These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

NDA 50-685

AP Ltr
AE Ltr
Draft LBL
mor
Bio

stat
pharm
micro
chem
SBA memo
NA Ltr

AP Ltr

Draft LBLG

AE Ltr

NA Ltr

NDA 50-685
NDA 50-686

DEC 20 1995

Schering-Plough Corporation
Attention: Alexander R. Giaquinto, Ph.D.
Senior Vice President
Worldwide Regulatory Affairs
Galloping Hill Road
Kenilworth, New Jersey 07033

Dear Dr. Giaquinto:

Reference is made to your new drug applications (NDA's) dated December 20, 1991 submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Cedax Capsules (ceftibuten capsules), NDA 50-685 and Cedax Oral Suspension (cefibuten for oral suspension), NDA 50-686.

We acknowledge receipt of your amendment dated November 20, 1995 submitted to each application.

Please also refer to the Food and Drug Administration's (FDA) nonapprovable letter for NDA 50-685 dated March 22, 1993 and the approvable letters for both NDA's 50-685 and 50-686 dated December 29, 1994 and September 7, 1995.

We have completed the review of these applications as amended, 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 dated December 20, 1995. Accordingly, the applications are approved effective on the date of this letter.

Marketing these products with labeling that is not identical to the enclosed labeling dated December 20, 1995, may render these products unapproved new drug products.

Please submit fifteen copies of final printed labeling (FPL), identical to the enclosed labeling dated December 20, 1995. Seven copies of the final printed label should be individually mounted on heavy-weight paper or similar material. These submissions should be designated for administrative purposes as "FPL for approved NDA's 50-685 and 50-686." Approval of these submissions by the FDA is not required before the labeling may be used.

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

Please note that any advertising or promotional labeling for Cedax® Capsules and Cedax® Oral Suspension will be considered false and misleading under Section 502 of the Act if it utilizes *in vitro* microbiologic data to imply clinical efficacy or to imply clinical superiority over other drug products if such indications or clinical superiority have not been established in adequate and well-controlled clinical trials. *In vitro* microbiologic data establish *in vitro* microbiologic activity. Appropriate use of such data in advertising and promotional labeling requires a balanced presentation of how such data should be interpreted in view of the human pharmacokinetic properties of and the established clinical efficacy of these drug products.

In addition, any advertising or promotional labeling for Cedax® Capsules and Cedax® Oral Suspension will be considered false and misleading under Section 502 of the Act if it attempts to minimize, by print size or presentation emphasis, the fact that clinical data from adequate and well-controlled trials are not available establishing efficacy of this drug product in treating diseases due to the organisms contained in the "not clinically supported" (i.e., the second) grouping of organisms in the *Microbiology* subsection of the drug products labeling.

Finally, any advertisement or promotional labeling for Cedax® Capsules and Cedax® Oral Suspension will be considered false and misleading under the Act if it does not include the entire **INDICATIONS AND USAGE** AND **DOSAGE AND ADMINISTRATION** sections of the labeling when referring to the indications or dosing regimens for which this product is approved. The "NOTES" and other added statements in these sections are considered integral parts of the approved indication and dosing regimens and may not be deleted or edited. Also, in advertising or promotional labeling, the "NOTES" and other added statements may not be spatially separated from the wording in the initial part of the **INDICATIONS AND USAGE** or **DOSAGE AND ADMINISTRATION** sections so as to minimize their impact. Such information must be presented in advertising or promotional pieces in at least the same print size and with at least the same impact as any other information from this section of the labeling.

This guidance constitutes notice of activities that may be considered to be violations of the Act. Failure to comply with this guidance may result in regulatory action without further notice.

We request that you submit, in triplicate, the advertising and promotional materials you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy of the materials to the Division of Anti-Infective Drug Products and two copies of the materials to the Division of Drug Marketing, Advertising and Communications, HFD-240, Room 17B-05, 5600 Fishers Lane, Rockville, Maryland, 20857. Please submit all proposed promotional and advertising materials in draft or mock-up form, not in final print. Also, please do not use form FDA 2253 for this submission; that form is for routine use, not proposed materials.

Please submit one market package for each of the drug products of the drug when it is available.

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

If you have any questions regarding these applications, please contact Mr. Carmen DeBellas of the Project Management Staff at 301-827-2125.

Sincerely yours,

David W. Feigal 12/20/95

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

cc: Orig NDA
District Office

HFD-2
HFD-85
HFD-240
HFD-500
HFD-683
HFD-735
HFD-100
HFD-230
HFD0520/SMO/Albrecht 12/20/95
HFD-520/MO/Leissa 12/20/95
HFD-520/MO/Soreth noted 12/20/95
HFd-520/Micro/Dionne
HFD-520/CSO/DeBellas 12/20/95
HFD-520/label file
APPROVAL

Concurrence:

HFD-520/DivDir/Fanning 12/20/95
HFD-520/SCSO/Bona 12/20/95
HFD-520/SMicro/Sheldon
HFD-520/SPharm/Osterberg

RA

NDA 50-685
NDA 50-685

Alexander R. Giaquinto, Ph.D.
Senior Vice President
Worldwide Regulatory Affairs
Schering Corporation
Galloping Hill Road
Kenilworth, New Jersey 07033

SEP 7 1995

Dear Dr. Giaquinto:

Please refer to your new drug applications submitted December 20, 1991, pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for Cedax® Capsules (ceftibuten capsules), NDA 50-685; and Cedax® Oral Suspension (ceftibuten for oral suspension), NDA 50-686.

We also acknowledge receipt of your additional communications dated April 27, May 2, May 15, May 31, and June 23, 1995 as well as the agency approvable letter dated December 29, 1994.

We have completed the review of these two applications, as amended, and they are approvable at this time. Before the applications may be approved, however, we request that you revise the proposed package labeling and submit draft labeling that is identical to the enclosed draft labeling dated September 7, 1995, prepared by the Division of Anti-Infective Drug Products. Please note that there are several areas in the draft labeling where the Agency has modified the wording provided by your company. These areas are addressed below:

1. In the **Tissue Penetration** subsection of the **CLINICAL PHARMACOLOGY** section, we have not revised the text of the *Middle ear fluid (MEF)* paragraph. In Study C88-082-16, the MEF levels at 4 and 12 hours are higher than plasma levels; you need to provide an explanation for these discrepancies before the results of this study can be accepted.

2. We have revised the **Microbiology** subsection of the **CLINICAL PHARMACOLOGY** section, deleted various organisms from the *in vitro*-only list of pathogens, and revised the *Susceptibility Testing* subsection in accordance with the Divisional memorandum dated May 4, 1995, which provides guidance on the content and format of this subsection. The reasons for these decisions are as follow:

   a. While pathogens such as *Streptococcus* Group C or F are applicable to approvable indications, they cannot be added to the *in vitro* list because you provided data on only a few isolates. To include an organism in the *in vitro* list, we suggest approximately 100 isolates be tested.

b. The other pathogens which you propose to include in your *in vitro* list are applicable to indications such as urinary tract infections, gastrointestinal infections, etc., for which you have not submitted adequate and well-controlled studies supporting approval.

c. The NCCLS "MIC" and "Zone Diameter" criteria for aerobic non-fastidious organisms in the *SUSCEPTIBILITY TESTING* subsection are not applicable to the pathogens for which ceftibuten is approvable. Therefore, only information on applicable pathogens, *H. influenzae* and *S. pneumoniae*, is included in this subsection.

3. The **INDICATIONS AND USAGE** section, including the **Notes**, and the **DOSAGE AND ADMINISTRATION** section, specifically the table on dosage recommendations, have been revised to be consistent with Divisional policy. Specifically, we refer you to the approval action by the Center on Dynabac (dirithromycin) dated June 19, 1995. In the approved labeling for Dynabac, you will note that the text of the notes is similar to the text of the notes proposed for Cedax. In reviewing the documentation for Dynabac, it became evident that the clinical and statistical results of the studies met 95% confidence interval criteria, but that outcome for some pathogens did not meet Divisional criteria for approval. The scenario is comparable to Cedax, and, therefore, Cedax needs to carry this information in the package insert. For your information, a copy of the approved Dynabac package insert is enclosed.

4. We have added a **CLINICAL STUDIES** section to present the specific data on all pathogens tested.

5. We agree with you that, on the basis of all the information available from the ceftibuten-theophylline interaction study and the telephone conversations with the Agency, it is not necessary to conduct a Phase 4 study of oral ceftibuten and oral theophylline interaction.

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

Please submit, in triplicate, the advertising copy that you intend to use in your proposed introductory promotional and/or advertising campaign. Submit one copy to the Division of Anti-Infective Drug Products and two copies to the Division for Drug Marketing, Advertising and Communications, HFD-240, 5600 Fishers Lane, Rockville, Maryland, 20857. Submit all proposed materials in draft or mock-up form, not in final print. Do not use form FDA-2253 for this submission; that form is for routine use, not proposed materials.

We appreciate your acknowledgment of your responsibilities under Section 502 of the Act regarding promotion of these products. We again remind you of the specific concerns mentioned in our previous approvable letter of December 29, 1994 to you.

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, or follow one of the other alternatives under 21 CFR 314.110. In the absence of such action, the Food and Drug Administration (FDA) may take action to withdraw these applications.

These drugs may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions regarding these applications, please contact Mr. Carmen DeBellas of the Project Management Staff at 301-443-6797.

Sincerely yours,

David W Feigal 9-7-95

David Feigal, M.D.
Acting Deputy Director
Office fo Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE

CC: Orig NDA's
District Office
HF-2
HFD-2
HFD-85
HFD-240
HFD-500
HFD-683
HFD-735
HFD-100
HFD-230
HFD0520/SMO/Albrecht 9/7/95
HFD-520/MO/Soreth 9/7/95
Hfd-520/Micro/Dionne
HFD-520/CSO/DeBellas 9/7/95
HFD-520/label file
APPROVABLE

Concurrence:

HFD-520/DivDir/Fanning 9/7/95
HFD-520/SCSO/Bona
HFD-520/SMicro/Sheldon
HFD-520/SPharm/Osterberg

DEC 29 1994

NDA 50-685
NDA 50-686

Alexander R. Giaquinto, Ph.D.
Senior Vice President
Worldwide Regulatory Affairs
Schering Corporation
Galloping Hill Road
Kenilworth, New Jersey 07033

Dear Dr. Giaquinto:

Please refer to Schering's December 20, 1991 new drug applications (NDA's) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Cedax Capsules (ceftibuten capsules), NDA 50-685; and Cedax Oral Suspension (ceftibuten for oral suspension), NDA 50-686.

Please also refer the Food and Drug Administration's (FDA) non-approvable letter for NDA 50-685 dated March 22, 1993.

We acknowledge receipt of Schering's amendments to NDA 50-685 dated June 4, September 24, November 2 and 5, and December 13, 1993; February 28, March 2, and April 5, 1994. We also acknowledge Schering's amendments to NDA 50-686 dated February 6, March 13, April 1, June 3, August 21, October 19, and December 4, 1992; January 20, March 19, April 30, May 3, June 23 and 24, August 12, September 9, November 2, December 13, 1993; January 25, February 28, March 9 and 23, July 25, and August 9, 1994.

We have completed the review of these two applications, as amended, and they are approvable at this time. Before the applications may be approved, however, it will be necessary for you to submit the following items for FDA's review and concurrence:

(1) Draft labeling that is identical to the enclosed draft labeling dated December 29, 1994, prepared by the Division of Anti-Infective Drug Products. Please note that there are several areas in the draft labeling that have been highlighted. These areas should be completed by Schering with reference in the NDA to where the data that substantiate your completions can be located. Please note that final approval of certain parts of DAIDP's proposed draft labeling will depend upon satisfactory responses to the other items for clarification in this letter.

Please submit to the Division of Anti-Infective Drug Products fifteen copies of the final printed labels and other labeling. Ten of these copies should be individually mounted on heavy weight paper or similar material.

(2) In the Schering report on Study I88-115, SGOT abnormalities are listed as 17/97 (17.5%) for ceftibuten and 8/59 (13.6%) for cefaclor. "Abnormalities" are defined as value greater than three times the upper limit of normal for the laboratory value. In reviewing the clinical data base provided, the FDA medical reviewer was only able to identify five such ceftibuten patients and 1 such cefaclor patient. Please provide clarification as to the apparent discrepancy in the report and the clinical data base.

(3) In Study C90-037, study center #8 apparently used the 75 mL bottle instead of the 150 mL bottle required by the protocol. Please clarify how the study site was able to obtain a 75 mL bottle for this protocol.

(4) In Study 90-037, the patients enrolled appear to be less ill than patients in previous such studies. Likewise the outcomes from this study appear to be somewhat better than in previous such studies. In active control trials designed to test an equivalence hypothesis, there is always the concern that there could be patient selection bias if "less ill" patients were routinely selected so that both arms of the study would do better. Are there any enrollment logs that were maintained at the study sites that list why certain patients may not have been included in the trial? Were there any special instructions given the investigators concerning severity of illness that patients in this trial should have? Do you believe there was selection bias in this trial? If not, upon what do you base your opinion?

(5) In studies C90-045 and C88-044 six investigators enrolled 54% (201/373) and 42% (79/190) patients respectively. Why do you believe the FDA should consider these independent studies? As these were studies of patients with chronic bronchitis, were patients enrolled more than once in the trials, i.e., enrolled in both C90-045 and C88-044? When we examine the outcomes for the "non-common" investigators, there is a "worse" outcomes generally from those sites than from the "common" investigator sites. Such analyses raise concerns about the ability of studies conducted with common investigators to independently corroborate the outcomes of the individual studies. We note that there is also substantial overlap among the investigators in the US otitis media studies C88082, C90057 and C90886. Please address these issues.

(6) There is an apparent lower ceftibuten response rate in Europe to disease thought due to *S. pneumoniae* than in the United States. Please address this issue and any relevance it may have to proper use of this product in the United States.

(7) Please provide any information available that address the issue of *S. pneumoniae* penicillin binding proteins affinities (PBP) for ceftibuten.

(8) Please provide a regulatory update that should include copies, with English transiations, of all approved labeling for this product by foreign drug regulatory authorities, and a statement of all the countries to which marketing applications for this product have been filed and whether any have been rejected in whole or in part or whether Schering has withdrawn the product after approval or the marketing application prior to approval in any country.

(9) A safety update as required by 21 CFR 314.50(d)(5)(vi)(b).

(10) Mockups of final carton labeling including actual proposed colors, print size, and size of cartons for both samples and trade packaging. We acknowledge Schering's commitment to redesign the external packaging of the product so as to minimize any potential medication error from mistaking the 90 and 180 mg/5 cc products.

(11) Please provide an explanation for why Schering believes the formulations used in the clinical trials of ceftibuten suspension are either the same as or bioequivalent to the proposed to-be-marketed ceftibuten suspension.

In addition, we ask for a written commitment from Schering to conduct and submit within 1 year of the approval of this product results from a study that examines the potential interactions between ceftibuten and multiple doses of theophylline. This study should examine the potential effects on BOTH ceftibuten and theophylline pharmacokinetics.

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

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Please note that any advertising or promotional labeling for ceftibuten will be considered false and misleading under Section 502 of the Act if it utilizes *in vitro* microbiologic data to imply clinical efficacy or to imply clinical superiority over other drug products if such indications or clinical superiority have not been established in adequate and well-controlled clinical trials. *In vitro* microbiologic data establish *in vitro* microbiologic activity only. Appropriate use of such data in advertising and promotional labeling requires a balanced presentation of how such data should be interpreted in view of the human pharmacokinetic properties and the established clinical efficacy of these drug products.

In addition, any advertising or promotional labeling for ceftibuten will be considered false and misleading under Section 502 of the Act if it attempts to minimize, by print size or presentation emphasis, the fact that clinical data from adequate and well-controlled trials are not available establishing efficacy of this drug product in treating diseases due to the microorganisms contained in the "not clinically supported" (i.e., the second) grouping of organisms in the *Microbiology* subsection of the drug product labeling.

Finally, any advertisement or promotional labeling for ceftibuten will be considered false and misleading under the Act if it does not include the entire INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the labeling when referring to the indications or dosing regimens for which this product is approved. The "NOTES" and other added statements in these sections are considered integral parts of the approved indication and dosing regimens and may not be deleted or edited. In advertising or promotional labeling, the "NOTES" and other added statements may not be spatially separated from the wording in the initial part of the INDICATIONS AND USAGE or DOSAGE AND ADMINISTRATION sections so as to minimize their impact. Such information must be presented in advertising or promotional pieces in at least the same print size and with at least the same impact as any other information from this section of the labeling.

This guidance constitutes notice of activities that may be considered to be violations of the Act. Failure to comply with this guidance may result in regulatory action without further notice.

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

These drugs may not be legally marketed until you have been notified in writing that the applications are approved.

Should you have any questions, please contact:

Mr. Carmen DeBellas
Project Manager
Telephone: (301) 443-6797

Sincerely yours,

MML 12/29/94

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

cc:
Original NDA's
HF-2 (with label)
HFC-130/JAllen
HFD-80
HFD-500
HFD-520
HFD-240
HFD-638
HFD-730
HFD-520/CSO/DeBellas
HFD-520/SMO/Albrecht for 12/29/94
HFD-520/MO/Soreth
HFD-520/Micro/Dionne
HFD-520/Pharm/Buko
APPROVABLE

Concurrence:
HFD-520/SCSO/Bona for 12/29/94
HFD-520/Pharm/Osterberg
HFD-520/SMicro/Sheldon
HFD-520/DepDir/Gavrilovich HFD-2/Lumpkin

HFD-52

NDA 50-685

Alexander Giaquinto, Ph.D.
Vice President
Regulatory Affairs
Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

MAR 22 1993

Dear Dr. Giaquinto:

Reference is made to your New Drug Application (NDA) dated December 20, 1991, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Cedax® Capsules (ceftibuten capsules).

We also reference your amendments and correspondence dated February 13, March 12, 13, 25, 30, April 1, 2, May 6, June 3 and 25, July 1 and 17, August 21 and 31, September 24, and October 2 and 13, 1992.

We have completed our review of this NDA, as amended, and it is not approvable at this time. Under Section 507 of the Act and 21 CFR 314.125(b)(5) of the FDA implementing regulations, you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Cedax® Capsules will have the effect they are represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Specifically, the following deficiencies in the clinical and biopharmaceutics sections of the application have been identified.

CLINICAL DEFICIENCIES:

The discussion that follows refers to our assessments of the clinical data submitted in this NDA, with the exception of pneumonia patients where your clinical assessments were used. For the studies of ceftibuten in the treatment of acute bacterial exacerbation of chronic bronchitis (AECB) and in the treatment of secondary bacterial infection of acute bronchitis (SBB), the clinical outcome at the "test-of-cure" visit was considered the primary effectiveness parameter. In the studies of ceftibuten in the treatment of complicated urinary tract infections (including pyelonephritis), the bacteriologic outcome at the "test-of-cure" visit was considered the primary effectiveness parameter.

LOWER RESPIRATORY TRACT INFECTIONS:

In our review of the SBB and AECB indications, the comparative trials were grouped and evaluated as indicated in the following paragraphs:

1. Protocol C88044:

   Based on our analysis of the submitted data, the clinical success rates (cure and improvement) for patients with SBB, as determined at least 4 days after the completion of antimicrobial therapy, were 33/55 (60%) for ceftibuten 400 mg QD versus 15/19 (79%) for cefaclor 250 mg TID. The corrected two-tailed 95% CI around the difference between these two outcomes is {-45%, 7%}.

   For patients with AECB, the clinical success rates were 35/59 (59%) for ceftibuten 400 mg QD versus 17/26 (65%) for cefaclor 250 mg TID. The corrected two-tailed 95% CI around the difference between these two outcomes is {-31%, 19%}.

   The results of this study, for both SBB and AECB, failed to meet the divisional standard (two-tailed 95% CI delta of +/- 20%, in this case) by which "equivalence" of two active treatments is defined.

2. Protocols I88111, I88217, and I88327:

   Based on our analysis of the submitted data, the clinical success rates (cure and improvement) for patients with SBB, as determined at least 4 days after the completion of antimicrobial therapy, were 29/37 (78%) for ceftibuten 400 mg QD versus 8/10 (80%) for cefaclor 250 mg TID. The corrected two-tailed 95% CI around the difference between these two outcomes is {-36%, 33%}.

For patients with AECB, the clinical success rates were 27/51 (53%) for ceftibuten 400 mg QD versus 15/28 (54%) for cefaclor 250 mg TID. The corrected two-tailed 95% CI around the difference between these two outcomes is {-26%, 25%}.

The results of this study, for both SBB and AECB, failed to meet the divisional standard (two-tailed 95% CI delta of +/- 15%, in this case for SBB and +/- 20% in this case for AECB) by which "equivalence" of two active treatments is defined.

3. Analysis of combined results of Protocols C88044, I88111, I88217, and I88327:

We believe that the results from these four trials can properly be pooled together and a combined analysis be performed. This combined analysis yielded clinical success rates for patients with SBB of 62/92 (67%) for ceftibuten 400 mg QD versus 23/29 (79%) for cefaclor 250 mg TID. The corrected two-tailed 95% CI around the difference between these two outcomes is {-30%, 6%}. The results of this combined analysis for SBB patients failed to meet the divisional standard (two-tailed 95% CI delta of +/-20%, in this case) by which "equivalence" of two active treatments is defined.

For patients with AECB, clinical success rates were 62/110 (56%) for ceftibuten 400 mg QD versus 32/54 (59%) for cefaclor 250 mg TID. The corrected two-tailed 95% CI around the difference between these two outcomes is {-20%, 15%}; uncorrected = {-19%, 13%}. The results of this combined analysis for AECB patients just satisfies the divisional standard (two-tailed 95% CI delta of +/-20%) by which "equivalence" of two active treatments is defined.

Please note that the term "equivalence" in this letter refers to the power of a study to rule out the test antimicrobial being worse than the active comparator.

Because examination of data on patients with SBB who were treated with ceftibuten 400 mg QD failed to identify an adequate and well-controlled study supporting approval of ceftibuten for the treatment of this infection, it was judged that critical review of SBB patients receiving ceftibuten dosing regimens other than that requested in the draft labeling would be unproductive.

However, in view of the results from the combined analysis of patients with AECB treated in the four trials listed previously, we did critically review additional patients with AECB who received other ceftibuten dosing regimens. This included evaluation of patients in Protocols C87001, I87107, I87223, I87233, I87234, I87236, I87325 and I88230 who received ceftibuten 200 mg BID or cefaclor 250/500 mg TID.

4. Analysis of combined results of Protocols C87001, I87107, I87223, I87233, I87234, I87236, I87325, and I88230 (patients with AECB):

   The clinical success rates for AECB patients were 17/39 (44%) for ceftibuten 200 mg BID versus 24/41 (59%) for cefaclor 250/500 mg TID. The corrected two-tailed 95% CI around the difference between these two outcomes is {-39%, 9%}. The results of this combined analysis failed to meet the divisional standard (two-tailed 95% CI delta of +/- 20%, in this case) by which "equivalence" of two active treatments is defined.

5. Analysis of combined results from pneumonia patients across all clinical studies using ceftibuten 200 mg BID or cefaclor 500 mg TID (using Schering analyses):

   You reported cumulative clinical responses among your "valid" patients at the extended post-therapy visit to be 41/56 (73%) for ceftibuten patients and 36/43 (84%) for cefaclor patients. The corrected two-tailed 95% CI around the difference between these two outcomes is{-27%, 6%}. The analysis of these combined results failed to meet the

divisional standard (two-tailed 95% CI delta of +/- 15%, in this case) by which "equivalence" of two active treatments is defined.

Please also note that in study C88044, ceftibuten appeared to have reasonable bacterial activity against most pathogens requested in the draft labeling (**Indications and Usage** section). In the international studies, however, the eradication rates, overall, were lower than those demonstrated in the American trials. Moreover, eradication rates for *S. pneumoniae* appeared substantially lower. Based on the clinical and *in vitro* ceftibuten experience submitted with this application, we are concerned about ceftibuten's activity against *S. pneumoniae* in lower respiratory tract infections. Please address this concern and seeming discrepancy between the American and European outcome results for this significant pathogen.

For future reference, the following comments are made:

Regarding the proposed labeling of this product, the role of *Haemophilus parainfluenzae* and *Klebsiella pneumoniae* in the pathogenesis of AECB is not well defined by the infectious diseases community at large. At this time, as discussed in two Anti-Infective Advisory Committee meetings, the Division is not granting approval for the treatment of AECB secondary to these two pathogens.

In addition, while ceftibuten did not appear to have problems with β-lactamase-producing pathogens, the overall numbers of evaluable pathogens were small.

URINARY TRACT INFECTIONS:

1. Study C87069

Based on our analysis of patients with complicated urinary tract infections (UTI's) and pyelonephritis, the bacteriologic eradication at 5-9 days post-treatment was 41/47 (87%) in the

ceftibuten recipients and 22/25 (88%) in the TMP/SMX patients. The corrected two-tailed 95% CI around the difference between these two outcomes is {-20%, 18%}. The results of this study failed to meet the divisional standard (two-tailed 95% CI delta of +/- 15%, in this case) by which "equivalence" of two active treatments is defined.

It was observed that there was a greater proportion of men in the TMP/SMX group than in the ceftibuten group, and the men's bacteriologic response was worse compared to the response seen in women. This raises a concern about potential bias against TMP/SMX in the final study population selection (randomization). Please address this concern.

Eradication rates for *Escherichia coli* at the 5-9 day post-therapy visit were 26/31 (84%) for the ceftibuten recipients versus 14/15 (93%) for the TMP/SMX patients. The corrected 95% CI around the difference between these two outcomes is {-32%, 14%}. This raises a concern about the power of this study to demonstrate the "equivalence" of ceftibuten to an approved antimicrobial in the treatment of UTI's and pyelonephritis caused by the most common pathogen isolated. Please address this concern.

2. Studies I87247 and I87326:

In our analysis of these studies, the bacteriologic eradication rates for patients with complicated UTI's and pyelonephritis were 44/60 (73%) in ceftibuten recipients and 31/39 (80%) in TMP/SMX patients. The corrected two-tailed 95% CI around the difference between these two outcomes is {-25%, 18%}. The results of this study failed to meet the divisional standard (two-tailed 95% CI delta of +/- 15%, in this case) by which "equivalence" of two active treatments is defined.

Eradication rates for *Escherichia coli*, by the 5-9 day post-therapy visit, were 34/45 (76%) versus 24/28 (86%), respectively. The corrected 95% CI for these results was {-31%, 11%}. Again, this raises a concern about the power of this study to demonstrate the "equivalence" of ceftibuten to an approved antimicrobial in the treatment of UTI's and pyelonephritis caused by the most common pathogen isolated. Please address this concern.

3. Studies I87128, I89054, and I87232:

In our analysis of these studies, the bacteriologic eradication rates for patients with complicated UTI's and pyelonephritis were 52/76 (68%) in ceftibuten recipients and 36/43 (84%) in quinolone-treated patients. The corrected two-tailed 95% CI around the difference between these two outcomes is {-32%, 2%}. The results of this study failed to meet the divisional standard (two-tailed 95% CI delta of +/- 15%, in this case) by which "equivalence" of two active treatments is defined.

Eradication rates for *Escherichia coli*, by the 5-9 day post-therapy visit were 35/53 (66%) vs. 24/27 (89%), respectively. The corrected 95% CI for these results was {-43%, -3%}. This analysis indicated that ceftibuten was less effective than the quinolone regimens in the treatment of complicated UTI's/pyelonephritis due to *E. coli*, one of the most important uropathogens. Please address this concern.

4. Analysis of combined results of Protocols C87069, I87247 and I87326:

We performed a combined-analysis on the TMP/SMX-controlled clinical trials. This yielded bacterial eradication rates of 85/107 (79%) for ceftibuten versus 53/64 (83%) for TMP/SMX. The uncorrected 95% CI = {-15%, 9%}. Combining the studies increases the sample size so the results now just satisfy the Divisional standard for defining

"equivalence" between two active treatment regimens. When corrected, however, the 95% CI = {-17%, 10%}.

Based on the findings presented above for complicated urinary tract infections and pyelonephritis, no single study satisfied the 95% confidence interval for therapeutic equivalence.

When the TMP/SMX-controlled trials were combined, the Divisional standard for defining "equivalence" to an approved antimicrobial treatment regimen was met for overall bacteriological results; yet, the eradication rates for *Escherichia coli*, the primary uropathogen, were better (though not statistically) in the control arm.

In the quinolone-controlled study, ceftibuten was less effective, clinically and statistically, gainst *Escherichia coli* than the quinolone comparators. Furthermore, ceftibuten did not exhibit a safety advantage over the comparator drugs, including the quinolones, in the data submitted to the NDA.

Therefore, this NDA fails, at this time, to provide two adequate and well-controlled studies to support approval of ceftibuten in the treatment of complicated urinary tract infections (including pyelonephritis).

BIOPHARMACEUTICS:

1. Assay validation plasma samples from the pre-study were either directly injected onto the HPLC or a solid phase clean-up procedure was used. In at least two studies, the analytical method was modified by adding and/or using a column switching technique. In several other studies, the analytical method was not specifically mentioned. Please provide the analytical method used in <u>each</u> study and please submit validation data for the method in which the detergent and/or column switching were used.

2. Please provide stability data for ceftibuten in plasma and urine during sample collection, storage, and processing. Furthermore, please provide the individual recovery results from the Schering-Plough plasma method and recovery results from the other methods.

3. The NDA indicates that, compared to healthy younger volunteers, geriatric volunteers receiving the same dosage regimen exhibited higher C_{max} and AUC values and longer half-lives. Please provide any data you may have to explain this difference.

4. Please submit the following information on protein binding:

   a. The effect of ceftibuten on the binding of the other tested drugs if available,

   b. The number of replicates that were used to evaluate the *in vitro* protein binding, and

   c. A description and validation of the analytical method used.

5. Please provide the validation for the specificity accuracy and linearity of the analytical method used in the dissolution tests.

6. Because more than 90% of the capsule content was dissolved using
   we recommend using
   This speed, as previously tested, is more sensitive to batch-to-batch differences.

7. For studies C90-420-01 and C90-875-01, please submit the SAS output used to analyze and calculate the 90% confidence intervals.

8. For study C88-058-01, please provide an explanation of the following:

   a. The variability in the half-life values (ranged from hrs) in this study was unreasonably high.

   b. When compared to the other studies where a 200 mg dose of ceftibuten was administered, the individual and mean C_{max} and AUC values obtained in this study were relatively higher. These values were comparable to values obtained following ceftibuten 400 mg p.o. administration (cross study comparison).

9. Please provide the SAS output that was used to calculate the 90% confidence intervals in study C88-058-01.

10. For the 100 mg capsule used in study C88-058-01, please provide the formulation number, manufacturing site, batch size, etc.

11. Please explain why the C_{max} and AUC values obtained in study C90-876-01 were found to be relatively low when compared to other studies with similar design.

12. Based on simulation of plasma levels in each group by the two adjustment methods suggested in your draft labeling (dose and time interval), we recommend that dose adjustment, rather than adjustment in dosing interval, is more appropriate for renally-impaired patients.

PHARMACOLOGY

1. Please submit the pharmacology study referred to in "References for Application Summary " in Vol. 1.1 entitled Study #38 "Acute oral Toxicity Studies of SCH 39720 in Neonatal (8-day old), Juvenile (28-Day old), and Adult (8-week old) Rats. We are unable to locate this in either this NDA submission or in NDA 50-686.

Please also note that this NDA cannot be approved until we have received notification that all facilities involved in the manufacture, control, and testing of this product are in compliance with applicable CGMP's.

Please also note that this NDA cannot be approved until we have received and reviewed your version of the environmental impact statement than can be released publicly.

Within 10 days after the date of this letter, you are required to amend the application or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the Food and Drug Administration may take action to withdraw the application. A reply will not be processed as a major amendment unless all remaining outstanding deficiencies have been addressed.

If you have any questions concerning this NDA, please contact Mr. Carmen DeBellas, Project Management Staff, at 301-443-6797.

Sincerely yours,

3/19/93

James M. Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CC: orig NDA 50-685
District Office
HFC-130
HFD-82
HFD-240
HFD-638
HFD-500
HFD-520/DirDiv/Lumpkin
HFD-520/MO/Leissa
HFD-520/Micro/Dionne
HFD-520/Pharm/Buko
HFD-502/CSO/DeBellas
HFD-520/label file/DeSantis
NOT APPROVAL

Concurrence:
HFD-520/SMO/Albrecht
HFD-520/SCSO/Bona
HFD-520/Smicro/Sheldon
HFD-520/Spharm/Osterberg
HFD-420/Biopharm/Lam
HFD-710/Biometrics/Harkins

CC: orig NDA 50-685
District Office
HFC-130
HFD-82
HFD-240
HFD-638
HFD-500
HFD-520/DirDiv/Lumpkin
HFD-520/MO/Leissa
HFD-520/Micro/Dionne
HFD-520/Pharm/Buko
HFD-502/CSO/DeBellas
HFD-520/label file/DeSantis
NOT APPROVAL

Concurrence:
HFD-520/SMO/Albrecht initialed
HFD-520/SCSO/Bona
HFD-520/Smicro/Sheldon
HFD-520/Spharm/Osterberg

FDA APPROVED LABELING Revised: December 20, 1995

PRODUCT INFORMATION

CEDAX® Capsules (ceftibuten capsules)
CEDAX® ORAL SUSPENSION (ceftibuten for oral suspension)

FOR ORAL USE ONLY

DESCRIPTION

CEDAX CAPSULES (ceftibuten capsules) and CEDAX ORAL SUSPENSION (ceftibuten for oral suspension) contain the active ingredient ceftibuten as ceftibuten dihydrate. Ceftibuten dihydrate is a semisynthetic, cephalosporin antibiotic for oral administration. Chemically, it is (+)-(6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, dihydrate. Its molecular formula is $C_{15}H_{14}N_4O_6S_2 \cdot 2H_2O$. Its molecular weight is 446.43 as the dihydrate.

Ceftibuten dihydrate has the following structural formula:

[COMPANY TO INSERT FORMULA]

CEDAX CAPSULES contain ceftibuten dihydrate equivalent to 400 mg ceftibuten. Inactive ingredients contained in the capsule formulation include magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The capsule shell and/or band contains gelatin, sodium lauryl sulfate, titanium dioxide and polysorbate 80. The capsule shell may also contain benzyl alcohol, sodium propionate, edetate calcium disodium, butylparaben, propylparaben and methylparaben.

CEDAX ORAL SUSPENSION after reconstitution contains ceftibuten dihydrate equivalent to either 90 mg of ceftibuten per 5 mL or 180 mg of ceftibuten per 5 mL. Cedax Oral Suspension is cherry flavored and contains the inactive ingredients: cherry flavoring, polysorbate 80, silicon dioxide, simethicone, sodium benzoate, sucrose (approximately 1g/5 mL), titanium dioxide and xanthan gum.

CLINICAL PHARMACOLOGY
PHARMACOKINETICS
Absorption:
CEDAX CAPSULES:

Ceftibuten is rapidly absorbed after oral administration of CEDAX Capsules. The plasma concentrations and pharmacokinetic

parameters of ceftibuten after a single 400 mg dose of CEDAX Capsules to 12 healthy adult male volunteers (20 to 39 years of age) are displayed in the table below. When CEDAX capsules were administered once daily for 7 days, the average C_{max} was 17.9 μg/mL on day 7. Therefore, ceftibuten accumulation in plasma is about 20% at steady state.

CEDAX ORAL SUSPENSION:

Ceftibuten is rapidly absorbed after oral administration of CEDAX Oral Suspension. The plasma concentrations and pharmacokinetic parameters of ceftibuten after a single 9 mg/kg dose of CEDAX Oral Suspension to 32 fasting pediatric patients (6 months to 12 years of age) are displayed in the following table.

Parameter	Average Plasma Concentration (in μg/mL of ceftibuten after a single 400 mg dose) and Derived Pharmacokinetic Parameters (± 1 SD) (n=12 healthy adult males)	Average Plasma Concentration (in μg/mL of ceftibuten after a single 9 mg/kg dose) and Derived Pharmacokinetic Parameters (±1 SD) (n=32 pediatric patients)
1.0 h	6.1 (5.1)	9.3 (6.3)
1.5 h	9.9 (5.9)	8.6 (4.4)
2.0 h	11.3 (5.2)	11.2 (4.6)
3.0 h	13.3 (3.0)	9.0 (3.4)
4.0 h	11.2 (2.9)	6.6 (3.1)
6.0 h	5.8 (1.6)	3.8 (2.5)
8.0 h	3.2 (1.0)	1.6 (1.3)
12.0 h	1.1 (0.4)	0.5 (0.4)
C_{max}, μg/mL	15.0 (3.3)	13.4 (4.9)
T_{max}, h	2.6 (0.9)	2.0 (1.0)
AUC, h*μg/mL	73.7 (16.0)	56.0 (16.9)
T½, h	2.4 (0.2)	2.0 (0.6)
Total body clearance (Cl/F) mL/min/kg	1.3 (0.3)	2.9 (0.7)

The absolute bioavailability of Cedax Oral Suspension has not been determined. The plasma concentrations of ceftibuten in pediatric patients are dose proportional following single doses of Cedax Capsules of 200 and 400 mg and of Cedax Oral Suspension between 4.5 mg/kg and 9 mg/kg.

Distribution:

CEDAX CAPSULES

The average apparent volume of distribution (V/F) of ceftibuten in 6 adult subjects is 0.21 L/kg (± 1 SD=0.03 L/kg).

CEDAX ORAL SUSPENSION

The average apparent volume of distribution (V/F) of ceftibuten in 32 fasting pediatric patients is 0.5 (±1 SD=0.2 L/kg).

Protein Binding:

Ceftibuten is 65% bound to plasma proteins. The protein binding is independent of plasma ceftibuten concentration.

Tissue Penetration:

Bronchial secretions: In a study of 15 adults administered a single 400 mg dose of ceftibuten and scheduled to undergo bronchoscopy, the mean concentrations in epithelial lining fluid and bronchial mucosa were 15% and 37%, respectively, of the plasma concentrations.

Sputum: Ceftibuten sputum levels average approximately 7% of the concomitant plasma ceftibuten level. In a study of 24 adults administered ceftibuten 200 mg bid or 400 mg qd, the average C_{max} in sputum (1.5 μg/mL) occurred at 2 hours post-dose and the average C_{max} in plasma (17 μg/mL) occurred at 2 hours post-dose.

Middle ear fluid (MEF): Ceftibuten middle ear fluid levels average approximately 50% of the concomitant plasma ceftibuten level. In a study of 30 children administered 9 mg/kg of ceftibuten, the average C_{max} in MEF (2.9 ± 0.9 μg/mL) occurred at 4 hours post-dose and the average C_{max} in plasma (6.7 ± 1.9 μg/mL) occurred at 2 hours post-dose.

Tonsillar tissue:
Data on ceftibuten penetration into tonsillar tissue are not available.

Cerebrospinal fluid: Data on ceftibuten penetration into cerebrospinal fluid are not available.

Metabolism and Excretion:
A study with radiolabeled ceftibuten administered to 6 healthy adult male volunteers demonstrated that *cis*-ceftibuten is the predominant component in both plasma and urine. About 10% of ceftibuten is converted to the *trans*-isomer. The *trans*-isomer is approximately 1/8 as antimicrobially potent as the *cis*-isomer.

Ceftibuten is excreted in the urine; 95% of the administered radioactivity was recovered either in urine or feces. In 6 healthy adult male volunteers, approximately 56% of the administered dose of ceftibuten was recovered from urine and 39% from the feces within 24 hours. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment. (See **DOSAGE AND ADMINISTRATION.**)

Food Effect on Absorption:
Food affects the bioavailability of ceftibuten from Cedax Capsules and Cedax Oral Suspension.

The effect of food on the bioavailability of Cedax Capsules was evaluated in 26 healthy adult male volunteers who ingested 400 mg CEDAX Capsules after an overnight fast or immediately after a standardized breakfast. Results showed that food delays the time of C_{max} by 1.75 hours, decreases the C_{max} by 18%, and decreases the extent of absorption (AUC) by 8%.

The effect of food on the bioavailability of Cedax Oral Suspension was evaluated in 18 healthy adult male volunteers who ingested 400 mg CEDAX Oral Suspension after an overnight fast or immediately after a standardized breakfast. Results obtained demonstrated a decrease in C_{max} of 26% and in AUC of 17% when Cedax Oral Suspension was administered with a high fat breakfast, and a decrease in C_{max} of 17% and in AUC of 12% when Cedax Oral Suspension was administered with a low calorie nonfat breakfast. (See **PRECAUTIONS.**)

Bioequivalence of Dosage Formulations:
A study in 18 healthy adult male volunteers demonstrated that a 400-mg dose of CEDAX Capsules produced equivalent concentrations to a 400-mg dose of CEDAX for Oral Suspension. Average C_{max} values were 15.6 (3.1) μg/mL for the capsule and 17.0 (3.2) μg/mL for the suspension. Average AUC values were 80.1 (14.4) μg*hr/mL for the capsule and 87.0 (12.2) μg*hr/mL for the suspension.

Special Populations:

Geriatric patients: Ceftibuten pharmacokinetics have been investigated in elderly (65 years of age and older) men (n=8) and women (n=4). Each volunteer received ceftibuten 200 mg capsules twice daily for 3½ days. The average C_{max} was 17.5 (3.7) μg/mL after 3½ days of dosing compared to 12.9 (2.1) μg/mL after the first dose; ceftibuten accumulation in plasma was 40% at steady state. Information regarding the renal function of these volunteers was not available; therefore, the significance of this finding for clinical use of CEDAX Capsules in elderly patients is not clear. Ceftibuten dosage adjustment in elderly patients may be necessary. (See **DOSAGE AND ADMINISTRATION.**)

Patients with renal insufficiency: Ceftibuten pharmacokinetics have been investigated in adult patients with renal dysfunction. The ceftibuten plasma half-life increased and apparent total clearance (Cl/F) decreased proportionately with increasing degree of renal dysfunction. In 6 patients with moderate renal dysfunction (creatinine clearance 30 to 49 mL/min), the plasma half-life of ceftibuten increased to 7.1 hours and Cl/F decreased to 30 mL/min. In 6 patients with severe renal dysfunction (creatinine clearance 5 to 29 mL/min), the half-life increased to 13.4 hours and Cl/F decreased to 16 mL/min. In 6 functionally anephric patients (creatinine clearance < 5 mL/min), the half-life increased to 22.3 hours and Cl/F decreases to 11 mL/min (a 7- to 8-fold change compared to healthy volunteers). Hemodialysis removed 65% of the drug from the blood in 2 to 4 hours. These changes serve as the basis for dosage adjustment recommendations in adult patients with mild to severe renal dysfunction. (See **DOSAGE AND ADMINISTRATION.**)

Microbiology:

Ceftibuten exerts its bactericidal action by binding to essential target proteins of the bacterial cell wall. This binding leads to inhibition of cell-wall synthesis.

Ceftibuten is stable in the presence of most plasmid-mediated beta-lactamases, but it is not stable in the presence of chromosomally-mediated cephalosporinases produced in organisms such as *Bacteroides, Citrobacter, Enterobacter, Morganella,* and *Serratia.* Like other beta-lactam agents, ceftibuten should not be used against strains resistant to beta-lactams due to general mechanisms such as permeability or penicillin-binding protein changes like penicillin-resistant *S. pneumoniae.*

Ceftibuten has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections: (See **INDICATIONS AND USAGE** section.):

Gram-positive aerobes:

Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Gram-negative aerobes:

Haemophilus influenzae
(including β-lactamase-producing strains)
Moraxella catarrhalis
(including β-lactamase-producing strains)

There are no known organisms which are potential pathogens in the indications approved for ceftibuten for which ceftibuten exhibits *in vitro* activity but for which the safety and efficacy of ceftibuten in treating clinical infections due to these organisms have not been established in adequate and well-controlled trials.

NOTE: Ceftibuten is INACTIVE *in vitro* against *Acinetobacter, Bordetella, Campylobacter, Enterobacter, Enterococcus, Flavobacterium, Hafnia, Listeria, Pseudomonas, Staphylococcus,* and *Streptococcus* (except *pneumoniae* and *pyogenes*) species. In addition, it shows little *in vitro* activity against most anaerobes,

including most species of *Bacteroides*.

SUSCEPTIBILITY TESTING
Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth, agar, or microdilution) or equivalent with standardized inoculum concentrations and standardized concentrations of ceftibuten powder. The MIC values should be interpreted according to the following criteria when testing *Haemophilus* species using Haemophilus Test Media (HTM):

MIC (µg/mL)	Interpretation
≤ 2	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" implies that an infection due to the strain may be appropriately treated with the dosage of antimicrobial agent recommended for that type of infection and infecting species, unless otherwise contraindicated.

Ceftibuten is indicated for penicillin-susceptible only strains of *Streptococcus pneumoniae*. A pneumococcal isolate that is susceptible to penicillin (MIC ≤0.06 µg/mL) can be considered susceptible to ceftibuten for approved indications. Testing of ceftibuten against penicillin-intermediate or penicillin-resistant isolates is not recommended. Reliable interpretive criteria for ceftibuten are not currently available. Physicians should be informed that clinical response rates with ceftibuten may be lower in strains that are not penicillin-susceptible.

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

Organism	MIC range (µg/mL)
Haemophilus influenzae ATCC 49274	0.25-1.0

Diffusion Techniques:
Quantitative methods that require measurement of zone diameters also provide 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 30-µg ceftibuten to test the susceptibility of microorganisms to ceftibuten.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg ceftibuten disk should be interpreted according to the following criteria when testing *Haemophilus* species using Haemophilus Test Media (HTM):

Zone diameter (mm)	Interpretation
≥ 28	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

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

Ceftibuten is indicated for penicillin-susceptible only strains of *Streptococcus pneumoniae*. Pneumococcal isolates with oxacillin zone sizes of ≥ 20 mm are susceptible to penicillin and can be considered susceptible for approved indications. Reliable disk diffusion tests for ceftibuten do not yet exist.

As with standardized dilution techniques, diffusion methods require use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg ceftibuten disk should provide the following zone diameters in these laboratory quality control strains:

Organism	Zone diameter (mm)
Haemophilus influenzae ATCC 49247	29-35

Cephalosporin class disks should not be used to test for susceptibility to ceftibuten.

INDICATIONS AND USAGE
Cedax (ceftibuten) is indicated for the treatment of individuals with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. (*See* **DOSAGE AND ADMINISTRATION** and **CLINICAL STUDIES** sections.)

Acute Bacterial Exacerbations of Chronic Bronchitis due to *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains only).

> ***NOTE:*** In acute bacterial exacerbations of chronic bronchitis clinical trials where *Moraxella catarrhalis* was isolated from infected sputum at baseline, ceftibuten clinical efficacy was 22% less than control.

Acute Bacterial Otitis Media due to *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *Streptococcus pyogenes*.

> ***NOTE:*** Although ceftibuten used empirically was equivalent to comparators in the treatment of clinically and/or microbiologically documented acute otitis media, the efficacy against *Streptococcus pneumoniae* was 23% less than control. Therefore, ceftibuten should be given empirically **only** when adequate antimicrobial coverage against *Streptococcus pneumoniae* has been previously administered.

