

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50760

ADMINISTRATIVE DOCUMENTS

MEMORANDUM
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

Date: July 13, 1998

To: Stephen Trostle, Jose Cintron
Consumer Safety Officer HFD-520

Subject: NDA 50-760 Amoxil for Oral Suspension
(This NDA was formerly designated NDA 50-542 (SE2-013))

From: Dr. Kenneth A. Seethaler
Pharmacologist/Toxicologist HFD-520

Through: Dr. Robert E. Osterberg *ROE 7/14/98*
Pharmacology Team Leader HFD-520

This NDA requests approval of two new strengths of amoxicillin (200 and 400 mg/5 ml) oral suspension, and a change in the dosing regimen in pediatric patients from three times a day to twice daily. The request is based on bioequivalence data.

The NDA does not contain any preclinical safety assessment data, and thus does not require a Pharmacology/Toxicology review.

IS/ *07/14/98*
Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.
Pharmacologist/Toxicologist
HFD-520/CDER/FDA

Copy:

NDA 50-760

HFD-520/K. Seethaler

HFD-520/R. Osterberg

HFD-520/L. Gavrilovich

HFD-520/G. Chikami

HFD-520/S. Trostle

lg 7/17/98

NDA 50-760

Amoxil® (amoxicillin) for Oral Suspension
Pediatric q12h dosing

Item 16

Debarment Certification

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

d) Did the applicant request exclusivity?

YES /___/ NO //

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO //

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO //

If yes, NDA # _____.

Drug Name _____

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

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

YES /___/ NO //

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES // NO /___/

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

NDA# 50-542 Amoxil (amoxicillin)
NDA# 50-754 Amoxil (amoxicillin) Tablets
NDA# _____

2. Combination product.

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

YES / / NO / /

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

NDA# _____
NDA# _____
NDA# _____

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

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

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

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

YES / / NO / /

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

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

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

YES /___/ NO /___/

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

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /___/

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

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

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

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

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____
! _____
!

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____
! _____
!

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

Investigation #1

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

Investigation #2

YES /___/ Explain _____

NO /___/ Explain _____

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

YES /___/

NO /___/

If yes, explain: _____

IS/

4/15/99

Signature

Date

Title: Regulatory Health Project Manager

IS/

4/16/99

Signature of Office/
Division Director

Date

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: <u>50760</u>	Trade Name: <u>AMOXIL(AMOXICILLIN)ORAL SUS 200MG/400MG</u>
Supplement Number:	Generic Name: <u>AMOXICILLIAN</u>
Supplement Type:	Dosage Form: <u>Suspension; Oral</u>
Regulatory Action: <u>AP</u>	Proposed Indication: <u>The new amoxil suspension, two strengths: 200mg and 400 mg per 5 cc, is matched in amoxicillin content to the Augmentin, amoxicillin/clavulanate potassium, suspensions, previously approved for q12 hr dosing in pediatric patients, Ref. NDA 50-725 , approved May 31, 1996.</u>

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 months-12 Years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy	<u>Adequate for SOME pediatric age groups</u>
Formulation Status	<u>NEW FORMULATION developed with this submission</u>
Studies Needed	<u>No further STUDIES are needed</u>
Study Status	<u>Protocols are submitted and approved</u>

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
See NDA 50-725

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JOSE CINTRON

Signature

JS

Date

4-5-99

MEMORANDUM OF MEETING

Date: June 3, 1997
NDA: 50-760/761
Drug: Amoxil (amoxicillin) Chewable Tablets and Amoxil Oral Suspension q12h dosing
Sponsor: SmithKline Beecham
Indication: New Amoxil Tablets (two strengths: 200 mg and 400 mg/ 5 mL) in divided doses q12h (children) for susceptible microorganisms

PARTICIPANTS FROM FDA:

Dr. Gary Chikami, M.D. Act. Division Director, HFD-520
Dr. Mercedes Albuerne, M.D., Team Leader, HFD-520
Dr. Dikoe Makhene, M.D. Medical Officer, HFD-520
Dr. Frank Pelsor, Team Leader Biopharmaceutics, HFD-880
Dr. He Sun, Biopharmaceutics, HFD-880
Dr. Dave Katague, TL Chemistry, HFD-830
Dr. Andrew Yu, Chemistry, HFD-830
Dr. Sousan Altaie, Microbiology, HFD-520
Mr. Jose R. Cintron, R.Ph., M.A., Project Manager, HFD-520

SUBJECT: Determination of the fileability of Amoxil Chewable Tablets and Amoxil Oral Suspension.

