation).
Applicant:	SmithKline Beecham Pharmaceuticals Philadelphia, PA
Contact Person:	Sharon W. Shapowal, R.Ph. 215-751-3468
Date Submitted:	August 22, 1996
Date Received by M.O.:	November 22, 1996
Date Review Completed:	December 18, 1996

Background Information:
This review will be applicable to all 6 NDA supplements listed above. The information submitted to each NDA file by the applicant is identical.

At the time of approval for NDA 50-720, it was noted that the Augmentin labels (for the formulations approved at that time) had a minimal amount of information dealing with overdosage of this medication. The applicant agreed to review supporting data and to draft a new **OVERDOSAGE** section for the labeling. These labeling supplements contain a proposed updated **OVERDOSAGE** section, and also include additions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections.

Material Submitted:

One volume submission to each of the NDA files, containing the following:

1. Annotated draft labeling.
2. Individual patient case summaries of overdosage (both for amoxicillin overdosage and Augmentin).
3. Literature References for the Augmentin **OVERDOSAGE** section.
4. Hemodialysis Report, entitled "The pharmacokinetics of amoxycillin and clavulanic acid in haemodialysis patients following intravenous administration of Augmentin". Study HP/85/31 from Beecham Pharmaceuticals Research Division.
5. Individual patient case summaries of hemolytic anemia.
6. Individual patient case summaries of interaction with oral contraceptives.

Proposed Labeling Changes:

Medical Officer's Review of Proposed Labeling Changes:

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Conclusions:

1. The applicant's proposed changes to the Augmentin labeling are acceptable.

2. The proposed changes should be applied to the Amoxil® label as well, where applicable.

3. section of the label should be removed, as well as the reference strain included in the dilution techniques section. In addition, the section should be revised as well, with either removal of the paragraph discussing label only.

Recommendations:

It is recommended that the supplements be approved and the applicant be notified of the above items outlined in the Conclusions.

Alexander Rakowsky, M.D.
M.O./HFD-520

NDA files
#50-564
#50-575
#50-597
#50-720
#50-725

#50-726
HFD-520
HFD-520/MO/RAlivisatos
HFD-520/TeamLeader/BLeissa
HFD-520/MicroTeamLeader/ASheldon
HFD-520/Micro/PDionne
HFD-520/ProjMan/STrostle
HFD-880/Biopharm/FPelsor

Concurrence Only:
HFD-520/ActDivDir/DFeigal 3-5-97
HFD-520/MOTL/RRoberts
12/23/96

REFERENCES

1. Bolt HM, "Interactions between clinically used drugs and oral contraceptives", Environmental & Health Perspectives, Nov 1994; 102 Suppl 9: 35-8.

2. Zachariasen RD, "Loss of oral contraceptive efficacy by concurrent antibiotic administration", Women-Health, 1994; 22(1): 17-26.

3. Orme M and Back DJ, "Oral contraceptive steroids- pharmacological issues of interest to the prescribing physician", Advances in Contraception, Dec 1991; 7(4): 325-331.

4. Shenfield GM, "Oral contraceptives. Are drug interactions of clinical significance?", Drug Safety, July 1993; 9(1): 21-37.

5. Wright AJ and Wilkowske CJ, "The Penicillins" (part of the "Symposium on Antimicrobial Agents" series), Mayo Clinic Proceedings, October 1991; 66: 1047-1063.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA50-564/S-031,NDA50-575/S-022,NDA50-597/S-027,NDA50-720/S-002,NDA50-725/S-001,NDA50-726/S-001

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date AUG 28 1996

NDA No. 50-397

Sharon W. Shapowal, R.Ph.
SmithKline Beecham Pharmaceuticals
One Franklin Plaza
P. O. Box 7919
Philadelphia, PA 19101-7919
Attention: Sharon W. Shapowal, R.Ph.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Augmentin for Oral Suspension

NDA Number: 50-397

Supplement Number: S-027

Date of Supplement: August 22, 1996

Date of Receipt: August 23, 1996

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research

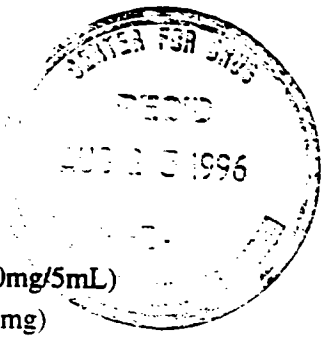
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA50-564/S-031,NDA50-575/S-022,NDA50-597/S-027,NDA50-720/S-002,NDA50-725/S-001,NDA50-726/S-001

CORRESPONDENCE

SmithKline Beecham
Pharmaceuticals

August 22, 1996



NDA 50-575 *
Augmentin® (amoxicillin/clavulanate potassium) for Oral Suspension
NDA 50-597 *
***Augmentin* Chewable Tablets**
NDA 50-725 (by cross reference, *Augmentin* for Oral Suspension, 200mg & 400mg/5mL)
NDA 50-726 (by cross reference, *Augmentin* Chewable Tablets, 200mg and 400mg)

NDA NO. 50597/SER. NO. S-027

David Feigal, 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

Supplement requiring FDA approval
Labeling Changes per 21 CFR 314.70(b)(3)

Dear Dr. Feigal:

Reference is made to the original New Drug Applications (NDAs) for Augmentin® (amoxicillin/clavulanate potassium) for Oral Suspension, NDA 50-575, and Chewable Tablets, NDA 50-597. Cross reference also is made to NDAs 50-725 and 50-726 for the 200 and 400mg strength formulations for q12h dosing in pediatric patients.

Further, reference is made to our correspondence of June 18, 1996 to NDAs 50-725 and 50-726, wherein the following commitment was made:

*** Full data package submitted to NDA 50-575 and 50-597. Submission by cross-reference to NDA 50-725 & 50-726.**

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At this time, we are submitting a labeling supplement, pursuant to 21 CFR 314.70(b)(3), and in fulfillment of the above, to revise the OVERDOSAGE section of labeling. The supplement also includes two additions to the PRECAUTIONS section, namely, the addition of a drug interaction with oral contraceptives and as a

Documentation to support these changes is enclosed. We have submitted the same data to NDA 50-564 and by cross-reference to 50-720 (the swallow tablet applications), as well. Annotated draft labeling is provided herein for your review.

If you have any questions or requests regarding this submission, please do not hesitate to contact me at (215) 751-3468.

Sincerely,

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

Desk Copy: Ms. Pauline Fogarty
Project Manager