Pharyngitis and tonsillitis due to *Streptococcus pyogenes*.

> ***NOTE:*** Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Ceftibuten is generally effective in the eradication of *Streptococcus pyogenes* from the oropharynx; however, data establishing the efficacy of Cedax for the prophylaxis of subsequent rheumatic fever are not available.

CONTRAINDICATIONS

Cedax is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEDAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEDAX, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEDAX OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftibuten and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

PRECAUTIONS

General:
As with other broad-spectrum antibiotics, prolonged treatment may result in the possible emergence and overgrowth of resistant organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

The dose of ceftibuten may require adjustment in patients with varying degrees of renal insufficiency, particularly in patients with creatinine clearance less than 50 mL/min or undergoing hemodialysis. (See **DOSAGE AND ADMINISTRATION**.) Ceftibuten is readily dialyzable. Dialysis patients should be monitored carefully, and administration of ceftibuten should occur immediately following dialysis.

Ceftibuten should be prescribed with caution to individuals with a history of gastrointestinal disease, particularly colitis.

Information to Patients:
Patients should be informed that:

- If the patient is diabetic, he/she should be informed that Cedax Oral Suspension contains 1 gram sucrose per teaspoon of suspension.

- Cedax Oral Suspension should be taken at least 2 hours before a meal or at least 1 hour after a meal. (See **CLINICAL PHARMACOLOGY**, Food Effect on Absorption.)

Drug Interactions:
Theophylline:
Twelve healthy male volunteers were administered one 200 mg ceftibuten capsule twice daily for 6 days. With the morning dose of ceftibuten on day 6, each volunteer received a single intravenous infusion of theophylline (4 mg/kg). The pharmacokinetics of theophylline were not altered. The effect of ceftibuten on the pharmacokinetics of theophylline administered orally has not been investigated.

Antacids or H_2 receptor antagonists:
The effect of increased gastric pH on the bioavailability of

ceftibuten was evaluated in 18 healthy adult volunteers. Each volunteer was administered one 400 mg ceftibuten capsule. A single dose of liquid antacid did not affect the C_{max} or AUC of ceftibuten; however, 150 mg of ranitidine q12h for 3 days increased the ceftibuten C_{max} by 23% and ceftibuten AUC by 16%. The clinical relevance of these increases is not known.

Drug/Laboratory Test Interactions:
There have been no chemical or laboratory test interactions with ceftibuten noted to date. False positive direct Coombs' tests have been reported during treatment with other cephalosporins. Therefore, it should be recognized that a positive Coombs' test could be due to the drug. The results of assays using red cells from healthy subjects to determine whether ceftibuten would cause direct Coombs' reactions *in vitro* showed no positive reaction at ceftibuten concentrations as high as 40 µg/mL.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long term animal studies have not been performed to evaluate the carcinogenic potential of ceftibuten. No mutagenic effects were seen in the following studies: *in vitro* chromosome assay in human lymphocytes, *in vivo* chromosome assay in mouse bone marrow cells, Chinese hamster ovary (CHO) cell point mutation assay at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus, and in a bacterial reversion point mutation test (AMES). No impairment of fertility occurred when rats were administered ceftibuten orally up to 2000 mg/kg/day (approximately 43 times the human dose based on mg/m²/day).

Pregnancy: *Teratogenic effects: Pregnancy Category B:*
Ceftibuten was not teratogenic in the pregnant rat at oral doses up to 400 mg/kg/day (approximately 8.6 times the human dose based on mg/m²/d). Ceftibuten was not teratogenic in the pregnant rabbit at oral doses up to 40 mg/kg/day (approximately 1.5 times the human dose based on mg/m²/day) and has revealed no evidence of harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:
Ceftibuten has not been studied for use during labor and delivery. Its use during such clinical situations should be weighed in terms

of potential risk and benefit to both mother and fetus.

Nursing Mothers:
It is not known whether ceftibuten (at recommended dosages) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ceftibuten is administered to a nursing woman.

Pediatric Use:
The safety and efficacy of ceftibuten capsules in infants less than 6 months of age have not been established.

Geriatric Patients:
The usual adult dosage recommendation may be followed for patients in this age group. However, these patients should be monitored closely, particularly their renal function, as dosage adjustment may be required.

ADVERSE REACTIONS
Clinical Trials:
CEDAX CAPSULES (adult patients):
In clinical trials, 1728 adult patients (1092 U.S. and 636 international) were treated with the recommended dose of ceftibuten capsules (400 mg per day). There were no deaths or permanent disabilities thought due to drug toxicity in any of the patients in these studies. Thirty-six of 1728 (2%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea, vomiting, or nausea. Six of 1728 (0.3%) patients were discontinued due to rash or pruritus thought related to ceftibuten administration.

In the U.S. trials, the following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to ceftibuten capsules in multiple-dose clinical trials (n = 1092 ceftibuten-treated patients).

ADVERSE REACTIONS CEFTIBUTEN CAPSULES U.S. CLINICAL TRIALS IN ADULT PATIENTS (n = 1092)		
Incidence equal to or greater than 1%	Nausea	4%
	Headache	3%
	Diarrhea	3%
	Dyspepsia	2%
	Dizziness	1%
	Abdominal pain	1%
	Vomiting	1%
Incidence less than 1% but greater than 0.1%	Anorexia	
	Constipation	
	Dry mouth	
	Dysuria	
	Dyspnea	
	Eructation	
	Fatigue	
	Flatulence	
	Loose stools	
	Moniliasis	
	Nasal congestion	
	Paresthesia	
	Pruritus	
	Rash	
	Somnolence	
	Taste perversion	
	Urticaria	
	Vaginitis	

LABORATORY VALUE CHANGES* CEFTIBUTEN CAPSULES U.S. CLINICAL TRIALS IN ADULT PATIENTS		
Incidence equal to or greater than 1%	↑ BUN ↑ Eosinophils ↓ Hemoglobin ↑ ALT (SGPT) ↑ Bilirubin	4% 3% 2% 1% 1%
Incidence less than 1% but greater than 0.1%	↑ Alk phosphatase ↑ Creatinine ↑ Platelets ↓ Platelets ↓ Leukocytes ↑ AST (SGOT)	

*Changes in laboratory values with possible clinical significance regardless of whether or not the investigator thought that the change was due to drug toxicity.

CEDAX ORAL SUSPENSION (pediatric patients):

In clinical trials, 1152 pediatric patients (772 U.S. and 380 international), 97% of whom were younger than 12 years of age, were treated with the recommended dose of ceftibuten (9 mg/kg once daily up to a maximum dose of 400 mg per day) for 10 days. There were no deaths, life-threatening adverse events or permanent disabilities in any of the patients in these studies. Eight of 1152 (<1%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. The discontinuations were primarily (7 out of 8) for gastrointestinal disturbances, usually diarrhea or vomiting. One patient was discontinued due to cutaneous rash thought possibly related to ceftibuten administration.

In the U.S. trials, the following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to ceftibuten oral suspension in multiple-dose clinical trials (n = 772 ceftibuten-treated patients).

ADVERSE REACTIONS CEFTIBUTEN ORAL SUSPENSION U.S. CLINICAL TRIALS IN PEDIATRIC PATIENTS (n = 772)		
Incidence equal to or greater than 1%	Diarrhea*	4%
	Vomiting	2%
	Abdominal pain	2%
	Loose Stools	2%
Incidence less than 1% but greater than 0.1%	Agitation	
	Anorexia	
	Dehydration	
	Diaper dermatitis	
	Dizziness	
	Dyspepsia	
	Fever	
	Headache	
	Hematuria	
	Hyperkinesia	
	Insomnia	
	Irritability	
	Nausea	
	Pruritus	
	Rash	
	Rigors	
	Urticaria	

*NOTE: The incidence of diarrhea in children ≤ 2 years old was 8% (23/301) compared with 2% (9/471) in children > 2 years old.

LABORATORY VALUE CHANGES* CEFTIBUTEN CAPSULES U.S. CLINICAL TRIALS IN PEDIATRIC PATIENTS		
Incidence equal to or greater than 1%	↑ Eosinophils ↑BUN ↓ Hemoglobin ↑ Platelets	3% 2% 1% 1%
Incidence less than 1% but greater than 0.1%	↑ ALT (SGPT) ↑ AST (SGOT) ↑Alk Phosphatase ↑ Bilirubin ↑ Creatinine	

*Changes in laboratory values with possible clinical significance regardless of whether or not the investigator thought that the change was due to drug toxicity.

In Post-marketing Experience:
In addition to the events reported during clinical trials with ceftibuten capsules, the following adverse experiences have been reported during worldwide post-marketing surveillance:

CEDAX CAPSULES: Aphasia, jaundice, psychosis, stridor, toxic epidermal necrolysis.

CEDAX ORAL SUSPENSION: Melena.

Cephalosporin class adverse reactions:
In addition to the adverse reactions listed above that have been observed in patients treated with ceftibuten capsules, the following adverse events and altered laboratory tests have been reported for cephalosporin-class antibiotics:

allergic reactions, anaphylaxis, drug fever, Stevens-Johnson syndrome, renal dysfunction, toxic nephropathy, hepatic cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive test for urinary glucose, neutropenia, pancytopenia, and agranulocytosis. Pseudomembranous colitis; onset of symptoms may occur during or after antibiotic treatment (see **WARNINGS**).

Several cephalosporins have been implicated in triggering seizures,

particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Ceftibuten is readily dialyzable and significant quantities (65% of plasma concentrations) can be removed from the circulation by a single hemodialysis session. Information does not exist with regard to removal of ceftibuten by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The recommended doses of CEDAX CAPSULES and ORAL SUSPENSION are presented in the table below. **CEDAX ORAL SUSPENSION must be administered at least 2 hours before or 1 hour after a meal.**

Type of Infection (as qualified in the **INDICATIONS AND USAGE** section of this labeling)	**Daily Maximum Dose**	**Dose and Frequency**	**Duration**
ADULTS (12 years and older) Acute Bacterial Exacerbations of Chronic Bronchitis due to *H. influenzae* (including β-lactamase-producing strains), *M. catarrhalis* (including β-lactamase-producing strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains only). (See **INDICATIONS and USAGE - NOTE**) Pharyngitis and tonsillitis due to *S. pyogenes*. Acute Bacterial Otitis Media due to *H. influenzae* (including β-lactamase producing strains), *M. catarrhalis* (including ß-lactamase producing strains) or *S. pyogenes*. (See **INDICATIONS and USAGE - NOTE**)	400 mg	400 mg QD	10 days
CHILDREN: Pharyngitis and tonsillitis due to *S. pyogenes*. Acute Bacterial Otitis Media due to *H. influenzae* (including β-lactamase producing strains) and *M. catarrhalis* (including β-lactamase producing strains) or *S. pyogenes*. (See **INDICATIONS and USAGE - NOTE**)	400 mg	9 mg/kg QD	10 days

CEFTIBUTEN ORAL SUSPENSION - PEDIATRIC DOSAGE CHART		
CHILD'S WEIGHT	90 mg/5 mL	180 mg/5 mL
10 kg 22 lbs	1 tsp QD	1/2 tsp QD
20 kg 44 lbs	2 tsp QD	1 tsp QD
40 kg 88 lbs	4 tsp QD	2 tsp QD

Children weighing more than 45 kgs should receive the maximum daily dose of 400 mg.

Renal Impairment:
CEDAX CAPSULES and CEDAX ORAL SUSPENSION may be administered at normal doses in the presence of impaired renal function with creatinine clearance of 50 mL/min or greater. The recommendations for dosing in patients with varying degrees of renal insufficiency are presented in the following table.

Creatinine Clearance (mL/min)	Recommended Dosing Schedules
>50	9 mg/kg or 400 mg Q24h (normal dosing schedule)
30-49	4.5 mg/kg or 200 mg Q24h
5-29	2.25 mg/kg or 100 mg q24h

Hemodialysis Patients:
In patients undergoing hemodialysis two or three times weekly, a single dose 400 mg dose of ceftibuten capsules or a single dose of 9 mg/kg (maximum of 400 mg of ceftibuten) oral suspension may be administered at the end of each hemodialysis session.

Directions for Mixing Cedax Oral Suspension:

DIRECTIONS FOR MIXING CEDAX ORAL SUSPENSION			
Final Concentration	Bottle Size	Amount of Water	Directions
90 mg per 5 mL	30 mL	Suspend in 28 mL of water.	First tap the bottle to loosen powder. Then add water in two portions, shaking well after each aliquot.
	60 mL	Suspend in 53 mL of water.	
	120 mL	Suspend in 103 mL of water.	
180 mg per 5 mL	30 mL	Suspend in 28 ml of water.	
	60 mL	Suspend in 53 mL of water.	
	120 mL	Suspend in 103 mL of water.	

After mixing, the suspension may be kept for 14 days and must be stored in the refrigerator. Keep tightly closed. Shake well before each use. Discard any unused portion after 14 days.

HOW SUPPLIED

CEDAX® CAPSULES, containing 400 mg of ceftibuten (as ceftibuten dihydrate) are white, opaque capsules imprinted with the product name and strength are available as follows:

20 Capsules/Bottle (NDC 0085-0691-01)
100 Capsules/Bottle (NDC 0085-0691-02)
Unit-dose dispensing (10 strips of 4 capsules each) (NDC 0085-0691-03).

Store the capsules between 2° and 25°C (36° and 77°F). Replace cap securely after each opening.

CEDAX ORAL SUSPENSION is an off-white to cream-colored powder that,

when reconstituted as directed, contains either ceftibuten equivalent to 90 mg/5 mL or 180 mg/5 mL, supplied as follows:

90 mg/5 mL

18 mg/mL	30 mL Bottle	NDC 0085-0777-03
18 mg/mL	60 mL Bottle	NDC 0085-0777-01
18 mg/mL	120 mL Bottle	NDC 0085-0777-02

180 mg/5 mL

36 mg/mL	30 mL Bottle	NDC 0085-0834-03
36 mg/mL	60 mL Bottle	NDC 0085-0834-01
36 mg/mL	120 mL Bottle	NDC 0085-0834-02

Prior to reconstitution, the powder must be stored between 2° and 25°C (36° and 77°F). Once it is reconstituted, the oral suspension is stable for 14 days when stored in the refrigerator between 2° and 8°C (36° and 46°F).

CLINICAL STUDIES:

Acute Bacterial Exacerbations of Chronic Bronchitis:
Three clinical trials (two domestic, the third abroad) have been conducted testing ceftibuten in the treatment of acute exacerbations of chronic bronchitis (AECB). Overall, the clinical outcome among patients who had signs and symptoms of AECB, who had a gram stain showing a predominance of PMN's and few epithelial cells, and who were evaluated at approximately one-to-two weeks after completing therapy is presented in the table below. The bacterial eradication rates of specific pathogens from these three trials are also presented:

CLINICAL AND BACTERIOLOGICAL OUTCOME
ACUTE BACTERIAL EXACERBATIONS OF CHRONIC BRONCHITIS

	ceftibuten 400 mg QD	control
Clinical Cure Rates	171/271 (63%)	147/216 (68%)
The 95% confidence interval around the difference in the means is (-14%, +4%).		
Bacteriological Eradications Rates		
Haemophilus influenzae	45/62 (73%)	26/36 (72%)
H. parainfluenzae	10/10	4/6
Moraxella catarrhalis	33/46 (72%)	32/34 (94%)
Streptococcus pneumoniae	23/35 (66%)	14/20 (70%)

Acute Bacterial Otitis Media:
Four clinical trials (three domestic, the fourth abroad) have been conducted testing ceftibuten in the treatment of acute bacterial otitis media. Overall, the clinical outcome among patients who had signs and symptoms of acute bacterial otitis media and who were evaluabled approximately 1-2 weeks after completing therapy is presented in the table below. Tympanocentesis was performed on patients in three of the above-mentioned studies; the bacterial eradication rates of specific pathogens from these three trials are also presented:

CLINICAL AND BACTERIOLOGICAL OUTCOME
ACUTE BACTERIAL OTITIS MEDIA

	ceftibuten 9 mg/kg QD	control
Clinical Cure Rates	266/365 (73%)	174/226 (77%)

The 95% confidence interval around the difference in the means is (-12%, +4%).

Bacteriological Eradications Rates		
Haemophilus influenzae	56/67 (81%)	29/38 (76%)
Moraxella catarrhalis	20/26 (77%)	13/17 (77%)
Streptococcus pneumoniae	68/105 (65%)	35/40 (88%)
Streptococcus pyogenes	13/15 (87%)	5/5

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically -- Third Edition. Approved Standard NCCLS Document M7-A3, Vol.13, No. 25, NCCLS, Villanova, PA. December, 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests -- Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

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Memorandum to the Record

To: NDA 50-685

From: Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Subject: Summary Basis of Approval

The Applicant has applied for the approval of Cedax^{R} (ceftibuten) Capsules and has submitted the necessary labeling and documentation.

The following reviews will serve as the summary basis of approval:

Medical Officer's Reviews: dated December 1992, December 1994, and September 1995.

Pharmacologist's Reviews: dated December 1992.

Biopharmaceutic's Review: dated December 1992 and ~~J~~une 1994.

Biometric's Review: dated February 1993.

Carmen DeBellas, PMS

December 1995

cc: orig NDA
HFD-82
HFD-500
HFD-520
HFD-520/Div Dir/M Fanning
HFD-520/DepDir/LGavrilovich
HFD-520/MO/BLeissa
HFD-520/Pharm/LBuko
HFD-520/Micro/PDionne
HFD-520/CSO/CDeBellas
Memorandum to the Record



Ceftibuten -- SMO Secondary Review
NDA 50-685 (capsules)

SMO Addendum #2 to MOR

August 9, 1994

Sponsor: Schering-Plough Corporation

Date of Original NDA: December 20, 1991
Date of Amendment: November 5, 1993

Name of Drug: ceftibuten (CEDAX) capsules

Related INDs: IND IND NDA 50-686 suspension

Related Reviews:
MOR by Dr. Leissa dated February 2, 1993
MOR by Dr. Soreth dated July 5, 1994
SMO addendum by Dr. Albrecht dated January 22, 1993

Requested Indications:

In the Original NDA

Acute Bronchitis and Acute Bacterial Exacerbations of Chronic Bronchitis. Dose Regimen: 400 mg QD x 5-14 days.

In the Amendment:
Acute Bacterial Exacerbations of Chronic Bronchitis. Dose Regimen: 400 mg QD x 5-14 days.

Background:

However, the Agency stated that the applicant had one study that showed favorable results for the indication of acute exacerbation of chronic bronchitis. A second study would need to be submitted in order for the drug to be approved for this indication.

The applicant has now submitted an amendment, and provided results of Study C90-045.

CLINICAL STUDY RESULTS:

ORIGINAL NDA RESULTS

The applicant and then the reviewer examined patient records to confirm the actual diagnosis: bronchitis acute exacerbation of chronic bronchitis

The original protocol(s) for the study of respiratory infections proposed to make the final assessment at the completion of therapy. The applicant was informed, and acknowledged in the end-of-Phase II meeting minutes, that a 1-2 week post-treatment follow-up was necessary to evaluate outcome of therapy in these patients.

In all protocols, patients with bronchitis and pneumonia were enrolled. The dosage regimens were to be 400 mg QD and 200 mg BID, respectively. For the purposes of this summary, and because the sponsor is not requesting approval
only the results of the bronchitis studies are presented.

Two groups of patients submitted to the original NDA are are summarized below (for further information, please refer to MOR 2/3/93 and SMO addendum 1/22/93):

1) Protocol C88-044: domestic, multicenter, randomized trial of patients with bronchitis who were treated with ceftibuten 200 mg capsules. For bronchitis, the dose was 400 mg QD The comparator was cefaclor 250 mg TID for bronchitis . Treatment was for 5-14 days.

Criteria for efficacy and safety evaluation:
Patients had baseline clinical and bacteriological evaluation, including assessment of cough, sputum, dyspnea, cyanosis, rales/rhonchi; an adequate gram stain had to be recorded (predominant organism, >25 WBC, <10 epithelial cells per LPF). Chest x-ray was requested but not required for diagnosis of bronchitis. Isolates from sputum culture were tested for susceptibility. Patients were re-evaluated at the end of treatment (EOT) and again at the 7-14 day post treatment follow-up (FU).

COMMENT: While the applicant considered the results from the EOT assessment as primary evidence in evaluating the efficacy of ceftibuten, the MO considered a patient evaluable for efficacy if the patient had a FU assessment documented between ≥4 days and 3 weeks for AECB and between ≥4 days and 4 weeks for after the end of treatment. Several subgroups were examined, as defined below.

Definitions:

The APPLICANT analyzed five subsets (intent to treat, modified intent to treat, clinical efficacy, valid, supportive).

The MO defined the three efficacy populations below, and examined each. Regulatory decisions were made on the "Clinical Test-of-Cure" population.

"CLINICAL EFFICACY" population: to be included in this category, the patient had to have signs and symptoms of bronchitis, an acceptable sputum gram stain, received 5-14 days of therapy, and have an evaluation at the end of treatment. (For this group, a positive bacterial culture and/or a post-treatment follow-up were not required.)

"CLINICAL TEST-OF-CURE" population: a patient had to have all the criteria as defined under Clinical Efficacy, above. In addition, the patient had to have a post-treatment follow-up evaluation between ≥4 days and 3 weeks for AECB and between ≥4 days and 4 weeks for acute bacterial bronchitis after the completion of therapy.

"VALID EFFICACY" population: a patient had to have all the criteria of Clinical Test-of-Cure and have a valid sputum culture, with the isolation of a "pathogen": *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Klebsiella pneumoniae.*

A total of 30 investigators enrolled 408 patients.

The applicant reported that 351 patients had bronchitis, 239 were randomized to the 400 mg QD ceftibuten regimen and 112 received cefaclor 250 mg TID. Clinical outcome at the EOT was reported as favorable in 165/190 (87%) of ceftibuten patients and 67/78 (86%) of cefaclor patients [95% C.I. = (-0.08, +0.10)]. The analysis of patients at the post-treatment follow-up did not include patients considered failures at EOT, and is not presented here.

The MO identified 348 patients with bronchitis. The breakdown by specific diagnosis, dose regimen, and outcome is presented in the table below:

	Secondary Bacterial Infections of Acute Bronchitis		Acute Exacerbation of Chronic Bronchitis	
	ceftibuten	cefaclor	ceftibuten	cefaclor
Parameter	400 mg QD	250 mg TID	400 mg QD	250 mg TID
Enrolled	107	50	128	63
Clinical efficacy	57/78 (73%)	27/31 (87%)	68/90 (76%)	27/36 (77%)
Clinical Test-of-Cure	33/55 (60%)	15/19 (79%)	35/59 (59%)	17/26 (65%)
	95% C.I. = (-0.45, +0.07)		95% C.I. = (-0.31, +0.19)	
Valid Efficacy	12/14 (86%)	4/4 (100%)	17/26 (65%)	9/13 (69%)
Eradication rates for individual pathogens				
Haemophilus influenzae	*7/8*	*3/3*	*10/14*	*3/6*
Haemophilus parainfluenzae	*2/2*	*1/1*	*7/7*	*2/2*
Moraxella catarrhalis	*2/3*	-	*3/5*	*2/2*
Streptococcus pneumoniae	*1/1*	-	*3/3*	*4/4*
Klebsiella pneumoniae	*1/1*	-	*2/2*	*1/1*
TOTAL	13/15 (87%)	4/4 (100%)	25/31 (81%)	12/15 (79%)

An analysis of drug related adverse clinical events and changes in laboratory determinations showed: six ceftibuten and three cefaclor patients died; 9 ceftibuten and 6 cefaclor patients discontinued therapy due to adverse events; 64/229 (28%) ceftibuten and 23/102 (23%) cefaclor patients experienced at least one adverse event. In the ceftibuten arm, headaches, somnolence, nausea, vomiting and diarrhea each occurred in at least 1% of patients. Laboratory tests were unremarkable, but a handful of patients had urinary WBC, RBC and protein detected (in both arms).

2) Protocols I88-111, I-88-217, I88-327: these multicenter international studies followed the same protocol and analyzed results using the same criteria as the C88-044 domestic clinical trial.

A total of 23 investigators enrolled 399 patients.

The applicant reported that 268 patients had bronchitis, 182 were randomized to the 400 mg QD ceftibuten regimen and 86 received cefaclor 250 mg TID. Clinical outcome at the EOT was reported as favorable in 150/169 (89%) of ceftibuten patients and 76/79 (96%) of cefaclor patients. The analysis of patients at the post-treatment follow-up did not include patients considered failures at EOT, and is not presented here.

The MO identified 261 patients with bror . The breakdown by specific diagnosis, dose regimen, and outcome is presented in the table bel

	Secondary Bacterial Infections of Acute Bronchitis		Acute Exacerbation of Chronic Bronchitis	
	ceftibuten	cefaclor	ceftibuten	cefaclor
Parameter	400 mg QD	250 mg TID	400 mg QD	250 mg TID
Enrolled	85	35	90	51
Clinical efficacy	73/80 (91%)	31/32 (97%)	70/86 (81%)	39/48 (81%)
Clinical Test-of-Cure	29/37 (78%) 95% C.I. = (-0.36, +0.33)	8/10 (80%)	27/51 (53%) 95% C.I. = (-0.26, +0.25)	15/28 (54%)
Valid Efficacy	16/21 (76%)	5/7 (71%)	20/39 (51%)	9/18 (50%)
Eradication rates for individual pathogens				
Haemophilus influenzae	*11/12*	-	*12/17*	*7/10*
Haemophilus parainfluenzae	*1/1*	-	*3/3*	*2/4*
Moraxella catarrhalis	*2/2*	-	*4/5*	*1/2*
Streptococcus pneumoniae	*2/5*	*4/6*	*8/16*	*3/5*
Klebsiella pneumoniae	*1/1*	*1/1*		-
TOTAL	17/21 (81%)	5/7 (71%)	30/45 (67%)	13/21 (82%)

An analysis of drug related adverse clinical events and changes in laboratory determinations showed: six ceftibuten and two cefaclor patients died; 2 ceftibuten and 2 cefaclor patients discontinued therapy due to adverse events; 20/177 (11%) ceftibuten and 11/88 (13%) cefaclor patients experienced at least one adverse event. In the ceftibuten arm, nausea, vomiting, diarrhea, hematuria and hypokalemia each occurred in at least 1% of patients. Laboratory tests showed elevated creatinine, and a handful of patients had urinary WBC, RBC and protein detected (in both arms).

COMMENTS:

In the treatment of patients with ceftibuten did not meet the lower limit of the 95% confidence interval in either the study.

In the treatment of , ceftibuten did not meet the lower limit of the 95% confidence interval in either the domestic study of in the international study.

Thus, the data were examined in another way. The results for patients with acute bacterial bronchitis were pooled, and the results for all patients with acute exacerbation of chronic bronchitis were pooled. These are presented below:

	ceftibuten 400 mg QD	*cefaclor 250 mg TID*
Acute Exacerbation of Chronic Bronchitis	*62/110 (56%)*	*32/54 (59%)*
	95% C.I. = (-0.20, +0.15)	

From these results, it is evident that the group does not meet the lower limit of the 95% C.I., while the group does meet the lower limit.

AMENDMENT RESULTS

3) Protocol C90-045: domestic, multicenter, randomized trial of patients with acute exacerbation of chronic bronchitis who were treated with ceftibuten 400 mg qd or cefixime 400 mg qd for 5-14 days.

Criteria for efficacy and safety evaluation:
Patients had baseline clinical and bacteriological evaluation, including assessment of cough, sputum, dyspnea, cyanosis, rales/rhonchi; an adequate gram stain had to be recorded (predominant organism, >25 WBC, <10 epithelial cells per LPF). Chest x-ray was requested to rule out pneumonia Isolates from sputum culture were tested for susceptibility. Patients were re-evaluated at the end of treatment (EOT, 0-6 days post therapy) and again at the 7-21 day post treatment follow-up (FU).

COMMENT: Although in the original NDA analysis the applicant considered the results from the EOT assessment as primary evidence in evaluating the efficacy of ceftibuten, in the amendment the applicant adopted the analysis used by the MO in the original NDA. Thus a patient was evaluable for efficacy if the patient was seen at the EOT visit (0-6 days), FU visit (7-21 days) with a four day window between the two visits. This differs somewhat from the criteria used in the NDA review by Dr. Leissa; a F/U assessment documented between ≥4 days and 3 weeks for AECB.

Requiring a "late" visit for evaluability helps explain why there is fairly close agreement between the applicant's and FDA's analysis.

The SMO requested that Dr. Soreth examine whether using a ≥4 to 3 week window for the patients in this trial would alter the results from this study. Because failures were "carried forward" by both reviewers and because the 7-21 captured a substantial portion of the returning patient, the only question remains is whether patients seen ≥4 to 6 or 22 to 3 weeks were excluded by Dr. Soreth while these would have been acceptable to Dr. Leissa. According to Dr. Soreth, examination of t data at ≥4 to 3 weeks did not alter the results of this trial.

Definitions:

The APPLICANT analyzed patients at EOT and FU.

The MO examined the outcome in the clinical population and the microbiologically evaluable population at EOT (visit 3, day 0-6) and again at FU (visit 4, 7-21 days). The test-of-cure visit was Visit 4.

A total of 23 investigators enrolled 373 patients with a diagnosis of AECB.

	Acute Exacerbation of Chronic Bronchitis	
	ceftibuten	cefixime
Parameter	400 mg QD	400 mg QD
Enrolled	161	162
Clinical Efficacy		
Cure	112/161 (70%)	114/162 (70%)
Improved		
Clinical Test of Cure		
Cure	109/161 (68%)	115/162 (71%)
Improved	15	16
	95% C.I. = (-0.14, +0.07) for cure	
	95% C.I. = (-0.135, +0.055) for cure + improved	
Microbiological Evaluable subset		
Clinical Efficacy		
Cure	36/58 (62%)	30/44 (68%)
Improved	3	4
Eradication rates for individual pathogens		
Haemophilus influenzae	*23/31 (74%)*	*16/20 (80%)*
Moraxella catarrhalis	*11/18 (61%)*	*15/15 (100%)*
Streptococcus pneumoniae	*12/16 (75%)*	*7/11 (64%)*
TOTAL	46/65 (71%)	38/46 (83%)

An analysis of drug related adverse clinical events and changes in laboratory determinations showed: one ceftibuten and one cefixime patient died; 3 ceftibuten and 9 cefixime patients discontinued therapy due to adverse events; 68/185 (37%) ceftibuten and 81/185 (44%) cefixime patients experienced at least one adverse event. In the ceftibuten arm, dry mouth, pain, headaches, dizziness, depression, insomnia, abdominal pain, diarrhea. dyspepsia, loose stools, nausea, vaginitis, bronchospasm, dyspnea, taste perversion, purpura each occurred in at least 1% of patients. Laboratory tests were unremarkable, but a handful of patients had urinary WBC, RBC and protein detected (in both arms).

SUMMARY AND CONCLUSIONS

Three clinical trials (two domestic, the third abroad) have been conducted testing ceftibuten in the treatment of AECB. Overall, the clinical outcome at the test-of-cure late follow up visit was

	ceftibuten	control
clinical TOC visit	171/271 (63%)	147/216 (68%)
	95% C.I. = (-0.138, +0.039)	

The confidence interval indicates there is no statistically significant difference between the two clinical outcomes.

The bacterial eradication rates of pathogens combined from all three trials are:
(H. parainfluenzae and K. pneumoniae were only evaluated in C88-044 and the I-88 protocols.)

Eradication rates for individual pathogens		
Haemophilus influenzae	45/62 (73%)	26/36 (72%)
beta-lactamase (-)	37/48 (77%)	21/28 (75%)
beta-lactamase (+)	5/7	2/5
beta-lactamase (?)	3/7	3/3
H. parainfluenzae	10/10	4/6
beta-lactamase (-)	9/9	4/6
beta-lactamase (+)	1/1	-
Moraxella catarrhalis	18/28 (64%)	18/19 (95%)
beta-lactamase (-)	5/5	5/6
beta-lactamase (+)	12/21	10/10
beta-lactamase (?)	1/2	3/3
Streptococcus pneumoniae	23/35 (66%)	14/20 (70%)
K. pneumoniae	5/6	1/1

The MIC 90's for the common respiratory pathogens are: *H. influenzae* 0.06; *M. catarrhalis* 2,4; *S. pneumoniae* 2; *S. pyogenes* 1.

A consistent pattern is seen in these bronchitis results. The activity of ceftibuten is comparable to the control agents against *H. influenzae*, which has a low MIC90. Ceftibuten demonstrated notably lower activity against *M. catarrhalis*, which has an MIC90 of 2 or 4. The activity against *S. pneumoniae* appears relatively comparable, with 55 total isolates evaluated (35 ceftibuten + 20 control). It is interesting to note that this pattern (poor *S. pneumoniae* eradication rate in otitis media but more comparable eradication in AECB) was also observed with the third-generation oral drug, cefixime: cefixime did not show acceptable activity at 8 mg/kg QD in *S. pneumoniae* otitis media, but did have acceptable activity at 200 mg BID or 400 mg QD against *S. pneumoniae* in bronchitis. A similar pattern is noted for ceftibuten.

From the above series of results and explanations, it can ceftibuten, 400 mg QD x 10 days, may be used as therapy for AECB, when *H. influenzae* (beta-lactamase negative and positive strains) or *S. pneumoniae* are suspected pathogens. However, there is problems with the activity against *M. catarrhalis*.

RECOMMENDATIONS:

An approvable letter should be issued for ceftibuten capsules in the treatment of AECB due to *H. influenzae* (beta-lactamase negative and positive strains) or *S. pneumoniae*. A note should be added (see MOR) that the agent should not be used as empiric therapy. A CLINICAL STUDIES section should present the results of ceftibuten compared to the control (see above). The dosage regimen should be 400 mg QD x 10 days.

cc: orig NDA
HFD-520
HFD-520/CSO/DeBellas
HFD-520/MO/Soreth
HFD-520/SMO/Albrecht
HFD-520/Pharm/Buko
HFD-520/Micro/Dionne
C:\review3\cefcaps

Renata Albrecht, M.D. 8/25/94

concurrence:
HFD-2/Lumpkin

12/26/94

Ceftibuten -- SMO Secondary Review
NDA 50-685 (capsules)

SMO Addendum to MOR

January 22, 1993

Sponsor: Schering-Plough Corporation

Date of Original NDA: December 20, 1991

Name of Drug: ceftibuten (CEDAX) capsules

Related INDs: IND IND NDA 50-686 suspension

Requested Indications:

Acute Bacterial Exacerbations of Chronic Bronchitis. Dose Regimen: 400 mg QD x 5-14 days.

Preclinical Background:

Ceftibuten is a cephalosporin for oral administration developed by the It is currently approved for marketing in seven countries for the treatment of various infections of the respiratory tract and urinary tract.

In animal and *in vitro* preclinical studies, the drug appeared to have low toxicity. The target organ after oral administration was the GI tract, with soft stools, diarrhea, edema, inflammation at doses 500 times the expected human dose mg/kg basis. No renal or hepatic toxicity was noted. Reproductive studies were negative.

Ceftibuten inhibits cell wall synthesis. It is stable against plasmid and chromosomal beta-lactamases of many species (except *Moraxella, Citrobacter, Enterobacter, Bacteroides fragilis).*

MIC for organisms requested in Indications:

GRAM-NEGATIVE	MIC 90 (µg/mL)
Enterobacter spp.	
Escherichia coli	
Haemophilus influenzae	
Haemophilus parainfluenzae	
Klebsiella pneumoniae	
Moraxella catarrhalis	
Proteus spp.	
GRAM-POSITIVE	
Streptococcus pneumoniae	

Proposed susceptibility cut-offs:

	Zone (mm)	MIC (µg/mL)
Susceptible		
Moderately susceptible		
Resistant		

Clinical Pharmacokinetics:
Clinical trials were conducted using 100-mg or 200-mg capsules.

Single and multiple dose pharmacokinetic studies were done using the 100-mg, 200-mg, 400-mg capsules and the suspension. The applicant reports that all formulations are bioequivalent.

After oral administration of 400 mg of ceftibuten, plasma Cmax values ranged from mcg/mL, and half-life was calculated between hours. (In glancing across all studies, the mean Cmax's appear to be near mcg/mL and the mean half-lives hover around 2.5 hours.)

COMMENT: However, the great variability in results was commented upon by the Division of Biopharmaceutics, and has been referred back to the applicant for an explanation. Final conclusions are pending.

The applicant reports bioavailability of %. In a radiolabeled study, 56% of radioactivity was recovered in urine, 39% in feces. Excretion is delayed in patients with renal failure. Hepatic failure does not affect elimination.

COMMENT: The original application requested approval for 400-mg capsule formulation.

CLINICAL STUDY RESULTS:

The applicant and then the reviewer examined patient records to confirm the actual diagnosis: bronchitis acute exacerbation of chronic bronchitis

The original protocol(s) for the study of proposed to make the final assessment at the completion of therapy. The applicant was informed, and acknowledged in the end-of-Phase II meeting minutes, that a 1-2 week post-treatment follow-up was necessary to evaluate outcome of therapy in these patients.

In all protocols, patients with bronchitis were enrolled. The dosage regimens were to be 400 mg QD and 200 mg BID, respectively. For the purposes of this summary,

only the results of the bronchitis studies are presented.

Four groups of patients are summarized below:

1) Protocol C88-044: domestic, multicenter, randomized trial of patients with bronchitis who were treated with ceftibuten mg capsules. For bronchitis, the dose was 400 mg QD The comparator was cefaclor 250 mg TID for bronchitis (500 mg TID for pneumonia). Treatment was for 5-14 days.

Criteria for efficacy and safety evaluation:
Patients had baseline clinical and bacteriological evaluation, including assessment of cough, sputum, dyspnea, cyanosis, rales/rhonchi; an adequate gram stain had to be recorded (predominant organism, >25 WBC, <10 epithelial cells per LPF). Chest x-ray was requested but not required for diagnosis of bronchitis. Isolates from sputum culture were tested for susceptibility. Patients were re-evaluated at the end of treatment (EOT) and again at the 7-14 day post treatment follow-up (FU).

COMMENT: While the applicant considered the results from the EOT assessment as primary evidence in evaluating the efficacy of ceftibuten, the MO considered a patient evaluable for efficacy if the patient had a FU assessment documented between ≥4 days and 3 weeks for AECB and between ≥4 days and 4 weeks for acute bacterial bronchitis after the end of treatment. Several subgroups were examined, as defined below.

The review of the NDA was hampered and delayed because of errors and inconsistencies in the paper and the electronic data base, and missing information mainly located in the comments pages of the actual case report forms. The MO requested corrections and clarification of the data. The MO's analysis reflects the information from the complete, updated and corrected data base. The applicant's results are taken from the NDA.

Definitions:

The APPLICANT analyzed five subsets (intent to treat, modified intent to treat, clinical efficacy, valid, supportive).

The MO defined the three efficacy populations below, and examined each. Regulatory decisions were made on the "Clinical Test-of-Cure" population.

"CLINICAL EFFICACY" population: to be included in this category, the patient had to have signs and symptoms of bronchitis, an acceptable sputum gram stain, received 5-14 days of therapy, and have an evaluation at the end of treatment. (For this group, a positive bacterial culture and/or a post-treatment follow-up were not required.)

"CLINICAL TEST-OF-CURE" population: a patient had to have all the criteria as defined under Clinical Efficacy, above. In addition, the patient had to have a post-treatment follow-up evaluation between ≥4 days and 3 weeks for AECB and between ≥4 days and 4 weeks for acute bacterial bronchitis after the completion of therapy.

"VALID EFFICACY" population: a patient had to have all the criteria of Clinical Test-of-Cure and have a valid sputum culture, with the isolation of a "pathogen": *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Klebsiella pneumoniae.*

A total of 30 investigators enrolled 408 patients.

The applicant reported that 351 patients had bronchitis, 239 were randomized to the 400 mg QD ceftibuten regimen and 112 received cefaclor 250 mg TID. Clinical outcome at the EOT was reported as favorable in 165/190 (87%) of ceftibuten patients and 67/78 (86%) of cefaclor patients [95% C.I. = (-0.08, +0.10)]. The analysis of patients at the post-treatment follow-up did not include patients considered failures at EOT, and is not presented here.

The MO identified 348 patients with bronchitis. The breakdown by specific diagnosis, dose regimen, and outcome is presented in the table below:

	Secondary Bacterial Infections of Acute Bronchitis		Acute Exacerbation of Chronic Bronchitis	
	ceftibuten	cefaclor	ceftibuten	cefaclor
Parameter	400 mg QD	250 mg TID	400 mg QD	250 mg TID
Enrolled	107	50	128	63
Clinical efficacy	57/78 (73%)	27/31 (87%)	68/90 (76%)	27/35 (77%)
Clinical Test-of-Cure	33/55 (60%) 95% C.I. = (-0.45, +0.07)	15/19 (79%)	35/59 (59%) 95% C.I. = (-0.31, +0.19)	17/26 (65%)
Valid Efficacy	12/14 (86%)	4/4 (100%)	17/26 (65%)	9/13 (69%)
Eradication rates for individual pathogens				
Haemophilus influenzae	*7/8*	*3/3*	*10/14*	*3/6*
Haemophilus parainfluenzae	*2/2*	*1/1*	*7/7*	*2/2*
Moraxella catarrhalis	*2/3*	-	*3/5*	*2/2*
Streptococcus pneumoniae	*1/1*	-	*3/3*	*4/4*
Klebsiella pneumoniae	*1/1*	-	*2/2*	*1/1*
TOTAL	13/15 (87%)	4/4 (100%)	25/31 (81%)	12/15 (79%)

When the patient numbers are pooled, the following results are seen:

Clinical Efficacy All Bronchitis Patients	ceftibuten 125/168 (74%) 95% C.I. = (-0.19, +0.04)	cefaclor 54/66 (82%)
Clinical Test of Cure All Bronchitis Patients	ceftibuten 68/114 (60%) 95% C.I. = (-0.27, +0.05)	cefaclor 32/45 (71%)

An analysis of drug related adverse clinical events and changes in laboratory determinations showed: six ceftibuten and three cefaclor patients died; 9 ceftibuten and 6 cefaclor patients discontinued therapy due to adverse events; 64/229 (28%) ceftibuten and 23/102 (23%) cefaclor patients experienced at least one adverse event. In the ceftibuten arm, headaches, somnolence, nausea, vomiting and diarrhea each occurred in at least 1% of patients. Laboratory tests were unremarkable, but a handful of patients had urinary WBC, RBC and protein detected (in both arms[1].

2) Protocols I88-111, I-88-217, I88-327: these multicenter international studies followed the same protocol and analyzed results using the same criteria as the C88-044 domestic clinical trial.

A total of 23 investigators enrolled 399 patients.

The applicant reported that 268 patients had bronchitis, 182 were randomized to the 400 mg QD ceftibuten regimen and 86 received cefaclor 250 mg TID. Clinical outcome at the EOT was reported as favorable in 150/169 (89%) of ceftibuten patients and 76/79 (96%) of cefaclor patients. The analysis of patients at the post-treatment follow-up did not include patients considered failures at EOT, and is not presented here.

The MO identified 261 patients with bronchitis. The breakdown by specific diagnosis, dose regimen, and outcome is presented in the table below:

	Secondary Bacterial Infections of Acute Bronchitis		Acute Exacerbation of Chronic Bronchitis	
	ceftibuten	cefaclor	ceftibuten	cefaclor
Parameter	400 mg QD	250 mg TID	400 mg QD	250 mg TID
Enrolled	86	35	90	51
Clinical efficacy	73/80 (91%)	31/32 (97%)	70/86 (81%)	39/48 (81%)
Clinical Test-of-Cure	29/37 (78%)	8/10 (80%)	27/51 (53%)	15/28 (54%)
	95% C.I. = (-0.36, +0.33)		95% C.I. = (-0.26, +0.25)	
Valid Efficacy	16/21 (76%)	5/7 (71%)	20/39 (51%)	9/18 (50%)
Eradication rates for individual pathogens				
Haemophilus influenzae	*11/12*	-	*12/17*	*7/10*
Haemophilus parainfluenzae	*1/1*	-	*3/3*	*2/4*
Moraxella catarrhalis	*2/2*	-	*4/5*	*1/2*
Streptococcus pneumoniae	*2/5*	*4/6*	*8/16*	*3/5*
Klebsiella pneumoniae	*1/1*	*1/1*	*3/4*	-
TOTAL	17/21 (81%)	5/7 (71%)	30/45 (67%)	13/21 (62%)

When the patient numbers are pooled, the following results emerge:

Clinical Efficacy All Bronchitis Patients	ceftibuten 143/166 (86%) 95% C.I. = (-0.10, +0.08)	cefaclor 70/80 (88%)
Clinical Test of Cure All Bronchitis Patients	ceftibuten 56/88 (64%) 95% C.I. = (-0.17, +0.24)	cefaclor 23/38 (61%)

An analysis of drug related adverse clinical events and changes in laboratory determinations showed: six ceftibuten and two cefaclor patients died; 2 ceftibuten and 2 cefaclor patients discontinued therapy due to adverse events; 20/177 (11%) ceftibuten and 11/88 (13%) cefaclor patients experienced at least one adverse event. In the ceftibuten arm, nausea, vomiting, diarrhea, hematuria and hypokalemia each occurred in at least 1% of patients. Laboratory tests showed elevated creatinine, and a handful of patients had urinary WBC, RBC and protein detected (in both arms).

COMMENTS:

In the treatment of patients with of acute bronchitis (acute bacterial bronchitis), ceftibuten did not meet the lower limit of the 95% confidence interval in either the domestic study of in the international study.

In the treatment of acute exacerbation of chronic bronchitis, ceftibuten did not meet the lower limit of the 95% confidence interval in either the domestic study of in the international study.

Thus, the data were examined in another way. The results for patients with

These are presented below:

	ceftibuten 400 mg QD	cefaclor 250 mg TID
Acute Exacerbation of Chronic Bronchitis	62/110 (56%) 95% C.I. = (-0.20, +0.15)	32/54 (59%)

From these results, it is evident that the group does not meet the lower limit of the 95% C.I., while the acute exacerbation of chronic bronchitis group does meet the lower limit.

Therefore, the data on patients with AECB treated with the 200 mg BID ceftibuten regimen were examined to determine whether they could serve as the "second" confirmatory study. (See below.)

3) Protocols C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, I87-325, I88-230: these multicenter international studies followed the same protocol and results analyzed using the same criteria as the C88-044 domestic clinical trial. For the reasons noted above, only information on patients with a diagnosis of acute exacerbation of chronic bronchitis who received either ceftibuten 200 mg BID or cefaclor 250 mg or 500 mg TID were evaluated.