OBJECTIVE: To determine the fileability of NDA 50-760/761

The meeting was convened to determine the adequacy of NDA 50-760/761. All sections of the NDA were evaluated in terms of the general content and format requirements.

Clinical: The NDAs is fileable, but Dosage and Administration section needs revision. The recommended doses are not consistent with those in the Augmentin label for the same indication.

Chemistry: The NDA is fileable

NDA 50-761 (Additional stability data (9 & 12 months) will be filed later per agreement with the Agency)
NDA 50-760 (Stability data shows that 1 batch failed after six months. Additional stability data (9 & 12 months) will be filed later per agreement with the Agency)

Pharm/Tox: All the products are currently approved. None

Microbiology: The NDA is fileable.

Statistics: None

NDA 50-760/761

Project Manger: The NDA is fileable.

It was concluded that the information in this NDA is acceptable and, therefore, the application would be filed.

15/

Jose R. Cintron, R.Ph., M.A
Project Manager, HFD-520

cc: original NDA 50-760 & 50-761

HFD-520/GChikami/Act. Division Director
HFD-520/MAlbuerne/Team Leader Medical
HFD-520/MMakhene/Medical Officer
HFD-520/SAltaie/Microbiology
HFD-830/DKatague/ Team Leader Chemistry
HFD-830/AYu/Chemistry
HFD-880/FPelsor/Team Leader Biopharmaceutics
HFD-880/HSun/Biopharmaceutics
HFD-520/PMS/JCintron

MEETING MINUTES (45-DAY)

NDA 50,760
NDA 50,761
Amoxil Chewable Tablet and Suspension

DATE of SUBMISSION
April 15, 1998

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

45-day filling comment

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

REVIEWER: HE SUN, Ph.D.

I BACKGROUND

The sponsor submitted these NDAs to support Amoxil (amoxicillin) Chewable tablet and suspension formulations, to allow for the change in the dosing regimen of amoxicillin from thrice daily to twice daily dosing in pediatric patient, and to provide support for the new formulations. These new Amoxil formulations (200 mg and 400 mg in strength) are matched to Augmentin (amoxicillin/clavulanate potassium) chewable tablet and suspension antibiotic containing amoxicillin that was approved for twice daily dosing (NDA 50-725 and NDA 50-726, approved May 31, 1996).

A three-way, cross-over bioequivalence study in 26 healthy adult volunteers (male and female) comparing the new 400-mg Amoxil formulations to the marketed *Augmentin* suspension formulation is the only study included in the submission.

II RECOMMENDATION

1. The submissions are fileable.
2. The BE study submitted provide the reviewer the opportunities to exam the amoxicillin bioavailability comparison between the new Amoxil formulations and marketed Augmentin formulation.
3. The to be marketed Amoxil 200 and 400 mg chewable and suspension formulations are new formulations, according to the general understand, at least one core food effect study is required for each formulation. Therefore, the NDAs are fileable while food effect study

should be conducted and submitted to support these new formulations. Below are recommended food effect study key design points:

1000 calories with 50% derived from fat.

240 ml water.

a.m. dosing (i.e., breakfast).

meal within ½ hours and drug administration within 5 minutes of meals.

S.D. 2-way crossover food effect study.

To claim "no effect," the average BE AUC fall in 80-125%, C_{max} falls in 70-143%.

Please conduct food effect studies for each formulation as soon as possible to avoid the delay in reviewing the NDA report.

4. Dissolution studies for the chewable tablets are found in the Chemistry Section of the NDAs. However, dissolution studies for the new suspension formulations (200 and 400 mg) are not included in the NDAs. It is required to conduct in vitro studies, such as dissolution study, to compare the 200mg and 400mg suspension formulations.

Please submit dissolution studies for the 200mg and 400mg chewable tablet and suspension formulations as soon as possible to avoid the delay in reviewing the NDA.

|S|

6/3/98

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

RD/FT Initialed by Frank Pelsor, Pharm. D.

|S|

6/3/98

cc:

NDA 50,760; 50,761

HFD-520 (Clinical, CSO)

HFD-340 (Viswanathan)

HFD-880 (Pelsor, Sun)

HFD-880 Div. File NDA 50,754(Amoxicillin)

HFD-850 Drug File (Mira Millison)