	Acute Exacerbation of Chronic Bronchitis		
Parameter	ceftibuten 200 mg BID	cefaclor 250/500 mg TID	
Enrolled	86	76	
Clinical efficacy	74	67	(success rates not calculated)
Clinical Test-of-Cure	17/39 (44%) 95% C.I. = (-0.39, +0.09)	24/41 (59%)	
Valid Efficacy	24	26	(success rates not calculated)
Eradication rates for individual pathogens			
Haemophilus influenzae	8/10	4/10	
Haemophilus parainfluenzae	4/5	3/7	
Moraxella catarrhalis	4/6	3/6	
Streptococcus pneumoniae	2/6	3/3	
Klebsiella pneumoniae	1/1	1/1	
TOTAL	19/28 (68%)	16/27 (59%)	

COMMENT: The applicant considered that the data from patients should be considered

supportive for the bronchitis indication, even though patients received a different dose
The MO examined whether the study results as presented by the sponsor met the 95% C.I. limit. As seen below, the applicant's analysis does not pass, therefore an independent MO review was not considered warranted.

4) All Protocols: all patients with the diagnosis of who received treatment with either ceftibuten 200 mg BID or cefaclor 500 mg TID were included in the analysis. The results provided below are based on the applicant's analysis of their data.

Parameter (per applicant)	ceftibuten 200 mg BID	cefaclor 500 mg TID	
Valid - End of Therapy	85/95 (89%)	59/64 (92%)	95% C.I. = (-0.13, +0.08) (uncorrected = (-0.12, +0.06))
Valid - at Follow-up	41/56 (73%)	36/43 (84%)	95% C.I. = (-0.27, +0.06)

SUMMARY AND CONCLUSIONS

From the above series of results and explanations, it can be seen that the applicant has failed to provide two adequate and well-controlled clinical trials upon which the indication of bronchitis could be approved. In fact, both clinically and statistically, there appears to be evidence that the ceftibuten 400 mg QD regimen is not as good as the cefaclor 250 mg TID regimen in the treatment of bronchitis. The weakest link appears to be the activity against *Streptococcus pneumoniae*.

The applicant conducted several trials at domestic and foreign centers. All sites used the 400 mg QD regimen.

Patients with including complicated recurrent uncomplicated were enrolled. The MO determined that the following groups represented separate subgroups for analysis

-- complicated (presence of anatomic normality/obstruction, indwelling catheter, functional/intrinsic renal disease, vesicoureteral reflux, renal transplant) along with uncomplicated and complicated pyelonephritis;

Study Criteria for evaluation of efficacy and safety:
Patients with signs and symptoms of documented underlying complication urinary culture positive for a pathogen with a colony count of $\geq 10^4$ CFU/mL, susceptible or moderately susceptible to ceftibuten. They were treated with a 10-14 day regimen of ceftibuten 400 mg QD or the control regimen (either TMP/SMX or quinolone, as specified under individual study summaries).

Repeat evaluations were done on therapy, at 5-9 days after the completion of therapy and again at 4-6 weeks after the completion of therapy.

Definitions:
The APPLICANT analyzed several subsets of patients (safety, modified intent-to-treat, expanded efficacy, efficacy, supportive).

The REVIEWER designated a "Valid" population, as defined below:

"VALID" population: patients with signs and symptoms of susceptible (or MS) pathogen, full course of therapy, evaluation at 5-9 days post therapy.

Patients were also evaluated at the 4-6 week follow-up and recurrence rates were assessed.

1) Protocol C87-069: domestic multicenter randomized trial comparing ceftibuten 400 mg QD to TMP/SMX 160/800 mg BID for 10-14 days.

Eight investigators enrolled 186 patients, 124 were randomized to ceftibuten and 62 to TMP/SMX.

Parameter	ceftibuten 400 mg QD	TMP/SMX 160/800 mg BID
Enrolled	124	62
APPLICANT's results at +5-+9 days:		
Clinical success	60/63 (95%) 95% C.I. = (-0.13, +0.03)	28/28 (100%)
Bacteriological eradication	63/69 (91%) 95% C.I. = (-0.15, +0.11)	29/31 (94%)
MEDICAL REVIEWER's results at +5-+9 days		
Clinical success	39/47 (83%) 95% C.I. = (-0.22, +0.21)	20/24 (83%)
Bacteriological eradication	41/47 (87%) 95% C.I. = (-0.20, +0.18)	22/25 (88%)
Eradication rates for individual pathogens		
Escherichia coli	*26/31 (84%)*	*14/15 (93%)*
Klebsiella pneumoniae	*5/5*	*5/5*
Proteus mirabilis	*1/1*	-
Proteus vulgaris	*0/1*	-
others	*10/10*	*4/6*
TOTAL	42/48 (88%)	23/26 (88%)
At 4-6 weeks post treatment°:		
Applicant Bacteriology Results	33/41 (80%)	16/17 (94%)
MO Bacteriology Results	16/30 (53%)	11/16 (69%)

*In the MO analysis, information on patients who were failures at the 5-9 days visit was carried forward into the 4-6 week tally.

Safety analysis showed that there were no deaths in this study; 4 ceftibuten and 4 TMP/SMX patients discontinued treatment due to adverse events; 22/211 (18%) ceftibuten and 12/61 (20%) TMP/SMX patients reported an adverse event. Diarrhea, nausea, vomiting, dyspepsia, headache and dizziness each were reported by at least 1% of patients.

2) Protocols 187-247, 187-326: international multicenter randomized trial comparing ceftibuten 400 mg QD to TMP/SMX 160/800 mg BID for 10-14 days.

Fifteen investigators enrolled 229 patients, 154 were randomized to ceftibuten and 75 to TMP/SMX.

Parameter	ceftibuten 400 mg QD	TMP/SMX 160/800 mg BID
Enrolled	154	75
APPLICANT's results at +5-+9 days:		
Clinical success	39/41 (95%)	19/20 (95%)
	95% C.I. = (-0.15, +0.15)	
Bacteriological eradication	37/50 (74%)	20/25 (80%)
	95% C.I. = (-0.29, +0.17)	
MEDICAL REVIEWER's results at +5-+9 days		
Clinical success	43/57 (75%)	31/39 (79%)
	95% C.I. = (-0.23, +0.15)	
Bacteriological eradication	44/60 (73%)	31/39 (80%)
	95% C.I. = (-0.25, +0.13)	
Eradication rates for individual pathogens		
Escherichia coli	*34/45 (76%)*	*24/28 (86%)*
Klebsiella pneumoniae	*5/7*	*1/?*
Proteus mirabilis	*2/2*	*1/1*
others	*3/7*	*5/7*
TOTAL	44/61 (72%)	31/38 (82%)
At 4-6 weeks post treatment*:		
Applicant Bacteriology Results	27/32 (84%)	12/15 (80%)
MO Bacteriology Results	34/55 (62%)	18/30 (60%)

*In the MO analysis, information on patients who were failures at the 5-9 days visit was carried forward into the 4-6 week tally.

Safety analysis showed that one patient died in each arm of the study; 10 ceftibuten and 5 TMP/SMX

patients discontinued treatment due to adverse events; 35/152 (23%) ceftibuten and 12/75 (15%) TMP/SMX patients reported an adverse event. Diarrhea, nausea, vomiting, abdominal pain, headache, dizziness and sweating each were reported by at least 1% of patients.

3) Protocols I87-128, I89-054, and I87-232: international multicenter randomized trial comparing ceftibuten 400 mg QD to norfloxacin 400 mg BID (I87-129, I89-054) or ofloxacin 200 mg BID (I87-232).

Fourteen investigators enrolled 217 patients, 147 were randomized to ceftibuten and 70 to quinolones.

Parameter	ceftibuten 400 mg QD	quinolone 200/400 mg BID
Enrolled	147	70
APPLICANT's results at +5-+9 days:		
Clinical success	53/53 (100%)	33/34 (97%)
	95% C.I. = (-0.05, +0.11)	
Bacteriological eradication	52/60 (87%)	35/38 (92%)
	95% C.I. = (-0.20, +0.09)	
MEDICAL REVIEWER's results at +5-+9 days		
Clinical success	60/76 (79%)	37/43 (86%)
	95% C.I. = (-0.23, +0.09)	
Bacteriological eradication	52/76 (68%)	36/43 (84%)
	95% C.I. = (-0.32, +0.02)	
Eradication rates for individual pathogens		
Escherichia coli	*35/53 (66%)*	*24/27 (89%)*
Klebsiella pneumoniae	*6/7*	*2/2*
Proteus mirabilis	*5/6*	*6/7*
Proteus vulgaris	*0/1*	-
others	*7/10*	*5/8*
TOTAL	53/77 (69%)	37/44 (84%)
At 4-6 weeks post treatment*:		
Applicant Bacteriology Results	40/46 (87%)	28/31 (90%)
MO Bacteriology Results	41/69 (59%)	27/38 (71%)

*In the MO analysis, information on patients who were failures at the 5-9 days visit was carried forward into the 4-6 week tally.

Safety analysis showed that two ceftibuten and one norfloxacin patient died in the study; 3 ceftibuten and 1 quinolone patient discontinued treatment due to adverse events; 25/147 (17%) ceftibuten and 4/70 (6%) of quinolone patients reported an adverse event. Gastrointestinal events were commonly reported in the ceftibuten arm. The actual table of adverse events from the MOR is included below:

All Adverse Clinical AE's by Severity
Protocols I87-128, I89-054, and I87-232 (According to applicant)

Clinical AE's	Ceftibuten (N=147) Mild	Mod	Severe	TOTAL	(%N)	Quinolone (N=70) Mild	Mod	Severe	TOTAL	(%N)
AT LEAST ONE AE				25	(17)				4	(6)
Gastrointestinal	7	10	2	18	(12)	2	0	1	3	(4)
Abdominal pain	4	1	-	5	(3)	-	-	-	0	
Diarrhea	-	5	1	6	(4)	-	-	-	0	
Dyspepsia	2	3	-	5	(3)	2	-	-	2	(3)
Loose stools	1	-	-	1	(<1)	-	-	-	0	
Nausea	-	2	-	2	(1)	-	-	-	0	
Vomiting	-	2	1	3	(2)	-	-	1	1	(1)
Neurologic	0	2	1	2	(1)	1	0	0	1	(1)
Headache	-	2	1	2	(1)	1	-	-	1	(1)
Tinnitus	-	-	-	0		1	-	-	1	(1)
Vertigo	-	-	-	0		1	-	-	1	(1)
Hypersensitivity	3	1	1	5	(3)	0	0	0	0	
Allergy	-	1	-	1	(<1)	-	-	-	0	
Pruritus	2	-	1	3	(2)	-	-	-	0	
Urticaria	1	-	-	1	(<1)	-	-	-	0	
Miscellaneous	0	0	0	0		1	0	1	2	(3)
Asthenia	-	-	-	0		1	-	1	2	(3)

4) Protocol C88-081: domestic multicenter noncomparative trial in which all patients received ceftibuten 400 mg QD for 10-14 days.

Three centers enrolled 92 patients. The sponsor considered 68 evaluable and reported that 64/68 (92%) had a bacteriological success. The MO calculated the following results for bacteriological outcomes:

Escherichia coli *51/54 (94%*

There were no deaths in this study, 6 patients discontinued because of adverse events and 26/91 (29%) of patients reported adverse events.

SUMMARY AND CONCLUSIONS

In all, four studies are summarized. In the first two, ceftibuten was compared to TMP/SMX, in the third ceftibuten was compared to quinolones; the majority of patients had complicated
The fourth study was noncomparative and enrolled mainly patients with cystitis.

The first two studies suggest that ceftibuten may be comparable to TMP/SMX, but the results do not reach statistical significance. If the two are pooled (meta-analysis), then the calculated outcomes are 85/107 (79%) and 53/64 (83%), the confidence interval is (-0.15, +0.09), and this might serve as one study. However, a second corroborative study is needed.

The third study, using quinolones as a control, might serve this purpose. However, the eradication rates with ceftibuten are lower. In the past, drugs with lower efficacy have been approved if it could be demonstrated that they offered a balancing advantage, e.g., a better safety profile. When the safety results were examined, in fact, ceftibuten patients reported overall more adverse events than the quinolone patients. In addition, the Division of Epidemiology was consulted and asked to provide safety profiles of marketed oral quinolones (ciprofloxacin, ofloxacin, norfloxacin) and "2nd","3rd" generation oral cephalosporins (cefaclor, cefuroxime axetil, cefixime) for the past five years. This revealed that quinolones had overall slightly fewer adverse events reported than the cephalosporins. In the quinolone groups, most events were CNS events; in the cephalosporin groups, most events were gastrointestinal, including diarrhea and pseudomembranous colitis. The consult cautioned against too much interpretation of the results from the Reporting System Database, but did state, "We do not believe that these data can be used to conclude that the cephalosporins are safer as a class than are quinolones."

The fourth noncomparative trial suggests that ceftibuten 400 mg QD may be effective in cystitis, but a corroborative, controlled trial is not available.

The results of the pediatric trial of UTI were not reviewed since it was considered very tenuous to extrapolate to a) a different population, b) receiving a different formulation and c) a different dose. To designate the pediatric trial as the second study, recognizing all the reservations noted above, would seem imprudent.

RECOMMENDATIONS:

A non-approval letter should be issued.

1) The sponsor might consider testing alternative regimens in the treatment of bronchitis, particularly in patients with *Streptococcus pneumoniae*.

2) It is possible that may be adequately treated with the 400 mg QD regimen, but a corroborative trial would need to be submitted to determine this. The efficacy in particularly those caused by *Escherichia coli* is disappointing; a different dosing regimen may need to be tested.

cc: orig NDA
HFD-520
HFD-520/CSO/DeBellas
HFD-520/MO/Leissa
HFD-520/SMO/Albrecht
HFD-520/Pharm/Buko
HFD-520/Micro/Dionne

Renata Albrecht, M.D.

concurrence:
HFD-520/DivDir/Lumpkin

9/19/93

MEDICAL OFFICER'S REVIEW

SEE VOLUME III

SAFETY UPDATE

SEE MEDICAL OFFICER'S REVIEW

[redacted]

MEDICAL OFFICER'S REVIEW OF NDA 50-685

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DATE APPLICATION SUBMITTED: December 20, 1991
DATE APPLICATION RECEIVED IN AGENCY: December 23, 1991
DATE REVIEW STARTED: January 2, 1992
DATE REVIEW COMPLETED: February 2, 1993

MATERIAL REVIEWED:
1) Original 300 volume submission dated December 20, 1991.
2) Amendments (including faxes and diskettes containing electronic data): 1/7/92, 1/8/92, 1/15/92, 1/16/92, 1/16/92, 1/27/92, 1/28/92, 1/29/92 x 2, 2/6/92, 2/11/92, 2/10/92, 2/12/92, 2/13/92, 3/3/92, 3/5/92, 3/12/92, 3/25/92, 3/26/92, 3/30/92, 4/1/92, 4/6/92, 4/16/92, 4/22/92, 4/27/92 x 2, 4/28/92, 5/4/92, 5/18/92, 5/21/92, 5/22/92, 5/29/92, 6/2/92, 6/3/92 x 2, 6/23/92, 6/26/92, 6/30/92, 7/1/92, 6/30/92, 7/8/92, 7/8/92, 7/16/92 x 2, 7/17/92, 7/20/92, 7/23/92, 7/24/92, 7/29/92, 7/31/92, 8/4/92, 8/11/92, 8/14/92, 8/19/92, 8/21/92, 8/25/92, 8/26/92, 8/27/92, 8/31/92, 9/2/92, 9/9/92, 9/10/92 x 2, 9/11/92, 9/16/92, 9/17/92, 9/18/92 x 2, 9/24/92, 9/25/92, 9/30/92, 10/2/92 x 2, 10/4/92, 10/8/92, 10/13/92, 10/23/92, 10/27/92, 10/30/92, 11/6/92, 11/18/92, 1/7/93, 1/12/93, 1/13/93.

MEETINGS WITH APPLICANT: 2/4/92 and 6/15/92.

APPLICANT: Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
(908) 298-2793

I. GENERAL INFORMATION:

GENERIC DRUG NAME: Ceftibuten

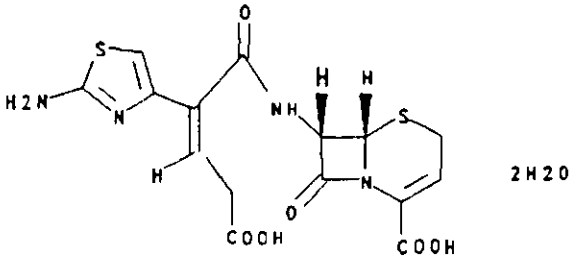
TRADE DRUG NAME REQUESTED: CEDAX®

CODE NAME: 7432-S; SCH 39720

DRUG CLASSIFICATION: 1-S

CHEMICAL NAME: (+)-(6R,7R)-7-[(Z)-2-(2-Amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo [4.2.0.] oct-2-ene-2-carboxylic acid, dihydrate

CHEMICAL STRUCTURE:



MOLECULAR FORMULA: $C_{15}H_{14}N_4O_6S_2 \bullet 2H_2O$

MOLECULAR WEIGHT: 446.43

U.S. PATENT No: 4,634,697 (expiration date, January 6, 2004)

ROUTE OF ADMINISTRATION: Oral

DOSAGE FORM: 400 mg capsule

> ***Medical Officer's Comment:*** In the original NDA submission, the applicant requested approval for ceftibuten dosage form 400 mg capsules. On September 24, 1992, the applicant submitted an amendment to the NDA containing revised proposed labeling.
>
> (The applicant currently is marketing a 200 mg formulation in foreign countries.)

RELATED IND's/NDA's: IND
IND
NDA 50-686 - suspension (pending review)

PHARMACOLOGIC CATEGORY:
Ceftibuten is an oral semisynthetic cephalosporin whose chemical structure is most similar to three other cephalosporins: cefixime, ceftriaxone, and ceftazidime. (Cefixime is an oral anti-infective drug; the latter two are administered parenterally.)

Ceftibuten contains a new side chain, carboxyethylidene, which differs from the phenylglycine found in most orally absorbed cephems. This moiety is responsible for oral absorption as well as stability against β-lactamases.

PROPOSED TREATMENT INDICATIONS:

(1) **Acute Bacterial Exacerbations of Chronic Bronchitis** due to *H. influenzae*, *M. catarrhalis*, *H. parainfluenzae*, *S. pneumoniae*, and *K. pneumoniae*.

Medical Officer's Comment: In the original NDA submission, the applicant requested approval for

On September 24, 1992, the applicant submitted an amendment to the NDA containing revised proposed labeling. In this submission, the "bronchitis" indication was reworded as noted above.

Medical Officer's Comment: When the applicant originally designed their clinical studies, treatment indication was sought.

In light of this, the applicant requested approval of a bronchitis treatment indication alone

II. MANUFACTURING AND CONTROLS:

The reader is referred to the microbiologist's manufacturing and controls review.

Ceftibuten dihydrate, the drug substance, is manufactured by:

The intermediate, benzyloxycaroxamide or prenyl half ester, is manufactured by:

Manufacturing, processing, packaging, and control operations for the drug substance will be performed by:

Schering Corporation
13900 N. W. 57th Court
Miami Lakes, Florida 33014

At the time of submission of this NDA, ceftibuten had not been approved in any other country. Yet, applications had been filed with 22 countries.

Medical Officer's Comment: The MO contacted the applicant on January 6, 1993, to inquire about the current status of ceftibuten marketing applications in other countries. The following was relayed to the reviewer by FAX on January 7, 1993.

Country	Date of Approval	Dosage Forms Approved	Indications Approved
Italy	3/92	200/400 mg caps & sachets 36 mg/mL susp	LRTI: Bronchitis, Pneumonia, Bronchopneumonia URTI: Tonsillitis/Pharyngitis, Sinusitis, Otitis Media UTI: Acute/Chronic Pyelonephritis, Cystopyelitis, Cystitis, Urethritis As second choice therapy in Acute Uncomplicated GC Urethritis **Launch planned for December 1992.**
Japan	10/92	100/200 mg caps*	Bronchitis, Bronchiectasis, Secondary Infections due to Chronic LRTI, Pyelonephritis, Cystitis, Acute Prostatitis, Gonococcal Urethritis.
Argentina	11/92	200/400 mg caps 18/36 mg/mL susp	"Argentina is not allowed to file indications."
Ecuador	7/92	200/400 mg caps 18/36 mg/mL susp	URTI: Tonsillitis/Pharyngitis, Scarlet Fever, Acute Sinusitis, Otitis Media LRTI: Acute Bronchitis, Acute Pneumonia (appropriate for oral therapy) Enteritis/Gastroenteritis and UTI
Greece	12/92	200/400 mg caps 18/36 mg/mL susp	URTI: Pharyngitis/Tonsillitis, Scarlet Fever, Acute Sinusitis, Chronic Purulent Otitis Media LRTI: Acute Bronchitis and Acute Pneumonia appropriate for oral therapy UTI: Complicated and Uncomplicated
Portugal	6/92	200/400 mg caps 18/36 mg/mL susp	URTI, LRTI, and UTI
Venezuela	7/92	200/400 mg caps 18/36 mg/mL susp	URTI, LRTI, UTI, and Enteritis/Gastroenteritis

* This formulation differs from the others.

NOTE: Ceftibuten capsule, internationally, with the exception of Japan, was approved for 400 mg p.o. q.d. dosing for all indications; except pneumonia where 200 mg p.o. b.i.d. was approved instead. In general, duration of therapy was approved for 5-10 days. In Japan, 200 mg p.o. b.i.d. was approved for all LRTI's, while 100 mg p.o. b.i.d. was approved for all urologic infections. (For the suspension, 9 mg/kg/day was approved for all indications in all countries with the exception of pediatric pneumonia which was not approved.)

DRUG PRODUCT COMPOSITION:

The composition of the to be marketed ceftibuten 400 mg capsule (formula #2383; see below) is as follows (excluding branding ink):

Substance	Approx. mg/capsule
Ceftibuten dihydrate	400
Microcrystalline cellulose NF	
Sodium starch glycolate NF	
Magnesium stearate NF	
approximate fill weight	mg
Band Seal Solution	
Polysorbate 80 NF	
Gelatin NF	
approximate band seal weight	mg

FORMULATIONS USED:

During the conduct of phase 1-3 studies, numerous dosage forms and formulations were investigated. These included the following:

Dosage Form	Formula No.
100 mg/cap	**1845**
200 mg/cap	2073
	2077*
	2136
	T6X01†
300 mg/cap	1943
	2089
	2090
	2279
400 mg/cap	2382
	2383
	2395

* 2077 was identical to 2136 with the exception of no band seal being present on the former.

† This formulation was used only once in a German pharmacokinetic study.

LRTI CLINICAL STUDIES FORMULATIONS USED

STUDY	CAPSULE FORMULA #	CENTER(S)
C88044	200 MG (#2136)	1-18,21-42,44
I88111	200 MG (#2136)	1-8
I88217	100 MG (#1845) 200 MG (#2136)	1-4,19,20,23,24 5-18,21,22
I88327	200 MG (#2136)	1-7
C87001	100 MG (#1845)	1-16
I87107	100 MG (#1845)	1,3-5
I87223	100 MG (#1845)	1,2,4,6
I87233	100 MG (#1845)	2,3
I87234	100 MG (#1845)	1-4
I87236	100 MG (#1845)	1,3
I87325	100 MG (#1845)	1-7,9
I88230	200 MG (#2136)	1-5

UTI CLINICAL STUDIES FORMULATION USED

STUDY	CAPSULE FORMULA #	CENTER(S)
C87069	100 MG (#1845) 200 MG (#2136)	1-7 1-6,8-12
I87247	200 MG (#2136)	2-4
I87326	100 MG (#1845) 200 MG (#2136)	2,3,5-8,13-23 3,4,9-12,24,25
I87128	100 MG (#1845) 200 MG (#2136)	1 2,3,7
I89054	200 MG (#2136)	50-55
I87232	100 MG (#1845) 200 MG (#2136)	1-5 5
C88081	200 MG (#2136)	1,3-5

Medical Officer's Comment: A 400/mg ceftibuten capsule was not administered in any of the clinical studies.

III. PHARMACOLOGY:

The reader is referred to the pharmacologist's review.

(1) TOXICOLOGY:
In animal acute, subacute, or chronic toxicology studies, ceftibuten appeared to have a low toxicity profile. The results from these studies are summarized in the following tables.

Several animal species were studied. Each study compared ceftibuten (SCH 39720) with cefaclor and the trans isomer of ceftibuten (SCH 39720-trans). According to the applicant, as the effects of ceftibuten and the trans isomer were very similar, the results for the isomer were not discussed.

In order to better correlate animal exposure with human exposure, the following table is provided:

Relationship Between Rat and Dog Plasma Ceftibuten Concentration After Toxicology Dose Compared to a Single Ceftibuten 400 mg Dose in Humans
(According to applicant and MO)

SPECIES	DOSE (mg/kg)	MULTIPLES OF HUMAN DOSE (5.7 mg/kg)	MULTIPLES OF HUMAN DOSE (mg/m^2)‡	C_{max} ($\mu g/mL$)	MULTIPLES OF HUMAN C_{max} (15.0 $\mu g/mL$)	AUC(tf)†	MULTIPLES OF HUMAN AUC (73.74 $\mu g \cdot hr/mL$)
Man	5.7*	-	-			73.7	-
Rat	300	53	8			144.3	2.
	1000	175	28			464.5	6.
	3000	525	84			1046.0	14.
Dog	200	35	19			552.2	8.
	400	70	37			704.3	9.
	800	140	75			1379.0	18.1

* Calculation based on 400 mg ceftibuten dose and 70 kg body weight.
† Area under the plasma concentration time curve from time zero to the last evaluabl time interval; 24 hours. (Except for 300 mg/kg dose rats where (tf) = 0-8 hours.)
‡ Calculation by MO. Reference for species specific calculation in mg/m^2: *Freireich EJ, Cancer Chemother. Repts. 50: 219, 1966.*

Medical Officer's Comment: In the clinical studies, the mean weight for evaluable ceftibuten bronchitis patients was 71.6 kg (males = 75.1 kg; females = 66.2 kg). In the evaluable patients, the mean weight was 69.2 kg (males = 80.0 kg; females = 65.8 kg). Hence, on average, a dose of 5.7 mg/kg of ceftibuten was administered to patients in clinical studies.

OVERVIEW OF ORAL CEFTIBUTEN TOXICOLOGY EXPERIENCE IN ADULT ANIMALS (According to applicant and MO; see footnote)

SPECIES	N	DURATION	DOSE RANGE (mg/kg)	TIMES HUMAN DOSE in mg/kg*	TIMES HUMAN DOSE in mg/m^2* (species specific)	APPLICANT'S FINDINGS/TOXICITIES
Rat	32	Single-Dose		876-1751	140-280	LD_{50} = >10,000 mg/kg
	160	1 Mo. & 1 Mo. post-dose		53-525	8-84	Abd. distention and soft stools ≥300 mg/kg.
	180	1 Mo. & 1 Mo. post-dose		53-525	8-84	Abdominal distention and soft stools ≥300 mg/kg. Enteritis at 3000 mg/kg. Kidney: dilation of tubules (≥1000 mg/kg). Cecum: necrosis, mononuclear cell infiltration (3000 mg/kg). Colon: inflammation (3000 mg/kg).
	80	35-91 days		525	84	No enteritis. (Study conducted to investigate reproducibility of enteritis seen in initial 3-month study @ 3000 mg/kg.)
	46	5-91 days		525	84	No enteritis.
	260	6 Mo. & 1 Mo. post-dose		18-180	3-28	Soft stool and abd. distention (≥300 mg/kg); Max. no effect dose = 100 mg/kg/d
Dog	8	Single-Dose		438-876	233-466	LD_{50} = >5,000 mg/kg
	48	1 Mo. & 1 Mo. post-dose		35-140	19-75	Soft/mucous/bloody stool &/or diarrhea (800 mg/kg). Small intestine: mucosal congestion (800 mg/kg)
	48	3 Mo. & 1 Mo. post-dose		35-140	19-75	Maximal no effect dose = 400 mg/kg/d
	40	6 Mo. & 1 Mo. post-dose		26-105	14-56	None

* Calculation per MO. Assuming 70 kg human received ceftibuten 400 mg: 5.7 mg/kg. Reference for species specific calculation in mg/m^2: *Freireich EJ, Cancer Chemother. Repts. 50: 219, 1966.*

j Vancomycin HCl administered q.d. 3-6 hours following ceftibuten dose.

In addition to the experience noted above for rats and dogs, ceftibuten did not produce a marked influence on gross behavior in **mice** when administered as a single dose (≤4000 mg/kg; 700 times the human dose in mg/kg; 57 times the human dose in mg/m^2) or b.i.d. for 5 consecutive days at ≤1000 mg/kg (175 times the human dose in mg/kg; 14 times the human dose in mg/m^2). However, hypoactivity was noted at ≥600 mg/kg (105 times the human dose in mg/kg; 9 times the human dose in mg/m^2) while hypothermia and loose stools occurred at ≥2000 mg/kg (350 times the human dose in mg/kg; 28 times the human dose in mg/m^2).

When **dogs** received a single 1000 mg/kg oral dose, a few animals vomited (175 times the human dose in mg/kg; 93 times the human dose in mg/m^2). When administered 1000 mg/kg b.i.d. x 5 days (350 times the human daily dose in mg/kg; 187 times the human daily dose in mg/m^2), dogs developed vomiting, mild loose stools, and stool with mucous/blood. No changes were noted in the neuromuscular system.

No renal effects were seen in **rats** with the exception of a decrease in the urine volume following a single 1000 mg/kg dose. When ceftibuten was administered as 1000 mg/kg b.i.d x 5 days, urinary excretion of electrolytes were decreased and urinary pH was lowered.

In **dogs**, no renal effects were seen following 600 mg/kg q.d. x 6 months (105 times the human dose in mg/kg; 56 times the human dose in mg/m^2).

No hepatic effects were seen in **rats** at a dose of 200 mg/kg/d x 7 days (35 times the human dose in mg/kg; 6 times the human dose in mg/m^2). Following a single 1000 mg/kg ceftibuten dose, no liver effects were seen; including following concomitant intravenous ethanol.

Immunogenicity:
No immunogenicity was seen in mice or guinea pigs when ceftibuten was given either bound to bovine gamma globulin with aluminum hydroxide, or in Freund's complete adjuvant. In the guinea pig, the SCH 39720 hapten cross-reacted with the ceftizoxime hapten only.

Erythrocyte osmotic fragility was evaluated in rats; none was seen.

Fertility and Reproduction:
Rats received ceftibuten 500-2000 mg/kg/d p.o. during segment I. No problems were noted.

Teratology:
No teratogenic effects were seen in rats given ceftibuten 62.5-4000 mg/kg in segment II, as well as rabbits given 2.5-40 mg/kg. No perinatal or postnatal toxicities were seen in adult rats given 125-2000 mg/kg.

Mutagenicity:
Mutagenicity was not noted for reverse point mutation, forward point mutation, or chromosomal aberrations.

"Related Compounds":
At the time of manufacture, impurities and degradation products ("related compounds") in ceftibuten drug substance are typically in the range of 1.5-3% and can increase by 1% after 2 years at -20°C storage. Product formulations can degrade an additional 5-10% over recommended shelf lives at 25°C.

These related compounds under went testing from a toxicologic standpoint. These compounds, being trans form T (SCH 39720-trans), sulfoxide forms L_2 and L_3, impurity I_1, decarboxylated product N_1, intramolecular ring closure product N_2, and 3-pyrroline forms L_4 and L_5, comprise approximately 30% of the total related compounds. Another group of compounds, Group X (X_1, X_2, and X_3) had been characterized only partially at the time of the NDA submission and comprise 40-60% of the related compounds. According to the applicant, 10% of the total related compounds are "unknown."

Toxicologic studies were conducted in animals using related compounds. No remarkable effects were described.

(2) METABOLISM:
When administered orally, ceftibuten demonstrated 51% absorption in rats, 56% in mice, 80% in dogs, 21% in rabbits, and 20% in cynomolgus monkeys. According to the applicant, absorption was dose proportional at low doses but tended to decrease at high doses.

There was no evidence of drug accumulation following multiple dosing or administration of high doses in animals.

Following administration of ceftibuten to rats, dogs, and man, SCH 9720-trans was the predominant conversion product in both plasma and urine, representing 4-25% of the urinary radioactivity. (A significant proportion of isomerization appears to occur in the stomach.) Two other minor metabolites,
were detectable in urine but not in plasma.

Ceftibuten did not induce or inhibit rat hepatic microsomal drug

metabolizing enzymes.

Following administration of a ^{14}C-labeled radioactive dose to rats, total biliary radioactivity was 7.4% of the dose.

In rabbits, ceftibuten is excreted primarily by proximal tubule secretion. In dogs, it is excreted primarily by glomerular filtration.

Tissue distribution:
In rats, the highest peak radioactive concentrations were seen in the kidney. Otherwise, plasma, lung, liver, heart, spleen, and fat demonstrated significant radioactive signals as well.

Ceftibuten concentrations in rats compared plasma with inflammatory fluid and CSF. In the former, the AUC and C_{max} were 57% and 27% of that obtained in plasma, respectively. For the latter, the AUC and C_{max} were both 9-10% of that measured in plasma.

Materno-fetal effects: The highest radioactive concentration seen in the maternal rat was the kidney followed by plasma. For the fetus, maximal concentrations were noted 4 hours post-dose; all tissues were involved with the exception of the intestine.

In the rat, radioactive milk concentrations peaked at 2 hours post-dose.

Plasma protein binding: Ceftibuten was <40% bound to the plasma proteins of mice, rats, and dogs. For monkey and man, per cent protein bindings were 55-80% and 60-64%, respectively.

The applicant states that pharmacokinetically the dog was the most similar to man. Yet, per cent plasma binding was most similar between primates and man.

IV. HUMAN PHARMACOKINETICS:

The reader is referred to the pharmacokineticist's review.

Overall, 46 pharmacokinetic and bioavailability studies were performed by Schering Co.

Single-dose, multiple-dose, special populations, and distribution into other body fluids are summarized in the following tables:

> ***Medical Officer's Comment:*** In study C88-058-01 (see below), the half-life values for ceftibuten ranged from 1.9 to 17.7 hours. Dr. Samara, the reviewing pharmacokineticist, has requested that the applicant explain this large discrepancy. In addition, according to Dr. Samara, mean plasma ceftibuten C_{max} values for studies varied from 8-28 µg/mL following a single 400 mg p.o. dose.

Bioavailability: Following a single-dose of ceftibuten, the drug is reported to have a bioavailability of 75-90% without food.

Following single-dose administration of radio-labeled ceftibuten (C88-080-01), 95% of the drug was recovered in the urine and feces (56% and 39%, respectively). Using an HPLC assay, 48% of the dose was recovered in the urine as unchanged ceftibuten, 11% as trans-ceftibuten. Small amount of metabolites were detected in the plasma and urine.

The Effect of Increasing Ceftibuten Dose on Protein binding: In an *in vitro* study, per cent protein binding was assessed at different ceftibuten concentrations. Per cent protein binding in human plasma samples was unaffected between µg/mL of ceftibuten. Beyond this concentration, per cent protein binding decreased accordingly.

> ***Medical Officer's Comment:*** As stated above, human ceftibuten per cent protein binding is approximately 60-64%.

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STUDY NO.	N	DOSE (mg)	FORMULA NO.	TIME OF DOSE	C_{max} (μg/mL)	T_{max} (hr.)	AUC(I) (hr•μg /mL)‡	$t_{½}$ (hr.)	URINARY EXCRETION (% of dose)	APPLICANT'S CONCLUSIONS/ COMMENTS
SINGLE DOSE										
C90-420-01 (2-way crossover)	18	400 cap. 400 susp.	2383 -	NA - not applicable					- -	Caps. & susp. bioequiv.
C88-058-01 (3-way crossover)	15	200 2x100 200	2077 1845 2073	NA					- - -	All 3 are bioequiv. (See MO Comment)
C89-243-01 (4-way crossover)	20	400 400 400 2x200	2382 2383 2395 2136	NA					- - - -	All 4 bioequiv.
C90-875-01 (3-way crossover)	20	400 2x200 2x200	2383** 2136 2136	NA					- - -	All 3 bioequiv.
C86-063-01 (rising dose; placebo-control)	18	200 2x200 4x200	T6X01 T6X01 T6X01	NA					68 62 53	7-10% excreted as SCH39720-trans isomer in urine
MULTIPLE DOSE										
C89-039-02	12	200 bid x 4 days	2136	1st dose 5th dose 7th dose			† † †		70 73 74	Steady state seen at days 3-4
C90-885-01	12	400 qd x 7 days	2382	1st dose 5th dose 7th dose			* * *		57 57 59	Accumulation factor did not exceed 1.14

** Final production batch.
‡ Area under the plasma concentration-time curve from time zero to infinity.
† AUC (0-12 hrs.)
* AUC (0-24 hrs.)

STUDY NO.	N	DOSE (mg)	FORMULA NO.	TIME OF DOSE / STRATIFICATION	C_{max} (μg/mL)	T_{max} (hr.)	AUC(I) (hr•μg /mL)	$t_{1/2}$ (hr.)	URINARY EXCRETION (% of dose)	APPLICANT'S CONCLUSIONS
FOOD EFFECT (single dose)										
C90-228-01 (4-way crossover)	18	400	2383	W/food 30' after 60' after 10 hr fast					- - - -	Food caused a decrease in the rate of absorption.
C90-229-02 (4-way crossover)	24	400	2383	1 hr after 2 hr after 4 hr after 10 hr fast					- - - -	No effect
C90-235-01 (3-way crossover)	18	400 susp	-	high calorie/fat low cal/non-fat fasting					- - -	Food resulted in a lower C_{max} and AUC.

* AUC (0-24)

Medical Officer's Comment: According to the reviewing pharmacokineticist, Dr. Samara, following the ingestion of food within 1 hour of drug administration, this decreases the rate and extent of ceftibuten absorption.

STUDY NO.	N	DOSE (mg)	FORMULA NO.	TIME OF DOSE / STRATIFICATION	C_{max} (μg/mL)	T_{max} (hr.)	AUC(I) (hr•μg /mL)	$t_{½}$ (hr.)	URINARY EXCRETION (% of dose)	APPLICANT'S CONCLUSIONS
SPECIAL POPULATIONS										
C88-098-01 Geriatric (65-76 yo)	12	200 bid x 7 doses	2136	1st dose 5th dose 7th dose					59 70 69†	C_{max}, AUC, accum. factor higher. $t_{½}$ prolonged.
C89-038-01 Chronic Liver Dis.	12	2x200 (single -dose)	2136	NA					55	Liver disease did not affect PK. Due to decreased GFR owing to age.
C87-091-01 Chronic Renal Dis.	31	3x100 (single -dose)	1845	C_{cr} >80 mL/min C_{cr} 50-80 mL/min C_{cr} 30-49 mL/min C_{cr} 5-29 mL/min C_{cr} <5 mL/min					68 53 41 31 18	65% of plasma ceftibuten removed during hemodialysis‡
C88-118-01 Lactating women	6	200 (single -dose)	2136	NA					-	<1.0 μg/mL detected in breast milk

* AUC (0-24)
† By day 4, 51% of the administered dose was identified in the urine as trans-ceftibuten.
‡ In Dr. Samara's review, he states that only 39% of the drug was eliminated with hemodialysis.

STUDY NO.	N	DOSE (mg)	FORMULA NO.	SAMPLING	C_{max} ($\mu g/mL$)	T_{max} (hr.)	AUC(I) (hr•μg /mL)	$t_{1/2}$ (hr.)	URINARY EXCRETION (% of lose)	APPLICANT'S CONCLUSIONS/ COMMENTS
BODY FLUID/TISSUE PENETRATION										
C90-070-01 (Blister fluid)	11	2x200 qd x 3 days	2136	Plasma Infl. fld.					- -	Ceftibuten penetrates into inflamm. fluid
C88-044-04 **C88-044-07** (Pts. w/LRTI)	12	2x200 qd or 200 bid	2136	Plasma Sputum					- -	Sputum level approx. 5% of plasma
C90-637-01 (Pts. w/trach)	12	2x200	2136	Plasma Sputum					- -	Sputum level approx. 8% of plasma

* AUC(tf)

In addition to the studies noted above, for study **C89-151-01**, ceftibuten 400 mg was administered as a single-dose to 15 patients with "pulmonary" conditions. Bronchial secretions, lung tissue, and plasma concentrations were assessed. According to the applicant, the mean concentrations in epithelial lining fluid and bronchial mucosa were 15% and 37%, respectively, of the plasma concentrations. However, these results were highly variable between patients.

Urinary Ceftibuten Pharmacokinetics:
According to data submitted in the NDA, ceftibuten urinary pharmacokinetic data are as follows:

Mean Urinary Concentrations (µg/mL) of Ceftibuten after a Single 400-mg Oral Dose (N=12)

Hours after Dosing	Concentration (µg/mL)
Pre	0.0
0-4	264.4
4-8	211.5
8-12	34.0
12-16	24.4
16-20	30.1
20-24	10.5

Drug Interactions:
The effect of ceftibuten on theophylline pharmacokinetics in 12 subjects was studied in **C88-119-01**. Ceftibuten, 200 mg b.i.d. x 7 days, was administered. A 15 minute infusion of theophylline was given at ceftibuten steady state. The applicant concluded that ceftibuten did not affect theophylline pharmacokinetics.

Co-administration with Mylanta® did not affect ceftibuten bioavailability. Ranitidine did not change ceftibuten's C_{max}, while the AUC increased by 15%.

> ***Medical Officer's Comment:*** The applicant contends that in their clinical studies, the 200 mg b.i.d. ceftibuten experience should be considered supportive of their 400 mg q.d. results. From pharmacokinetic studies C89-039-02 and C90-885-01 (see above), the extrapolated 24 hr. AUC for ceftibuten 200 mg b.i.d. administration was ≈110 hr•µg/mL compared to 80 hr•µg/mL for the 400 mg q.d. dosing. These 24 hr. AUC's differ significantly. A caveat to this is that, according to Dr. Samara, extreme pharmacokinetic variability existed between studies.

V. MICROBIOLOGY:

The reader is referred to the microbiologist's review.

Mechanism of Action:
Ceftibuten inhibits the growth of organisms by binding to penicillin-binding proteins (PBP's) leading to cell death through lysis. The drug has high affinity for PBP-3 in both *E. coli* and *P. vulgaris* and lower affinity for PBP-1a and -1b from *Proteus vulgaris*. High affinities were seen for PBP-2, -4, and -5 from *H. influenzae*. Ceftibuten has low affinity for PBP-2 and -3 of *S. aureus*. It has only moderate activity against strains containing SHV-4 and SHV-5.

Ceftibuten is stable in the presence of plasmid-mediated β-lactamases. It is stable against the chromosomally-mediated β-lactamases of *E. coli*, *Klebsiella spp.*, and *Haemophilus spp.* However, it is hydrolyzed by the chromosomally-mediated β-lactamases of *Moraxella spp.*, *Citrobacter spp.*, and *Enterobacter spp.* Ceftibuten is rapidly degraded by the β-lactamase of *Bacteroides fragilis* as well.

Resistance:
Ceftibuten is a weak inducer of the Class I chromosomal β-lactamases of *Enterobacter spp.*, *Serratia spp.*, and *Citrobacter spp.* The applicant postulates that resistance of clinical isolates to ceftibuten is "most likely to arise from the selection of stably-derepressed mutant strains that hyperproduce Class I β-lactamases rather than inducing the strains to produce more β-lactamase."

Miscellaneous Tests:

Inoculum effect: At 10^4 CFU/mL, MIC's were 2-fold lower than the standard inoculum of 10^5 CFU/mL. At 10^7 CFU/mL, only β-lactamase (+) strains had MIC's which increased ≥4-fold.

Media effect: When different agar media were studied, no differences in ceftibuten MIC's were observed. For all media, the MIC's were within 4-fold of the standard agar.

pH effect: When the pH of the media was changed, at pH's of 7.0 and 8.5, the MIC's were similar. However, at a pH of 5.5, they were 2 to 8-fold higher.

Serum effect: When horse serum (20-70%) was added to the media, no effect was seen on MIC results.

Bactericidal Activity:

Ampicillin-sensitive and -resistant *E. coli* strains were tested relative to ceftibuten's bactericidal activity. The MIC's and 24-hour MBC's were similar and the bactericidal activity against both *E. coli* groups were identical.

MIC's and MBC's were found to be within 2-fold of each other for *E. cloacae*, *K. oxytoca*, *M. catarrhalis*, and *H. influenzae*.

Synergism:
When ceftibuten was combined with a penem antibiotic, the effects were considered additive for only 25% of *Haemophilus spp.* and *Moraxella spp.* No effects were seen for anaerobes, while they were antagonistic in 80% of *Serratia spp.* and 30% of *Citrobacter spp.* and *Enterobacter spp.* tested. Ceftibuten and the aminoglycoside isepamicin were synergistic against *Pseudomonas spp.*

Activity of SCH-39720-trans:
The trans isomer of ceftibuten was 4-8 fold less potent than ceftibuten when tested against 108 various strains, many of which produced β-lactamase. Otherwise, the spectrum of activity for the metabolite was similar to the parent compound.

Effect on Fecal Flora:
Ceftibuten was administered as either 100 mg b.i.d. x 14 days or 200 mg b.i.d. x 7 days. No effect was seen on the amount of anaerobic bacteria, fungi, staphylococci, enterococci, or pseudomonas. Susceptible aerobic bacteria decreased during dosing but returned to pre-treatment levels several days after the last dose.

SUSCEPTIBILITY:

(1) *IN VITRO*: In one study, ceftibuten susceptibility was tested against 4735 clinical isolates. Ceftibuten inhibited 92% of the 3072 Enterobacteriaceae at ≤8 μg/mL.

***IN VITRO* CEFTIBUTEN SUSCEPTIBILITIES BY ASCENDING MIC**
(According to applicant)

	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
GRAM NEGATIVE		
Proteus mirabilis		
Proteus vulgaris		
Providencia		
Neisseria		
Haemophilus influenzae		
β-lactamase (-)		
β-lactamase (+)		
Amp-R; β-lactamase (-) (7 strains)		
Haemophilus parainfluenzae		
Salmonella		
Klebsiella pneumoniae		
Shigella		
Citrobacter diversus		
Escherichia coli		
Moraxella catarrhalis		
β-lactamase (-)		
β-lactamase (+)		
Mixed population		
Serratia		
Morganella morganii		
Citrobacter freundii		
Enterobacter cloacae		
Pseudomonas		
GRAM POSITIVE		
Streptococcus pyogenes		
Streptococcus pneumoniae		
PCN-susceptible		
PCN-resistant		
Mixed population		
Enterococci		
Streptococcus agalactiae		
Staphylococci		
OBLIGATE ANAEROBES		
Various anaerobes		

* Strains known to contain chromosomal cephalosporinases that hydrolyze ceftibuten.
† Two studies in Europe demonstrated MIC_{90}'s of µg/mL.
‡ Two studies in U.S. demonstrated MIC_{90}'s of µg/mL.
** The majority of pathogens (n=543) came from a Canadian study. However, there were 3 additional studies from the U.S. with penicillin-susceptible *S. pneumoniae* whose MIC_{90}'s ranged between µg/mL

Medical Officer's Comment: Combining all *in vitro* studies, the respective weighted MIC_{50}'s and MIC_{90}'s for *S. pneumoniae* are µg/mL.

The applicant has proposed the following susceptibility breakpoints for ceftibuten:

SUSCEPTIBILITY CRITERIA	ZONE (mm) 30-μg disk	MIC (μg/mL)
Susceptible	≥21	≤8
Moderate	18-20	16
Resistant	≤17	≥32

(2) *IN VIVO*; Animal studies:

Ceftibuten was compared to cefaclor in intraperitoneal, urinary, and respiratory infections in mice. Against gram-negative pathogens, in general, ceftibuten had an ED_{50} of ≤0.1 mg/kg while this was considerably larger for cefaclor. Against *Klebsiella spp.*, the ED_{50} was 1 mg/kg for ceftibuten and 8-15 mg/kg for cefaclor. For *S. pyogenes*, ceftibuten and cefaclor were similar, while ceftibuten had less activity than cefaclor in the treatment of infections due to *S. pneumoniae*.

In septicemia models using immunocompromised mice, ceftibuten had 10-100 fold greater activity than cefaclor. In
infections, 5-7 fold greater activity than cefaclor; in
infections, 25 fold greater activity.

VI. CLINICAL STUDIES:

According to the applicant, (using revised numbers submitted as an amendment to the NDA) efficacy/safety clinical studies were conducted comprising 2327 patients who were treated and a case report form for that subject was submitted to Schering. The infections treated consisted of (the latter is an indication that the applicant is not seeking approval for at this time). Of the 2327 patients, 1646 received ceftibuten, of which, 1062 received ceftibuten 400 mg q.d., 397 received ceftibuten 200 mg b.i.d, 187 ceftibuten 300 mg b.i.d. (See following table.)

In addition, 2279 patients received ceftibuten in studies carried out by No CRF's were made available to Schering for these subjects.

According to the applicant, the total ceftibuten capsule enrollment in clinical trials at the time of this NDA submission is presented in the following table (including comparators):

> ***Medical Officer's Comment:*** The applicant submitted efficacy data to the NDA for patients from studies C87001 *et al*, C88044 *et al*, and I88230. For efficacy data was presented for C87069 *et al*, I87128 *et al*, and C88081. No sinusitis efficacy data were submitted. (See specific study reviews below for further description.)

STUDY	DRUG DOSING	PATIENTS ENROLLED
LOWER RESPIRATORY TRACT INFECTIONS		**TOTAL 1500**
C87001 *et al* (completed)	Ceftibuten 200 bid	187
	Ceftibuten 300 bid	187
	Cefaclor 250 tid	2
	Cefaclor 500 tid	169
	Augmentin® 1000 bid	13
		TOTAL 558
	Ceftibuten 400 qd	413
	Ceftibuten 200 bid	120
	Cefaclor 250 tid	193
	Cefaclor 500 tid	63
		TOTAL 789
	Ceftibuten 400 qd Ceftibuten 200 bid Ceftriazine 500 tid	
	Ceftibuten 200 bid	52
	Cefaclor 250 tid	21
	Cefaclor 500 tid	9
		TOTAL 82
	Ceftibuten 200 bid Ceftin® 250 bid Ceftin® 500 tid	
	Ceftibuten 200 bid	38
	Ceftriaxone 1 g qd	33
		TOTAL 71
	Ceftibuten 200 bid Ceftin® 500 tid	
URINARY TRACT INFECTIONS		**TOTAL 627**
C87069 *et al* (completed)	Ceftibuten 400 qd	273
	TMP/SMX 160/800 bid	138
		TOTAL 411
	Ceftibuten 400 qd	146
	Norfloxacin 400 bid	50
	Ofloxacin 200 bid	20
		TOTAL 216
C88061 (completed)	Ceftibuten 400 qd	92
SINUSITIS		**TOTAL 200**
C89135 (completed)	Ceftibuten 400 qd	117
	Augmentin® 500 tid	62
		TOTAL 179
	Ceftibuten 400 qd	21
ALL CLINICAL STUDIES		**2327**

Medical Officer's Comment: Following review of the applicant's data base, the MO found numeric discrepancies with those numbers presented by the applicant above. The numbers represented in the specific study reviews are correct.

SPECIAL NOTE:

Following submission of the NDA, the data base for the clinical studies was submitted in a computerized format. At multiple times during the review process, the MO noted discrepancies in the data. The MO informed the applicant of these problems. Multiple submissions containing "corrections" followed. In light of these changes, the applicant's recent changes to the efficacy data base are not reflected. However, the MO's data is up-to-date.

In this review, the applicant's analysis reflects the data as originally presented in the NDA and does not include the numerous "corrections." The MO believes that it is beyond reasonable expectations for the reviewer to update the sponsor's analysis of the data. The MO's analysis that follows reflects all reasonable "corrections" to the data base and serves as the basis upon which approvability of this application was made.

Pages 27-43

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N A Indication

EVALUATION OF STUDY C88044 *et al*:

Medical Officer's Comment: C88044 *et al* is differentiated in the evaluation section into two portions: C88044, the domestic study, and the 3 international studies, I88111, I88217, and I88327.

DOMESTIC STUDY C88044

Study Investigators/Centers:

C88-044-02
William Mogabgab, MD
Tulane University School of Medicine
1430 Tulane Avenue
New Orleans, LA 70112

C88-044-04
Robert E. McCabe, MD
VA Medical Center
150 Muir Road
Martinez, CA 94553

C88-044-06
Thomas M. Nolen, MD
Columbiana Clinic
200 Milner Street
Columbiana, AL 35051

C88-044-07
Richard J. Perrotta, MD
Doctor's Clinic
2300 Fifth Avenue
Vero Beach, FL 32960

C88-044-09
Galen Toews, MD
Univ. of Michigan Medical Ctr.
Dept of Internal Medicine
3916 Taubman Center
Ann Arbor, MI 48109

C88-044-10
Charles J. Schleupner, MD
Veterans Administration Medical Center
1970 Boulevard
Salem, VA 24153

C88-044-11
Jack M. Bernstein, MD
Veterans Administration Medical Center
4100 West Third Street
Dayton, OH 45428

C88-044-12
Luis E. Jauregui, MD
St. Vincent's Hospital and Medical Center
Suite 204
2213 Cherry Street
Toledo, OH 43608

C88-044-15
Johanna Goldfarb, MD
Rainbow Babies & Children's Hospital
Dept of Pediatric Pharm. & Critical Care
2101 Adelbert Road
Cleveland, OH 44106

C88-044-16
Stephen R. Jones, MD
Good Samaritan Hospital
Department of Medicine
2222 Northwest Lovejoy
Portland, OR 97210

C88-044-17
Nazir A. Memon, MD
Atlantic Pulmonary and
Critical Care Assoc.
307 White Horse Pike
Suite 7-10
Absecon, NJ 08201

C88-044-21
Kirk D. Jacobson, MD
Sacred Heart General Hospital
1255 Hilyard Street
Eugene, OR 97401

C88-044-22
Barry McLean, MD
Brookwood Internal Medicine
Suite 101
Prof. Off. Building
2018 Brookwood Medical
Center Drive
Birmingham, AL 35209

C88-044-24
C. Andrew DeAbate, MD
Medical Research Center
3655 Veterans Memorial Blvd
Metairie, LA 70002

C88-044-25
Charles Hiller, MD
Univ of Arkansas for
Medical Sciences
4301 W. Markham
Little Rock, AR 72205

C88-044-26
Fred Deiss, MD
Univ of Wyoming Family
Practice Residency at Casper
1522 East A. Street
Casper, WY 82601

C88-044-27
David J. Miller, DO
Pennsbury Prof. Center
201 Woolston Drive
Morrisville, PA 19067

C88-044-29
John H. Ahrendt, MD
Snellville Medical Group, PC
2356 Lenora Church Road
Snellville, GA 30278

C88-044-30
Mark Striebel, DO
Future Healthcare Research Ctr
3100 Olentangy River Road
Columbus, OH 43202

C88-044-31
Pierre d'Hemecourt, MD
4930 Del Ray Ave.
Suite 401
Bethesda, MD 20814

C88-044-32
Ray Brodie, MD
NCRC of Baltimore
600-A North Eutaw Street
Baltimore, MD 21201

C88-044-33
Frank Listello, MD
NCRC of Suburban Maryland
6136 Landover Road
Cheverly, MD 20785

C88-044-34
Steven Zeig, MD
NCRC of Hollywood
6714 Hollywood Blvd
Pembroke Pines, FL 33024

C88-044-35
Chaikitch Lucas, MD
NCRC of Northern Virginia
3803 Fairfax Drive
Suite 502-S
Arlington, VA 22203

C88-044-36
Robert Botti, MD
25701 N. Lakewood Blvd, #101
Euclid, Ohio 44132

C88-044-37
Bruce Berlow, MD
Sansum Medical Clinic
317 West Pueblo Street
Santa Barbara, CA 93105

C88-044-38
Sidney Friedlaender, MD
7106 NE 11th Place
Gainesville, FL 32605

C88-044-40
John Selner, MD
Allergy Respiratory Institute
of Colorado, PC
5840 E. Evans
Denver, CO 80222

C88-044-42
Michael McCarthy, MD
1130 US Highway 202 South
Bldg B
Raritan, NJ 08869

C88-044-43[1]
Sydney Harvey, PhD
Nichols Institute
Reference Laboratories
26441 Via De Anza
San Juan Capistrano, CA 92675

C88-044-44
William H. Ziering, MD
4747 N. 1st Street
Suite 177
Fresno, CA 93726

Medical Officer's Comment: None of the investigators listed above are named in the DISD's Restricted Investigator List as of January 1992.

Based on the curriculum vitae submitted, the following investigators did not have prior experience in the conduct of clinical drug trials: Berlow, Botti, Brodie, Citron, Corona, Deiss, d'Hemecourt, Listello, Lucas, Memon, Perrotta, Toews, Zeig, and Ziering. One of the investigators, Dr. Brodie, according to his curriculum vitae, is a urologist.

The following centers did not receive drug and thus did not enroll patients: 1, 3, 13, 14, 19, 20, 23, 28, and 39. The following centers received study drug but did not enroll patients: 5, 8, 18, and 41. Center 43 was the research microbiology lab used for this study. In summary, out of 44 centers, 30 enrolled patients, 4 received drug but did not enroll, 9 never received drug, and 1 was the central microbiologic lab.

[1] Central laboratory used for microbiological determinations.

ENROLLMENT & EVALUABILITY:
According to the applicant, in C88044, there were 408 patients enrolled with a (See Table 1.)

Following review of the patient profiles and submission of multiple "corrections" to the data base, the MO determined the composition of acute bacterial bronchitis and AECB patients (See Table 2.) The remaining diagnoses were either pneumonia (n=56), bronchiectasis (n=2), lung abscess (n=1), or viral bronchitis (n=1). 4 pneumonia, 1 lung abscess, and 1 viral bronchitis patient received ceftibuten 400 mg q.d. Two were originally thought to have "bronchitis," but were switched from ceftibuten 400 mg q.d. to 200 mg b.i.d. after it was determined the patients actually had pneumonia.

The MO examined the applicant's and the reviewer's evaluability for C88044 bronchitis patients. (See Tables 3-5.) According to the applicant, approximately 20% of bronchitis patients were microbiologically and clinically evaluable. For the reviewer, for the clinical test-of-cure population, 40-50% were evaluable; evaluability was lower in the cefaclor group. When microbiologically and clinically evaluable patients were examined, the "valid" population, this fell to approximately 20% overall.

Despite the existence of 30 centers in C88044, Center 4, Dr. McCabe, represented 37/159 (23%) of the reviewer's clinical test-of-cure bronchitis patients.

Table 1
Summary of Evaluability, Dosing Regimens, and Underlying (C88044)
(According to applicant)

	Bronchitis/Tracheitis		Pneumonia/Bronchiectasis		
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID	Ceftibuten 200 mg BID	Cefaclor 500 mg TID	Total
Enrolled	**239**	**112**	**36†**	**21**	**408**
Excluded	3	2	0	0	5
Safety	236	110	36†	21	403
Clinical efficacy	190	78	-	-	268
Modified intent-to-treat	5	3	1†	-	9
Expanded efficacy	14	3	1	3	21
Supportive	8	0	1	0	1
Valid	51	22	10	7	90

† Includes a patient with a lung abscess who received ceftibuten 400 mg QD

Table 2
Summary of Evaluability, Dosing Regimens, for Type of Bronchitis (C88044)
(According to reviewer)

	Acute bacterial bronchitis		AECB		
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID	Ceftibuten 400 mg QD	Cefaclor 250 mg TID	Total
Enrolled	**107***	**50****	**128†**	**63‡**	**348**
Excluded	4	3	2	4	13
Safety	103*	47**	126†	59	335
Clinical efficacy	78	31	90†	35	234
Clinical test-of-cure	55	19	59†	26	159
Valid	14	4	26†	13	57

* Includes 3 who received ceftibuten 200 mg b.i.d., and 2 who received ceftibuten 200 mg q.d.
** Includes 1 who received cefaclor 250 mg b.i.d., and 1 who received cefaclor 500 mg t.i.d.
† Includes 1 who received ceftibuten 200 mg b.i.d.
‡ Includes 2 who received cefaclor 250 mg b.i.d.
NOTE: 2 patients, not included in this table, received ceftibuten 400 mg q.d.; both were included in the reviewer's safety population; C8804411103 had a lung abscess and C8804430105 had viral bronchitis.

Medical Officer's Comment: In the reviewer's classification of all LRTI patients, the reviewer reclassified "tracheitis" patients (n=5) as either acute bacterial bronchitis (n=4) or AECB (n=1) patients. The MO loosely equates these patients with "tracheobronchitis," not with acute bacterial tracheitis, as this usually involves very ill patients.

Medical Officer's Comment: The two major reasons for there being fewer patients in the reviewer's valid population compared with the applicant is that the MO limited "pathogens" to *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *K. pneumoniae*, and *H. parainfluenzae*, and patients in this

group were required to have a follow-up assessment on day +4 or later.

The MO excluded from clinical evaluation those patients the reviewer could identify who had inappropriate baseline sputa containing either fewer than 25 WBC/LPF (including investigators' reports of "rare" or "few" WBC's), many epithelial cells, or it wasn't done. There were 39 patients identified. (See below.) These consisted of 13 cefaclor and 26 ceftibuten patients; 13 acute bacterial bronchitis and 26 AECB patients.

center 04: 101,107,108,111,142
center 07: 102
center 12: 107
center 15: 108
center 17: 111,121,123
center 24: 102,105,107,108,112,113,114,115,117,
118,119,120,123,124,126,127,128,130
center 34: 102
center 44: 105,106,107,108,111,114,117,118,119

Table 3
Investigator/Drug Enrollment and Evaluability for Valid Bronchitis/Tracheitis Patients Who Received Either Ceftibuten 400 mg q.d., Ceftibuten 200 mg b.i.d., or Cefaclor 250 mg t.i.d.
(According to applicant)

		No. Clin. Eval./No. Enrolled (% Clin. Eval.)					
		Ceftibuten 400 mg qd		Cefaclor 250 mg tid		Combined	
C88-044-02	Mogabgab	1/1	(100)	0/1	(0)	1/2	(50)
C88-044-04	McCabe	20/42	(48)	7/21	(33)	27/63	(43)
C88-044-06	Nolen	2/8	(25)	3/4	(75)	5/12	(42)
C88-044-07	Perrotta	6/19	(32)	3/10	(30)	9/29	(31)
C88-044-09	Toews	2/9	(22)	0/4	(0)	2/13	(15)
C88-044-10	Schleupner	0/3	(0)	0/1	(0)	0/4	(0)
C88-044-11	Bernstein	1/2	(50)	1/1	(100)	2/3	(67)
C88-044-12	Jauregui	2/5	(40)	0/2	(0)	2/7	(29)
C88-044-15	Goldfarb	1/6	(17)	1/3	(33)	2/9	(22)
C88-044-16	Jones	0/1	(0)	0		0/1	(0)
C88-044-17	Memon	0/14	(0)	0/7	(0)	0/21	(0)
C88-044-21	Jacobson	5/8	(63)	4/4	(100)	9/12	(75)
C88-044-22	McLean	1/1	(100)	0		1/1	(100)
C88-044-24	DeAbate	3/20	(15)	1/10	(10)	4/30	(13)
C88-044-25	Hiller	0/9	(0)	0/3	(0)	0/12	(0)
C88-044-26	Deiss	1/2	(50)	0		1/2	(50)
C88-044-27	Miller	0/12	(0)	1/5	(20)	1/17	(6)
C88-044-29	Ahrendt	1/7	(14)	1/3	(33)	1/10	(10)
C88-044-30	Striebel	0/3	(0)	0/2	(0)	0/5	(0)
C88-044-31	d'Hemecourt	0/5	(0)	0/3	(0)	0/8	(0)
C88-044-32	Brodie	1/5	(20)	0/2	(0)	1/7	(14)
C88-044-33	Listello	0/1	(0)	0		0/1	(0)
C88-044-34	Zeig	1/17	(6)	0/9	(0)	1/26	(4)
C88-044-35	Lucas	0/6	(0)	0/2	(0)	0/8	(0)
C88-044-36	Botti	1/1	(100)	0		1/1	(100)
C88-044-37	Berlow	0/1	(0)	0		0/1	(0)
C88-044-38	Friedlaender	0/13	(0)	0/6	(0)	0/19	(0)
C88-044-40	Selner	1/2	(50)	0/1	(0)	1/3	(33)
C88-044-42	McCarthy	1/3	(33)	0/1	(0)	1/4	(25)
C88-044-44	Ziering	0/13	(0)	0/7	(0)	0/20	(0)
Total		**51/239**	**(21)**	**22/112**	**(20)**	**73/351**	**(21)**

Table 4
Investigator/Center Drug Enrollment for Clinical Test-of-Cure Bronchitis Patients Who Received Either Ceftibuten 400 mg q.d., Ceftibuten 200 mg b.i.d., or Cefaclor 250 mg t.i.d.
(According to reviewer)

		No. Clin. T-O-C/No. Enrolled (%Evaluable)		
		Ceftibuten 400 mg qd	Cefaclor 250 mg tid	Combined
ACUTE BACTERIAL BRONCHITIS				
C88-044-02	Mogabgab	0	0/1 (0)	0/1 (0)
C88-044-04	McCabe	5/10 (50)	1/1 (100)	6/11 (55)
C88-044-06	Nolen	3/5 (60)	0/1 (0)	3/6 (50)
C88-044-07	Perrotta	3/8 (38)	4/7 (57)	7/15 (47)
C88-044-09	Toews	3/3 (100)	0/1 (0)	3/4 (75)
C88-044-10	Schleupner	0	0/1 (0)	0/1 (0)
C88-044-11	Bernstein	0/1 (0)	0	0/1 (0)
C88-044-12	Jauregui	2/4 (50)	1/2 (50)	3/6 (50)
C88-044-15	Goldfarb	1/5 (20)	0/1 (0)	1/6 (17)
C88-044-16	Jones	0/1 (0)	0	0/1 (0)
C88-044-17	Memon	0/2 (0)	0/1 (0)	0/3 (0)
C88-044-21	Jacobson	3/4 (75)	2/2 (100)	5/6 (83)
C88-044-22	McLean	0	0	0
C88-044-24	DeAbate	3/9 (33)	1/4 (25)	4/13 (31)
C88-044-25	Hiller	1/3 (33)	0	1/3 (33)
C88-044-26	Deiss	0/2 (0)	0	0/2 (0)
C88-044-27	Miller	4/6 (67)	1/5 (20)	5/11 (45)
C88-044-29	Ahrendt	3/3 (100)	0/1 (0)	3/4 (75)
C88-044-30	Striebel	0/2 (0)	2/2 (100)	2/4 (50)
C88-044-31	d'Hemecourt	1/1 (100)	1/2 (50)	2/3 (67)
C88-044-32	Brodie	0	0/2 (0)	0/2 (0)
C88-044-33	Listello	0	0	0
C88-044-34	Zeig	6/14 (43)	1/5 (20)	7/19 (37)
C88-044-35	Lucas	0/2 (0)	0/2 (0)	0/4 (0)
C88-044-36	Botti	0	0	0
C88-044-37	Berlow	0	0	0
C88-044-38	Friedlaender	11/12 (92)	3/5 (67)	14/17 (82)
C88-044-40	Selner	2/2 (100)	0	2/2 (100)
C88-044-42	McCarthy	3/3 (100)	1/1 (100)	4/4 (100)
C88-044-44	Ziering	1/3 (33)	1/1 (100)	2/4 (50)
Total		**55/105 (52)**	**19/48 (40)**	**74/153 (48)**

(Contd.)

Table 4 (contd.)

		No. Clin. T-O-C/No. Enrolled (%Evaluable)		
		Ceftibuten 400 mg qd	Cefaclor 250 mg tid	Combined
AECB				
C88-044-02	Mogabgab	1/1 (100)	0	1/1 (100)
C88-044-04	McCabe	20/30 (67)	11/20 (55)	31/50 (62)
C88-044-06	Nolen	1/3 (33)	1/3 (33)	2/6 (33)
C88-044-07	Perrotta	4/11 (36)	2/3 (67)	6/14 (43)
C88-044-09	Toews	1/6 (17)	0/3 (0)	1/9 (11)
C88-044-10	Schleupner	1/3 (33)	0	1/3 (33)
C88-044-11	Bernstein	0	1/1 (100)	1/1 (100)
C88-044-12	Jauregui	0/2 (0)	0	0/2 (0)
C88-044-15	Goldfarb	1/1 (100)	0/2 (0)	1/3 (33)
C88-044-16	Jones	0	0	0
C88-044-17	Memon	0/10 (0)	2/6 (33)	2/16 (13)
C88-044-21	Jacobson	4/4 (100)	2/2 (100)	6/6 (100)
C88-044-22	McLean	0/1 (0)	0	0/1 (0)
C88-044-24	DeAbate	3/11 (27)	1/6 (17)	4/17 (24)
C88-044-25	Hiller	3/6 (50)	0	3/6 (50)
C88-044-26	Deiss	0	0	0
C88-044-27	Miller	1/6 (17)	0	1/6 (17)
C88-044-29	Ahrendt	4/4 (100)	2/2 (100)	6/6 (100)
C88-044-30	Striebel	0	0	0
C88-044-31	d'Hemecourt	0/4 (0)	0/1 (0)	0/5 (0)
C88-044-32	Brodie	3/5 (60)	0	3/5 (60)
C88-044-33	Listello	1/1 (100)	0	1/1 (100)
C88-044-34	Zeig	1/3 (33)	1/4 (25)	2/7 (29)
C88-044-35	Lucas	1/4 (25)	0	1/4 (25)
C88-044-36	Botti	1/1 (100)	0	1/1 (100)
C88-044-37	Berlow	1/1 (100)	0	1/1 (100)
C88-044-38	Friedlaender	1/1 (100)	1/1 (100)	2/2 (100)
C88-044-40	Selner	0	1/1 (100)	1/1 (100)
C88-044-42	McCarthy	0	0	0
C88-044-44	Ziering	6/9 (67)	1/6 (17)	7/15 (47)
Total		59/128 (46)	26/61 (43)	85/189 (45)
GRAND TOTAL		*114/233 (49)**	*45/109 (41)*	*159/342 (46)*

* Includes 4 patients, C8804404009, a valid patient, and 3 safety patients, who received ceftibuten 200 mg b.i.d.

Table 5
Investigator/Center Drug Enrollment for Valid Bronchitis Patients Who Received Either Ceftibuten 400 mg q.d., Ceftibuten 200 mg b.i.d., or Cefaclor 250 mg t.i.d.
(According to reviewer)

		No. Valid Eff./No. Enrolled (%Evaluable)		
		Ceftibuten 400 mg qd	Cefaclor 250 mg tid	Combined
ACUTE BACTERIAL BRONCHITIS				
C88-044-02	Mogabgab	0	0/1 (0)	0/1 (0)
C88-044-04	McCabe	5/10 (50)	1/1 (100)	6/11 (55)
C88-044-06	Nolen	0/5 (0)	0/1 (0)	0/6 (0)
C88-044-07	Perrotta	0/8 (0)	0/7 (0)	0/15 (0)
C88-044-09	Toews	0/3 (0)	0/1 (0)	0/4 (0)
C88-044-10	Schleupner	0	0/1 (0)	0/1 (0)
C88-044-11	Bernstein	0/1 (0)	0	0/1 (0)
C88-044-12	Jauregui	0/4 (0)	0/2 (0)	0/6 (0)
C88-044-15	Goldfarb	0/5 (0)	0/1 (0)	0/6 (0)
C88-044-16	Jones	0/1 (0)	0	0/1 (0)
C88-044-17	Memon	0/2 (0)	0/1 (0)	0/3 (0)
C88-044-21	Jacobson	2/4 (50)	2/2 (100)	4/6 (67)
C88-044-22	McLean	0	0	0
C88-044-24	DeAbate	1/9 (11)	1/4 (25)	2/13 (15)
C88-044-25	Hiller	0/3 (0)	0	0/3 (0)
C88-044-26	Deiss	0/2 (0)	0	0/2 (0)
C88-044-27	Miller	1/6 (17)	0/5 (0)	1/11 (9)
C88-044-29	Ahrendt	2/3 (67)	0/1 (0)	2/4 (50)
C88-044-30	Striebel	0/2 (0)	0/2 (0)	0/4 (0)
C88-044-31	d'Hemecourt	0/1 (0)	0/2 (0)	0/3 (0)
C88-044-32	Brodie	0	0/2 (0)	0/2 (0)
C88-044-33	Listello	0	0	0
C88-044-34	Zeig	2/14 (14)	0/5 (0)	2/19 (11)
C88-044-35	Lucas	0/2 (0)	0/2 (0)	0/4 (0)
C88-044-36	Botti	0	0	0
C88-044-37	Berlow	0	0	0
C88-044-38	Friedlaender	0/12 (0)	0/5 (0)	0/17 (0)
C88-044-40	Selner	0/2 (0)	0	0/2 (0)
C88-044-42	McCarthy	1/3 (33)	0/1	1/4 (25)
C88-044-44	Ziering	0/4 (0)	0/1 (0)	0/4 (0)
Total		**14/105 (13)**	**4/48 (8)**	**18/153 (12)**

(Contd.)

Table 5 (contd.)

		No. Valid/No. Enrolled (%Evaluable)		
		Ceftibuten 400 mg qd	Cefaclor 250 mg tid	Combined
AECB				
C88-044-02	Mogabgab	0/1 (0)	0	0/1 (0)
C88-044-04	McCabe	14/30 (47)	7/20 (35)	20/50 (40)
C88-044-06	Nolen	0/3 (0)	1/3 (33)	1/6 (17)
C88-044-07	Perrotta	0/11 (0)	0/3 (0)	0/14 (0)
C88-044-09	Toews	1/6 (17)	0/3 (0)	1/9 (11)
C88-044-10	Schleupner	0/3 (0)	0	0/3 (0)
C88-044-11	Bernstein	0	0/1 (0)	0/1 (0)
C88-044-12	Jauregui	0/2 (0)	0	0/2 (0)
C88-044-15	Goldfarb	0/1 (0)	0/2 (0)	0/3 (0)
C88-044-16	Jones	0	0	0
C88-044-17	Memon	0/10 (0)	0/6 (0)	0/16 (0)
C88-044-21	Jacobson	4/4 (100)	2/2 (100)	6/6 (100)
C88-044-22	McLean	0/1 (0)	0	0/1 (0)
C88-044-24	DeAbate	1/11 (9)	0/6 (0)	1/17 (6)
C88-044-25	Hiller	1/6 (17)	0	1/6 (17)
C88-044-26	Deiss	0	0	0
C88-044-27	Miller	0/6 (0)	0	0/6 (0)
C88-044-29	Ahrendt	0/4 (0)	0/2 (0)	0/6 (0)
C88-044-30	Striebel	0	0	0
C88-044-31	d'Hemecourt	0/4 (0)	0/1 (0)	0/5 (0)
C88-044-32	Brodie	2/5 (40)	0	2/5 (40)
C88-044-33	Listello	0/1 (0)	0	0/1 (0)
C88-044-34	Zeig	0/3 (0)	0/4 (0)	0/7 (0)
C88-044-35	Lucas	0/4 (0)	0	0/4 (0)
C88-044-36	Botti	0/1 (0)	0	0/1 (0)
C88-044-37	Berlow	1/1 (100)	0	1/1 (100)
C88-044-38	Friedlaender	0/1 (0)	1/1 (100)	1/2 (50)
C88-044-40	Selner	0	1/1 (100)	1/1 (100)
C88-044-42	McCarthy	0	0	0
C88-044-44	Ziering	2/9 (22)	1/6 (17)	3/15 (20)
Total		**26/128 (20)**	**13/61 (21)**	**39/189 (21)**
GRAND TOTAL		***40/233 (17)***	***17/109 (16)***	***56/342 (16)***

Completion Status for Enrolled Patients:
According to the applicant, the reviewer determined the noncompletion reasons for enrolled bronchitis patients; 193/351 (55%) completed the study. (See Table 6.) Both treatment groups were equally represented. The most common reason for noncompletion cited was "did not meet entrance criteria," i.e., patient had a negative baseline culture and was subsequently withdrawn.

Table 6
Noncompletion Reasons for Bronchitis Patients (C88044)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Total # of Patients Enrolled	239	112
Completed study	134 (56)	59 (53)
D/C adverse experience	10 (4)	6 (5)
D/C concurrent illness	3 (1)	1 (<1)
D/C death	1 (<1)	1 (<1)
D/C did not meet entry criteria	68 (28)	29 (26)
D/C non-compliance	7 (3)	2 (2)
D/C pt. did not return	11 (5)	13 (12)
D/C treatment failure	5 (2)	1 (<1)

Summary of Nonevaluability:
Both the applicant and reviewer examined reasons for nonevaluability. (See Tables 7 and 8.) The applicant's primary efficacy population was their "clinical efficacy" population. In the reviewer's table, patients were excluded from the MO's clinical test-of-cure population as they were not assessed clinically beyond day +3. For the reviewer, the major reason patients were excluded from the clinical efficacy population but retained in the safety population was insufficient medication to determine a clinical response (i.e., fewer than 5 days of drug for the determination of clinical improvement, or fewer than 3 days of drug therapy if the patient had a poor response), or an inadequate baseline sputum (i.e., patient did not have the required baseline sputum of >25 WBC's and <10 epithelial cells per LPF). Proportionally more cefaclor patients had insufficient medication.

Table 7
Summary of Patient Status for Bronchitis Patients and Reasons for Exclusion from Clinical Efficacy Population (C88044)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Total # of Patients Enrolled	239	112
Safety Population	236 (99)	110 (98)
Clinical Efficacy Population	190 (80)	78 (70)
Excluded from All Populations	3 (1)	2 (2)
Never Received Medication	3 (1)	2 (2)
(No further exclusion reason)	1	0
Drop-out/lost to follow-up	1	0
No pathogen isolated pretherapy	1	2
Excluded from Clinical Efficacy Population, But Included in Safety Population	46 (19)	32 (29)
Concurrent Illness	0	1 (<1)
Drop-out/Admin. Reasons	0	1*
Did Not Meet Entrance Criteria	38 (16)	28 (25)
No pathogen isolated pretherapy	36	26
Pathogen not susceptible	2	0
Pathogen resistant to comparator	0	1
Pathogen resistant to ceftibuten	0	1
Insufficient Efficacy Data	7 (3)	2 (2)
(No further exclusion reason)	0	2
Drop-out/Admin. reasons	2	0
Drop-out/Adverse reaction	1	0
Drop-out/Death	1	0
Drop-out/Lost to follow-up	3	0
Misrandomized	1 (<1)	1 (<1)
Drop-out/Admin. reasons	1	0
No pathogen isolated pretherapy	0	1

* C8804404148, a cefaclor patient, developed a life-threatening aortic aneurysm on day 1 of therapy and was removed from the study.

Table 8
Summary of Patient Status for Bronchitis Patients and Reasons for Exclusion from Clinical Efficacy Population (C88044)
(According to reviewer)

	No. of Patients (%) Ceftibuten	Cefaclor
Total # of Patients Enrolled	235**	113[1]
Safety Population	229 (97)	106 (94)
Clinical Efficacy Population	168 (71)	66 (58)
Excluded from All Populations	6 (3)	7 (6)
Did not return after first visit	6	4
Never received medication	0	3
Excluded from Clinical T-O-C Population, But Included in Clinical Eff. Population	54 (23)	21 (19)
Excluded from Clinical Efficacy Population, But Included in Safety Population	61 (26)	40 (35)
Insufficient medication[‡]	24 (10)	19 (17)
Inadequate baseline sputum	26 (11)	12 (11)
Insufficient efficacy data (unable to assess)	3 (1)	5 (4)
Improper dosing of drug	6 (3)	3 (3)
Unacceptable concom. anti-infective Rx	1†(<1)	1‡(<1)
Active tuberculosis*	1 (<1)	0

** Includes 4 ceftibuten 200 mg b.i.d. and 1 ceftibuten 200 mg q.d. patient.
[1] Includes 3 cefaclor 250 mg b.i.d. and 1 cefaclor 500 mg t.i.d.
[‡] For example, C8804434125 took only 9 doses of cefaclor over a 6 day period. C8804406109, another cefaclor recipient who "failed," received only 7 doses (the reviewer considers this insufficient medication). Having received insufficient medicine, their responses were nonassessable.
† C8804409103 had a good clinical outcome but received ampicillin concurrently between days -6 to 5. The reviewer believes that the ampicillin could have contributed to the patient's favorable outcome and thus should not be included in the clinical efficacy population.
‡ C8804404123 TMP/SMX added on day 5 of cefaclor therapy in light of "noncompliance." The patient received 14 doses of cefaclor in 6 days. At the time cefaclor was discontinued, the investigator considered the patient improved. As the TMP/SMX may have affected the patient's outcome, this patient was considered nonevaluable by the reviewer.
* C8804411101 was recently diagnosed with tuberculosis and at the time of enrollment had just recently been started on INH and rifampin. The patient's baseline sputum did not grow a pathogen, yet the patient was a failure. The reviewer believed that the patient's poor outcome could be due to the underlying tuberculosis and thus was not included in the clinical efficacy population.

Applicant and Reviewer Evaluability Differences:
The applicant and reviewer differed with regard to the evaluability of several "valid" bronchitis patients. (See Tables 9 and 10.)

General reasons for evaluability differences include the following. Specific examples can be found in the footnotes to the tables.

1) There were numerous patients whom the applicant considered clinically evaluable whom the MO noted had either a negative or unevaluable baseline sputum Gram's stain.
2) The MO included patients who grew "intermediate" susceptibility pathogens while the applicant excluded them.
3) There were patients whom the applicant stated were unevaluable due to insufficient efficacy data where the reviewer found sufficient efficacy data following review of

the patient profiles and comment pages of the CRF.

4) There were numerous patients who were "misrandomized." However, following discussions with the applicant, it was apparent that the blind was maintained intact.
5) C8804437102 was excluded by the applicant because of "concurrent illness" when in fact the patient was a failure and progressed on to develop pneumonia.
6) C8804411101 had active tuberculosis, a likely cause for the symptoms.
7) Some individuals were excluded from the valid population due to "lack of a baseline pathogen." However, following review of the data base, it was apparent that a baseline pathogen had been present.

In general, where the reviewer changed patients from the valid to the clinical test-of-cure populations, this was due to the patient not growing a baseline "pathogen" (i.e., *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, *K. pneumoniae*, or *S. pneumoniae*). All patients reassigned to the Clin Eff population were excluded from the "valid" population in that they were not assessed beyond day +3 and had not failed prior to this visit.

Table 9
Bronchitis Patients Considered "Valid" by the Applicant and the Reviewer's Assessment of Their Evaluability (C88044)
(According to reviewer - using applicant's bronchitis diagnoses)

MO's Evaluability	Ceftibuten 400 mg QD (n=51)	Cefaclor 250 mg TID (n=22)
Valid	25	10
Clinical Test-of-Cure	10	4
Clinical Efficacy	10	5
Safety	6[A]	3[B]

A C8804404107, C8804404142, C8804412107, and C8804424107 had nonpurulent baseline sputa; C8804411101 had active tuberculosis; C8804404155 had improper dosing of the study drug.
B C8804404101 and C8804404108 had nonpurulent baseline sputa; C8804406109 only received 7 doses of cefaclor and had a poor clinical response.

Table 10
Bronchitis Patients Considered "Valid" by the Reviewer Whom the Applicant Did Not Consider Valid (C88044)
(According to reviewer - using MO's bronchitis diagnoses)

Applicant's Evaluability	Ceftibuten 400 mg QD (n=14)	Cefaclor 250 mg TID (n=7)
Supportive	1[A]	-
Expanded Efficacy	6[B]	2
Clinical Efficacy	6[C]	5[D]
Modified Intent-to-Treat	1	0

A C8804404130 was excluded by the applicant because the *H. influenzae* was "resistant" to cefaclor when it was only moderately susceptible (cefaclor zone=20mm).

B C8804437102 was excluded by the applicant because of "concurrent illness" when in fact the patient was a failure and progressed on to develop pneumonia; C8804434119 was excluded from the valid population due to "insufficient efficacy data." However, data provided showed that the patient relapsed after completing therapy.

C C8804404140 was listed as "no pretherapy pathogen." However, the baseline culture was listed as *H. parainfluenzae*. C8804404150 was listed as "no pretherapy pathogen." However, the baseline culture grew *H. influenzae* ("intermediate" susceptibility). C8804421107 was excluded by the applicant because the *H. influenzae* was "resistant" to cefaclor when it was only moderately susceptible (cefaclor zone=17mm). C8804425110 was excluded by the applicant because the *H. influenzae* was "resistant" to ceftibuten when it was only moderately susceptible (ceftibuten zone=20mm). C8804444102 was excluded by the applicant because the *S. pneumoniae* was "resistant" to ceftibuten when it was only moderately susceptible (ceftibuten zone=20mm). C8804444115 was excluded by the applicant because the patient was "misrandomized." However, following conversations with the applicant, it was apparent that the misrandomization did not break the study blind.

D C8804404129 was excluded by the applicant because the *M. catarrhalis* was "resistant" to cefaclor when it was only moderately susceptible (cefaclor zone=15mm). C8804404137 was listed as "no pretherapy pathogen." However, the baseline culture grew *H. influenzae*. C8804404158 was excluded by the applicant because the *H. influenzae* was "resistant" to cefaclor when it was only moderately susceptible (cefaclor zone=14mm). C8804444113 was excluded by the applicant because the patient was "misrandomized." (See C8804444115 above.)

Baseline Demographics:
For the **enrolled population**, using the reviewer's diagnoses, treatment groups were fairly equally matched. This also applied to the types of underlying bronchitis. (See Tables 11 and 12) However, there was a trend that within the AECB group, proportionately more cefaclor patients were hospitalized inpatients, presumably more ill.

For **clinical test-of-cure** patients, the trend was more pronounced that cefaclor patients were hospitalized inpatients more frequently than ceftibuten patients; especially for AECB patients. (See Tables 13 and 14.)

When comparing acute bacterial bronchitis and AECB patients, as would be expected the latter tended to be older. There were proportionally more males in the AECB group as well.

Medical Officer's Comment: As patients were administered 400 mg of ceftibuten p.o. q.d.; on a mg/kg basis, clinical test-of-cure patients received, on average, 5.4 mg/kg/day of ceftibuten.

Table 11
Demographic Data for All Enrolled Patients with Bronchitis* (C88044)
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten (n=235)	Cefaclor (n=113)
Sex		
Male	130 (55)	58 (51)
Female	105 (45)	55 (49)
Race		
White	180 (77)	88 (78)
Black	38 (16)	20 (18)
Other	15 (6)	5 (4)
Not recorded	2 (<1)	0
Patient Status†		
Inpatient	28 (12)	20 (18)
Outpatient	206 (88)	89 (79)
Not recorded	1 (<1)	4 (4)
Age (yr)		
Mean	49.4	50.4
Median	49.0	52.0
Range (min-max)		
Weight (kg)		
Mean	76.2	77.3
Median	74.3	74.8
Range (min-max)		
Not Recorded	2	3
Diagnosis		
Acute Bacterial Bronchitis	107 (46)	50 (44)
AECB	128 (54)	63 (56)

* This table uses the diagnoses reassigned by the reviewer.
† According to the MO, the $\chi^2 = 2.52$ with corresponding p-value >0.1

Table 12
Demographic Data for Enrolled Bronchitis Patients According to Type of Bronchitis (C88044)
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten	Cefaclor
Acute Bacterial Bronchitis	(n = 107)	(n = 50)
Sex		
Male	55 (51)	23 (46)
Female	52 (49)	27 (54)
Race		
White	83 (78)	38 (76)
Black	20 (19)	10 (20)
Other	3 (3)	2 (4)
Not recorded	1 (<1)	0
Patient Status		
Inpatient	5 (5)	2 (4)
Outpatient	102 (95)	46 (96)
Not recorded	0	2
Age (yr)		
Mean	44.1	43.1
Median	42.0	39.0
Range (min-max)		
Weight (kg)		
Mean	76.1	76.8
Median	74.1	74.6
Range (min-max)	44-127	50-137
Not Recorded	1	1
AECB	(n = 128)	(n = 63)
Sex		
Male	75 (59)	35 (56)
Female	53 (41)	28 (44)
Race		
White	97 (76)	50 (80)
Black	18 (14)	10 (16)
Other	12 (9)	3 (5)
Not recorded	1 (<1)	0
Patient Status†		
Inpatient	23 (18)	18 (29)
Outpatient	104 (82)	43 (68)
Not recorded	1 (<1)	2
Age (yr)		
Mean	53.7	56.3
Median	57.0	59.0
Range (min-max)		
Weight (kg)		
Mean	76.3	77.7
Median	74.1	75.0
Range (min-max)		
Not Recorded	1	3

† According to the MO, the $\chi^2 = 3.14$ with corresponding p-value = $0.05<p<0.1$. However, if corrected, $\chi^2 = 2.51$, p-value >0.1

Table 13
Demographic Data for "Bronchitis" Patients in the Clinical Test-of-Cure Population (C88044)
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten 400 mg QD (n=114)*	Cefaclor 250 mg TID (n=45)
Sex		
Male	61 (54)	24 (53)
Female	53 (46)	21 (47)
Race		
White	95 (83)	37 (82)
Black	11 (10)	7 (16)
Other	7 (6)	1 (2)
Not recorded	1 (<1)	0
Patient Status†		
Inpatient	13 (11)	11 (24)
Outpatient	101 (89)	34 (76)
Age (yr)		
Mean	48.2	51.0
Median	49.0	52.0
Range (min-max)		
Weight (kg)		
Mean	73.9	79.5
Median	72.7	76.8
Range (min-max)		
Not Recorded	1	2
Diagnosis		
Acute Bacterial Bronchitis	55 (48)	19 (42)
AECB	59 (52)	26 (58)

* Includes a single ceftibuten 200 mg p.o. b.i.d. patient.
† According to the MO, the $\chi^2 = 4.28$ with corresponding p-value = $0.02<p<0.05$. However, if corrected, $\chi^2 = 3.32$, p-value $0.05<p<0.1$.

Table 14
Demographic Data for Patients in the Clinical Test-of-Cure Population According to Type of Bronchitis (C88044)
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(n = 55)	(n = 19)
Sex		
Male	26 (47)	6 (32)
Female	29 (53)	13 (68)
Race		
White	48 (87)	16 (84)
Black	5 (9)	2 (11)
Other	1 (2)	1 (5)
Not recorded	1 (2)	0
Patient Status		
Inpatient	3 (5)	1 (5)
Outpatient	52 (95)	18 (95)
Age (yr)		
Mean	42.7	43.1
Median	35.0	39.0
Range (min-max)	18-78	25-71
Weight (kg)		
Mean	73.3	74.2
Median	72.7	69.8
Range (min-max)		
Not Recorded	1	1
AECB	(n = 59)*	(n = 26)
Sex		
Male	35 (59)	18 (69)
Female	24 (41)	8 (31)
Race		
White	47 (80)	21 (81)
Black	6 (10)	5 (19)
Other	6 (10)	0
Patient Status†		
Inpatient	10 (17)	10 (38)
Outpatient	49 (83)	16 (62)
Age (yr)		
Mean	53.4	56.8
Median	56.0	59.0
Range (min-max)		
Weight (kg)		
Mean	74.5	83.7
Median	72.7	79.6
Range (min-max)		
Not Recorded	0	2

* Includes a single ceftibuten 200 mg p.o. b.i.d. patient.
† According to the MO, the $\chi^2 = 4.64$ with corresponding p-value = $0.02<p<0.05$. However, if corrected, $\chi^2 = 3.52$, p-value $0.05<p<0.1$.

Baseline Clinical Features:

> ***Medical Officer's Comment:*** As stated earlier, the investigators initially identified patients as having bronchitis. Following completion of the study, the Schering project monitors further classified the patients into AECB, depending on data provided in the case report form. Neither severity of illness, *per se*, nor duration of illness prior to enrollment were provided in the data base for the NDA.

The reviewer examined the baseline signs & symptoms for the MO's "bronchitis" clinical efficacy population. (See Tables 15 and 16.) These clinical findings were graded on a scale from 0-3 for each specific clinical parameter. (See footnote for Table 15.) The MO calculated a mean symptom value score for the patients who had a response recorded (i.e, excluded missing values).

These groups appeared to be equally matched. On average, the most severe clinical parameter for both treatment groups was cough and sputum production. When type of underlying bronchitis is looked at, the groups remain well matched. As one would expect, on average, the AECB patients tended to have more severe baseline dyspnea.

> ***Medical Officer's Comment:*** The applicant performed an analysis similar to that in Table 18. However, in their analysis they only included those patients who had a response other than "0" (none/absent) at baseline. The reviewer believes the analysis in Table 15 is more representative of the clinical efficacy population as a whole and thus the applicant's analysis is not included here.

For the MO's "bronchitis" clinical efficacy group, the average baseline temperature was 98.7°F for both treatment groups (range 96.2-103.1°F; n=168 for the ceftibuten recipients; range 96-101.6°F; n=66 for cefaclor). In addition, among the ceftibuten group, 13 (8%) had a baseline temperature greater than 100.4°F, while there were only 6 (9%) for cefaclor. (Data not shown.)

Table 15
Baseline Clinical Features of MO's Bronchitis
Clinical Efficacy Population by Mean Symptom Value* (C88044)
(According to reviewer)

	No. Recorded		Mean Symptom Value	
	Ceftibuten 400 mg qd (n=168)†	Cefaclor 250 mg qd (n=66)†	Ceftibuten 400 mg qd	Cefaclor 250 mg qd
Chills	150	61	0.5	0.4
Dyspnea	150	61	1.1	1.1
Cough	150	61	2.3	2.2
Sputum (prod. cough)	150	61	2.1	2.1
Rales/Rhonchi	139	59	1.2	1.3
Consolidation	139	59	0.05	0.05
Pleuritic chest pain	138	59	0.4	0.4

* Mean symptom value was calculated using baseline scores of 0=none/absent, 1=slight/mild, 2=moderate, 3=severe/marked. Baseline visit used was day 1. No patients had cyanosis reported at baseline. Wheeze, fatigue, diaphoresis were reported only erratically.

† "n" is the number of clinical efficacy patients. The "No. recorded" include the patients where a baseline score was provided. For example, of the 168 clinical efficacy ceftibuten "bronchitis" patients, 150 had day 1 "chills" scores of 0, 1, 2, or 3. For the 18 remaining patients, this information was not provided. Some patients had their baseline scores recorded on day -1 or earlier.

Table 16
Baseline Clinical Features of MO's Clinical Efficacy Population According to Type of Bronchitis and by Mean Symptom Value* (C88044)
(According to reviewer)

	No. Recorded		Mean Symptom Value	
	Ceftibuten 400 mg qd	Cefaclor 250 mg qd	Ceftibuten 400 mg qd	Cefaclor 250 mg qd
Acute Bact. Bronch.	**(n=78)**	**(n=31)**		
Chills	70	27	0.6	0.5
Dyspnea	70	27	0.7	0.6
Cough	70	27	2.3	2.1
Sputum (prod. cough)	70	27	2.1	2.1
Rales/Rhonchi	68	26	1.1	1.3
Consolidation	68	26	0.04	0.07
Pleuritic chest pain	67	26	0.5	0.5
AECB	**(n=90)**	**(n=35)**		
Chills	80	34	0.4	0.3
Dyspnea	80	34	1.5	1.5
Cough	80	34	2.3	2.2
Sputum (prod. cough)	80	34	2.2	2.2
Rales/Rhonchi	71	33	1.2	1.3
Consolidation	71	33	0.06	0.03
Pleuritic chest pain	71	33	0.3	0.3

* Mean symptom value calculated using baseline scores of 0=none/absent, 1=slight/mild, 2=moderate, 3=severe/marked. Baseline visit used was day 1. No patients had cyanosis reported at baseline. Wheeze, fatigue, diaphoresis were reported only erratically.

Underlying medical conditions:

> ***Medical Officer's Comment:*** In the applicant's NDA review, the applicant did not compare underlying medical conditions between the two treatment groups *per se*.

The applicant assigned patients general body system diagnoses for the underlying medical conditions as well as secondary diagnoses. (See Table 17.) From the reviewer's analysis of this data, fewer patients enrolled had no past medical history recorded, in contrast to the AECB patients where more did.

The reviewer identified specific underlying medical conditions of interest. (See Table 18.) As to be expected, the AECB patients experienced more chronic illnesses (both pulmonary and nonpulmonary).

> ***Medical Officer's Comment:*** One patient had a noteworthy underlying illness: C8804434123, also a ceftibuten recipient, had "colitis" prior to enrollment. This patient was discontinued from the study after 2 days due to "severe" GI bleeding ("tarry black stools").

Table 17
Underlying Medical Conditions by Body System for Enrolled Patients According to Type of Bronchitis (C88044)
(According to reviewer)

	No. of Patients (%)			
	Ceftibuten		Cefaclor	
Acute Bact. Bronchitis	(n=107)		(n=50)	
None	23	(21)	10	(20)
Allergic	25	(23)	16	(32)
Audiologic	8	(7)	2	(4)
Cardiovascular	23	(21)	13	(26)
Dermatologic	8	(7)	8	(16)
Endocrine	7	(7)	8	(16)
Gastrointestinal	27	(25)	15	(30)
Genitourinary	29	(27)	13	(26)
Hematologic	6	(6)	3	(6)
Musculoskeletal	24	(22)	13	(26)
Neurologic	6	(6)	7	(14)
Ophthalmologic	20	(19)	13	(26)
Psychological	9	(8)	6	(12)
Pulmonary	37	(35)	14	(28)
Systemic	7	(7)	3	(6)
AECB	(n=128)		(n=63)	
None	0		1	(2)
Allergic	41	(32)	16	(25)
Audiologic	12	(9)	6	(10)
Cardiovascular	52	(41)	27	(43)
Dermatologic	19	(15)	10	(16)
Endocrine	16	(13)	7	(11)
Gastrointestinal	37	(29)	17	(27)
Genitourinary	45	(35)	21	(33)
Hematologic	5	(4)	4	(6)
Musculoskeletal	45	(35)	17	(27)
Neurologic	12	(9)	7	(11)
Ophthalmologic	20	(16)	8	(13)
Psychological	20	(16)	11	(17)
Pulmonary	121	(95)	61	(97)
Systemic	7	(5)	0	

Table 18
Specific Underlying Medical Conditions for Enrolled Patients According to Type of Bronchitis (C88044)*
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten	Cefaclor
Acute Bact. Bronchitis	(n=107)	(n=50)
Pulmonary Disease		
Chronic‡	0	0
Asthma	5	0
Diabetes mellitus	2	5
Cancer		
Lung	0	0
All others	0	0
Immunodeficiency*	4	2
ETOH/IVDA**	1	2
H/O Tuberculosis	4	2
AECB	(n=128)	(n=63)
Pulmonary Disease		
Chronic‡	63 (50)	41 (65)
Asthma	48 (38)	12 (19)
Diabetes mellitus	10	3
Cancer		
Lung	0	0
All others	8	4
Immunodeficiency*	3	3
ETOH/IVDA**	7	4
H/O Tuberculosis	4	1

‡ Includes COPD (emphysema), chronic bronchitis, bronchiectasis, sarcoidosis, scleroderma, pulmonary fibrosis, and silicosis. Excludes lung cancer and "recurrent bronchitis."
* Immunodeficiencies included connective tissue disease (i.e., SLE, scleroderma), HIV, anemia, leukopenia, post-splenectomy, and pancytopenia.
** Alcohol and/or intravenous drug abuse

There were 2 ceftibuten recipients who had **concurrent infections** involving other anatomic sites at the time of enrollment. Patient C8804431103 had a infection." However, this diagnosis was based solely on a urine with minimal pyuria and hematuria. A urine culture was never obtained. This individual only received one dose of ceftibuten before being discontinued from the study in light of a negative entry sputum culture. Patient C8804444102 had at onset. Following 10 days of therapy the AECB had resolved. The response to therapy for is not specified. (One cefaclor patient had sinusitis at the time of study entry as well.)

In addition, there were some patients who developed concurrent infections, other than the during the study. Ceftibuten patient, C8804407123, developed otitis media following 11 days of ceftibuten therapy. Another ceftibuten recipient, C8804421109, developed sinusitis on day 5 of therapy that subsequently improved following the initiation of Afrin® nasal spray and Tylenol® with codeine. (Two cefaclor patients developed sinusitis and prostatitis at end-of-therapy,

respectively.)

Concomitant Medications:

Systemic Anti-Infective Drug Use:
The reviewer examined the database for concurrent systemic anti-infective drug used in pretherapy time period. For this indication, the reviewer did not consider topical anti-infective, antifungal, antipneumocystis, or antiviral therapy significant. Furthermore, the reviewer limited interest to those systemic anti-infectives administered between days -30 through the posttherapy follow-up visit; the reviewer does not believe that anti-infective use prior to this is of particular significance with regard to its effect on the population studied. The reviewer undertook this to determine whether any subgroup experienced greater pretherapy systemic anti-infective drug use than another - this could select for greater pathogen resistance as well as indicate a population with a preponderance for bacterial infections prior to enrollment.

From the reviewer's analysis, for enrolled patients, there appeared to be proportionately more pretherapy anti-infective use in both the ceftibuten and AECB groups. (See Table 19.)

Table 19
Pretherapy Systemic Anti-Infective Use for Enrolled Patients According to Type of Bronchitis (C88044)*
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten	Cefaclor
Pretherapy	(n=107)	(n=50)
AECB	**(n=128)**	**(n=63)**
Pretherapy	15 (12)	3 (5)

* Last use within 30 days prior to enrollment; excludes antituberculous therapy, antifungals, topical anti-infective therapy, and pentamidine.

Nonanti-Infective Drug Use:
The MO also evaluated the concurrent nonanti-infective drug use in enrolled patients. (See Table 20.) The reviewer was most interested in concomitant "pulmonary" drug use (i.e., methylxanthines, β-agonist bronchodilators (systemic and inhalant), corticosteroids (systemic and inhalant), cromolyn, and inhalant anticholinergic bronchodilators).

As to be expected, patients with AECB used more pulmonary drugs than patients. However, there was no difference in drug use between the two treatment groups. Oxygen use was recorded for only 5 patients - 4 ceftibuten and 1 cefaclor; 4 AECB

Table 20
Concomitant Nonanti-Infective Therapy for Enrolled Patients According to Type of Bronchitis (C88044)*
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten	Cefaclor
Acute Bact. Bronchitis	(n=107)	(n=50)
Pulmonary drugs*	12 (11)	2 (4)
Methylxanthines	1 (<1)	0
Inhalant steroids	1 (<1)	0
Systemic immunosup.‡	5 (5)	1 (2)
AECB	(n=128)	(n=63)
Pulmonary drugs*	83 (65)	44 (70)
Methylxanthines	53 (41)	28 (44)
Inhalant steroids	18 (14)	3 (5)
Systemic immunosup.‡	35 (27)	22 (35)

* "Pulmonary drugs" include methylxanthines, β-agonist bronchodilators (systemic and inhalant), corticosteroids (systemic and inhalant), cromolyn, oxygen, and inhalant anticholinergic bronchodilators.
‡ Systemic corticosteroids, infrequently, were prescribed for reasons other than bronchospasm. However, their co-administration may have had ameliorative effects on a patient's respiratory symptoms.

Of interest, the MO reviewed concomitant "pulmonary" drug use for the clinical test-of-cure population **initiated during therapy or during the posttherapy follow-up period.** The reviewer identified 34 patients (23 ceftibuten, 11 cefaclor; 5 acute bacterial bronchitis and 29 AECB). All acute bacterial bronchitis patients who received one or more pulmonary medications were in the ceftibuten group; for AECB, this consisted of 18 ceftibuten and 11 cefaclor recipients. Thus, concomitant pulmonary drug use initiated over the study period appeared to be comparable for the two treatment groups (although greater use in the acute bacterial bronchitis ceftibuten group was noted, albeit small).

Study Drug Administration:

Medical Officer's Comment: During the NDA review, it became apparent that there were significant discrepancies between the total days of therapy and total doses administered. The MO requested that the applicant reevaluate the data base. The corrected data on doses were submitted over a span of several clinical amendments.

According to the reviewer, evaluating various efficacy populations (clinical efficacy, clinical test-of-cure, and valid), the mean duration of therapy appeared to be comparable between populations. When type of bronchitis was looked at separately, dosing remained comparable. (See Tables 21 and 22.) Approximately 80% of patients had received their full course of therapy by day 11-12.

Table 21
Distribution of Duration of Therapy (Days) by Treatment Group for the "Bronchitis" Population According to MD's Evaluability (C88044)
(According to reviewer)

Duration (Days)	No. of Patients (cumulative %)					
	Clinical Efficacy		Clinical Test-of-Cure		Valid	
	Ceftibuten 400 mg QD (n=167)	Cefaclor 250 mg TID (n=66)	Ceftibuten 400 mg QD (n=113)	Cefaclor 250 mg TID (n=45)	Ceftibuten 400 mg QD (n=39)	Cefaclor 250 mg TID (n=17)
No record*	1 (<1)	0	0	0	0	0
3-4	10 (7)	4 (6)	10 (9)	4 (9)	2 (5)	0
5-6	43 (32)	9 (20)	24 (30)	2 (13)	3 (13)	0
7-8	26 (48)	13 (39)	18 (46)	11 (38)	11 (41)	8 (47)
9-10	52 (79)	17 (65)	40 (81)	10 (60)	15 (80)	2 (59)
11-12	12 (86)	14 (86)	8 (88)	12 (87)	3 (87)	3 (76)
13-14	19 (98)	5 (94)	11 (98)	2 (91)	3 (95)	2 (88)
15-16	4 (100)	4 (100)	2 (100)	4 (100)	2 (100)	2 (100)
Mean Days	8.6	9.4	8.5	9.6	9.2	10.2
Mean Doses	8.6	25.9	8.5	26.4	9.4	27.7

* One ceftibuten patients with "no record" of days of therapy, C8804407130, according to the patient profile, received 5 doses of study drug.
NOTE: This table excludes the single ceftibuten 200 mg b.i.d. patient.

Table 22
Distribution of Duration of Therapy (Days) for the MO's Clinical Test-of-Cure Populations According to Type of Bronchitis (C88044)
(According to reviewer)

	No. of Patients (cumulative %)			
	Acute Bact. Bronchitis		*AECB*	
Duration (Days)	Ceftibuten 400 mg QD (n=55)	Cefaclor 250 mg TID (n=19)	Ceftibuten 400 mg QD (n=59)	Cefaclor 250 mg TID (n=26)
3-4	4 (7)	3 (16)	6 (10)	1 (4)
5-6	14 (33)	0 (16)	10 (28)	2 (12)
7-8	9 (49)	5 (42)	9 (43)	6 (35)
9-10	18 (82)	5 (53)	22 (81)	5 (54)
11-12	3 (87)	4 (89)	5 (90)	8 (85)
13-14	6 (98)	0 (89)	5 (98)	2 (92)
15-16	1 (100)	2 (100)	1 (100)	2 (100)
Mean Days	8.5	9.3	8.6	9.9
Mean Doses	8.4	25.7	8.5	26.9

NOTE: This table excludes the single ceftibuten 200 mg b.i.d. patient.

EFFICACY EVALUATION:

CLINICAL EFFICACY EVALUATION:

Medical Officer's Comment: As previously stated, the main difference between the applicant and the reviewer in the clinical evaluation of the two study drugs is the "test-of-cure" visit. For the applicant, this was day +0-+3; represented by the applicant's **clinical efficacy** population. For the MO, this was day +4 or later; the MO's **clinical test-of-cure** population.

Clinical Efficacy at End-of-Therapy:
According to the applicant, by EOT for the **clinical efficacy** population, independent of the type of bronchitis, 165/190 (87%) and 67/78 (86%) of ceftibuten and cefaclor patients, respectively, were either improved or cured. (See Table 23.)

For the applicant's **valid** population, the success rate at EOT, independent of type of bronchitis, was 46/51 (90%) for ceftibuten recipients versus 18/22 (82%) for cefaclor. (See Table 24.)

According to the reviewer, for the sake of completeness, the reviewer assessed the MO's **clinical efficacy** population, analogous to the applicant's clinical efficacy population. (Albeit, this is not the reviewer's primary efficacy population.) (See Table 26.) Independent of the type of bronchitis, a

positive (successful) response was noted for 125/168 (74%) of ceftibuten patients in contrast to 54/66 (82%) of cefaclor recipients. The greatest difference was seen in the acute bacterial bronchitis group.

The reviewer also looked at the end-of-therapy response rates for the **clinical test-of-cure** population, the reviewer's primary efficacy population. (See Table 27.) Overall, the success rates were lower than those seen for the clinical efficacy population - for ceftibuten, 71/114 (62%); for cefaclor, 33/45 (73%). Between the two types of bronchitis, this difference was again greatest in the acute bacterial bronchitis patients.

For the reviewer's **valid** population (patients with a documented baseline pathogen) at end-of-therapy, few patients were assessable. Success rates appeared to be higher for the **acute bacterial bronchitis** population than those for the clinical efficacy and clinical test-of-cure populations. (See Table 28.)

Clinical Efficacy at Posttherapy Follow-up:
For the applicant, only the **"valid"** population was assessed at the posttherapy visit (days +7-+14). (See Table 25.) In addition, when the applicant assessed success rates, their denominator did not include patients who had failed earlier but only those patients who had a positive response at the end-of-therapy visit and were seen again later.

Hence, according to the applicant, for all "bronchitis" patients, 25/27 (93%) ceftibuten patients and 13/13 cefaclor recipients had a sustained positive extended therapy response. Numbers are too small to make differential assessments between types of bronchitis and don't include failures identified earlier during the course of the study.

According to the reviewer, who did carry end-of-therapy clinical failure responses forward as the posttherapy response, for the **clinical test-of-cure** population overall "cumulative" sustained positive responses for the two treatment groups were: 68/114 (60%) for ceftibuten versus 32/45 (71%) for cefaclor. (See Table 27.) Furthermore, there were 3 relapses in the ceftibuten and 1 in the cefaclor group.

For the reviewer's **valid** population, at follow-up, there was only 1 relapse seen in each group. (See Table 28.)

Table 23
Clinical Responses for the Bronchitis/Tracheitis Clinical Efficacy Populations at the End-of-Therapy Visit (C88044)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N= 88)*	(N= 37)
Cure/Improvement	74 (84)	31 (84)
(Cure)	53 (60)	22 (60)
(Improvement)	21 (24)	9 (24)
Failure	14 (16)	6 (16)
AECB	(N=102)	(N= 40)
Cure/Improvement	91 (89)	35 (88)
(Cure)	61 (60)	27 (68)
(Improvement)	30 (29)	8 (20)
Failure	11 (11)	5 (13)
Tracheitis	(N= 0)	(N= 1)
Cure/Improvement	0 (--)	1 (100)
(Cure)	0 (--)	1 (---)
(Improvement)	0 (--)	0 (---)
Failure	0 (--)	0 (---)
All Diagnoses	(N=190)*	(N= 78)
Cure/Improvement	165 (87)	67 (86)
(Cure)	114 (60)	50 (64)
(Improvement)	51 (27)	17 (22)
Failure	25 (13)	11 (14)

* includes an acute bacterial bronchitis patient, C8804404144, who received ceftibuten 200 mg b.i.d.

Table 24
Clinical Response of Valid Bronchitis Patients at the End-of-Therapy Visit (C88044)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N= 19)	(N= 10)
Cure/Improvement	16 (84)	9 (90)
(Cure)	14 (74)	9 (90)
(Improvement)	2 (11)	0
Failure	3 (16)	1 (10)
AECB	(N= 32)	(N= 12)
Cure/Improvement	30 (94)	9 (75)
(Cure)	21 (66)	7 (58)
(Improvement)	9 (28)	2 (17)
Failure	2 (6)	3 (25)
All Diagnoses	(N= 51)	(N= 22)
Cure/Improvement	46 (90)	18 (82)
(Cure)	35 (69)	16 (77)
(Improvement)	11 (22)	2 (9)
Failure	5 (10)	4 (18)

Table 25
Clinical Response of Valid Bronchitis Patients at the Posttherapy Visit (C88044)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N= 9)	(N= 6)
Sustained Cure/Improvement	9 (100)	6 (100)
(Cure)	7 (78)	6 (100)
(Improvement)	2 (22)	0
AECB	(N=18)	(N= 7)
Sustained Cure/Improvement	16 (89)	7 (100)
(Cure)	11 (61)	5 (71)
(Improvement)	5 (28)	2 (29)
Relapse	2 (11)	0
All Diagnoses	(N=27)	(N=13)
Sustained Cure/Improvement	25 (93)	13 (100)
(Cure)	18 (67)	11 (85)
(Improvement)	7 (26)	2 (15)
Relapse	2 (7)	0

Medical Officer's Comment: In the applicant's analysis of the extended therapy response for the valid population, early failures were not carried forward for the posttherapy follow-up response.

Table 26
Clinical Responses for the MO's Clinical Efficacy Population at End-of-Therapy Visit According to the Type of Bronchitis (C88044)*
(According to reviewer)

Clinical Response	No. of Patients (%)			
	ACUTE BACT. BRONCHITIS		*AECB*	
	Ceftibuten 400 mg QD (n=78)	Cefaclor 250 mg TID (n=31)	Ceftibuten 400 mg QD (n=90)	Cefaclor 250 mg TID (n=35)
Positive response	57 (73)	27 (87)	68 (76)	27 (77)
Cure	30 (38)	14 (45)	40 (44)	18 (51)
Improvement	27 (35)	13 (42)	28 (30)	9 (26)
Failure	21 (27)	4 (13)	22 (26)	8 (23)

* Assessment made between days +0–+3.

Table 27
Clinical Responses for the Clinical Test-of-Cure Population According to the Type of Bronchitis (C88044)*
(According to reviewer)

Clinical Response	No. of Patients (%)			
	ACUTE BACT. BRONCHITIS		*AECB*	
	Ceftibuten 400 mg QD (n=55)	Cefaclor 250 mg TID (n=19)	Ceftibuten 400 mg QD (n=59)	Cefaclor 250 mg TID (n=26)
At End-of-Therapy				
Positive response	34 (62)	15 (79)	37 (63)	18 (69)
Cure	20 (36)	9 (47)	19 (32)	12 (46)
Improvement	14 (25)	6 (32)	18 (31)	6 (23)
Failure	21 (38)	4 (21)	22 (37)	8 (31)
At Follow-up				
Positive response	33 (60)	15 (79)	35 (59)	17 (65)
Cure	28 (51)	14 (74)	26 (44)	15 (58)
Improvement	5 (9)	1 (5)	9 (15)	2 (8)
Negative response	22 (40)	4 (21)	24 (41)	9 (35)
Early Failure*	21 (38)	4 (21)	22 (37)	8 (31)
Relapse	1 (2)	0	2 (3)	1 (4)

* Failures at end-of-therapy carried forward as the extended follow-up visit response.

Table 28
Clinical Responses for the MO's Valid Population According to the Type of Bronchitis (C88044)*
(According to reviewer)

Clinical Response	No. of Patients (%)			
	ACUTE BACT. BRONCHITIS		*AECB*	
	Ceftibuten 400 mg QD (n=14)	Cefaclor 250 mg TID (n=4)	Ceftibuten 400 mg QD (n=26)	Cefaclor 250 mg TID (n=13)
At End-of-Therapy				
Positive response	13 (93)	4 (100)	18 (69)	10 (77)
Cure	8 (57)	2 (50)	8 (31)	7 (54)
Improvement	5 (36)	2 (50)	10 (38)	3 (23)
Failure	1 (7)	-	8 (31)	3 (23)
At Follow-Up				
Positive response	12 (86)	4 (100)	17 (65)	9 (69)
Cure	8 (57)	3 (75)	12 (46)	8 (62)
Improvement	4 (29)	1 (25)	5 (19)	1 (8)
Negative response	2 (14)	-	9 (35)	4 (31)
Early Failure*	1 (7)	-	8 (31)	3 (23)
Relapse	1 (7)	-	1 (4)	1 (8)

* Failures at end-of-therapy carried forward as posttherapy follow-up response of "early failure."

Resolution of Signs & Symptoms:
The time required for the resolution of signs and symptoms in patients who had clinical cure/improvement in the U.S. clinical efficacy bronchitis/tracheitis population was evaluated by the applicant. (See Table 29.) According to the applicant, some signs and symptoms appeared to resolve more quickly while on ceftibuten treatment.

However, there is a cautionary note to this analysis using the applicant's IADR results; a patient may have had disappearance of a sign or symptom followed by reappearance of that same symptom the next day. For example, a patient might have resolution of sputum (by diary) on day 5. The following day, the symptom may have reappeared and could have either persisted or disappeared again at a later date. Yet, the IADR would be assigned to day 5.

Table 29. Time in Days to Resolution of Signs and Symptoms in Patients in the US Bronchitis and Tracheitis Clinical Efficacy Population with a Clinical Response of Cure or Improvement (C88-044). (According to the applicant)

	Tracheitis		Acute Exacerbation Chronic Bronchitis		Acute Bacterial Bronchitis		Combined	
	Ceftibuten 400 mg QD	Cefaclor 250 mg Q8H	Ceftibuten 400 mg QD	Cefaclor 250 mg Q8H	Ceftibuten 400 mg QD	Cefaclor 250 mg Q8H	Ceftibuten 400 mg QD	Cefaclor 250 mg Q8H
Chills								
Mean	--	--	4.89	4.36	4.37	4.50	4.63	4.43
Median	--	--	4.00	4.00	4.00	4.50	4.00	4.00
Range	--	--	1 - 13	2 - 11	2 - 11	2 - 12	1 - 13	2 - 12
No. Patients	0	0	27	11	27	12	54	23
Dyspnea								
Mean	--	3.00	7.86	8.62	7.23	6.95	7.62	7.84
Median	--	3.00	7.00	7.00	5.50	4.00	7.00	4.00
Range								
No. Patients	0	1	73	29	44	20	117	50
Cough								
Mean	--	27.00	9.54	10.74	9.59	11.37	9.56	11.27
Median	--	27.00	10.00	10.00	9.00	10.00	9.00	10.00
Range								
No. Patients	0	1	87	35	68	30	155	66
Sputum								
Mean	--	10.00	9.51	10.69	9.10	9.52	9.33	10.15
Median	--	10.00	9.00	10.00	8.00	9.00	9.00	10.00
Range								
No. Patients	0	1	87	35	68	29	155	65
Cyanosis								
Mean	--	--	6.67	--	1.00	--	5.25	--
Median	--	--	5.00	--	1.00	--	5.00	--
Range								
No. Patients	0	0	3	0	1	0	4	0
Rales/Rhonchi								
Mean	--	--	7.58	8.27	8.02	9.95	7.79	9.02
Median	--	--	6.00	7.50	8.00	7.00	7.00	7.00
Range								
No. Patients	0	0	57	26	50	21	107	47
Signs of Consolidation								
Mean	--	--	7.33	--	7.20	5.33	7.25	5.33
Median	--	--	6.00	--	5.00	5.00	5.50	5.00
Range								
No. Patients	0	0	3	0	5	3	8	3
Pleuritic Chest Pain								
Mean	--	3.00	6.32	8.60	7.05	12.38	6.69	10.36
Median	--	3.00	5.00	8.00	5.50	9.50	5.00	8.50
Range								
No. Patients	0	1	19	5	20	8	39	14

BACTERIOLOGIC EFFICACY EVALUATION:

In the bacteriologic evaluation of bronchitis, the applicant considered various bacterial isolates as "pathogens." In contrast, the reviewer limited bacteriologic evaluation to those "pathogens" in the applicant's proposed label: *H. influenzae*, *H. parainfluenzae*, *K. pneumoniae*, *S. pneumoniae*, and *M. catarrhalis*. Furthermore, for the reviewer's purposes, bacteriologic evaluation was limited to the MO's **valid** population. Bacteriologic responses were either documented or presumptive. Furthermore, the applicant excluded pathogens with "intermediate" susceptibility while the reviewer included them - the MO noted the clinical/bacteriologic outcomes of these moderately susceptible pathogens separately. (See below.)

> ***Medical Officer's Comment:*** In the NDA submission, the applicant did not include the β-lactamase activity for specific pathogens. Following the MO's request, the applicant submitted this data as a clinical amendment. (See below.)

Bacteriologic Efficacy at End-of-Therapy:
According to the applicant, independent of type of bronchitis, 47/50 (94%) ceftibuten and 18/21 (86%) cefaclor patients experienced bacteriologic eradication. (See Table 30.) With regard to types of bronchitis, albeit small numbers, ceftibuten was more effective than cefaclor in the treatment of AECB.

The applicant evaluated bacteriologic response rates at EOT according to specific pathogens. (See Table 31.) Combining diagnoses, pathogen eradication rates were similar to patient eradication rates.

> ***Medical Officer's Comment:*** The reviewer assigned eradication rates only to those patients and pathogens assessable beyond day +4. (Unless they failed prior to this time.) Thus, no MO's assessment at end-of-therapy.

Table 30
Bacteriologic Response of Valid Patients with Bronchitis/Tracheitis at EOT (C88044)
(According to applicant)

	Number (%) of Patients	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N = 19)	(N = 10)
Total Eradication¶	17 (89)	9 (90)
(Eradication)	16 (84)	9 (90)
(W/ superinfection)	0	0
(W/ colonization)	1 (5)	0
Persistence#	2 (11)	1 (10)
AECB	(N = 31)§	(N = 11)§
Total Eradication¶	30 (97)	9 (82)
(Eradication)	28 (90)	7 (64)
(W/ superinfection)	1 (3)	1 (9)
(W/ colonization)	1 (3)	1 (9)
Persistence#	1 (3)	2 (18)
All Diagnoses	(N = 50)§	(N = 21)§
Total Eradication¶	47 (94)	18 (86)
(eradication)	44 (88)	16 (76)
(W/ superinfection)	1 (2)	1 (5)
(W/ colonization)	2 (4)	1 (5)
Persistence#	3 (6)	3 (14)

§ One patient each in both ceftibuten and cefaclor groups with an indeterminate response were not included in the denominator for calculation of response.
¶ Includes eradication and eradication with colonization, or superinfection.
Includes patients with a multiple response.

Table 31
Individual "Pathogen" Eradication Rates for Valid Patients with Bronchitis/Tracheitis at the EOT Visit (C88044)
(According to applicant)

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis		
Moraxella (Branhamella) catarrhalis	2/3 (67)	0/0 (---)
Haemophilus influenzae	7/7 (100)	3/4 (75)
Haemophilus parainfluenzae	3/3 (100)	1/1 (100)
Klebsiella pneumoniae	1/1 (100)	1/1 (100)
Streptococcus pneumoniae	1/1 (100)	2/2 (100)
Other§	10/11 (91)	2/2 (100)
Subtotal	24/26 (92)	9/10 (90)
AECB		
Moraxella (Branhamella) catarrhalis	2/2 (100)	1/1 (100)
Haemophilus influenzae	10/11 (91)	1/2 (50)
Haemophilus parainfluenzae	5/5 (100)	2/3 (67)
Klebsiella pneumoniae	1/1 (100)	1/1 (100)
Streptococcus pneumoniae	4/4 (100)	3/3 (100)
Other§	13/13 (100)	3/3 (100)
Subtotal	35/36 (97)	11/13 (85)
All Diagnoses		
Moraxella (Branhamella) catarrhalis	4/5 (80)	1/1 (100)
Haemophilus influenzae	17/18 (94)	4/6 (67)
Haemophilus parainfluenzae	8/8 (100)	3/4 (75)
Klebsiella pneumoniae	2/2 (100)	2/2 (100)
Streptococcus pneumoniae	5/5 (100)	5/5 (100)
Other§	23/24 (96)	5/5 (100)
Total	**59/62 (95)**	**20/23 (87)**

§ Includes *Citrobacter freundii, Enterobacter aerogenes, Enterobacter agglomerans, Enterobacter cloacae, Escherichia coli, Haemophilus* sp., *Klebsiella oxytoca, Klebsiella* sp, *Micrococcus luteus, Neisseria meningitides, Neisseria mucosa, Neisseria sicca, Proteus mirabilis, Proteus* sp, *Streptococcus* sp.

Bacteriologic Efficacy at Posttherapy:
Acccrding to the applicant, the bacteriologic responses for valid **patients** (independent of type of bronchitis) who had an extended posttherapy visit (days +7-+14) showed 88% (15/17) eradication in the ceftibuten group in comparison with 100% (6/6) in the cefaclor population. (See Table 32.)

For specific **pathogens**, eradication rates for the two drugs were 19/21 (90%) and 6/6, respectively. (See Table 33.)

> *Medical Officer's Comment:* As previously stated, the applicant did not carry their end-of-therapy failure responses forward to the extended response; the MO did.

According to the reviewer, independent of type of bronchitis, the cumulative bacteriologic eradication rates for **patients** with "bronchitis," was 32/40 (80%) for ceftibuten and 14/17 (82%) for cefaclor. (See Table 34.) According to type of bronchitis, albeit small numbers, the success rates of treatment arms for AECB were comparable.

With respect to bacteriologic efficacy relative to the MO's "**pathogens**," independent of type of bronchitis, for ceftibuten, 38/46 (83%) were eradicated while this was 16/19 (84%) for cefaclor. (See Table 35.) Acute bacterial bronchitis pathogens appeared to have higher eradication rates. Due to small numbers of specific pathogens isolated, it is difficult to contrast pathogen specific eradication rates between the two treatment arms. A single bacteriologic relapse occurred; a β-lactamase (-) *H. influenzae* in the cefaclor group.

With regard to β-lactamase activity, owing to small pathogen numbers, here too it is difficult to reach conclusions. For ceftibuten, of the β-lactamase (+) *H. influenzae* and *M. catarrhalis*, eradication (presumptive or documented) occurred in 4/8 (50%). There were 2 cefaclor patients with β-lactamase (+) *H. influenzae* or *M. catarrhalis*; both were eradicated.

Table 32
Bacteriologic Response for Valid Patients with Bronchitis/Tracheitis at F/U (C88044)
(According to applicant)

	Ceftibuten 400 mg QD (N=17)[‡]	Cefaclor 250 mg TID (N= 6)
Total Eradication[¶]	15 (88)	6 (100)
(Eradication)	13 (76)	5 (83)
(W/ colonization)	2 (6)	1 (17)
Persistence	2 (12)	0

‡ One patient with an indeterminate response was not included in the denominator for calculation of response in the ceftibuten treatment group.
¶ Includes eradication and eradication with colonization.

Table 33
Bacteriologic Response for Valid Bronchitis/Tracheitis Pathogens at F/U (C88044)
(According to applicant)

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Moraxella (Branhamella) catarrhalis	1/1 (100)	1/1 (100)
Haemophilus influenzae	6/7 (86)	1/1 (100)
Haemophilus parainfluenzae	2/2 (100)	1/1 (100)
Other[§]	10/11 (91)	3/3 (100)
Total	19/21 (90)	6/6 (100)

§ Includes *Enterobacter aerogenes*, *E. agglomerans*, *Escherichia coli*, *Haemophilus* sp, *Klebsiella* sp, *Klebsiella Oxytoca*, *Neisseria meningitides*, *Neisseria mucosa*, *Neisseria sp*, *Proteus* sp, *Streptococcus* sp.

Table 34
Cumulative Bacteriologic Responses for MO's Valid Bronchitis/Tracheitis Patients at F/U (C88044)
(According to reviewer)

	Number (%) of Patients	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N = 14)	(N = 4)
Eradication	12 (86)	4 (100)
Persistence	1 (7)	-
Multiple response#	1 (7)	-
AECB	(N = 26)	(N = 13)
Eradication	20 (77)	10 (77)
Persistence	5 (19)	1 (8)
Relapse	-	1 (8)
Multiple response#	1 (4)	1 (8)

Includes responses of eradication and persistence; patients had more than one baseline pathogen.

Table 35
Cumulative "Pathogen" Eradication Rates for MO's Valid Bronchitis Pathogens at F/U (C88044)
(According to reviewer)

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis		
Moraxella (Branhamella) catarrhalis		
β-lactamase (-)†	1/1 (100)	0
β-lactamase (+)	1/2 (50)	0
Haemophilus influenzae		
β-lactamase (-)	6/7 (86)	2/2 (100)
β-lactamase (+)	1/1 (100)	1/1 (100)
Haemophilus parainfluenzae		
β-lactamase (-)	2/2 (100)	1/1 (100)
β-lactamase (+)	-	0
Klebsiella pneumoniae	1/1 (100)	0
Streptococcus pneumoniae	1/1 (100)	0
Total	**13/15 (87)**	**4/4 (100)**
AECB		
Moraxella (Branhamella) catarrhalis		
β-lactamase (-)	1/1 (100)	1/1 (100)
β-lactamase (+)	2/4 (50)	1/1 (100)
Haemophilus influenzae		
β-lactamase (-)	10/13 (77)	3/6● (50)
β-lactamase (+)	0/1 (0)	0
Haemophilus parainfluenzae		
β-lactamase (-)	6/6 (100)	2/2 (100)
β-lactamase (+)	1/1 (100)	0
Klebsiella pneumoniae	2/2 (100)	1/1 (100)
Streptococcus pneumoniae	3/3 (100)	4/4 (100)
Total	**25/31 (81)**	**12/15 (80)**

* Eradication is the absence of the causative organism(s) at or immediately after termination of therapy (documented), or the complete disappearance of the culture source (e.g., sputum) so that follow-up culture is impossible (presumptive).
† Includes pathogens not tested for β-lactamase activity.
● = Designates pathogens with bacteriologic relapse.

Bacteriologic Superinfections/Reinfections:
The reviewer identified 1 bacteriologic superinfection (due to one of the five pathogens) which occurred in the U.S. study - a cefaclor patient. There were no bacteriologic reinfections documented. Details follow:

C8804429108 (cefaclor, AECB): On day +3, this individual became infected with *H. influenzae*, β-lactamase negative. (cefaclor zone 30mm; susceptible pathogen). This patient was a clinical failure.

COMBINED CLINICAL/BACTERIOLOGIC EFFICACY:

Both the applicant and reviewer evaluated the relationship of clinical and bacteriologic responses for bronchitis patients in this study. It is generally accepted, that for many AECB patients, following a course of effective anti-infective therapy, although they may be clirically cured, the baseline pathogen will persist - indeed their "normal flora." In other words, the anti-infective therapy may have been successful in decreasing the respiratory pathogen load.

According to the applicant, at EOT, only a single acute bacterial bronchitis cefaclor recipient showed persistence of the baseline pathogen associated with clinical cure. (See Table 36.) In contrast, there were two patients (one from each group) who experienced bacterio c eradication, yet the patient clinically failed.

At F/U, excluding earlier failures, the applicant noted that all patients who had a follow-up visit experienced both a successful outcome and concurrent bacteriologic eradication (documented and presumptive). (See Table 37.)

According to the reviewer, combined clinical/bacteriologic responses for patients and specific pathogens, including β-lactamase activity, were looked at for valid patients. (See Table 38.) No patients experienced persistence of pathogens with a successful outcome - colonization with the baseline pathogen. There were more patients with AECB who experienced clinical failure with documented bacteriologic eradication; none attributed to reinfection.

Table 36
Correlation of Bacteriologic Response and Clinical Response for Valid Patients with Bronchitis/Tracheitis at EOT (C88044)
(According to applicant)

Bacteriological Response	Clinical Response	Number of Patients (%) Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis			
		N=19	N=10
Eradication§	Cure/Improvement	16 (84)	8 (80)
	(Cure)	14 (74)	8 (80)
	(Improvement)	2 (11)	0
	Failure	1 (5)	1 (10)
Persistence	Cure/Improvement	0	1 (10)
	(Cure)	0	1 (10)
	Failure	2 (11)	0
Acute Exacerbation of Chronic Bronchitis			
		N=31¶	N=11¶
Eradication§	Cure/Improvement	30 (97)	9 (75)
	(Cure)	21 (68)	7 (58)
	(Improvement)	9 (29)	2 (17)
Persistence	Failure	1 (3)	2 (17)
Indeterminate	Failure	1	1
All Diagnoses			
		N= 50¶	N=20¶
Eradication§	Cure/Improvement	46 (92)	17 (85)
	(Cure)	35 (70)	15 (75)
	(Improvement)	11 (22)	2 (10)
	Failure	1 (2)	1 (5)
Persistence	Cure/Improvement	0	1 (5)
	(Cure)	0	1 (5)
	Failure	3 (6)	1 (5)
Indeterminate	Failure	1	1

§ Includes eradication and eradication with: colonization, superinfection, and reinfection.
¶ One patient with an indeterminate bacteriologic response, from each group was not included in the denominator.

Medical Officer's Comment: This table, copied from the NDA, has been corrected by the MO. In the applicant's original table, the "indeterminate" bacteriologic response with clinical "failure" was originally included with the "persistence" bacteriologic response group for cefaclor and ignored for ceftibuten.

Table 37
Correlation of Bacteriologic Response and Clinical Response for Valid Patients with Bronchitis/Tracheitis at F/U (C88044)
(According to applicant)

Bacteriological Response	Clinical Response	Number of Patients (%) Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis			
		N= 4	N= 1
Eradication§	Cure/Improvement	4 (100)	1 (100)
	(Cure)	4 (100)	1 (100)
Acute Exacerbation of Chronic Bronchitis			
		N=10¶	N= 4
Eradication§	Cure/Improvement	10 (100)	4 (100)
	(Cure)	7 (70)	3 (75)
	(Improvement)	3 (30)	1 (25)
All Diagnoses			
		N= 14¶	N= 5
Eradication§	Cure/Improvement	14 (100)	5 (100)
	(Cure)	11 (79)	4 (80)
	(Improvement)	3 (21)	1 (20)

§ Includes eradication and eradication with colonization or superinfection.
¶ One ceftibuten patient with an "indeterminate" bacteriologic response, but clinical relapse, was not included in the denominator.

Table 38
Correlation of Bacteriologic Response and Extended Clinical Response for Valid Patients According to Type of Infection (C88044)
(According to reviewer)

	Number (%) of Isolates			
	Ceftibuten 400 mg QD		Cefaclor 250 mg TID	
	Cure/Improve	Fail/Relapse‡	Cure/Improve	Fail/Relapse‡
Acute Bacterial Bronchitis				
ERADICATION*				
Moraxella (Branhamella) catarrhalis				
β-lactamase (-)†	1	-	-	-
β-lactamase (+)	1	-	-	-
Haemophilus influenzae				
β-lactamase (-)	6	-	2	-
β-lactamase (+)	1	-	1	-
Haemophilus parainfluenzae				
β-lactamase (-)	2	-	1	-
Klebsiella pneumoniae	1	-	-	-
Streptococcus pneumoniae	-	1[A]	-	-
PERSISTENCE/RELAPSE				
Moraxella (Branhamella) catarrhalis				
β-lactamase (+)	-	1[A]	-	-
Haemophilus influenzae				
β-lactamase (-)	-	1		-
Total Acute Bronchitis Pathogens	12	3	4	-
Total Acute Bronchitis Patients	12	2	4	-
Acute Exacerbations of Chronic Bronchitis				
ERADICATION*				
Moraxella (Branhamella) catarrhalis				
β-lactamase (-)	1[B]	-	1	-
β-lactamase (+)	2[D,E]	-	1	-
Haemophilus influenzae				
β-lactamase (-)	8[B,C]	2	2[H]	1
Haemophilus parainfluenzae				
β-lactamase (-)	6[E]	-	2	-
β-lactamase (+)	1[D]	-	-	-
Klebsiella pneumoniae	1	1[F]	-	1[G]
Streptococcus pneumoniae	2[C]	1	4[H]	-
PERSISTENCE/RELAPSE				
Moraxella (Branhamella) catarrhalis				
β-lactamase (+)	-	2[F]	-	-
Haemophilus influenzae				
β-lactamase (-)	-	3	-	3[G,•]
β-lactamase (+)	-	1	-	-
Total AECB Pathogens	21	10	10	5
Total AECB Patients	17	9	9	4

Note: Superscript letters represent more than one pathogen isolated from the same patient.

‡ "Early failures" were carried forward as the extended posttherapy response (day +4 or later).

* Eradication is the absence of the causative organism(s) at or immediately after termination of therapy, or the complete disappearance of the culture source (eg, sputum) so that follow-up culture is impossible.

† Includes pathogens not tested for β-lactamase activity.

• Bacteriologic relapse

ADDITIONAL CLINICAL/BACTERIOLOGIC INFORMATION

Progression to Pneumonia While Receiving Therapy:
There was 1 ceftibuten patient (and 1 cefaclor patient) who **progressed on to pneumonia** during the study after receiving a minimum of 3 days of therapy. C8804437102, a valid AECB patient, developed pneumonia after 3 days of therapy. β-lactamase (+) *M. catarrhalis* (ceftibuten zone=28mm) grew at baseline; no follow-up cultures were obtained at the time of pneumonia diagnosis.

Development of Bacteriologic Resistance While Receiving Therapy:
The MO assessed all patients in C88044 who grew one of the 5 "pathogens" during therapy or during the posttherapy period that also had been isolated at baseline to look for the development of resistance (using zone susceptibilities as no MIC's were done).

There were 122 ceftibuten susceptible "pathogens" isolated at baseline from 106 patients (an additional 4 baseline pathogens did not undergo susceptibility testing). For cefaclor there were 116 cefaclor susceptible baseline pathogens isolated from 104 patients (6 additional baseline pathogens did not undergo susceptibility testing).

The MO identified a single β-lactamase (-) *H. influenzae* isolated from a cefaclor recipient (C8804406108) that was susceptible (cefaclor zone=26mm) at entry, became resistant (cefaclor zone=12mm) on day 3, and then was susceptible (cefaclor zone=18mm) again on day 7 (typing was not done to assess possible superinfection).

Clinical/Bacteriologic Efficacy of Study Drugs Against Valid Baseline Pathogens with "Intermediate" Susceptibility:

There were three bronchitis patients in the valid **ceftibuten**-treated population who grew baseline pathogens with "intermediate" susceptibility. The MO's clinical/bacteriologic responses follow (2/3 were clinical successes):

C8804404150: AECB; β-lactamase (-) *H. influenzae* (Zone=20mm). At EOT, the patient was clinically improved followed by **cure** at F/U. Bacteriologic response was documented **eradication**.

C8804425110: AECB; β-lactamase (-) *H. influenzae* (Zone=20mm). By day 11, the patient was a clinical **failure** with presumptive **persistence**.

C8804444102: AECB; *S. pneumoniae* (Zone=20mm). At EOT, the patient was clinically **cured** with sustainment of this response at F/U. Bacteriologic response was documented **eradication**.

****

Likewise, there were two patients in the valid **cefaclor**-treated population who grew baseline pathogens with "intermediate" susceptibility. The MO's responses follow (1/2 were clinical

successes):

C8804404129: AECB; β-lactamase (+) *M. catarrhalis* (Zone=15mm). The patient was not assessed at EOT. However, at F/U, the patient was clinically cured with presumptive eradication.

C8804404158: AECB; β-lactamase (-) *H. influenzae* (Zone=14mm). This patient was a clinical failure after 7 days of therapy with documented persistence.

Clinical/Bacteriologic Efficacy for Ceftibuten-Resistant Pathogens: The reviewer did not consider any of the following patients or pathogens "valid." (2/3 were clinical successes.)

C8804404111 (ceftibuten x 7 days, acute bacterial bronchitis, Safety): This individual grew *H. influenzae* (Zone=15 mm; no MIC was performed; "I" susceptible to cefaclor) from the sputum but did not have a productive cough at baseline; a nonevaluable patient. The applicant considered this patient a clinical cure.

C8804404106 (ceftibuten x 9 days, AECB, Clin Eff): Grew *H. influenzae* at baseline (Zone=17 mm; no MIC was performed; "I" susceptible to cefaclor). By day 3, the *H. influenzae* had been eradicated. End-of-therapy responses (clinical-bacteriologic) were cure and documented eradication, respectively.

C8804410104 (ceftibuten x 7 days, AECB, Clin TOC): Grew *S. pneumoniae* (Zone=9 mm; no MIC was performed; "S" to cefaclor). Extended responses (clinical-bacteriologic) were failure and persistence, respectively.

Outcomes for Patients with Other LRTI's at Baseline Who Received Ceftibuten 400 mg p.o. q.d.: There were 7 such patients in C88044. For the MO, this is an important clinical issue, as not infrequently, patients who have pneumonia at presentation may be misdiagnosed and treated as if they have a less severe LRTI, i.e., bronchitis.

C8804404109: Originally this patient was diagnosed incorrectly By day 2 the patient was considered a failure and placed on I.V. ceftizoxime. *H. influenzae* was isolated at baseline. On day +2, after failing, *S. aureus* was isolated from the sputum. By day +11, "the bilateral infiltrates were worse." According to the applicant, the patient expired on day +17 due to "complications secondary to lung cancer." However, according to the death certificate, the patient died of "postobstructive pneumonia."

C8804404112: This patient was misdiagnosed at baseline with AECB and had pneumonia. Following 10 days of therapy, the patient was considered a clinical cure. The patient remained clinically well up through day +15; the CXR at that time noted "clearing of right lung infiltrate." *Neisseria spp.* was isolated at baseline.

C8804404162: This patient with metastatic colorectal CA and DM was misdiagnosed with *H. influenzae* and *S. pneumoniae* were both isolated at baseline. (The latter had intermediate susceptibility to ceftibuten.) Following 9 days of therapy, the patient was "cured." However, by day +9, there is the new appearance of moderate rales/rhonchi. Also on day +9, *S. pneumoniae* was reisolated from the sputum. Yet, the CXR on day +13 was "normal." This patient also received 5-FU from day 7→+2.

C8804407122: Due to a misdiagnosis at entry of "bronchitis", when the patient actually had pneumonia, this patient was inadvertently placed on ceftibuten, 400 mg p.o. q.d. x 3 days, until this error was detected. The patient was subsequently switched to 200 mg p.o. b.i.d. for the remaining 11 days and was subsequently cured.

C8804411103: This individual with was initially diagnosed with AECB when in actuality a cavitary lung abscess was present. Ceftibuten, 400 mg p.o. q.d. was given for 5 days. The sputum grew "normal flora." However, the patient clinically failed and was switched to I.V. penicillin G.

C8304438004: This patient received ceftibuten, 400 mg p.o. q.d. x 17 days, for "AECB" when pneumonia was actually present. The patient grew *Haemophilus spp.* from the baseline sputum, which was subsequently eradicated. However, the patient clinically failed.

C8804444116: Although being misdiagnosed with "AECB" and had pneumonia. 5 days of ceftibuten 400 mg q.d. therapy were given. This patient was removed from the study due to a "concurrent illness." No clinical assessments were recorded by the investigator beyond baseline. *H. influenzae* grew at baseline.

Ceftibuten Bacteremic Patients:

No patients in C88044 with "bronchitis" experienced bacteremia during the study period. However, there were 3 ceftibuten **pneumonia** patients (1 cefaclor) who grew bacteria from blood cultures during this study - all bacterial isolates were possible contaminants; all ceftibuten patients listed below received 200 mg p.o. b.i.d. dosing:

C8804411002: grew *S. aureus* at baseline (no susceptibilities). Patient also grew *S. pneumoniae* from sputum the same day. The follow-up blood culture on day 6 was negative. This *S. aureus* was probably a contaminant.

C8804427002: grew *S. epidermidis* from blood at baseline; patient had another blood culture the same day which was negative. This was probably a contaminant.

C8804434001: *Staphylococcus spp.* grew at baseline. Follow-up blood culture was negative after 3 days of therapy despite the onset of "sepsis" on day 3. The patient did not grow a pathogen from the sputum at anytime.

> ***Medical Officer's Comment:*** There was another ceftibuten patient, C8804409001, whose blood culture result was listed as "normal flora." Following communication with the applicant, it was determined that this was an error and should have been identified as "sterile" instead.

SAFETY EVALUATION:

The following section contains assessments of all patients (those who were not excluded) who received either ceftibuten 400 mg q.d. or cefaclor 250 mg t.i.d with the exception of deaths where other dosing regimens are included. There were 40 ceftibuten and 24 cefaclor patients who received other dosing regimens, who were not "excluded" and are not included here. Instead, they are included in the MO's review of the overall integrated summary of safety.

Patients Discontinued From Therapy Due to AE:
According to the applicant, 15 patients (9 ceftibuten, 6 cefaclor) were discontinued from the study due to the development of an AE. The specifics follow.

CEFTIBUTEN:

C8804404119: (AECB) This patient developed right upper quadrant pain and "mild" increases of SGOT and SGPT (SGOT and SGPT, 19 IU and 23 IU, respectively, increased to 62 IU and 209, respectively by day 8; normal range up to 45 IU) and "abnormal WBC" (WBC increased from 13,900/mm^3 at baseline to 28,700/mm^3 at day 5. On day 8, ceftibuten was discontinued (WBC = 20,300/mm^3). The investigator considered the LFT abnormalities "probably" due to the study drug; the WBC changes "possibly" due to the study drug.

> ***Medical Officer's Comment:*** Clinically, by end-of-therapy, the applicant considered this patient an "improvement" while the MO considered this patient a "failure." The patient was begun on TMP/SMX on day +4 for persistent productive cough, which may explain the elevated WBC.

C8804411103: See deaths.

C8804415105: After 6 days of therapy, this patient experienced moderate abdominal pain on day 2, pharyngitis on the last day of therapy, mild asthenia, and diaphoresis beginning on day +2. The applicant considered the former "probably" related to ceftibuten while the latter 3 were "unrelated." The abdominal pain disappeared once ceftibuten was discontinued. Of interest, there were mild rises in SGOT (120 IU), SGPT (82 IU), and total bilirubin (1.3 mg/dL) - these were not followed.

C8804421110: This patient only received 1½ doses and discontinued due to mild vomiting, followed by postural hypotension, and syncope. The investigator considered the former "possibly" due to ceftibuten, the latter 2 "unrelated." The patient was placed on erythromycin.

C8804425102: (AECB) Beginning on day 3 of therapy, mild pruritic urticaria developed, which was considered "probably" due to the study drug. Ceftibuten was discontinued on day 6. According to the CRF, the urticaria required additional "therapy." This patient was supposedly allergic to "mycins" and tetracycline. She was switched to TMP/SMX.

C8804425111: (AECB) This patient received 4 days of therapy. On day 3, the patient experienced worsening moderate cough. The investigator considered this "unrelated" to the study drug.

> ***Medical Officer's Comment:*** The MO considered this patient a clinical failure; the applicant's clinical response was "unknown."

C8804431108: (AECB) On the first day of therapy, this patient experienced

severe "colitis." The drug was discontinued that day and the symptoms lasted for 4 more days. The patient was hospitalized, but the investigator considered this "unrelated" to ceftibuten. Patient underwent lower endoscopy and "cultures"; all were negative.

C8804438113: On day 5 of therapy, moderate diarrhea began. Ceftibuten was discontinued on day 8 and the diarrhea resolved. The investigator considered this "possibly" related to ceftibuten. The patient was "treated" with yoghurt for 2 days.

C8804444110: (AECB) Beginning on day 1, moderate dyspepsia ("heartburn") ensued. Ceftibuten was discontinued and the patient improved. The patient also noted "flu-like" symptoms on day 4. The applicant considered the former "probably" related to ceftibuten, the latter "unrelated."

CEFACLOR:

C8804404121: (AECB) Following 6 days of cefaclor, moderate dizziness and moderate blurred vision developed. The drug was discontinued and both symptoms continued. The investigator considered both "unrelated" to study drug.

C8804406108: (AECB) Following 8 days of cefaclor, moderate cardiac failure and lobar pneumonia developed. The investigator considered both "unrelated" to study drug. The patient was hospitalized. The patient was considered a failure and was started on ceftriaxone and furosemide.

C8804406109: (AECB) After having received 3 days of therapy, severe "congestion" and severe nausea/vomiting ensued - two doses were missed. The patient was hospitalized, cefaclor was discontinued, new "antibiotic" therapy was started, and the patient improved. The investigator considered all "unrelated" to the study drug. The patient was receiving theophylline, 300 mg b.i.d. at the time on a chronic dose.

C8804427112: This 52 y.o. male hypertensive, on day 4 of therapy, developed severe chest pain. The patient was hospitalized and the investigator considered this "unrelated" to study cefaclor.

C8804435106: On day 4 of therapy, mild abdominal pain developed lasting 6 days. The study drug was discontinued.

C8804444106: (AECB) Following the 2nd dose of drug, severe chest pain, pruritus, urticaria, and respiratory distress developed. The investigator considered all "related" to the study drug. Cefaclor was discontinued. The patient had a history of atopic dermatitis. Patient given epinephrine and bronchodilators.

DEATHS: There were a total of 9 deaths over the course of this study; 6 ceftibuten, 3 cefaclor. The following includes ALL patients from C88044, independent of drug or underlying LRTI.

CEFTIBUTEN:

C8804404003: (Ceftibuten 200 mg q12h x 13 days; This 67-year-old white male with prostatic adenocarcinoma metastatic to the brain, died on day+8. The investigator considered this "unrelated" to ceftibuten. This patient was a clinical failure despite eradication of the baseline *M. catarrhalis*. According to the CRF, the pneumonia worsened.

C8804404109: (Ceftibuten 400 mg q.d. x 2 days; This 61-year-old

white male clinically failed ceftibuten therapy. At baseline, *H. influenzae* grew; subsequently *S. aureus* grew. Due to the isolation of *S. aureus*, he was switched to ceftizoxime therapy. On day+17 the patient died from complications secondary to lung cancer for which he received large doses of decadron. The death certificate listed this as "post-obstructive pneumonia." However, the investigator states, "I do not believe post-obstructive pneumonia played a significant role in his course." The investigator considered this death "unrelated" to study drug.

C8804404151: (Ceftibuten 400 mg q.d. x 1 day; AECB) This 78-year-old white male with CHF and CAD developed severe oliguria, "unrelated" to ceftibuten, and died the next day. At baseline, the patient's creatinine was 2.4 mg/dL. No follow-up creatinine was reported. The investigator considered this death "unrelated" to study drug. According to the CRF, the patient was admitted with "theophylline toxicity."

C8804404156: (Ceftibuten 400 mg q.d. x 7 days; AECB) This 72-year-old white male with NIDDM and "left hilar mass" died on day +6 due to respiratory insufficiency. According to the investigator, this death was "unexplained, probably due to tracheal obstruction by lymphoma or CAD; at autopsy there was no evidence of infection." Interestingly, the day ceftibuten was discontinued, the patient demonstrated an increased WBC (12,800/mm^3) and a left shift (35% bands). These abnormalities were not present at baseline. According to another section of the CRF, the patient underwent fine needle aspiration of the mediastinal mass "which probably led to bleeding and tracheal obstruction." At baseline, the patient grew *Serratia marcescens* from the sputum and was clinically cured. Subsequent sputum cultures were negative.

C8804410103: (Ceftibuten 400 mg q.d. x 2 days; AECB) This 63-year-old white male with "end-stage COPD" died on day +9; per death certificate this was described as cardiopulmonary arrest due to severe COPD. The investigator considered this "unrelated" to study drug. The patient also had mild pancytopenia. The baseline sputum culture was negative.

C8804411103: (Ceftibuten 400 mg q.d. x 5 days; lung abscess) This 68-year-old white male experienced severe "seizure" on the last day of therapy, day 5, was taken to the ICU and was placed on phenytoin. The investigator considered this "possibly" due to ceftibuten. The patient was receiving theophylline, 300 mg b.i.d. at the time. The theophylline dose had been decreased from 300 mg t.i.d. 2 days prior to this event. There was no history of neurologic problems.

On day +2, the patient died. According to the investigator, this was due to cardiopulmonary arrest and the development of bradycardia. The patient was considered a failure; all cultures were negative.

CEFACLOR:

C8804411011: (Cefaclor 500 mg q8 hrs. x 9 days; This 60-year-old white male with COPD developed SOB prior to discharge from the hospital and was found later in extremis and died on day +5. The investigator does not consider this related to the study drug. This patient grew β-lactamase (+) *M. catarrhalis* at baseline that was "I" susceptibility to cefaclor and subsequently was a clinical "cure." On day +2, *P. aeruginosa*, cefaclor-resistant, grew from the sputum.

C8804411102: (Cefaclor 250 mg q8 hrs. x 11 days; AECB) This 55-year-old white male with CA, metastatic to the lung, died on day +17. The patient was under a "do not resuscitate" order. The investigator considered this "unrelated" to cefaclor. Although the patient was considered a clinical failure. This patient also only received 23 doses of cefaclor over 11 days; a dosing protocol violation. *Haemophilus spp.* and *Pseudomonas spp.* grew at baseline.

At day +17, *Pseudomonas spp.* persisted. No susceptibilities were done for the latter isolate.

C8804417004: (Cefaclor 500 mg q8hrs. x 8 days; This 58-year-old white male with COPD and polymyositis died on day +26. The patient was pulseless for less than 1 min, considered due to a cardiac arrhythmia. The investigator considered this "unrelated" to the study drug. The patient had a seizure disorder and was on chronic phenytoin. The patient was also on chronic theophylline, the dose having been increased on day 5 to 300 mg t.i.d. At baseline, cefaclor-resistant *P. aeruginosa* was isolated. No subsequent cultures were obtained.

CLINICAL ADVERSE EVENTS:

> ***Medical Officer's Comment:*** Combining all studies, no patients experienced diarrhea attributed to *C. difficile*. Only one patient developed colitis. (See above.) No patients were given vancomycin or metronidazole for "diarrhea."

During the course of this study, 64/229 (28%) ceftibuten 400 mg q.d. and 23/102 (23%) cefaclor 250 mg t.i.d. patients experienced at least one AE, independent of relatedness to the drug. Likewise, 39/229 (17%) ceftibuten 400 mg q.d. and 16/102 (16%) cefaclor 250 mg t.i.d. patients experienced a minimum of one AE, which was considered to be at least possibly-related to the drug. (See Tables 39 & 40.)

Independent of relatedness of the AE to the study drugs, in genera , gastrointestinal and neurologic (esp. headache) AE's were seen with greater frequency in the ceftibuten arm equally represented between the 2 treatment arms. (See Table 39.)

When AE's were looked at specifically with regard to relatedness (possibly, probably, and definitely drug-related), there were still proportionally more headaches in the ceftibuten group. (See Table 40.) Otherwise, gastrointestinal AE's were similar.

Table 39
All Clinical AE's by Severity for All Patients who Received Either Ceftibuten 400 mg Q.D. or Cefaclor 250 mg T.I.D. (C88044)
(According to applicant)

Clinical AE's	Ceftibuten (N=229)					Cefaclor (N=102)				
	Mild	Mod	Severe	TOTAL	(%N)	Mild	Mod	Severe	TOTAL	(%N)
AT LEAST ONE AE				64	(28)				23	(23)
Gastrointestinal	21	5	2	28	(12)	5	2	3	9	(9)
Abdominal pain	1	1	-	2	(<1)	1	1	-	2	(2)
Colitis	-	-	1	1	(<1)	-	-	-	0	
Constipation	1	-	-	1	(<1)	-	-	-	0	
Diarrhea	5	1	-	6	(3)	1	1	1	3	(3)
Dyspepsia	1	1	1	3	(1)	-	-	-	0	
Flatulence	1	-	-	1	(<1)	-	-	-	0	
Hemorrhoids	1	-	-	1	(<1)	-	-	-	0	
Loose stools	1	-	-	1	(<1)	-	-	-	0	
Nausea	9	2	-	11	(5)	4	-	2	6	(6)
Oral mucositis	1	-	-	1	(<1)	-	-	-	0	
Vomiting	3	-	-	3	(1)	-	-	2	2	(2)
Neurologic	10	9	4	22	(10)	2	2	1	5	(5)
Agitation	-	-	-	0		-	-	1	1	(1)
Convulsions	-	-	1	1	(<1)	-	-	-	0	
Dizziness	1	-	-	1	(<1)	1	1	0	2	(2)
Headache	5	6	3	14	(6)	2	-	-	2	(2)
Insomnia	2	1	-	0		-	1	-	1	(1)
Miosis	1	-	-	1	(<1)	-	-	-	0	
Mouth dry	1	-	-	1	(<1)	-	-	-	0	
Nervousness	-	1	-	1	(<1)	-	-	-	0	
Taste perv.	1	1	-	2	(<1)	-	-	-	0	
Vision abnl.	-	-	-	0		-	1	-	1	(1)
Hypersensitivity	5	1	1	7	(3)	0	1	1	2	(2)
Pruritus	2	0	1	3	(1)	-	-	1	1	(1)
Rash	1	1	0	2	(<1)	-	1	-	1	(1)
Urticaria	2	0	0	2	(<1)	-	-	-	0	

(Continued)

Table 39 contd.

Clinical AE's	Ceftibuten (N=229) Mild	Mod	Severe	TOTAL	(%N)	Cefaclor (N=102) Mild	Mod	Severe	TOTAL	(%N)
Miscellaneous	14	8	3*	24	(10)	5	2	6	12	(12)
Asthenia	1	-	-	1	(<1)	-	-	-	0	
Back pain	1	-	-	1	(<1)	1	-	-	1	(1)
Cardiac failure	-	-	-	0		-	1	-	1	(1)
Chest pain	-	1	-	1	(<1)	-	-	2	2	(2)
Congestion	-	-	-	0		-	-	1	1	(1)
Coughing	-	1	-	1	(<1)	-	-	2	2	(2)
Dyspnea	-	-	-	0		-	-	1	1	(1)
Epistaxis	1	-	-	1	(<1)	-	-	-	0	
Fatigue	1	1	-	2	(<1)	-	-	-	0	
Gingival bleeding	-	1	-	1	(<1)	-	-	-	0	
Hemoptysis	1	-	-	1	(<1)	-	-	-	0	
Leukorrhoea	-	1	-	1	(<1)	-	-	-	0	
Moniliasis	1	-	-	1	(<1)	-	-	-	0	
Myalgia	1	-	-	1	(<1)	-	-	-	0	
Myocard. infarct.	-	-	1	1	(<1)	-	-	-	0	
Palpitation	1	-	-	1	(<1)	-	-	-	0	
Pharyngitis	2	-	-	2	(<1)	-	-	-	0	
Pleural pain	-	-	-	0		1	-	-	1	(1)
Pneumonia lobar	-	-	-	0		-	1	-	1	(1)
Pneumothorax	1	-	-	1	(<1)	-	-	-	1	(1)
Pruritus genital	-	-	-	0		1	1	1	3	(3)
Renal fail., acute	-	-	1	1	(<1)	-	-	-	0	
Resp. insuff.	-	-	1	1	(<1)	-	-	-	0	
Rhinitis	1	1	-	2	(<1)	-	-	-	0	
SGOT increased	1	-	-	1	(<1)	-	-	-	0	
SGPT increased	1	1	-	2	(<1)	-	-	-	0	
Sneezing	1	-	-	1	(<1)	-	-	-	0	
Somnolence	2	1	-	3	(1)	-	-	-	0	
Tachycardia	-	-	-	0		-	-	1	1	(1)
Vaginitis	-	1	-	1	(<1)	1	-	1	2	(2)
WBC abnormal, NOS	1	-	-	1	(<1)	-	-	-	0	

NOTE: "N" does not include "excluded" patients.
* All three were life-threatening

Table 40
Clinical AE's by Severity Considered Possibly, Definitely, or Probably Drug-Related for All Patients who Received Either Ceftibuten 400 mg Q.D. or Cefaclor 250 mg T.I.D.
(C88044)
(According to applicant)

Clinical AE's	Ceftibuten (N=229)					Cefaclor (N=102)				
	Mild	Mod	Severe	TOTAL	(%N)	Mild	Mod	Severe	TOTAL	(%N)
AT LEAST ONE AE				39	(17)				16	(16)
Gastrointestinal	15	4	1	20	(9)	4	2	2	7	(7)
Abdominal pain	1	1	-	2	(<1)	1	1	-	2	(2)
Constipation	1	-	-	1	(<1)	-	-	-	0	
Diarrhea	2	1	-	3	(1)	1	1	1	3	(3)
Dyspepsia	1	1	1	3	(1)	-	-	-	0	
Flatulence	1	-	-	1	(<1)	-	-	-	0	
Loose stools	1	-	-	1	(<1)	-	-	-	0	
Nausea	7	1	-	8	(3)	3	-	1	4	(4)
Oral mucositis	1	-	-	1	(<1)	-	-	-	0	
Vomiting	2	-	-	2	(<1)	-	-	1	1	(1)
Neurologic	5	6	3	13	(6)	2	1	0	3	(3)
Anxiety	-	-	-	0		-	-	-	0	
Convulsions	-	-	1	1	(<1)	-	-	-	0	
Dizziness	-	-	-	0		1	-	-	1	(1)
Headache	3	4	2	9	(4)	2	-	-	2	(2)
Insomnia	-	-	-	0		-	1	-	1	(1)
Mouth dry	1	-	-	1	(<1)	-	-	-	0	
Nervousness	-	1	-	1	(<1)	-	-	-	0	
Taste perv.	1	1	-	2	(<1)	-	-	-	0	
Hypersensitivity	2	1	1	4	(2)	0	1	1	2	(2)
Pruritus	1	-	-	1	(<1)	-	-	1	1	(1)
Rash	-	1	-	1	(<1)	-	1	-	1	(1)
Urticaria	-	-	2	2	(<1)	-	-	-	0	
Miscellaneous	4	4	0	8	(3)	2	1	3	6	(6)
Chest pain	-	-	-	0		-	-	1	1	(1)
Coughing	-	-	-	0		-	-	2	2	(2)
Fatigue	-	1	-	1	(<1)	-	-	-	0	
Gingival bleeding	-	1	-	1	(<1)	-	-	-	0	
Granulocytopenia	-	-	-	0		-	-	-	0	
Hematuria	-	-	-	0		-	-	-	0	
Leukorrhoea	-	1	-	1	(<1)	-	-	-	0	
Moniliasis	1	-	-	1	(<1)	-	-	-	0	
Pruritus genital	-	-	-	0		1	1	1	3	(3)
Rigors	-	-	-	0		-	-	-	0	
SGOT increased	1	-	-	1	(<1)	-	-	-	0	
SGPT increased	1	-	-	1	(<1)	-	-	-	0	
Somnolence	2	1	-	3	(1)	-	-	-	0	
Vaginitis	-	1	-	1	(<1)	1	-	-	1	(1)
WBC abnormal, NOS	1	-	-	1	(<1)	-	-	-	0	

NOTE: "N" does not include "excluded" patients.

LABORATORY ADVERSE EVENTS:
According to the applicant, the following laboratory AE's are found in Table 41. From their assessment, more patients in the ceftibuten arm experienced an increase in urinary WBC's. Otherwise, laboratory AE's were comparable.

The reviewer developed different criteria to assess the significance of laboratory AE's. (See appendix.) Laboratory changes were not assessed relative to their relatedness to drug therapy as this information was not provided.

For a patient to have "evaluable" laboratory results, the patient was required to have baseline and at least one follow-up result for that specific laboratory parameter.

Using the criteria developed by the MO, in general, few laboratory AE's were noted. Laboratory changes of significance were limited to the urinalyses; more proteinuria and pyuria in ceftibuten arm; more hematuria with cefaclor. (See Table 42.)

Table 42
Abnormal Laboratory Values for Bronchitis/Tracheitis Patients (C88044)§
(According to applicant)

	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Eosinophils	7/192 (4%)	4/80 (5%)
Hemoglobin	11/202 (5%)	3/87 (3%)
Platelets (above 700)	1/195 (<1%)	0/81 (0%)
Platelets (below 100)	1/195 (<1%)	0/81 (0%)
WBC	0/202 (0%)	0/87 (0%)
BUN	9/196 (5%)	7/86 (8%)
Creatinine	0/198 (0%)	0/85 (0%)
SGOT ↑	0/186 (0%)	1/80 (1%)
SGPT ↑	4/182 (2%)	1/78 (1%)
Total bilirubin	3/180 (2%)	4/76 (5%)
Alkaline phosphatase	1/185 (<1%)	0/78 (0%)
Specific Gravity	3/194 (2%)	0/89 (0%)
pH	18/153 (12%)	11/71 (15%)
Glucose	3/152 (2%)	5/71 (7%)
Hemoglobin	7/152 (5%)	4/71 (6%)
Protein	9/152 (6%)	2/71 (3%)
Urine WBC	18/152 (12%)	0/89 (0%)
Urine RBC	18/152 (12%)	10/69 (15%)
Epithelial	32/152 (21%)	12/69 (17%)
Bacteria	21/152 (14%)	8/69 (12%)
Crystals	20/152 (13%)	10/69 (14%)

Criteria for abnormal findings:

SGOT, SGPT - 3 times above the upper limit of normal range.
BUN, Total bilirubin - 25% increase above baseline value and above the upper limit of normal range.
Alkaline phosphatase - above 1.5 times the upper limit of normal range if baseline value is within normal range, otherwise 50% increase above baseline value.
Creatinine - 0.5 mg/dl increase from baseline value and above the upper limit of normal range OR for S.I. Units ≥133 moles/L.
Eosinophils - above 700 mm^3 if baseline value is within normal range.
Hemoglobin - 2 G decrease from baseline.
WBC - below 2.5/mm^3
Platelets - below 100 or above 700 and more than 50% change from baseline value.
Specific gravity - ≤ 1.00 or ≥ 1.075.
pH - ±2.0 units from baseline.
Glucose - 1+ or greater, otherwise increase of 1 from baseline.
Hemoglobin - 1+ or greater, otherwise increase of 1 from baseline.
Protein - if baseline is within the normal range (0/trace) a reading of 1+ or greater. If baseline is initially abnormal than any increase from baseline.
Microscopic U/A:
- WBC - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.
- RBC - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.
- Epithelium - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.
- Bacteria - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.
- Crystals - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.

§ The denominators reflect the total number of patients that had a baseline laboratory assessment with subsequent assessment(s) during treatment.

Table 42
Laboratory AE'S For Patients Who Received Either Ceftibuten 400 mg Q.D. or Cefaclor 250 mg T.I.D. (C88044)*
(According to reviewer)

Patients with baseline labs.	Ceftibuten (N=225)	Cefaclor (N=98)
Eval. Hemoglobin	(n=196)	(n=87)
Drop of ≥3 g/dL	1 (<1)	1 (1)
Eval. WBC	(n=196)	(n=87)
F/U WBC <3.5, drop of ≥1.0	3 (2)	0
Eval ANC	(n=177)	(n=75)
F/U ANC <1.0; NL @ baseline	0	2 (3)
Eval. Eosinophils	(n=188)	(n=80)
F/U Eos >500/mm^3 (2x baseline)	6 (3)	1 (1)
Eval. Platelets	(n=189)	(n=81)
F/U ≤150,000 (drop ≥100,000)	0	0
F/U ≥600,000 (1.5x baseline)	1 (<1)	1 (1)
Eval. Prothrombin time	(n=0)	(n=0)
Eval. Glucose	(n=3)	(n=1)
Inc. or Dec.	0	0
Eval. BUN	(n=188)	(n=86)
F/U flagged & 2x NL baseline	0	0
Eval. Creatinine	(n=190)	(n=85)
F/U flagged & inc. by 25%	1 (<1)	1 (1)
Eval. AST	(n=179)	(n=79)
F/U 3x ULN & baseline	0	0
Eval. ALT	(n=175)	(n=77)
F/U 3x ULN & baseline	1 (<1)	0
Eval. Alkaline phosphatase	(n=178)	(n=78)
F/U 2x ULN & baseline	0	0
Eval. Bilirubin (total)	(n=179)	(n=78)
F/U 1.5x ULN or inc. 1 mg/dL if baseline WNL.	1 (<1)	1 (1)
Eval. Urine glucose	(n=104)	(n=45)
Baseline WNL, F/U ≥+2	0	2 (4)
Eval. Urine protein	(n=104)	(n=45)
Baseline WNL, F/U ≥+1	7 (7)	1 (2)
Eval. Urine [illegible]	(n=104)	(n=45)
Baseline F/U ≥+1	6 (6)	4 (9)
Eval. Urine WBC'S	(n=105)	(n=44)
Baseline WNL, F/U ≥6/LPF	7 (7)	1 (2)
Eval. Urine RBC's	(n=105)	(n=44)
Baseline WNL, F/U ≥6/LPF	4 (4)	5 (11)

* Laboratory changes were not assessed relative to their relatedness to drug therapy. "Excluded" patients are not included in this table.

CONCLUSIONS:

Using the **clinical test-of-cure** population as the primary efficacy population (those patients who were clinically assessed on day +4 or later), independent of type of bronchitis, the success rate for ceftibuten was 68/114 (60%) versus 32/45 (71%) for cefaclor. Using the 95% C.I. approach, corrected for unequal sample sizes, this is {-29%, 6%}. Uncorrected, this is {-27%, 5%}. If these groups are separated into type of underlying bronchitis, numbers are too small to reach statistical significance.

If the MO's **clinical efficacy** population is looked at, analogous to the applicant's clinical efficacy population, the following is seen. A positive (successful) response was noted for 125/168 (74%) of ceftibuten patients in contrast to 54/66 (82%) of cefaclor recipients; uncorrected, this is {-19%, 4%}. Either way, this doesn't meet the 95% CI approach. There exists a trend here that ceftibuten was less effective than cefaclor.

Of interest, when the reviewer looked at the clinical outcomes for the valid population, in general, these patients tended to have a better outcome than the clinical test-of-cure population. Of course, the only difference between these two groups was the isolation of a "pathogen" at baseline. The better outcome in valid patients is potentially explained by the inclusion of patients in the clinical populations who either did not have a bacteriologic cause for their illness **despite** a "positive" baseline Gram's stain - thus anti-infective therapy would be ineffective, OR inclusion of bacterial isolates, other than the 5 "pathogens" looked for in this review. Furthermore, a clinical population would include "resistant" pathogens.

According to the applicant, by EOT for their **clinical efficacy** population (those patients seen right at end-of-therapy), independent of the type of bronchitis, 165/190 (87%) and 67/78 (86%) of ceftibuten and cefaclor patients, respectively experienced a successful response. The uncorrected 95% CI = {-8%, 10%}.

When separated into types of bronchitis, for acute bacterial bronchitis, success rates are 74/88 (84%) vs. 31/37 (84%), respectively. Corrected 95% CI = {-16%, 16%}. This barely exceeds the -15% acceptable for the lower limit of the 95% CI when the success rates are in the % range. For AECB, 91/102 (89%) vs. 35/40 (88%) with the following 95% CI, both corrected and uncorrected: {-12%, 15%}; {-10%, 14%}. According to the applicant's findings, ceftibuten is as effective as cefaclor in the treatment of AECB.

With regard to bacteriologic efficacy, there were few "pathogens" evaluable. The most common pathogens were *H. influenzae* and *H.*

parainfluenzae. If all pathogens are combined, from the reviewer's assessment the following eradication rates are seen (combined presumptive and documented): for ceftibuten, 38/46 (83%) vs. 16/19 (84%) for cefaclor. The corrected 95% CI = {-25%, 22%}.

Relative to <u>safety</u>, when only clinical AE's considered related to the study drug are looked at, more patients complained or neurologic AE's. Otherwise, the drugs were comparable. With regard to laboratory AE's assessed by the MO, the only differences between the study drugs noted included urinalysis changes. No cases of *C. difficile* were identified.

INTERNATIONAL STUDIES I88111, I88217, and I88327:

Medical Officer's Comment: I88111 centers were located in Central and South America; I88217 centers were located in Western Europe; I88327 centers were located in Canada.

Study Investigators/Centers:

I88-111-01
Pedro Leal Del Rosal, MD
Clinica Del Parque
Calle 12 y de la Llave
Chihuahua, Chih.
MEXICO

I88-111-02
Jorge M. Hill Juarez, MD
Hospital 20 De Noviembre
(I.S.S.S.T.E.)
Félix Cuevas y Ave. Coyoacàn
Mexico City, MEXICO

I88-111-03
Francisco Maglio, MD
Hospital Naval Bs. As.
Patricias Argentinas 351
Buenos Aires, ARGENTINA

I88-111-04
Luis Soto Roman, MD
National Institute for
Respiratory Diseases and
Thoracic Surgery
José M. Infante 711
Santiago, CHILE

I88-111-05
Paulo E. Marques, MD
La Universidad del Zulia
Maracaibo, VENEZUELA

I88-111-06
Eduardo Rodriguez Noriega, MD
Hospital Civil
Justo Sierra 2350- 1er.P1S0
Guadalajara, Jal 44680
MEXICO

I88-111-07
Luis Soto Roman, MD
National Institute for
Respiratory Diseases and
Thoracic Surgery
José M. Infante 711
Santiago, CHILE

I88-111-08
Pedro Manuel Pacheco, MD
Hospital Santa Clara
Carrera 15 No. 1-59 S
Bogota, COLOMBIA

I88-217-01
Alan G. Wade, MD/
Gordon M. MacDonald, MD[2]
Clydebank Health Centre
Kilbowie Road, Clydebank
Glasgow G81 2TQ
UNITED KINGDOM

I88-217-02
R.M. Rudd, MD
London Chest Hospital
Bonner Road, London F29JX
UNITED KINGDOM

[2] Sub-investigator.

I88-217-03
Alan G. Wade, MD/
Rosemary Dargie, MD[3]
Clydebank Health Centre
Kilbowie Road, Clydebank
Glasgow G81 2TQ
UNITED KINGDOM

I88-217-04
R. Rawlins, MD
The Surgery
Ancho Road, Coleford, Bath
Avon BA3 5PG

UNITED KINGDOM

I88-217-05
P. Mary, MD
Clinique Ste Anne
Place de la Vaillance
14A-1070
Bruxelles, BELGIUM

I88-217-06
Philippe Lefebvre, MD
Centre De Sante Des Fagnes
Boulevard Louise 18
6460 Chimay, BELGIUM

I88-217-07
Pal Boelcskei, MD
Clinical Center Nuremberg,
Center for Internal Medicine,
Department of Pneumology
Flurstrasse 17, D-8500
Nuremberg 91, GERMANY

I88-217-08
Gerhard Siemon, MD
Hospital Donaustauf
Ludwigstrasse 68
D8405 Donaustauf
GERMANY

I88-217-09
Ralf Wettengel, MD
Karl Hansen Clinic for
Respiratory Tract Diseases
and Allergy
Antoniusstrasse 19
D-4792 Bad Lippsringe
GERMANY

I88-217-11
Pentti Hänninen, MD
Department of Infectious
Diseases, University of
Turku
Kommunalsjokhusvägen 20
SF-20 700 Turku,
FINLAND

I88-217-12
Stig Cronberg, MD
Infektionskliniken
Malmö Allmänna Sjukhus
214 01 Malmö, SWEDEN

I88-217-13
Johan Carlson, MD
Infektionskliniken
Akademiska Sjukhuset
751 85 Uppsala, SWEDEN

I88-217-14
Per Niklasson, MD
Infektionskliniken,
Vaxjo lasurett
351 85 Växjö, SWEDEN

I88-217-15
John Kosmidis, MD
The General Hospital of
Athens
Mesoghion Street
Athens, GREECE

[3] Sub-investigator.

I88-217-16
George Saroglous, MD
Alexandra Hospitals
Vess. Sophias-Lourou Street
11528 Athens, GREECE

I88-217-17
Otto Brändli, MD
Zurcher Höhenklinik Wald
CH-8639 Faltigberg
SWITZERLAND

I88-217-18
Helen Giamarellou, MD
Laikon Hospital
University of Athens
17, Ag. Thomas Street
Athens, GREECE

I88-217-19
Michael Grillage, MD
Northbrook Health Centre
Northbrook Road
W. Midlands B90 3LX
UNITED KINGDOM

I88-217-20
A. Wade, MD
Clydebank Health Centre
Kilbowie Road, Clydebank
Glasgow 681 2TQ
UNITED KINGDOM

I88-217-21
Paolo Conti, MD
Divisione di Pneumologia
Ospedale Pneumologico
Corso Casale 31, 13100
Vercelli, ITALY

I88-217-22
Massimo Andreoni, MD
Divisione di Medicina Infetivi
Ospedale Maggiore
Corso Mazzini 18
28100 Novara, ITALY

I88-217-23
S.P. Wadera, MBBS, DA
The Surgery
478 Landseer Road
Ipswich, Suffolk
UNITED KINGDOM

I88-217-24
R.B. Baghdjian, MD
The Health Centre
Collison Road
Chorley, Lancs
UNITED KINGDOM

I88-327-01
Joe Dylewski, MD
St. Mary's Hospital
3830 Lacombe Avenue
Montreal, Quebec H3T 1M5
CANADA

I88-327-02
Hovsep Baghdalian, MD
Lakeshore General Hospital
160 Stillview
Pointe Claire, Quebec H9R 242
CANADA

I88-327-03
Hugh G. Robson, MD
Royal Victoria Hospital
687 Pine Avenue West
Montreal, Quebec H3A 1A1
CANADA

I88-327-04
Thomas J. Louie, MD
Calgary General Hospital
841 Centre Ave., East
Calgary, Alberta T2E 0A1
CANADA

I88-327-05
Bya Clecner, MD
Hôtel-Dieu de St. Jérôme
Quebec J7Z 5T3
CANADA

I88-327-06
Irving Salit, MD
Toronto General Hospital
200 Elizabeth Street
Toronto, Ontario
CANADA

I88-327-07
Charles K. Chan, MD
The Wellesley Hospital
Jones Building, Suite 242
160 Wellesley Street, East
Toronto, Ontario M4Y 1J3
CANADA

Based on the curriculum vitae submitted, the following investigators did not have prior experience in the conduct of clinical drug trials: Drs. Soto-Roman, Marques, Pacheco, Rudd, Rawlins, Mary, Lefebvre, Boelcskei, Cronberg, Carlson, Niklasson, Brändli, Conti, Andreoni, Wadera, Baghdjian, Baghdalian, and Salit.

The following centers did not enroll any patients: I88111, centers 5,6,8; I88217, centers 4,10,12,13,16; I88327, centers 2,4,5. I88217, center 11, and I88327, center 6, did not enroll bronchitis/tracheitis patients. Furthermore, in study I88111, centers 4 and 7, as well as for study I88217, centers 1, 3 and 20, were run by the same investigators.

ENROLLMENT & EVALUABILITY:
According to the applicant, in the international studies, there were 399 patients enrolled

For the reviewer, following a detailed review of the data base and CRF's, 261 patients were identified with bronchitis. (See Table 2.)

The reviewer also reviewed the enrollments and evaluabilities for specific centers and according to type of bronchitis. (See Tables 3-5.) According to the applicant, approx. 45% of bronchitis patients were clinically and microbiologically evaluable. For the reviewer, for the clinical test-of-cure population, 40-50% were evaluable; evaluability was lower in the cefaclor group. When microbiologically and clinically evaluable patients were examined, the "valid" population, this fell to approximately 20-50% overall.

As in C88044, the MO excluded from clinical evaluation those patients the reviewer could identify who had inappropriate baseline sputa. There were 4 patients as listed below. These

consisted of 1 cefaclor and 3 ceftibuten patients.

I88217: center 18: 111
center 21: 107
center 24: 101
I88327: center 07: 001

Medical Officer's Comment: The international studies, in general, were less likely to contain information concerning the baseline sputum Gram's stain in the comment section of the CRF, in contrast to the domestic study. Hence, it is likely that there may be other patients from the international centers who, in reality, had unacceptable baseline sputa.

Table 1
Summary of Evaluability, Dosing Regimens, and Underlying (International)
(According to applicant)

	Bronchitis/Tracheitis		Pneumonia/Bronchiectasis		
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID	Ceftibuten 200 mg BID	Cefaclor 500 mg TID	Total
Enrolled	**182**	**86**	**87****	**44***	**399**
Excluded	7	4	1	1	13
Safety	175	82	86**	43*	386
Clinical Efficacy	169	79	-	-	248
Modified intent-to-treat	5	3	0	1	9
Expanded Efficacy	9	7	4	0	20
Supportive Population	4	0	5	0	9
Valid	83	39	56	22	200

* Includes one bronchiectasis patient treated with cefaclor 250 mg t.i.d.
** Includes one bronchiectasis patient treated with ceftibuten 400 mg q.d.

Table 2
Summary of Evaluability, Dosing Regimens, for Type of Bronchitis (International)
(According to reviewer)

	Acute bacterial bronchitis		AECB		
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID	Ceftibuten 400 mg QD	Cefaclor 250 mg TID	Total
Enrolled	**85**	**35**	**90***	**51**	**261**
Excluded	2	1	1	0	4
Safety	83	34	89*	51	257
Clinical efficacy	80	32	86*	48	246
Clinical test-of-cure	37	10	51*	28	126
Valid	21	7	39	18	85

* Includes one AECB patient treated with ceftibuten 200 mg t.i.d.

Medical Officer's Comment: In the reviewer's classification of all LRTI patients, the reviewer reclassified "tracheitis" patients (n=5) as either acute bacterial bronchitis (n=3), AECB (n=1), or pneumonia (n=1) patients.

Table 3
Investigator/Drug Enrollment and Evaluability for Valid Bronchitis/Tracheitis Patients Who Received Either Ceftibuten 400 mg q.d., Ceftibuten 200 mg b.i.d., or Cefaclor 250 mg t.i.d.
(According to applicant)

		No. Evaluable/No. Enrolled (%Evaluable)					
		Ceftibuten 400 mg qd		Cefaclor 250 mg tid		Combined	
I88-111-01	Del Rosal	3/5	(60)	1/2	(50)	4/7	(57)
I88-111-02	Hill-Juarez	9/9	(100)	5/5	(100)	14/14	(100)
I88-111-03	Maglio	7/7	(100)	3/3	(100)	10/10	(100)
I88-111-04	Soto-Roman	2/5	(40)	0/3	(0)	2/8	(25)
I88-111-07	Soto-Roman	4/6	(67)	3/4	(75)	7/10	(70)
I88-217-01	Wade	3/14	(21)	1/4	(25)	4/18	(22)
I88-217-02	Rudd	0		0/1	(0)	0/1	(0)
I88-217-03	Wade	0/12	(0)	0/6	(0)	0/18	(0)
I88-217-05	Mary	1/4	(25)	0/1	(0)	1/5	(20)
I88-217-06	Lefebvre	1/1	(100)	1/1	(100)	2/2	(100)
I88-217-07	Boelcskei	4/5	(80)	0		4/5	(80)
I88-217-08	Siemon	3/7	(43)	1/4	(25)	4/11	(36)
I88-217-09	Wettengel	12/20	(60)	6/10	(60)	18/30	(60)
I88-217-14	Niklasson	0/4	(0)	0/4	(0)	0/8	(0)
I88-217-15	Kosmidis	3/5	(60)	2/3	(67)	5/8	(63)
I88-217-17	Brändli	6/14	(43)	2/6	(33)	8/20	(40)
I88-217-18	Giamarellou	9/17	(53)	5/9	(56)	14/26	(54)
I88-217-19	Grillage	2/5	(40)	0/2	(0)	2/7	(29)
I88-217-20	Wade	2/12	(17)	2/6	(33)	4/18	(22)
I88-217-21	Conti	4/6	(67)	3/3	(100)	7/9	(78)
I88-217-22	Andreoni	1/4	(25)	2/2	(100)	3/6	(50)
I88-217-23	Wadera	2/11	(20)	1/4	(25)	3/15	(20)
I88-217-24	Baghdjian	0/1	(0)	0		0/1	(0)
I88-327-01	Dylewski	3/4	(75)	0/2	(0)	3/6	(50)
I88-327-03	Robson	1/3	(33)	0		1/3	(33)
I88-327-07	Chan	0		1/1	(100)	1/1	(100)
Total		**83/182**	**(46)**	**39/86**	**(45)**	**122/268**	**(46)**

Table 4
Investigator/Center Drug Enrollment for Clinical Test-of-Cure Bronchitis Patients Who Received Either Ceftibuten 400 mg q.d., Ceftibuten 200 mg b.i.d., or Cefaclor 250 mg t.i.d.
(According to reviewer)

		No. Clin. T-O-C/No. Enrolled (%Evaluable)		
		Ceftibuten 400 mg qd	Cefaclor 250 mg tid	Combined
ACUTE BACTERIAL BRONCHITIS				
I88-111-01	Del Rosal	0/1 (0)	0/1 (0)	0/2 (0)
I88-111-02	Hill-Juarez	5/5 (100)	3/3 (100)	8/8 (100)
I88-111-03	Maglio	0/6 (0)	0/2 (0)	0/8 (0)
I88-111-04	Soto-Roman	0/1 (0)	1/2 (50)	1/3 (33)
I88-111-07	Soto-Roman	0	0/1 (0)	0/1 (0)
I88-217-01	Wade	2/11 (18)	0/4 (0)	2/15 (13)
I88-217-02	Rudd	0	0	0
I88-217-03	Wade	1/10 (10)	0/5 (0)	1/15 (7)
I88-217-05	Mary	1/3 (33)	0	1/3 (33)
I88-217-06	Lefebvre	0	0	0
I88-217-07	Boelcskei	0/1 (0)	0	0/1 (0)
I88-217-08	Siemon	1/2 (50)	0/1 (0)	1/3 (33)
I88-217-09	Wettengel	1/1 (100)	1/1 (100)	2/2 (100)
I88-217-14	Niklasson	3/4 (75)	1/2 (50)	4/6 (67)
I88-217-15	Kosmidis	4/4 (100)	1/1 (100)	5/5 (100)
I88-217-17	Brändli	0	0	0
I88-217-18	Giamarellou	1/1 (100)	0	1/1 (100)
I88-217-19	Grillage	4/5 (80)	0/1 (0)	4/6 (67)
I88-217-20	Wade	2/11 (18)	0/6 (0)	2/17 (12)
I88-217-21	Conti	1/2 (50)	0	1/2 (50)
I88-217-22	Andreoni	1/3 (33)	1/2 (50)	2/5 (40)
I88-217-23	Wadera	7/7 (100)	1/1 (100)	8/8 (100)
I88-217-24	Baghdjian	0/1 (0)	0	0/1 (0)
I88-327-01	Dylewski	1/3 (33)	1/2 (50)	2/5 (40)
I88-327-03	Robson	2/3 (67)	0	2/3 (67)
I88-327-07	Chan	0	0	0
Total		**37/85 (44)**	**10/35 (29)**	**47/120 (39)**

(Contd.)

Table 4 (contd.)

		No. Evaluable/No. Enrolled (%Evaluable)		
		Ceftibuten 400 mg qd	Cefaclor 250 mg tid	Combined
AECB				
I88-111-01	Del Rosal	1/4 (25)	0/1 (0)	1/5 (20
I88-111-02	Hill-Juarez	1/1 (100)	1/1 (100)	2/2 (100
I88-111-03	Maglio	0/1 (0)	0/1 (0)	0/2 (0)
I88-111-04	Soto-Roman	4/4 (100)	1/1 (100)	5/5 (100)
I88-111-07	Soto-Roman	4/6 (67)	2/3 (67)	6/9 (67)
I88-217-01	Wade	0/1 (0)	0/2 (0)	0/3 (0)
I88-217-02	Rudd	0	0/1 (0)	0/1 (0)
I88-217-03	Wade	1/2 (50)	0/1 (0)	1/3 (33)
I88-217-05	Mary	1/1 (100)	0/1 (0)	1/2 (50)
I88-217-06	Lefebvre	1/1 (100)	1/1 (100)	2/2 (100)
I88-217-07	Boelcskei	2/4 (50)	0	2/4 (50)
I88-217-08	Siemon	2/4 (50)	1/3 (33)	3/7 (43)
I88-217-09	Wettengel	16/19 (84)	7/9 (78)	23/28 (82)
I88-217-14	Niklasson	0	2/2 (100)	2/2 (100)
I88-217-15	Kosmidis	1/1 (100)	2/2 (100)	3/3 (100)
I88-217-17	Brändli	9/14 (64)	3/6 (50)	12/20 (60)
I88-217-18	Giamarellou	3/15 (20)	3/9 (33)	6/24 (25)
I88-217-19	Grillage	0	1/1 (100)	1/1 (100)
I88-217-20	Wade	0/1 (0)	0	0/1 (0)
I88-217-21	Conti	0/4 (0)	2/3 (67)	2/7 (29)
I88-217-22	Andreoni	0/1 (0)	0	0/1 (0)
I88-217-23	Wadera	3/4 (75)	2/2 (100)	5/6 (83)
I88-217-24	Baghdjian	0	0	0
I88-327-01	Dylewski	1/1 (100)	0	1/1 (100)
I88-327-03	Robson	0	0	0
I88-327-06	Salit	1/1 (100)	0	1/1 (100)
I88-327-07	Chan	0	0/1 (0)	0/1 (0)
Total		**51/90 (57)***	**28/51 (55)**	**79/141 (56)**
GRAND TOTAL		***88/175 (50)****	***38/86 (44)***	***125/261 (48)***

* Includes one clinical test-of-cure patient, who received ceftibuten 200 mg b.i.d.

Table 5
Investigator/Center Drug Enrollment for Valid Bronchitis Patients Who Received Either Ceftibuten 400 mg q.d., Ceftibuten 200 mg b.i.d., or Cefaclor 250 mg t.i.d.
(According to reviewer)

		No. Valid Eff./No. Enrolled (%Evaluable)		
		Ceftibuten 400 mg qd	Cefaclor 250 mg tid	Combined
ACUTE BACTERIAL BRONCHITIS				
I88-111-01	Del Rosal	0/1 (0)	0/1 (0)	0/2 (0)
I88-111-02	Hill-Juarez	4/5 (80)	3/3 (100)	7/8 (88)
I88-111-03	Maglio	0/6 (0)	0/2 (0)	0/8 (0)
I88-111-04	Soto-Roman	0/1 (0)	1/2 (50)	1/3 (33)
I88-111-07	Soto-Roman	0	0/1 (0)	0/1 (0)
I88-217-01	Wade	1/11 (9)	0/4 (0)	1/15 (7)
I88-217-02	Rudd	0	0	0
I88-217-03	Wade	0/10 (0)	0/5 (0)	0/15 (0)
I88-217-05	Mary	1/3 (33)	0	1/3 (33)
I88-217-06	Lefebvre	0	0	0
I88-217-07	Boelcskei	0/1 (0)	0	0/1 (0)
I88-217-08	Siemon	1/2 (50	0/1 (0)	1/3 (33)
I88-217-09	Wettengel	1/1 (100)	1/1 (100)	2/2 (100)
I88-217-14	Niklasson	1/4 (25)	0/2 (0)	1/6 (17)
I88-217-15	Kosmidis	4/4 (100)	1/1 (100)	4/5 (80)
I88-217-17	Brändli	0	0	0
I88-217-18	Giamarellou	1/1 (100)	0 (0)	1/1 (100)
I88-217-19	Grillage	2/5 (40)	0/1 (0)	2/6 (33)
I88-217-20	Wade	1/11 (9)	0/6 (0)	1/17 (6)
I88-217-21	Cont.	0/2 (0)	0	0/2 (0)
I88-217-22	Andreoni	0/3 (0)	0/2 (0)	0/5 (0)
I88-217-23	Wadera	3/7 (43)	0/1 (0)	3/8 (38)
I88-217-24	Baghdjian	0/1 (0)	0	0/1 (0)
I88-327-01	Dylewski	1/3 (33)	1/2 (50)	2/5 (40)
I88-327-03	Robson	0/3 (0)	0	0/3 (0)
I88-327-07	Chan	0	0	0
Total		**21/85 (25)**	**7/35 (20)**	**28/120 (23)**

Contd.

Table 5 (contd.)

		No. Evaluable/No. Enrolled (%Evaluable)		
		Ceftibuten 400 mg qd	Cefaclor 250 mg tid	Combined
AECB				
I88-111-01	Del Rosal	1/4 (25)	0/1 (0)	1/5 (20)
I88-111-02	Hill-Juarez	1/1 (100)	1/1 (100)	2/2 (100)
I88-111-03	Maglio	0/1 (0)	0/1 (0)	0/2 (0)
I88-111-04	Soto-Roman	4/4 (100)	1/1 (100)	5/5 (100)
I88-111-07	Soto-Roman	3/6 (50)	1/3 (33)	4/9 (44)
I88-217-01	Wade	0/1 (0)	0/2 (0)	0/3 (0)
I88-217-02	Rudd	0	0/1 (0)	0/1 (0)
I88-217-03	Wade	0/2 (0)	0/1 (0)	0/3 (0)
I88-217-05	Mary	1/1 (100)	0/1 (0)	1/2 (50)
I88-217-06	Lefebvre	1/1 (100)	1/1 (100)	2/2 (100)
I88-217-07	Boelcskei	0/4 (0)	0	0/4 (0)
I88-217-08	Siemon	2/4 (50)	0/3 (0)	2/7 (29)
I88-217-09	Wettengel	15/19 (79)	7/9 (78)	22/28 (79)
I88-217-14	Niklasson	0	1/2 (50)	1/2 (50)
I88-217-15	Kosmidis	1/1 (100)	1/2 (50)	2/3 (67)
I88-217-17	Brändli	6/14 (43)	1/6 (17)	7/20 (35)
I88-217-18	Giamarellou	3/15 (20)	3/9 (33)	6/24 (25)
I88-217-19	Grillage	0	0/1 (0)	0/1 (0)
I88-217-20	Wade	0/1 (0)	0	0/1 (0)
I88-217-21	Conti	0/4 (0)	0/3 (0)	0/7 (0)
I88-217-22	Andreoni	0/1 (0)	0	0/1 (0)
I88-217-23	Wadera	0/4 (0)	1/2 (50)	1/6 (17)
I88-217-24	Baghdjian	0	0	0
I88-327-01	Dylewski	1/1 (100)	0	1/1 (100)
I88-327-03	Robson	0	0	0
I88-327-06	Salit	0/1	0	0/1
I88-327-07	Chan	0	0/1 (0)	0/1 (0)
Total		39/90 (43)	18/51 (35)	57/141 (40)
GRAND TOTAL		*60/175 (34)*	*25/86 (29)*	*85/261 (33)*

Completion Status of Enrolled Patients:
From the applicant's data, the reviewer determined that 239/268 (89%) of bronchitis/tracheitis patients completed the study. (See Table 6.) Many more patients in the international study completed it than they did in the domestic study, C88044.

Table 6
Noncompletion Reasons for Bronchitis Patients (International)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Total # of Patients Enrolled	182	86
Completed study	164 (90)	75 (87)
D/C adverse experience	2 (1)	2 (2)
D/C death	1 (<1)	0
D/C did not meet entry criteria	4 (2)	2 (2)
D/C pt. did not return	6 (3)	6 (7)
D/C treatment failure	5 (3)	1 (1)

Summary of Nonevaluability:
Both the applicant and reviewer examined reasons for nonevaluability. (See Tables 7 and 8.) Very few were excluded specifically from the reviewer's clinical efficacy population. However, a greater proportion were excluded from the clinical test-of-cure population in comparison to C88044.

> ***Medical Officer's Comment:*** As previously stated, following discussions with the applicant, for the patients who were "misrandomized," Schering **was** able to determine with certainty which drug treatment these patients received.

Table 7
Summary of Patient Status for Bronchitis Patients and Reasons for Exclusion from Clinical Efficacy Population (International)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Total # of Patients Enrolled	182	86
Safety Population	175 (96)	82 (95)
Clinical Efficacy Population	169 (93)	79 (92)
Excluded from All Populations	7 (4)	4 (5)
Misrandomized (unknown rx)	5 (3)	4 (5)
Never Received Medication	2 (1)	0
Drop-out/lost to follow-up	1	0
No pathogen isolated pretherapy	1	0
Excluded from Clinical Efficacy Population, Included in Safety Population	6 (3)	3 (3)
Did not Meet Entrance Criteria	3 (2)	2 (2)
No pathogen isolated pretherapy	3	2
Insufficient Efficacy Data	3 (2)	1 (2)
Drop-out/adverse reaction	1	0
Drop-out/lost to follow-up	2	1

Table 8
Summary of Patient Status for Bronchitis Patients and Reasons for Exclusion from Clinical Efficacy Population (International)
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Total # of Patients Enrolled	175*	86
Safety Population	172 (98)*	85 (99)
Clinical Efficacy Population	166 (95)*	80 (93)
Excluded from All Populations	3 (2)	1 (1)
Did not return after first visit	1	1
Never received medication	2	0
Excluded from Clinical T-O-C Population, But Included in Clinical Eff. Population	78 (45)	42 (49)
Excluded from Clinical Efficacy Population, But Included in Safety Population	6 (3)	5 (6)
Insufficient medication	3	1
Inadequate baseline sputum	2	1
Insufficient efficacy data	0	1
Unacceptable concom. anti-infective Rx	0	2‡
Wrong diagnosis	1†	0

* Includes a single patient who received ceftibuten 200 mg b.i.d.
† I8821701112 had infectious mononucleosis
‡ I8821718112 received ampicillin for one day prior to entry which may have contributed (the patient grew H. parainfluenzae at baseline); I8821718126 received Augmentin® for two days prior to entry which may have contributed (the patient grew H. parainfluenzae at baseline).

Applicant and Reviewer Evaluability Differences:
The applicant and reviewer differed with regard to the evaluability of several "valid" bronchitis patients. (See Tables 9 and 10.) Specific examples can be found in the footnotes to the tables. For further discussion, the reader is referred to the review of C88044.

Table 9
Bronchitis Patients Considered "Valid" by the Applicant and the Reviewer's Assessment of Their Evaluability (International)
(According to reviewer - using applicant's bronchitis diagnoses)

MO's Evaluability	Ceftibuten 400 mg QD (n=83)	Cefaclor 250 mg TID (n=39)
Valid	42	15
Clinical Test-of-Cure	4*	5
Clinical Efficacy	33	16
Safety	1[A]	2[B]

* Includes a single ceftibuten 200 mg b.i.d. patient.
A I8821721107 did not have a productive cough at baseline.
B I8821718112 received ampicillin for one day prior to entry which may have contributed to the patients good clinical response (the patient grew *H. parainfluenzae* at baseline); I8821718126 received Augmentin® for two days prior to entry which may have contributed as well (the patient grew *H. parainfluenzae* at baseline).

Table 10
Bronchitis Patients Considered "Valid" by the Reviewer Whom the Applicant Did Not Consider Valid (International)
(According to reviewer - using MO's bronchitis diagnoses)

Applicant's Evaluability	Ceftibuten 400 mg QD (n=18)	Cefaclor 250 mg TID (n=10)
Supportive	3[A]	-
Expanded Efficacy	4[B]	4
Clinical Efficacy	8[C]	3[F]
Modified Intent-to-Treat	2[D]	2[G]
Excluded	1[E]	1[H]

A I8811107102, I8821717117, and I8821718114 all grew pathogens which were susceptible to ceftibuten; but "intermediate" susceptibility to cefaclor.
B I8821709128 was excluded from the valid population by the applicant due to "unacceptable concomitant therapy." However, this therapy was ofloxacin which the patient was placed on due to "failure."
C I8811104101 grew "I" susceptible *S. pneumoniae* at baseline; I8811104106 grew "I" susceptible *S. pneumoniae* at baseline; I8821705107 did not have baseline susceptibilities recorded in contrast to the applicant's exclusion reason of "resistant"; I3821709103 grew "I" susceptible *S. pneumoniae* at baseline; I8821709119 grew "I" susceptible *S. pneumoniae* at baseline; I8821709120 grew "I" susceptible *H. influenzae* at baseline; I8821715102 grew "I" susceptible *H. influenzae* at baseline; I8821715106 grew "I" susceptible *M. catarrhalis* at baseline.
D Both patients were excluded from the valid population by the applicant due to "unacceptable concomitant therapy. However, I8821709130 was treated with ofloxacin due to "failure"; I8821717113 was treated with Augmentin® due to "failure."
E I8821714003 was excluded to due "misrandomization." However, the investigator did not become unblinded.
F I8811104102, I8821709108, I8821709123 all grew pathogens which were susceptible to cefaclor, but "I" susceptibility to ceftibuten.
G Both patients were excluded from the valid population by the applicant due to "unacceptable concomitant therapy. Both, I8821709126 and I8821709129 were treated with amoxicillin due to "failure."
H I8821714005 was excluded to due "misrandomization." However, the investigator did not become unblinded.

Baseline Demographics:
For the **enrolled population**, slightly more patients with AECB were enrolled in the cefaclor arm. (See Tables 11 and 12.) Otherwise, treatment groups appeared to be well-matched.

In the **clinical test-of-cure** group, the difference in proportion of AECB patients between treatment arms was greater here. (See Tables 13 and 14.) A greater proportion of AECB patients were inpatients.

Medical Officer's Comment: For the international studies, on average, patients received approximately 5.8 mg/kg/day of ceftibuten.

Table 11
Demographic Data for All Enrolled Patients with Bronchitis* (International)
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten 400 mg QD (n=175)**	Cefaclor 250 mg TID (n=86)
Sex		
Male	113 (65)	55 (64)
Female	61 (35)	31 (36)
Not recorded	1 (<1)	0
Race		
White	166 (95)	83 (97)
Black	3 (2)	0
Other	6 (3)	2 (2)
Not recorded	0	1 (1)
Patient Status		
Inpatient	86 (49)	44 (51)
Outpatient	85 (49)	42 (48)
Not recorded	4 (2)	2 (1)
Age (yr)		
Mean	56.1	55
Median	59	59
Range (min-max)		
Weight (kg)		
Mean	69.3	68.4
Median	69.5	68.0
Range (min-max)		
Not Recorded	1	1
Diagnosis		
Acute Bacterial Bronchitis	85 (49)	35 (41)
AECB	90 (51)	51 (58)

* This table includes the diagnoses reassigned by the reviewer.
** Includes a single patient who received ceftibuten 200 mg b.i.d.

Table 12
Demographic Data for the Enrolled Bronchitis Patients According to the Type of Bronchitis (International)
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten	Cefaclor
Acute Bacterial Bronchitis	(n=85)	(n=35)
Sex		
Male	53 (62)	23 (66)
Female	32 (38)	12 (34)
Race		
White	82 (96)	34 (97)
Black	2 (2)	0
Other	1 (1)	1 (3)
Patient Status		
Inpatient	20 (24)	7 (20)
Outpatient	63 (74)	28 (80)
Not recorded	2 (2)	0
Age (yr)		
Mean	50.3	45.5
Median	53	51
Range (min-max)		
Weight (kg)		
Mean	71.4	71.8
Median	70	70.2
Range (min-max)		
Not recorded	0	1
AECB	(n=90)*	(n=51)
Sex		
Male	60 (67)	32 (63)
Female	29 (32)	19 (37)
Not recorded	1 (1)	0
Race		
White	84 (93)	49 (96)
Black	1 (1)	0
Other	5 (6)	1 (2)
Not recorded	0	1 (2)
Patient Status		
Inpatient	66 (73)	37 (73)
Outpatient	23 (26)	14 (27)
Not recorded	1 (1)	0
Age (yr)		
Mean	61.6	66.8
Median	62	62
Range (min-max)		
Weight (kg)		
Mean	67.4	66.1
Median	69	65
Range (min-max)		
Not Recorded	1	0

* Includes a single patient who received ceftibuten 200 mg b.i.d.

Table 13
Demographic Data for "Bronchitis" Patients in the Clinical Test-of-Cure Population (International)
(According to reviewer)

	Ceftibuten 400 mg QD (n=88)	Cefaclor 250 mg TID (n=38)
Sex		
Male	57 (65)	25 (66)
Female	31 (35)	13 (34)
Race		
White	83 (94)	38 (100)
Black	3 (4)	0
Other	2 (2)	0
Patient Status		
Inpatient	42 (48)	21 (55)
Outpatient	44 (50)	17 (48)
Not recorded	2 (2)	0
Age (yr)		
Mean	58	61
Median	59	61
Range (min-max)	27-89	24-83
Weight (kg)		
Mean	69.5	67.2
Median	69.5	67
Range (min-max)	42-94.6	44.7-88.4
Not Recorded	0	1
Diagnosis		
Acute Bacterial Bronchitis	37 (42)	10 (26)
AECB	51 (58)	28 (74)

Table 14
Demographic Data for Patients in the Clinical Test-of-Cure Population According to Type of Bronchitis (International)
(According to reviewer)

	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis*	(n = 37)	(n = 10)
Sex		
Male	22 (59)	8 (80)
Female	15 (41)	2 (20)
Race		
White	35 (95)	10 (100)
Black	2 (5)	0
Patient Status		
Inpatient	5 (14)	2 (20)
Outpatient	30 (81)	8 (80)
Not recorded	2 (5)	0
Age (yr)		
Mean	53	52
Median	54	57
Range (min-max)		
Weight (kg)		
Mean	72.0	72.6
Median	74	74.5
Range (min-max)		
Not Recorded	0	1
AECB	(n = 51)	(n = 28)
Sex		
Male	35 (69)	17 (61)
Female	16 (31)	11 (39)
Race		
White	48 (94)	28 (100)
Black	1 (2)	0
Other	2 (4)	0
Patient Status		
Inpatient	37 (73)	19 (68)
Outpatient	14 (27)	9 (32)
Age (yr)		
Mean	60	63
Median	60	63
Range (min-max)		
Weight (kg)		
Mean	67.2	65.4
Median	67.3	65
Range (min-max)		

Baseline Clinical Features:
As for the domestic study, the reviewer examined the baseline signs & symptoms of the MO's "bronchitis" clinical efficacy population. (See Tables 15 and 16.) As with the domestic study, the most significant baseline symptoms were cough and sputum (productive cough). On average, rales/rhonchi were of greater severity at baseline in the international study compared with the domestic one. Dyspnea was also more pronounced for the AECB population.

With regard to baseline temperature for the MO's bronchitis clinical efficacy population, the average temperature for the ceftibuten group was 37.0°C (range 35-39.7°C; n=166) and 37.1°C (range 36-38.8°C; n=80) for the cefaclor group. Among the ceftibuten patients, 26 had a baseline temperature greater than 38°C, while there were 13 for the cefaclor group. (Data not shown.)

Table 15
Baseline Clinical Features of MO's Bronchitis Clinical Efficacy Population by Mean Symptom Value* (International)
(According to reviewer)

	No. of Occurrences		Mean Symptom Value	
	Ceftibuten 400 mg qd (n=166)†	Cefaclor 250 mg qd (n=80)†	Ceftibuten 400 mg qd	Cefaclor 250 mg qd
Chills	162	79	0.4	0.5
Dyspnea	160	79	1.4	1.6
Cough	161	79	2.2	2.3
Sputum (prod. cough)	161	79	2.2	2.3
Rales/Rhonchi	159	78	1.8	1.9
Consolidation	160	78	0.02	0.04
Pleuritic chest pain	159	78	0.15	0.19

* Mean symptom value was calculated using baseline scores of 0=none/absent, 1=slight/mild, 2=moderate, 3=severe/marked. Baseline visit used was day 1. No patients had cyanosis at baseline. Wheeze, fatigue, diaphoresis were reported erratically.

† "n" is the number of clinically evaluable patients. The "occurrences" include the patients where a baseline score was provided. For example, of the 166 clinically evaluable ceftibuten "bronchitis" patients, 162 with "chills" had a baseline score of 0, 1, 2, or 3, while for 3 patients, this information was not provided.

Table 16
Baseline Clinical Features of MO's Clinical Efficacy Population According to Type of Bronchitis and by Mean Symptom Value* (International)
(According to reviewer)

	No. of Occurrences		Mean Symptom Value	
	Ceftibuten 400 mg qd	Cefaclor 250 mg qd	Ceftibuten 400 mg qd	Cefaclor 250 mg qd
Acute Bact. Bronch.	**(n=80)**	**(n=32)**		
Chills	80	32	0.5	0.5
Dyspnea	80	32	1.0	0.9
Cough	80	32	2.0	2.1
Sputum (prod. cough)	80	32	2.1	2.2
Rales/Rhonchi	79	31	1.9	1.8
Consolidation	80	31	-	0.1
Pleuritic chest pain	79	31	0.2	0.2
AECB	**(n=80)**	**(n=48)**		
Chills	81	46	0.2	0.5
Dyspnea	79	46	1.8	2.0
Cough	80	46	2.3	2.4
Sputum (prod. cough)	80	46	2.3	2.3
Rales/Rhonchi	80	46	1.8	2.0
Consolidation	80	46	0.04	-
Pleuritic chest pain	80	46	0.1	0.2

* Mean symptom value calculated using baseline scores of 0=none/absent, 1=slight/mild, 2=moderate, 3=severe/marked. Baseline visit used was day 1. If this was not available, day -1 was used instead. No patients had cyanosis at baseline.

Underlying medical conditions:
From the assessment of medical conditions by body system for enrolled patients, the groups were equally represented. (See Table 17.)

Upon division of the enrolled patients according to type of bronchitis, few specific underlying diagnoses were noted in the acute bacterial bronchitis group. (See Table 18.) For the AECB population, treatment groups were equally represented.

Table 17
Underlying Medical Conditions by Body System for Enrolled Patients According to Type of Bronchitis (International)
(According to applicant)

	No. of Patients (%)			
	Ceftibuten		Cefaclor	
Acute Bact. Bronchitis	(n=85)		(n=35)	
None	43	(51)	19	(54)
Allergic	2	(2)	-	
Audiologic	1	(1)	2	(6)
Cardiovascular	11	(13)	6	(17)
Dermatologic	1	(1)	3	(9)
Endocrine	6	(7)	4	(11)
Gastrointestinal	17	(20)	6	(17)
Genitourinary	9	(11)	3	(9)
Hematologic	-		1	(3)
Musculoskeletal	14	(16)	5	(14)
Neurologic	4	(5)	1	(3)
Ophthalmologic	4	(5)	1	(3)
Psychological	1	(1)	1	(3)
Pulmonary	3	(4)	3	(9)
Systemic	-		-	
AECB	(n=90)		(n=51)	
None	0		1	(2)
Allergic	7	(8)	6	(12)
Audiologic	3	(3)	2	(4)
Cardiovascular	38	(42)	21	(41)
Dermatologic	5	(6)	5	(10)
Endocrine	13	(14)	3	(6)
Gastrointestinal	24	(27)	11	(22)
Genitourinary	12	(13)	7	(14)
Hematologic	4	(4)	2	(4)
Musculoskeletal	17	(19)	5	(10)
Neurologic	8	(9)	3	(6)
Ophthalmologic	11	(12)	1	(2)
Psychological	3	(3)	3	(6)
Pulmonary	83	(92)	46	(90)
Systemic	5	(6)	1	(2)

Table 18
Specific Underlying Medical Conditions for Enrolled Patients According to Type of Bronchitis (International)*
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bact. Bronchitis	**(n=85)**	**(n=35)**
Pulmonary Disease		
Chronic‡	0	0
Asthma	0	0
Diabetes mellitus	2	2
Cancer		
Lung	0	0
All others	2	1
Immunodeficiency*	0	0
ETOH/IVDA**	0	0
Tuberculosis	0	1
AECB	**(n=90)**	**(n=51)**
Pulmonary Disease		
Chronic‡	56 (66)	32 (63)
Asthma	23 (26)	12 (24)
Diabetes mellitus	5	2
Cancer		
Lung	1	0
All others	0	0
Immunodeficiency*	4	2
ETOH/IVDA**	1	0
Tuberculosis	9	3

‡ Includes COPD (emphysema), chronic bronchitis, bronchiectasis, sarcoidosis, scleroderma, pulmonary fibrosis, and silicosis. Excludes lung cancer and "recurrent bronchitis."

* Immunodeficiencies included connective tissue disease (i.e., SLE, scleroderma), HIV, anemia, post-splenectomy, and pancytopenia.

** Alcohol and/or intravenous drug abuse

There was one ceftibuten patient who had a **concurrent infection** involving an anatomic site other than the lower respiratory tract at the time of enrollment. Patient I8821709111 had a urinary tract infection due to *E. coli* which was persistent on day +6; no susceptibilities were provided. (One cefaclor patient had staphylococcal impetigo at the time of enrollment.)

Two nonrespiratory tract infections developed during the study for ceftibuten recipients. I8821705105 developed an "eye infection" on day 4 of therapy which was treated with chloramphenicol ophthalmologic solution through day +8. No cultures were obtained. Although not mentioned in the applicant's patient profiles, according to the CRF comment page, I8821703111 developed pyuria posttherapy with 10^4-10^5 CFU/mL enterococci in urine; Septra® was given for 7 days. (There were no cefaclor patients who developed other infections over the course of the study.)

Concomitant Medications:

Systemic Anti-Infective Drug Use:
As with C88044, the reviewer examined the pretherapy systemic anti-infective use for enrolled patients. (See Table 19.) There was no pretherapy anti-infective use in the acute bacterial bronchitis group.

Table 19
Pretherapy Systemic Anti-Infective Use for Enrolled Patients According to Type of Bronchitis (International)*
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bact. Bronchitis	**(n=85)**	**(n=35)**
Pretherapy	0	0
AECB	**(n=90)**	**(n=51)**
Pretherapy	11 (12)	4 (8)

* Last use within 30 days prior to enrollment; excludes antituberculous therapy, antifungals, and pentamidine.

Nonanti-Infective Drug Use:
As with the domestic study, the MO evaluated concomitant nonanti-infective drug use with potential ameliorative effects on the pulmonary system. (See Table 20.) In general, in comparison to the domestic study, more patients in the international studies received nonanti-infective therapy either before, during, or posttherapy; especially the AECB group.

Table 20
Concomitant Nonanti-Infective Therapy for Enrolled Patients According to Type of Bronchitis (International)*
(According to reviewer)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bact. Bronchitis	(n=85)	(n=35)
Pulmonary drugs*	13 (15)	2 (6)
Methylxanthines	8 (9)	1 (3)
Inhalant steroids	2 (2)	0
Systemic immunosup.‡	9 (11)	1 (3)
AECB	(n=90)	(n=51)
Pulmonary drugs*	76 (84)	44 (86)
Methylxanthines	64 (71)	30 (59)
Inhalant steroids	29 (32)	16 (31)
Systemic immunosup.‡	66 (73)	35 (69)

* "Pulmonary drugs" include methylxanthines, β-agonist bronchodilators (systemic and inhalant), corticosteroids (systemic and inhalant), cromolyn, oxygen, and inhalant anticholinergic bronchodilators.
‡ Systemic corticosteroids, infrequently, may have been prescribed for reasons other than bronchospasm. However, their co-administration may have had ameliorative effects on a patient's respiratory symptoms.

As with the U.S. study, the MO reviewed concomitant "pulmonary" drug use for the clinical test-of-cure population **initiated during therapy or during the posttherapy follow-up period.** (Data not shown.) The reviewer identified 44 patients (10 cefaclor, 34 ceftibuten; 7 acute bacterial bronchitis and 37 AECB - all acute bacterial bronchitis patients were ceftibuten recipients; for AECB, 28 received ceftibuten and 9 cefaclor) who received one or more pulmonary medications during the course of the study - initiated during therapy or during the posttherapy follow-up period.

Study Drug Administration:
The reviewer compared the dosing of the study drugs for various efficacy populations. (See Tables 21 and 22.) Groups are comparable.

Table 21
Distribution of Duration of Therapy (Days) by Treatment Group for the "Bronchitis" Population According to MO's Evaluability (International)
(According to reviewer)

	No. of Patients (cumulative %)					
	Clinical Efficacy		Clinical Test-of-Cure		Valid	
Duration (Days)	Ceftibuten 400 mg QD (n=165)	Cefaclor 250 mg TID (n=80)	Ceftibuten 400 mg QD (n=37)*	Cefaclor 250 mg TID (n=38)	Ceftibuten 400 mg QD (n=60)	Cefaclor 250 mg TID (n=25)
3-4	4 (2)	0	4 (5)	0	2 (3)	0
5-6	51 (33)	20 (25)	22 (30)	5 (13)	14 (27)	2 (8)
7-8	32 (53)	22 (53)	19 (52)	11 (42)	13 (48)	8 (40)
9-10	45 (80)	17 (74)	24 (79)	11 (71)	17 (77)	7 (68)
11-12	15 (89)	14 (91)	8 (89)	7 (89)	7 (88)	4 (84)
13-14	13 (97)	5 (98)	7 (97)	3 (97)	5 (9[illegible])	3 (96)
15-16	5 (100)	2 (100)	3 (100)	1 (100)	2 (100)	1 (100)
>16	0	0	0	0	0	0
Mean Days	8.4	8.7	8.6	9.3	8.8	9.6
Mean Doses	8.4	25.2	8.6	27.2	8.8	23.4

* Excludes a single ceftibuten 200 mg p.o. b.i.d. patient who received 20 doses over 11 days.

Table 22
Distribution of Duration of Therapy (Days) for the MO's Clinical Test-of-Cure Populations According to Type of Bronchitis (International)
(According to reviewer)

	No. of Patients (cumulative %)			
	Acute Bact. Bronchitis		*AECB*	
Duration (Days)	Ceftibuten 400 mg QD (n=37)	Cefaclor 250 mg TID (n=10)	Ceftibuten 400 mg QD (n=50)	Cefaclor 250 mg TID (n=28)
3-4	2 (5)	0	2 (4)	0
5-6	10 (32)	2 (20)	12 (28)	3 (11)
7-8	6 (49)	3 (50)	13 (54)	8 (39)
9-10	13 (84)	2 (70)	11 (76)	9 (71)
11-12	2 (89)	1 (80)	6 (88)	6 (93)
13-14	3 (97)	2 (100)	4 (96)	1 (96)
15-16	1 (100)	0 (100)	2 (100)	1 (100)
Mean Days	8.4	9.2	8.7	9.3
Mean Doses	8.6	26.8	8.6	27.4

NOTE: This table excludes the single ceftibuten 200 mg b.i.d. patient.

EFFICACY EVALUATION:

CLINICAL EFFICACY EVALUATION:

Medical Officer's Comment: As previously stated, the main difference between the applicant and the reviewer in the clinical evaluation of the two study drugs is the "test-of-cure" visit. For the applicant, this was day +0-+3; represented by the applicant's **clinical efficacy** population. For the MO, this was day +4 or later; the MO's **clinical test-of-cure** population.

Clinical Efficacy at End-of-Therapy:
According to the applicant, by EOT for the **clinical efficacy** population, independent of the type of bronchitis, 150/169 (89%) and 76/79 (96%) of ceftibuten and cefaclor patients, respectively, were either improved or cured. (See Table 23.)

For the applicant's **valid** population at EOT, the overall success rate was 74/83 (89%) and 36/39 (92%), respectively. (See Table 24.)

According to the reviewer, for the MO's **clinical efficacy** population, independent of type of bronchitis, a successful outcome was seen for 143/166 (86%) ceftibuten and 70/80 (88%). (See Table 26.) Success rates for the two treatment arms among the AECB patients were comparable.

For the **clinical test-of-cure** population, the reviewer's primary efficacy population, at EOT, independent of diagnosis, respective success rates were 65/88 (74%) and 28/38 (74%). (See Table 27.) Success rates were comparable when looked at relative to type of bronchitis. As with the domestic study, these were lower than that for the clinical efficacy population above.

For the reviewer's **valid** population at end-of-therapy, success rates were comparable to the clinical efficacy populations discussed above. (See Table 28.) This contrasted somewhat with the findings in C88044 which showed higher success rates.

Clinical Efficacy at Posttherapy Follow-up:
According to the applicant, for the **valid** population, success rates were comparable between the two groups; 33/35 (94%) vs. 16/16 (100%). (See Table 25.) As for the domestic study, only those patients who were clinical successes at EOT were considered assessable at F/U (i.e., poor clinical responses by the EOT visit were NOT carried forward to the posttherapy follow-up visit by the applicant).

According to the reviewer, where end-of-therapy clinical failure responses were carried forward as the patient's posttherapy

response, for the clinical test-of-cure population overall "cumulative" sustained successful responses for the two treatment groups were 56/88 (64%) and 23/38 (61%). (See Table 27.) There were 8 relapses in the ceftibuten group 4 for cefaclor; 1 late failure in each group. The majority of relapses were in the AECB population.

For the valid population, similar, albeit smaller, numbers were found. (See Table 28.)

Table 23
Clinical Responses for the Bronchitis/Tracheitis
Clinical Efficacy Populations at the End-of-Therapy Visit
(International)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N= 92)	(N= 37)
Cure/Improvement	85 (92)	37 (100)
(Cure)	69 (75)	29 (78)
(Improvement)	16 (17)	8 (22)
Failure	7 (8)	0 (0)
AECB	(N= 73)	(N= 41)
Cure/Improvement	61 (84)	38 (93)
(Cure)	41 (56)	25 (61)
(Improvement)	20 (27)	13 (32)
Failure	12 (16)	3 (7)
Tracheitis	(N= 4)	(N= 1)
Cure/Improvement	4 (100)	1 (100)
(Cure)	4 (100)	1 (100)
(Improvement)	0 (---)	0 (---)
Failure	0 (---)	0 (---)
All Diagnoses	(N=169)	(N= 79)
Cure/Improvement	150 (89)	76 (96)
(Cure)	114 (67)	55 (70)
(Improvement)	36 (21)	21 (27)
Failure	19 (11)	3 (4)

Table 24
Clinical Response of Valid Bronchitis Patients at the End-of-Therapy Visit (International)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N=37)	(N=16)
Cure/Improvement	33 (89)	16 (100)
(Cure)	26 (70)	12 (75)
(Improvement)	7 (19)	4 (25)
Failure	4 (11)	0
AECB	(N=42)	(N=22)
Cure/Improvement	37 (88)	19 (86)
(Cure)	26 (62)	13 (59)
(Improvement)	11 (26)	6 (27)
Failure	5 (12)	3 (14)
Tracheitis	(N=4)	(N=1)
Cure/Improvement	4 (100)	1 (100)
(Cure)	4 (100)	1 (100)
(Improvement)	0	0
Failure	0	0
All Diagnoses	(N=83)	(N=39)
Cure/Improvement	74 (89)	36 (92)
(Cure)	56 (67)	26 (67)
(Improvement)	18 (22)	10 (26)
Failure	9 (11)	3 (8)

Table 25
Clinical Response of Valid Bronchitis/Tracheitis Patients at the Posttherapy Visit (International)
(According to applicant)

	No. of Patients (%)	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N=19)	(N= 7)
Sustained Cure/Improvement	18 (95)	7 (100)
(Cure)	16 (84)	5 (71)
(Improvement)	2 (11)	2 (29)
Relapse	1 (5)	0
AECB	(N=13)	(N= 8)
Sustained Cure/Improvement	12 (92)	8 (100)
(Cure)	8 (62)	6 (75)
(Improvement)	4 (31)	2 (25)
Relapse	1 (8)	0
Tracheitis	(N=3)	(N=1)
Sustained Cure/Improvement	3 (100)	1 (100)
(Cure)	3 (100)	1 (100)
(Improvement)	0	0
Relapse	0	0
All Diagnoses	(N=35)	(N=16)
Sustained Cure/Improvement	33 (94)	16 (100)
(Cure)	27 (77)	12 (75)
(Improvement)	6 (17)	4 (25)
Relapse	2 (6)	0

Table 26
Clinical Responses for the MO's Clinical Efficacy Population at End-of-Therapy According to the Type of Bronchitis (International)*
(According to reviewer)

	No. of Patients (%)			
	ACUTE BACT. BRONCHITIS		*AECB*	
Clinical Response	Ceftibuten 400 mg QD (n=80)	Cefaclor 250 mg TID (n=32)	Ceftibuten 400 mg QD (n=86)	Cefaclor 250 mg TID (n=48)
Positive response	73 (91)	31 (97)	70 (81)	39 (81)
Cure	54 (68)	25 (78)	42 (49)	20 (42)
Improvement	19 (24)	6 (19)	28 (33)	19 (40)
Failure	7 (9)	1 (3)	16 (19)	9 (19)

* Assessment made between days +0-+3.

Table 27
Clinical Responses for the Clinical Test-of-Cure Population According to the Type of Bronchitis (International)*
(According to reviewer)

	No. of Patients (%)			
	ACUTE BACT. BRONCHITIS		*AECB*	
Clinical Response	Ceftibuten 400 mg QD (n=37)	Cefaclor 250 mg TID (n=10)	Ceftibuten 400 mg QD (n=51)	Cefaclor 250 mg TID (n=28)
At End-of-Therapy				
Positive response	30 (81)	9 (90)	35 (69)	19 (68)
Cure	18 (49)	7 (70)	14 (27)	9 (32)
Improvement	12 (32)	2 (20)	21 (41)	10 (36)
Failure	7 (19)	1 (10)	16 (31)	9 (32)
At Follow-up				
Positive response	29 (78)	8 (80)	27 (53)	15 (54)
Cure	23 (62)	7 (70)	22 (43)	10 (36)
Improvement	6 (16)	1 (10)	5 (10)	5 (18)
Negative response	8 (22)	2 (20)	24 (47)	13 (46)
Early Failure*	7 (19)	1 (10)	16 (31)	9 (32)
Late Failure**	0	0	1 (2)	1 (4)
Relapse	1 (3)	1 (10)	7 (14)	3 (11)

* Failures at end-of-therapy carried forward as the extended follow-up visit response.

** Late failures were improved or not assessable at end-of-therapy, followed by a poor clinical response at the posttherapy follow-up visit (i.e., inadequate sustained improvement).

Table 28
Clinical Responses for the MO's Valid Population According to the Type of Bronchitis (International)*
(According to reviewer)

Clinical Response	No. of Patients (%) ACUTE BACT. BRONCHITIS Ceftibuten 400 mg QD (n=21)	ACUTE BACT. BRONCHITIS Cefaclor 250 mg TID (n=7)	AECB Ceftibuten 400 mg QD (n=39)	AECB Cefaclor 250 mg TID (n=18)
At End-of-Therapy				
Positive response	17 (81)	6 (86)	26 (67)	10 (56)
Cure	13 (62)	5 (71)	12 (31)	6 (33)
Improvement	4 (19)	1 (14)	14 (36)	4 (22)
Failure	4 (19)	1 (14)	13 (33)	8 (44)
At Follow-Up				
Positive response	16 (76)	5 (71)	20 (51)	9 (50)
Cure	13 (62)	4 (57)	17 (44)	7 (39)
Improvement	3 (14)	1 (14)	3 (8)	2 (11)
Negative response	5 (24)	2 (29)	19 (49)	9 (50)
Early Failure*	4 (19)	1 (14)	13 (33)	8 (44)
Late Failure**	0	0	1 (3)	0
Relapse	1 (5)	1 (14)	5 (13)	1 (6)

* Failures at end-of-therapy carried forward as posttherapy follow-up response of "early failure."
** Late failures were improved or not assessable at end-of-therapy, followed by a poor clinical response at the posttherapy follow-up visit (i.e., inadequate sustained improvement).

Resolution of Signs & Symptoms:
The investigator's assessment of the day of resolution (IADR) for the clinical parameters as presented by the applicant for the applicant's clinical efficacy population is found in Table 29.

As with C88044, using the IADR of the individual clinical parameters, the MO evaluated cough and sputum (productive cough) for the reviewer's clinical efficacy population. For the acute bacterial bronchitis/tracheitis group, **productive cough** resolved within a mean of 7.8 and 7.4 days for acute bacterial bronchitis ceftibuten and cefaclor patients, respectively. For AECB, 8.3 and 9 days. With regard to **cough**, for the acute bacterial bronchitis group, 8.9 and 7.5 days, respectively. For AECB, 8.8 and 9.4 days. (Data not shown.)

Table 29. Time in Days to Resolution of Signs and Symptoms in Patients in the International Bronchitis and Tracheitis Clinical Efficacy Population with a Clinical Response of Cure or Improvement, (I88-111, I88-217, I88-327)* (According to applicant)

	Tracheitis		Acute Exacerbation Chronic Bronchitis		Acute Bacterial Bronchitis		Combined	
	Ceftibuten 400 mg QD	Cefaclor 250 mg Q8H	Ceftibuten 400 mg QD	Cefaclor 250 mg Q8H	Ceftibuten 400 mg QD	Cefaclor 250 mg Q8H	Ceftibuten 400 mg QD	Cefaclor 250 mg Q8H
Chills								
Mean	3.67	3.00	3.17	3.69	4.31	3.80	3.93	3.71
Median	4.00	3.00	3.00	2.00	4.00	2.50	3.00	2.50
Range								
No. Patients	3	1	12	13	26	10	41	24
Dyspnea								
Mean	4.00	--	7.96	8.68	6.77	6.76	7.30	7.79
Median	4.00	--	7.00	8.00	6.00	6.00	7.00	7.00
Range								
No. Patients	2	0	55	34	56	29	113	63
Cough								
Mean	6.25	5.00	8.73	9.45	8.89	7.92	8.75	8.64
Median	6.00	5.00	8.00	8.00	8.00	7.00	8.00	7.50
Range								
No. Patients	4	1	60	38	80	37	144	76
Sputum								
Mean	5.50	5.00	8.42	9.08	8.01	7.73	8.11	8.36
Median	5.50	5.00	8.00	8.00	7.00	7.00	8.00	7.00
Range								
No. Patients	4	1	60	37	81	37	145	75
Cyanosis								
Mean	--	--	8.83	9.00	9.00	--	8.88	9.00
Median	--	--	9.50	9.00	9.00	--	9.00	9.00
Range								
No. Patients	0	0	6	3	2	0	8	3
Rales/Rhonchi								
Mean	4.75	5.00	8.70	9.11	7.23	6.74	7.75	7.92
Median	5.00	5.00	7.00	8.00	6.00	7.00	7.00	7.00
Range								
No. Patients	4	1	56	36	78	34	138	71
Signs of Consolidation								
Mean	--	--	7.50	--	7.00	10.00	7.25	10.00
Median	--	--	7.50	--	7.00	10.00	7.50	10.00
Range								
No. Patients	0	0	2	0	2	1	4	1
Pleuritic Chest Pain								
Mean	2.50	--	5.33	7.75	4.92	4.00	4.80	5.67
Median	2.50	--	5.00	7.50	5.00	3.00	5.00	4.00
Range								
No. Patients	2	0	6	4	14	5	20	9

BACTERIOLOGIC EFFICACY EVALUATION:

NOTE: Please refer to the beginning of the bacteriologic efficacy evaluation section for the C88044 study for a discussion of its review.

Bacteriologic Efficacy at End-of-Therapy:
According to the applicant, independent of type of bronchitis, overall, 69/82 (84%) ceftibuten and 33/39 (85%) cefaclor patients experienced eradication of their baseline pathogen. (See Table 30.) Eradication rates were higher for the acute bacterial bronchitis group.

With regard to the eradication rates for specific **pathogens** at the end-of-therapy visit, the respective eradication rates independent of type of bronchitis for the two treatment groups was 77/90 (86%) and 33/40 (83%). (See Table 31.) Compared to other pathogens, the *S. pneumoniae* eradication rates were the lowest for ceftibuten.

Table 30
Bacteriologic Response of Valid Patients with Bronchitis/Tracheitis at EOT (International)
(According to applicant)

	Number (%) of Patients	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N=36)§	(N=16)
Total Eradication¶	31 (86)	14 (88)
(Eradication)	29 (81)	13 (81)
(W/ superinfection)	2 (6)	1 (6)
(W/ colonization)	0	0
Persistence#	5 (14)	2 (13)
AECB	(N=42)	(N=22)
Total Eradication	34 (81)	18 (82)
(Eradication)	29 (69)	14 (64)
(W/ superinfection)	1 (2)	3 (14)
(W/ colonization)	4 (10)	1 (5)
Persistence#	8 (19)	4 (18)
Tracheitis	(N= 4)	(N= 1)
Total Eradication	4 (100)	1 (100)
(Eradication)	4 (100)	1 (100)
(W/ superinfection)	0	0
(W/ colonization)	0	0
Persistence#	0	0
All Diagnoses	(N=82)§	(N=39)
Total Eradication¶	69 (84)	33 (85)
(Eradication)	62 (76)	28 (72)
(W/ superinfection)	3 (5)	4 (10)
(W/ colonization)	4 (7)	1 (3)
Persistence#	13 (16)	6 (15)

§ One ceftibuten acute bacterial bronchitis patient with an indeterminate response was not included in the denominator for calculation of response.
¶ Includes eradication and eradication with colonization, or superinfection.
Includes patients with a multiple response.

Table 31
Individual "Pathogen" Eradication Rates for Valid Patients with Bronchitis/Tracheitis at the EOT Visit (International)
(According to applicant)

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis		
Moraxella (Branhamella) catarrhalis	2/2 (100)	2/ 2 (100)
Haemophilus influenzae	15/16 (94)	2/ 2 (100)
Haemophilus parainfluenzae	3/ 3 (100)	0/ 0 (---)
Klebsiella pneumoniae	1/ 1 (100)	2/ 2 (100)
Streptococcus pneumoniae	8/11 (73)	6/ 8 (75)
Streptococcus pyogenes	1/ 1 (100)	0/ 0 (----)
Other§	2/ 3 (67)	2/ 2 (100)
Subtotal	32/37 (86)	14/16 (88)
AECB		
Moraxella (Branhamella) catarrhalis	6/ 6 (100)	0/ 1 (0)
Haemophilus influenzae	14/15 (93)	10/12 (83)
Haemophilus parainfluenzae	4/ 5 (80)	4/ 4 (100)
Klebsiella pneumoniae	5/ 6 (83)	0/ 0 (---)
Streptococcus pneumoniae	6/11 (55)	1/ 2 (50)
Other§	6/ 6 (100)	3/ 4 (75)
Subtotal	41/49 (84)	18/23 (78)
Tracheitis		
Moraxella (Branhamella) catarrhalis	2/ 2 (100)	0/ 0 (---)
Haemophilus influenzae	1/ 1 (100)	0/ 0 (---)
Streptococcus pneumoniae	0/ 0 (---)	1/ 1 (100)
Streptococcus pyogenes	1/ 1 (100)	0/ 0 (---)
Other§	0/ 0 (---)	0/ 0 (---)
Subtotal	4/ 4 (100)	1/ 1 (100)
All Diagnoses		
Moraxella (Branhamella) catarrhalis	10/10 (100)	2/ 3 (67)
Haemophilus influenzae	30/32 (94)	12/14 (86)
Haemophilus parainfluenzae	7/ 8 (88)	4/ 4 (100)
Klebsiella pneumoniae	6/ 7 (86)	2/ 2 (100)
Streptococcus pneumoniae	14/22 (64)	8/11 (73)
Streptococcus pyogenes	2/ 2 (100)	0/ 0 (---)
Other§	8/10 (80)	5/ 6 (83)
Total	**77/90 (86)**	**33/40 (83)**

§ Includes *Acinetobacter calcoaceticus, Citrobacter* sp, *Enterobacter cloacae, Escherichia coli, Haemophilus* sp, *Proteus mirabilis, Serratia marcescens.*

Bacteriologic Efficacy at Posttherapy:
According to the applicant, eradication rates for valid **patients**, independent of type of bronchitis, who had an extended posttherapy visit (day +7-+14) were 14/16 (88%) for ceftibuten and 7/8 (88%) for cefaclor patients. (See Table 32.) For **pathogens**, respective eradication rates were 16/18 (89%) and 7/8 (88%). (See Table 33.)

> ***Medical Officer's Comment:*** As previously stated, in their analysis, the applicant did not carry forward the end-of-therapy failures for the extended responses.

According to the reviewer, the cumulative eradication rates, for **patients** with "bronchitis" were 42/60 (70%) for ceftibuten and 15/25 (60%) for cefaclor. (See Table 34.) There were 2 bacteriologic relapses in the AECB ceftibuten arm.

With respect to the eradication rates for the MO's "**pathogens**," overall, for ceftibuten, 47/66 (71%) were eradicated in contrast to 18/28 (64%) for cefaclor. (See Table 35.)

In contrast to the domestic study, both treatment arms experienced lower efficacy in the eradication of *S. pneumoniae*. Moreover, many more *S. pneumoniae* were isolated in the international studies compared with the domestic one.

With regard to β-lactamase activity, as with the domestic study, there were few β-lactamase (+) pathogens isolated - four. Three of the three were eradicated. It is difficult to make conclusions based on these small numbers.

There were two ceftibuten (no cefaclor) patients who experienced initial eradication of their baseline β-lactamase (-) *H. influenzae* followed by bacteriologic relapse with this same pathogen. (Of course, without serotyping reinfection cannot be ruled out, but relapse is assumed in this situation.)

Table 32
Overall Bacteriologic Response for Valid Patients with Bronchitis/Tracheitis at F/U (International)
(According to applicant)

	Ceftibuten 400 mg QD (N=16)§	Cefaclor 250 mg TID (N= 8)§
Total Eradication¶	14 (88)	7 (88)
(Eradication)	13 (81)	6 (75)
(W/ superinfection)	0 (--)	1 (13)
(W/ reinfection)	1 (6)	0 (--)
Relapse	2 (13)	1 (13)

§ Eight patients with an indeterminate response were not included in the denominator for calculation of response in the ceftibuten treatment group and three patients in the cefaclor treatment group. According to the applicant, "many of these patients were classified as indeterminate because they were treated with another antimicrobial medication."
¶ Includes eradication and eradication with superinfection or reinfection.

Table 33
Bacteriologic Response for Valid Bronchitis/Tracheitis Pathogens at F/U (International)*
(According to applicant)

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Haemophilus influenzae	7/9 (78)	2/2 (100)
Haemophilus parainfluenzae	1/1 (100)	1/1 (100)
Klebsiella pneumoniae	2/2 (100)	1/1 (100)
Streptococcus pneumoniae	6/6 (100)	1/1 (100)
Other§	0/0 (---)	2/3 (67)
Total	16/18 (89)	7/8 (88)

§ Includes *Acinetobacter calcoaceticus*, *Citrobacter* sp, *Haemophilus* sp.

Table 34
Cumulative Bacteriologic Responses for MO's Valid Bronchitis/Tracheitis Patients at F/U (International)
(According to reviewer)

	Number (%) of Patients	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis	(N=21)	(N=7)
Eradication	17 (81)	5 (71)
Persistence	4 (19)	2 (29)
AECB	(N=39)	(N=18)
Eradication	25 (64)	10 (56)
Persistence	9 (13)	6 (33)
Relapse	2 (23)	0
Multiple response*	3 (8)	2 (11)

* Includes responses of eradication and persistence; patients had more than one baseline pathogen.

Table 35
Cumulative "Pathogen" Eradication Rates for MO's Valid Bronchitis Pathogens at F/U (International)
(According to reviewer)

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis		
Moraxella (Branhamella) catarrhalis		
β-lactamase (-)†	2/2 (100)	0
β-lactamase (+)	0	0
Haemophilus influenzae		
β-lactamase (-)	9/10 (90)	0
β-lactamase (+)	2/2 (100)	0
Haemophilus parainfluenzae		
β-lactamase (-)	1/1 (100)	0
β-lactamase (+)	0	0
Klebsiella pneumoniae	1/1 (100)	1/1 (100)
Streptococcus pneumoniae	2/5 (40)	4/6 (67)
Total	**17/21 (81)**	**5/7 (71)**
AECB		
Moraxella (Branhamella) catarrhalis		
β-lactamase (-)	3/3 (100)‡	1/2 (50)
β-lactamase (+)	1/2 (50)	0
Haemophilus influenzae		
β-lactamase (-)	12/17 (71)••	7/10 (70)‡
β-lactamase (+)	0	0
Haemophilus parainfluenzae		
β-lactamase (-)	3/3 (100)	2/4 (50)
β-lactamase (+)	0	0
Klebsiella pneumoniae	3/4 (75)	0
Streptococcus pneumoniae	8/16 (50)	3/5 (60)‡
Total	**30/45 (67)**	**13/21 (62)**

* Eradication is the absence of the causative organism(s) at or immediately after termination of therapy (documented), or the complete disappearance of the culture source (e.g., sputum) so that follow-up culture is impossible (presumptive).
† Includes pathogens not tested for β-lactamase activity.
• Designates pathogens with documented relapse.

Bacteriologic Superinfections/Reinfection:
The reviewer identified 5 bacteriologic **superinfections** in the international study - 2 ceftibuten, 3 cefaclor - due to one of the 5 "pathogens." The details follow:

I8821717111 (ceftibuten, AECB): On day +4, the patient became superinfected with β-lactamase (-) *M. catarrhalis* (ceftibuten zone = 23mm; susceptible). The patient had begun to clinically fail prior to this. The patient also had persistence of the baseline pathogen, *S. pneumoniae*.

I8821714001 (ceftibuten, acute bacterial bronchitis): The reviewer considered this patient a clinical failure at end-of-therapy. However, a culture was not obtained until day +4 at which time β-lactamase (-) *H. parainfluenzae* was isolated (cefaclor zone = 51mm; susceptible).

I8821709112 (cefaclor, acute bacterial bronchitis): On day 6, the patient grew β-lactamase (-) *H. influenzae, de novo* (cefaclor zone = 22mm; susceptible) from the sputum. At EOT, the patient was switched to ofloxacin. The patient was a clinical failure. The patient also had persistence of the baseline pathogen, *S. pneumoniae*.

I8821709126 (cefaclor, AECB): The reviewer considered this patient a clinical failure at end-of-therapy; amoxicillin was begun. However, a culture was not obtained until day +4 at which time β-lactamase (-) *H. influenzae* was isolated (cefaclor zone = 25mm; susceptible). The patient also had persistence of the baseline pathogen, *S. pneumoniae*.

I8821714002 (cefaclor, AECB): On day +1, the patient grew *H. parainfluenzae de novo* (a cefaclor zone was not obtained). The patient was a late clinical failure. The patient was begun on TMP/SMX and subsequently improved.

> ***Medical Officer's Comment:*** Even though this patient did not fail until beyond day +3, the reviewer considered this a superinfection as the new pathogen was isolated earlier.

The reviewer also identified 4 **reinfections**; 3 ceftibuten and 1 cefaclor. The details follow:

I8821705103 (ceftibuten, AECB): Patient clinically relapsed (patient treated with parenteral penicillin and amikacin) and *S. pneumoniae* was isolated *de novo* on day +5 (ceftibuten zone = 32mm; susceptible).

I8821717104 (ceftibuten, AECB): Patient clinically relapsed with pneumonia on or before day +21 (patient not admitted to the hospital until day +21). At that time, day +21, β-lactamase (-) *M. catarrhalis* was cultured (ceftibuten zone not done). The patient died 10 days later.

I8821717115 (ceftibuten, acute bacterial bronchitis): Patient clinically relapsed and grew β-lactamase (-) *H. influenzae* on day +11 (ceftibuten zone = 37mm; susceptible).

I8832701102 (cefaclor, acute bacterial bronchitis): Patient clinically relapsed and grew β-lactamase (-) *H. influenzae* on day +5 (cefaclor zone = 39mm; susceptible). The patient also demonstrated persistence of the original baseline pathogen, *S. pneumoniae*.

COMBINED CLINICAL/BACTERIOLOGIC EFFICACY:

According to the applicant, at EOT, there were a total of 11 patients who experienced bacteriologic persistence of their baseline pathogen associated with clinical cure/improvement. (See Table 36.) In contrast, there were 3 patients who experienced bacteriologic eradication with clinical failure.

At the extended posttherapy visit, for those patients who had not previously failed, there were two ceftibuten patients who experienced clinical relapse with bacteriologic eradication; no cefaclor relapses. Otherwise, there were no "persisters." (See Table 37.)

According to the reviewer, combined clinical/bacteriologic responses, including β-lactamase activity for specific pathogens, are summarized in Table 38 for the MO's valid patients. There were 2 ceftibuten patients and 1 cefaclor patient who had clinical success with associated colonization (persistence) of the baseline pathogen. There were a significant number of pathogens associated with clinical failure/relapse, but bacteriologic eradication; mostly *H. influenzae*.

Table 36
Correlation of Bacteriologic Response and Clinical Response for Valid Patients with Bronchitis/Tracheitis at EOT (International)
(According to applicant)

Bacteriological Response	Clinical Response	Number of Patients: Ceftibuten 400 mg QD	Number of Patients: Cefaclor 250 mg TID
Acute Bacterial Bronchitis			
		N=36¶	N=16
Eradication§	Cure/Improvement	30 (83)	14 (88)
	(Cure)	26 (72)	12 (75)
	(Improvement)	4 (11)	2 (13)
	Failure	1 (3)	0
Persistence	Cure/Improvement	3 (8)	2 (13)
	(Cure)	0	0
	(Improvement)	3 (8)	2 (13)
	Failure	2 (6)	0
Acute Exacerbation of Cnronic Bronchitis			
		N=42	N=22
Eradication§	Cure/Improvement	33 (79)	17 (77)
	(Cure)	25 (60)	12 (55)
	(Improvement)	8 (19)	5 (23)
	Failure	1 (2)	1 (5)
Persistence	Cure/Improvement	4 (10)	2 (9)
	(Cure)	1 (2)	1 (5)
	(Improvement)	3 (7)	1 (5)
	Failure	4 (10)	2 (9)
Tracheitis			
		N=4	N=1
Eradication§	Cure	4 (100)	1 (100%)
All Diagnoses			
		N= 82¶	N=39
Eradication§	Cure/Improvement	67 (82)	32 (82)
	(Cure)	55 (67)	25 (64)
	(Improvement)	12 (15)	7 (18)
	Failure	2 (2)	1 (3)
Persistence	Cure/Improvement	7 (9)	4 (10)
	(Cure)	1 (1)	1 (3)
	(Improvement)	6 (7)	3 (8)
	Failure	6 (7)	2 (5)

§ Includes eradication and eradication with colonization or superinfection.
¶ One ceftibuten patient with an indeterminate bacteriologic response, but a clinical failure, was eliminated from the denominator.

Table 37
Correlation of Bacteriologic Response and Clinical Response for Valid Patients with Bronchitis/Tracheitis at F/U (International)
(According to applicant)

Bacteriological Response	Clinical Response	Number of Patients: Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis			
		N= 6	N= 2
Eradication§	Cure/Improvement	5 (83)	2 (100)
	(Cure)	5 (83)	1 (50)
	(Improvement)	0	1 (50)
	Relapse	1 (17)	0
Acute Exacerbation of Chronic Bronchitis			
		N= 8¶	N= 3
Eradication§	Cure/Improvement	7 (88)	3 (100)
	(Cure)	3 (38)	2 (67)
	(Improvement)	4 (50)	1 (33)
	Relapse	1 (13)	0
All Diagnoses			
		N= 14¶	N= 5¶
Eradication§	Cure/Improvement	12 (86)	5 (100)
	(Cure)	8 (57)	3 (60)
	(Improvement)	4 (29)	2 (40)
	Relapse	2 (14)	0

§ Includes eradication and eradication with: colonization or superinfection.
¶ One patient with an indeterminate response was eliminated from denominator.

Table 38
Correlation of Bacteriologic Response and Extended Clinical Response for Valid Patients According to Type of Infection (International)
(According to reviewer)

	Number (%) of Isolates			
	Ceftibuten 400 mg QD		Cefaclor 250 mg TID	
	Cure/Improve	Fail/Relapse‡	Cure/Improve	Fail/Relapse‡
Acute Bacterial Bronchitis				
ERADICATION*				
Moraxella (Branhamella) catarrhalis				
β-lactamase (-)†	2	-	-	-
Haemophilus influenzae				
β-lactamase (-)	9	-	-	-
β-lactamase (+)	1	1	-	-
Haemophilus parainfluenzae				
β-lactamase (-)	1	-	-	-
Klebsiella pneumoniae	1	-	1	-
Streptococcus pneumoniae	2	-	4	-
PERSISTENCE/RELAPSE				
Moraxella (Branhamella) catarrhalis				
β-lactamase (-)	-	1	-	-
Streptococcus pneumoniae	-	3	-	2
Total Acute Bronchitis Pathogens	**16**	**5**	**5**	**2**
Total Acute Bronchitis Patients	**16**	**5**	**5**	**2**
Acute Exacerbations of Chronic Bronchitis				
ERADICATION*				
Moraxella (Branhamella) catarrhalis				
β-lactamase (-)	1	2^{C}	1	-
β-lactamase (+)	1^{A}	-	-	-
Haemophilus influenzae				
β-lactamase (-)	7^{B}	$5^{D,E}$	5^{G}	2^{H}
Haemophilus parainfluenzae				
β-lactamase (-)	2	1	1	1^{I}
Klebsiella pneumoniae	3^{A}	-	-	-
Streptococcus pneumoniae	6^{B}	2	2^{G}	1
PERSISTENCE/RELAPSE				
Moraxella (Branhamella) catarrhalis				
β-lactamase (-)	-	-	-	1^{I}
β-lactamase (+)	-	1^{F}	-	-
Haemophilus influenzae				
β-lactamase (-)	1	$4^{C,e,e}$	-	3
Haemophilus parainfluenzae				
β-lactamase (-)	-	-	1	1
Klebsiella pneumoniae	-	1	-	-
Streptococcus pneumoniae	1	$7^{D,E,F}$	-	2^{H}
Total AECB Pathogens	**22**	**23**	**10**	**11**
Total AECB Patients	**20**	**19**	**9**	**9**

Note: Superscript letters represent more than one pathogen isolated from the same patient.

‡ "Early failures" were carried forward as the extended posttherapy response (day +4 or later).

* Eradication is the absence of the causative organism(s) at or immediately after termination of therapy, or the complete disappearance of the culture source (eg, sputum) so that follow-up culture is impossible.

† Includes pathogens not tested for β-lactamase activity.

e Individual bacteriologic relapses.

ADDITIONAL CLINICAL/BACTERIOLOGIC INFORMATION:

Progression to Pneumonia While Receiving Therapy:
There were two patients who **progressed on to pneumonia** during the course of the study having received a minimum of 3 days of therapy; both were ceftibuten patients. The details follow:

I8811107102 (AECB): This patient received 10 days of ceftibuten but failed. At baseline, the patient grew β-lactamase (-) *H. influenzae* at entry which was eradicated. However, by day +4 of therapy, the patient had a RLL infiltrate on CXR. On days 5 and +1, the sputum grew *Neisseria spp.* and α-hemolytic streptococci, no further speciation performed (the latter could potentially represent *S. pneumoniae*). The patient was switched to ampicillin.

I8821717104 (AECB; "chronic lipoid pneumonia"): This patient received 8 days of study drug. *P. aeruginosa* (ceftibuten zone = 16; resistant) grew at baseline from the sputum, which was eradicated At end-of-therapy the patient was considered clinically improved. The patient was readmitted to the hospital on day +21 with pneumonia due to β-lactamase (-) *M. catarrhalis*; no susceptibilities were done. The patient subsequently expired on day +31.

Development of Bacteriologic Resistance While Receiving Therapy:
As with C88044, the reviewer assessed all patients in the international studies who grew one of the "pathogens" during therapy or during the posttherapy period that also had been isolated at baseline to look for the development of resistance on therapy.

There were 222 ceftibuten susceptible (by zone or MIC) "pathogens" isolated at baseline from 207 patients (13 baseline pathogens did not undergo ceftibuten susceptibility testing). There were four pathogens that showed the development of resistance. The details follow:

I8811101005: *M. catarrhalis* had a baseline ceftibuten zone of 31 mm. By day 3, upon reisolation, it had a ceftibuten zone size of 0 mm.

I8811101012: *M. catarrhalis* had a baseline ceftibuten zone of 27 mm. By day 3, upon reisolation, the new ceftibuten zone was 0 mm.

I8821706006: *S. pneumoniae* had a baseline ceftibuten zone of 30 mm. By day the last day of therapy, the ceftibuten zone was reported as "R" although a specific zone size was not recorded.

I8821709002: *H. influenzae* had a baseline ceftibuten zone of 25 mm. By the last day of therapy, the ceftibuten zone was 17 mm.

For cefaclor there were 243 pathogens isolated at baseline from 226 patients that were susceptible to cefaclor (by zone or MIC). 12 baseline pathogens did not undergo cefaclor susceptibility testing. A single patient, I8821718107, grew β-lactamase (-) *H. influenzae* which changed from a baseline cefaclor zone size of 18mm to 6mm by day 7.

Clinical/Bacteriologic Efficacy of Study Drugs Against Valid Baseline Pathogens with "Intermediate" Susceptibility: There were 8 patients in the valid **ceftibuten**-treated population who grew baseline pathogens with "intermediate" susceptibility to ceftibuten; all had AECB. The MO's clinical bacteriologic responses follow: (There were no valid **cefaclor**-treated patients who grew pathogens with "intermediate" susceptibility to cefaclor.) (4/8 were clinical successes.)

I8811104101: AECB; *S. pneumoniae* (Zone=20mm). At EOT, the patient was clinically improved followed by **sustained improvement** at F/U; however, the pathogen **persisted.**

I8811104106: AECB; *S. pneumoniae* (Zone=18mm). At EOT the patient had **failed.** The pathogen **persisted.**

I8821709103: AECB; *S. pneumoniae* (Zone=20mm). At EOT the patient had **failed.** The pathogen was **persisted.**

I8821709119: AECB; *S. pneumoniae* (Zone=20mm). At EOT the patient was considered cured with **sustained cure** at F/U. The baseline pathogen was **eradicated,** but then the patient became **recolonized** with *S. pneumoniae.*

I8821709120: AECB; β-lactamase (-) *H. influenzae* (Zone=18mm). By EOT the patient was improved but subsequently **relapsed.** There was documented **eradication** of the baseline pathogen.

I8821709130: AECB; *S. pneumoniae* (Zone=20mm). Patient **failed** by EOT. Patient had **persistence** of the baseline pathogen.

I8821715102: AECB; β-lactamase (-) *H. influenzae* (Zone=20mm). Patient was cure at EOT with **sustained cure** at F/U. Patient had **eradication** of the baseline pathogen.

I8821715106: AECB; β-lactamase (-) *M. catarrhalis* (Zone=20mm). At EOT the patient was improved. By F/U patient was **cured.** The baseline pathogen was **eradicated.**

Clinical/Bacteriologic Efficacy for Ceftibuten-Resistant Pathogens: There were no ceftibuten-resistant "pathogens" (i.e., the five major pathogens) isolated at baseline in ceftibuten recipients.

Outcomes for Patients Treated with Other LRTI's at Baseline Who Received Ceftibuten 400 mg p.o. q.d.:

> ***Medical Officer's Comment:*** These patients were treated with a lower study drug dosage than that proscribed in the protocol relative to their baseline infection; none of these patients were considered evaluable by the reviewer, but their responses are noted.

I8811102108: (pneumonia; initially diagnosed with AECB.) This patient with IDDM received ceftibuten, 400 mg p.o. q.d., for 10 days. A transtracheal aspirate grew β-lactamase (-) *H. catarrhalis* at baseline (day -2) which was subsequently eradicated. The patient was cured at end-of-therapy with **sustained cure** two weeks post-treatment. The day +16 CXR was "normal."

I8811102111: (pneumonia; initially diagnosed with tracheitis.) The patient

received ceftibuten, 400 mg p.o. q.d., for 7 days. A transtracheal aspirate grew β-lactamase (-) *H. catarrhalis* on day -1 which was subsequently eradicated. The patient was a sustained cure two weeks posttreatment with a "normal" CXR on day +22.

I88111102113: (pneumonia; initially diagnosed incorrectly with "acute bacterial bronchitis.") The patient received ceftibuten, 400 mg p.o. q.d., for 9 days. A transtracheal aspirate grew *S. pneumoniae* on day -2 which was subsequently eradicated. The patient was a sustained cure two weeks posttreatment with a "normal" CXR on day +27.

I88217105101: (bronchiectasis) This patient received ceftibuten, 400 mg p.o. q.d., for 13 days (15 doses). The patient had a negative baseline sputum culture and was clinically cured at end-of-therapy.

I88217108110: (pneumonia; initially diagnosed incorrectly with "acute bacterial bronchitis.") This patient, who had an underlying pulmonary embolism, received ceftibuten, 400 mg p.o. q.d., for 7 days. *E. coli* grew from the baseline sputum and persisted throughout the study. In addition, *S. aureus* (ceftibuten susceptible) was isolated from the sputum, *de novo*, on day +3. The patient was considered a clinical failure. The CXR remained abnormal at day +1.

I88217118102: (pneumonia; initially diagnosed with AECB.) Ceftibuten, 400 mg p.o. q.d., was administered for 10 days (15 doses as patient did not return unused drug) having failed a 6-day course of ampicillin, 2 gm q8 hours. β-lactamase (-) *H. parainfluenzae* was grown at baseline (resistant to ampicillin). The patient was considered clinically cured at end-of-therapy with presumptive eradication of the baseline pathogen. By day +16, the CXR was reported to be "normal."

Ceftibuten Bacteremic Patients:

In the international study. there were 3 patients who experienced bacteremia during the course of the study. The details follow:

I88217105001 (ceftibuten 200 mg b.i.d. x 7 days; diagnosed with pneumonia, but actually had endocarditis). *S. pneumoniae* was isolated from the sputum. However, the patient was subsequently diagnosed with endocarditis due to *Streptococcus bovis* after being isolated from the blood on day 4. It was ceftibuten resistant (zone = 15mm). The patient was switched to IV penicillin (also used to treat persistent *S. pneumoniae* from repeated bronchoscopy specimens). No follow-up blood cultures were done. Patient underwent an aortic valve replacement on day +20.

I88217105107: See DEATHS. (Although not "bacteremic," this patient died of "sepsis" following isolation of *S. pneumoniae* at baseline.)

I88217107009 (ceftibuten 200 mg b.i.d. x 5 days; pneumonia). This patient had pneumonia due to *S. pneumoniae*; the individual was bacteremic with this pathogen at entry - it was ceftibuten susceptible. No follow-up blood cultures were done. The patient was considered a "failure" on day 5 and was switched to IV penicillin on day +5.

I88327101007 (ceftibuten 200 mg b.i.d. x 4 days; pneumonia). This patient had pneumonia and concurrent bacteremia due to *S. pneumoniae* - a susceptible pathogen. The patient was a failure having persistence of *S. pneumoniae* in both blood and sputum and was switched to IV penicillin on day 4.

SAFETY EVALUATION:

The following section contains assessments for all LRTI patients (those who were not excluded) who received either ceftibuten 400 mg q.d. or cefaclor 250 mg t.i.d with the exception of deaths where other dosing regimens were included. (87 ceftibuten 200 mg b.i.d. and 43 cefaclor 500 mg b.i.d. "safety" patients are not included in this section. Instead, they are included in the MO's review of the overall integrated summary of safety.

Patients Discontinued From Therapy Due to AE:
According to the applicant, 4 patients (2 ceftibuten, 2 cefaclor) were discontinued from the study due to the development of an AE. The specifics follow.

CEFTIBUTEN:

I8821724101: On the first day of therapy, this patient developed severe "rigors" lasting 5 days - these rigors were due to the development of pneumonia. The patient required hospitalization and treatment with erythromycin. The investigator considered this "unrelated" to the study drug.

I8832701106: On the first day of therapy, 5 hours after her first dose, severe nausea and vomiting developed. The drug was stopped and the patient quickly improved. The investigator considered this "possibly" related to ceftibuten.

CEFACLOR:

I8821718126: (AECB) After 10 days of therapy, this patient developed moderate "erythema (allergic reaction)." The drug was discontinued and the patient returned to baseline within 2 days. The investigator considered this "probably" due to cefaclor. There was no history of allergy.

I8821720106: On the first day of therapy, moderate vomiting occurred. The drug was discontinued and this resolved within 2 days. The investigator considered this "unrelated" to cefaclor therapy.

DEATHS: There were a total of 8 deaths experienced during the course of this study; 6 ceftibuten, 2 cefaclor. The following includes ALL patients from the I88111, I88217, or I88327, independent of drug or underlying LRTI.

CEFTIBUTEN:

I8821705004: (Ceftibuten 200 mg q12h x 15 days; - however CXR report = "bronchopneumonia") This 83-year-old white male with "adenocarcinoma" and NIDDM died on day +19 of "cardiac failure." The investigator considered this "unrelated" to drug therapy. The patient had a persistent right basilar infiltrate by day +10. The baseline sputum grew *S. aureus* - no susceptibilities done.

I8821705104: (Ceftibuten 400 mg q d. x 15 days;
This 92-year-old white male hospitalized with a hip fracture and a history of atrial fibrillation died on day +5 of "cardiac decompensation." The patient was a clinical cure at end-of-therapy and grew *S. pneumoniae* at baseline which was presumptively eradicated. The investigator considered this "unrelated" to the study drug.

I8821705107: (Ceftibuten 400 mg q.d. x 4 days; there was no baseline CXR obtained.) This 84-year-old white male died on day 4 of therapy. On day 3, the patient experienced "strong shivers" and died that night of "SEPSIS"; The patient grew *S. pneumoniae* from the sputum at baseline; no susceptibilities done to ceftibuten. A blood culture obtained at that same time was negative. The investigator considered this "unrelated" to the study drug.

I8821707110: (Ceftibuten 400 mg q.d. x 7 days; AECB) This 78-year-old white female with cor pulmonale died of "heart insufficiency" with resultant pleural and pericardial effusions on day +15. *Haemophilus spp.* was isolated at baseline. At EOT, the patient was considered improved. The investigator considered this "unrelated" to the study drug.

I8821707112: (Ceftibuten 400 mg q.d. x 7 days; AECB) This 62-year-old white male with cor pulmonale and a history of TB died on day +16 in light of "circulatory breakdown." Clinically this patient was considered a cure. *E. coli* and *Haemophilus spp.* grew at baseline. The investigator considered this "unrelated" to the study drug.

I8821717104: (Ceftibuten 400 mg q.d. x 8 days; AECB) This 41-year-old white male with "chronic lipoid pneumonia" died on day +31 due to pneumonia. The investigator considered this "unrelated" to the study drug. (See section on superinfections/reinfections.)

CEFACLOR:

I8832701006: (Cefaclor 500 mg q8h x 7 days; pneumonia) This 83-year-old white male with COPD and ETOH abuse died on day +4 of "disease progression." The patient was a clinical failure with *S. pneumoniae* isolated at baseline. At end-of-therapy, there was no *S. pneumoniae* present. Instead both *Enterobacter cloacae* and *K. pneumoniae* were found. The investigator considered this "unrelated" to the study drug.

I8821706101: (Cefaclor 250 mg q8h x 9 days; AECB) This 59-year-old white female with COPD, s/p treatment for TB, died of "cardiorespiratory arrest with CO_2 retention" on day +12. The patient was a clinical failure; both *M. catarrhalis* and *H. parainfluenzae* were isolated at baseline. The former persisted. The investigator considered this "unrelated" to the study drug.

CLINICAL ADVERSE EVENTS:

During the course of this study, 20/177 (11%) ceftibuten 400 mg q.d. and 11/88 (13%) cefaclor 250 mg t.i.d. patients experienced at least one AE, independent of relatedness to the drug. Likewise, 14/177 (8%) ceftibuten 400 mg q.d. and 7/88 (8%) cefaclor 250 mg t.i.d. patients experienced a minimum of one AE, which was considered to be at least possibly-related to the drug. (See Tables 39 & 40.)

Independent of relatedness to study drug, more cefaclor patients experienced "neurologic" AE's than did the ceftibuten arm. (See Table 39.)

When AE's are looked at specifically with regard to relatedness, fewer were seen, and they appeared to be fairly equally represented between treatment groups. (See Table 40.) This smaller number of AE's contrast with that seen in the domestic study.

Table 39
All Clinical AE's by Severity for All Patients who Received Either Ceftibuten 400 mg Q.D. or Cefaclor 250 mg T.I.D. (International)
(According to applicant)

Clinical AE's	Ceftibuten (N=177) Mild	Mod	Severe	TOTAL	(%N)	Cefaclor (N=88) Mild	Mod	Severe	TOTAL	(%N)
AT LEAST ONE AE				20	(11)				11	(13)
Gastrointestinal	5	2	3	10	(6)	2	2	0	4	(5)
Diarrhea	1	1	2	4	(2)	-	-	-	0	
Dyspepsia	1	-	-	1	(<1)	-	-	-	0	
Hemorrhage,rectum	-	-	-	0		1	-	-	1	(1)
Nausea	2	1	2	5	(3)	1	1	-	2	(2)
Oral thrush	1	-	-	1	(<1)	-	-	-	0	
Vomiting	1	1	2	4	(2)	1	1	-	2	(2)
Neurologic	1	2	0	3	(2)	3	1	0	4	(5)
Agitation	-	1	-	1	(<1)	-	-	-	0	
Dizziness	-	-	-	0		1	-	-	1	(1)
Headache	-	1	-	1	(<1)	1	-	-	1	(1)
Nervousness	-	1	-	1	(<1)	-	-	-	0	
Paresthesia	1	-	-	1	(<1)	-	-	-	0	
Syncope	-	-	-	0		1	-	-	1	(1)
Vertigo	-	-	-	0		-	1	-	1	(1)
Hypersensitivity	0	0	0	0		0	1	0	1	(1)
Erythema	-	-	-	0		-	1	-	1	(1)
Miscellaneous	6*	0	1	7	(4)	3	1	2†	6	(7)
Asthenia	-	-	-	0		1	-	-	1	(1)
Backache	-	-	-	0		1	-	-	1	(1)
Cardiac arrest	-	-	-	0		-	-	1†	1	(1)
Hematuria	2	-	-	2	(1)	-	-	-	0	
Hypokalemia	3	-	-	3	(2)	-	-	-	0	
Infection, fungal	-	-	-	0		-	1	1	2	(2)
Musc. skel. pain	-	-	-	0		1	-	-	1	(1)
Nasal congestion	1	-	-	1	(<1)	-	-	-	0	
Rigors	-	-	1	1	(<1)	-	-	-	0	

NOTE: "N" does not include "excluded" patients.
* 5/6 had no severity assessment; the MO arbitrarily assigned severity scores of mild.
† Designates a single "life-threatening" AE.

Table 40
Clinical AE's by Severity Considered Possibly, Definitely, or Probably Drug-Related for All Patients who Received Either Ceftibuten 400 mg Q.D. or Cefaclor 250 mg T.I.D. (International)
(According to applicant)

Clinical AE's	Ceftibuten (N=177)					Cefaclor (N=88)				
	Mild	Mod	Severe	TOTAL	(%N)	Mild	Mod	Severe	TOTAL	(%N)
AT LEAST ONE AE				14	(11)				7	(8)
Gastrointestinal	4	0	2	6	(3)	1	1	0	2	(2)
Diarrhea	-	-	1	1	(<1)	-	-	-	0	
Dyspepsia	1	-	-	1	(<1)	-	-	-	0	
Nausea	2	-	1	3	(2)	1	1	-	2	(2)
Oral thrush	2	-	-	2	(1)	-	-	-	0	
Vomiting	2	-	1	3	(2)	-	-	-	0	
Neurologic	1	1	0	2	(1)	2	1	0	3	(3)
Agitation	-	1	-	1	(<1)	-	-	-	0	
Dizziness	-	-	-	0		1	-	-	1	(1)
Headache	-	-	-	0		1	-	-	1	(1)
Nervousness	-	1	-	1	(<1)	-	-	-	0	
Paresthesia	1	-	-	1	(<1)	-	-	-	0	
Vertigo	-	-	-	0		-	1	-	1	(1)
Hypersensitivity	0	0	0	0		0	1	0	1	(1)
Erythema	-	-	-	0		-	1	-	1	(1)
Miscellaneous	6*	0	0	6	(3)	1	1	1	3	(3)
Backache	-	-	-	0		1	-	-	1	(1)
Hematuria	2	-	-	2	(1)	-	-	-	0	
Hypokalemia	3	-	-	3	(2)	-	-	-	0	
Infection, fungal	-	-	-	0		-	1	1	1	(1)
Nasal congestion	1	-	-	1	(<1)	-	-	-	0	

NOTE: "N" does not include "excluded" patients.
* 5/6 had no severity assessment; the MO arbitrarily assigned severity scores of mild.

LABORATORY ADVERSE EVENTS:
According to the applicant, the laboratory AE's are shown in Table 41. Laboratory AE's between the two groups are comparable.

Using different criteria (see Appendix), the reviewer's significant AE's are included in Table 42. These were comparable between treatment groups.

Table 41
Abnormal Laboratory Values for Bronchitis/Tracheitis Patients (International)§
(According to applicant)

	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Eosinophils	4/150 (3%)	2/69 (3%)
Hemoglobin	8/163 (5%)	3/76 (4%)
Platelets (above 700)	0/159 (0%)	0/76 (0%)
Platelets (below 100)	0/159 (0%)	1/76 (1%)
WBC	1/163 (<1%)	0/76 (0%)
BUN	12/125 (10%)	5/63 (8%)
Creatinine	22/164 (13%)	9/78 (12%)
SGOT	1/148 (<1%)	1/73 (1%)
SGPT	1/157 (<1%)	0/69 (0%)
Total Bilirubin	2/158 (1%)	2/74 (3%)
Alkaline Phosphatase	0/165 (0%)	0/74 (0%)
Specific gravity	41/118 (35%)	17/52 (33%)
pH	7/110 (6%)	3/49 (6%)
Glucose	3/108 (3%)	1/50 (2%)
Hemoglobin	3/107 (3%)	2/50 (4%)
Protein	2/107 (2%)	0/50 (0%)
Urine WBC	18/110 (16%)	9/50 (18%)
Urine RBC	13/109 (12%)	4/51 (8%)
Epithelial	19/110 (17%)	11/51 (22%)
Bacteria	5/110 (5%)	1/51 (2%)
Crystals	7/109 (6%)	7/51 (14%)

Criteria for abnormal findings:

SGOT, SGPT - 3 times above the upper limit of normal range.
BUN, Total bilirubin - 25% increase above baseline value and above the upper limit of normal range.
Alkaline phosphatase - above 1.5 times the upper limit of normal range if baseline value is within normal range, otherwise 50% increase above baseline value.
Creatinine - 0.5 mg/dl increase from baseline value and above the upper limit of normal range OR for S.I. Units ≥133 moles/L.
Eosinophils - above 700 mm^3 if baseline value is within normal range.
Hemoglobin - 2 G decrease from baseline.
WBC - below 2.5/mm^3
Platelets - below 100 or above 700 and more than 50% change from baseline value.
Specific gravity - ≤ 1.00 or ≥ 1.075.
pH - ±2.0 units from baseline.
Glucose - 1+ or greater, otherwise increase of 1 from baseline.
Hemoglobin - 1+ or greater, otherwise increase of 1 from baseline.
Protein - if baseline is within the normal range (0/trace) a reading of 1+ or greater. If baseline is initially abnormal then any increase from baseline.
Microscopic U/A:
- WBC - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.
- RBC - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.
- Epithelium - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.
- Bacteria - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.
- Crystals - if baseline is within normal range then an increase ≥ 10/high power field. If baseline is initially abnormal, then an increase of ≥20/high power field.

§ The denominators reflect the total number of patients that had a baseline laboratory assessment with subsequent assessment(s) during treatment.

Table 42
Laboratory AE'S For Patients Who Received Either Ceftibuten 400 mg Q.D. or Cefaclor 250 mg T.I.D. (International)*
(According to reviewer)

Patients with baseline labs.	Ceftibuten (N=175)	Cefaclor (N=87)
Eval. Hemoglobin	(n=167)	(n=83)
Drop of ≥3 g/dL	0	0
Eval. WBC	(n=167)	(n=83)
F/U WBC <3.5, drop of ≥1.0	4 (2)	2 (2)
Eval ANC	(n=85)	(n=84)
F/U ANC <1.0; NL @ baseline	1 (1)	0
Eval. Eosinophils	(n=154)	(n=76)
F/U Eos >500/mm^3 (2x baseline)	6 (4)	3 (4)
Eval. Platelets	(n=162)	(n=81)
F/U ≤150,000 (drop ≥100,000)	1 (<1)	2 (2)
F/U ≥600,000 (1.5x baseline)	0	1 (1)
Eval. Prothrombin time	(n=0)	(n=0)
Eval. Glucose	(n=4)	(n=1)
Inc. or Dec.	0	0
Eval. BUN	(n=165)	(n=85)
F/U flagged & 2x NL baseline	1 (<1)	1 (1)
Eval. Creatinine	(n=166)	(n=85)
F/U flagged & inc. by 25%	11 (7)	7 (8)
Eval. AST	(n=151)	(n=77)
F/U 3x ULN & baseline	0	1 (1)
Eval. ALT	(n=161)	(n=73)
F/U 3x ULN & baseline	0	0
Eval. Alkaline phosphatase	(n=167)	(n=80)
F/U 2x ULN & baseline	0	0
Eval. Bilirubin (total)	(n=159)	(n=80)
F/U 1.5x ULN or inc. 1 mg/dL if baseline WNL.	0	0
Eval. Urine glucose	(n=102)	(n=51)
Baseline WNL, F/U ≥+2	1 (1)	0
Eval. Urine protein	(n=101)	(n=51)
Baseline WNL, F/U ≥+1	1 (1)	1 (2)
Eval. Urine blood	(n=102)	(n=51)
Baseline WNL, F/U ≥+1	2 (2)	2 (4)
Eval. Urine WBC'S	(n=99)	(n=50)
Baseline WNL, F/U ≥6/LPF	9 (9)	3 (6)
Eval. Urine RBC's	(n=98)	(n=51)
Baseline WNL, F/U ≥6/LPF	3 (3)	1 (2)

* Laboratory changes were not assessed relative to their relatedness to drug therapy. "Excluded" patients are not included in this table.

CONCLUSIONS:

Medical Officer's Comment: As previously stated, in general, the international studies provided less clinical information than the domestic one did. The comment pages of the CRF were less like to be filled-out and concomitant drug use was less likely to be fully included.

Using the **clinical test-of-cure** population as the primary efficacy population (those patients who were clinically assessed on day +4 or later), independent of type of bronchitis, the success rate for ceftibuten was 56/88 (64%) versus 23/38 (61%) for cefaclor. Using the 95% C.I. approach, corrected for unequal sample sizes, this is {-17%, 24%}. Uncorrected, this is {-15%, 22%}. If these groups are separated into type of underlying bronchitis, numbers are too small to reach statistical significance.

If the MO's **clinical efficacy** population is looked at, analogous to the applicant's clinical efficacy population, the following is seen. A positive (successful) response was noted for 143/166 (86%) of ceftibuten patients in contrast to 70/80 (88%) of cefaclor recipients; uncorrected, this is {-10%, 8%}. If groups are separated into respective underlying forms of bronchitis, respective success rates and 95% CI's are: 73/80 (91%) vs. 31/32 (97%); {-16%, 5%} for acute bacterial bronchitis AND 70/86 (81%) vs. 39/48 (81%); {-15%, 16%} (uncorrected: {-14%, 14%}. Based on this, using the 95% CI approach, ceftibuten is shown to be equally efficacious to cefaclor in the treatment of AECB only.

According to the applicant, by EOT for their **clinical efficacy** population (those patients seen right at end-of-therapy), independent of the type of bronchitis, 150/169 (89%) and 76/79 (96%) of ceftibuten and cefaclor patients, respectively experienced a successful response. The uncorrected 95% CI = {-14%, -1%}. Using the applicant's primary efficacy population, overall, ceftibuten was less effective than cefaclor.

When separated into types of bronchitis, for acute bacterial bronchitis (including tracheitis), success rates are 89/96 (93%) vs. 38/38 (100%), respectively. Corrected 95% CI = {-14%, -0.3%}. Again, ceftibuten is less efficacious. For AECB, 61/73 (84%) vs. 38/41 (93%) with the following 95% CI, corrected: {-23%, 4%}.

With regard to bacteriologic efficacy, there were few "pathogens" evaluable. The most common pathogens were *H. influenzae* and *S. pneumoniae*. If all pathogens are combined, from the reviewer's assessment the following eradication rates are seen (combined presumptive and documented): for ceftibuten, 30/45 (67%) vs.

13/21 (62%) for cefaclor. The corrected 95% CI = {-24%, 33%}. For *S. pneumoniae*, combining both types of bronchitis, respective eradication rates for the two treatment groups are 10/21 (48%) vs. 7/11 (64%). Using χ^2 with Yate's correction for continuity, p>0.5. Although this difference isn't statistically significant, it is concerning how much lower the *S. pneumoniae* eradication rate is compared with other "pathogens" treated with ceftibuten.

Relative to safety, when only clinical AE's considered related to the study drug are looked at, very few were seen and the drugs appeared to be comparable. With regard to laboratory AE's assessed by the MO, no significant differences were seen.

EVALUATION OF AECB PATIENTS WHO RECEIVED CEFTIBUTEN 200 MG B.I.D. OR CEFACLOR IN STUDIES C87001 *et al* AND I88230:

Medical Officer's Comment: C87001 *et al* consisted of the domestic study C87001 and the international studies I87107, I87223, I87233, I87234, I87236, and I87325. I88230 was a different international study. (See below.)

Based on the ceftibuten 400 mg q.d. and cefaclor 250 t.i.d. bronchitis experience from C88044 *et al*, using the MO's clinical test-of-cure population, it is apparent that neither the domestic or international studies were able to satisfy the 95% confidence interval approach. Indeed, ceftibuten appeared to be less effective than cefaclor in the treatment of acute bacterial bronchitis. In light of these findings and the applicant's insistence that the ceftibuten 200 mg b.i.d. data should be considered "supportive" of ceftibuten 400 mg q.d. dosing, the MO decided to review only the AECB patients in these studies.

The review that follows is presented here in less detail than that for C88044 *et al* as those studies were considered pivotal. The data presented here involves selection of those patients across multiple studies (C87001 *et al* and I88230) who had AECB, and the patients received either ceftibuten 200 mg b.i.d. or cefaclor 250 mg t.i.d. and 500 mg t.i.d. (Few patients received cefaclor 250 mg t.i.d. in these studies.) The remaining patients are ignored with regard to efficacy. (For a breakdown of the these studies according to geographic location, the reader is referred to the introduction for the section.)

These studies were conducted similarly to the previous studies with the major exception being dosing regimens employed. In C87001 *et al*, patients with "bronchitis" or pneumonia/bronchiectasis were to be randomized (1:1:1) to either ceftibuten 200 mg b.i.d or 300 mg b.i.d. or cefaclor 500 mg t.i.d. Two of the centers in C87001 *et al*, I87234-01 and -03 both used Augmentin® 1 gram b.i.d as the comparator. In I88230, the same diagnoses were randomized (2:1) to receive either ceftibuten 200 mg b.i.d. or cefaclor 250 mg t.i.d.

The number of patients enrolled from these studies are represented in Table 1. Demographics in Table 2.

Table 1
Summary of Evaluability, Dosing Regimens, for AECB
(C87001 *et al* & I88230)
(According to reviewer)

	Ceftibuten 200 mg bid	Cefaclor 250 mg tid	Cefaclor 500 mg tid	Total
Enrolled	**86**	**18**	**58**	**162**
Excluded	0	0	0	0
Safety	86	18	58	162
Clinical efficacy	74	15	52	141
Clinical test-of-cure	39	36	5	80
Valid	24	4	22	50

Table 2
Demographic Data for All Enrolled
AECB Patients* (C87001 *et al* & I88230)
(According to reviewer)

	No. of Patients (%) Ceftibuten (n=86)	Cefaclor (n=78)
Sex		
Male	63 (73)	46 (61)
Female	23 (27)	30 (39)
Race		
White	79 (92)	70 (92)
Black	3 (3)	3 (4)
Other	4 (5)	3 (4)
Patient Status		
Inpatient	10 (12)	7 (9)
Outpatient	16 (19)	11 (14)
Not recorded	60 (70)	58 (76)
Age (yr)		
Mean	63.0	60.8
Median	65.0	65.0
Range (min-max)		
Weight (kg)		
Mean	71.2	67.4
Median	70	65.9
Range (min-max)		
Not Recorded	0	1

* This table uses the diagnoses reassigned by the reviewer.

With regard to study drug administration for the clinical test-of-cure population, for ceftibuten 200 mg b.i.d., on average 10 days of drug were given (19.3 doses). For cefaclor 250 or 500 mg t.i.d, 10.6 days; 30.7 doses.

Clinical and bacteriologic responses for clinical test-of-cure and valid patients, respectively, are represented in Tables 3 and 4.

Table 3
Clinical Responses for the Clinical Test-of-Cure
AECB Population*
(According to reviewer)

Clinical Response	No. of Patients (%) Ceftibuten (n=39)		Cefaclor (n=41)	
At End-of-Therapy				
Positive response	23	(59)	27	(66)
Cure	9	(23)	14	(34)
Improvement	14	(36)	13	(32)
Failure	16	(41)	14	(34)
At Follow-up				
Positive response	17	(44)	24	(59)
Cure	14	(36)	19	(46)
Improvement	3	(8)	5	(12)
Negative response	22	(56)	17	(41)
Early Failure*	16	(41)	14	(34)
Late Failure**	1	(3)	0	
Relapse	5	(13)	3	(7)

* Failures at end-of-therapy carried forward as the extended follow-up visit response.

** Late failures were improved or not assessable at end-of-therapy, followed by a poor clinical response at the posttherapy follow-up visit (i.e., inadequate sustained improvement).

Table 4
Cumulative "Pathogen" Eradication Rates for MO's
Valid AECB Pathogens at F/U
(According to reviewer)

	Number (%) of Isolates Ceftibuten	Cefaclor
Moraxella (Branhamella) catarrhalis		
β-lactamase (-)†	3/4 (75)	1/1 (100)
β-lactamase (+)	1/2 (50)	2/5 (40)
Haemophilus influenzae		
β-lactamase (-)	7/9 (78)*	3/8 (38)
β-lactamase (+)	1/1 (100)	1/2 (50)
Haemophilus parainfluenzae		
β-lactamase (-)	4/5 (80)	5/7 (71)
β-lactamase (+)	0	0
Klebsiella pneumoniae	1/1 (100)	1/1 (100)
Streptococcus pneumoniae	2/6 (33)	3/3 (100)
Total	**19/28 (68)**	**16/27 (59)**

* Eradication is the absence of the causative organism(s) at or immediately after termination of therapy (documented), or the complete disappearance of the culture source (e.g., sputum) so that follow-up culture is impossible (presumptive).

† Includes pathogens not tested for β-lactamase activity.

* Designates pathogens with documented relapse.

There were 9 **superinfections** in the ceftibuten arm and 3 in the cefaclor group. For ceftibuten, the specific pathogens were *S. pneumoniae* (4), *H. influenzae* (2), and *M. catarrhalis* (3). For cefaclor, *S. pneumoniae* (3).

There were 2 **reinfections**; 1 from each treatment group. For ceftibuten, *M. catarrhalis*; cefaclor, *H. influenzae*. Neither was β-lactamase (+).

No patients were bacteremic. One patient developed pneumonia, I8723402004, a ceftibuten recipient. Following 7 days of therapy, this patient experienced "sudden **DEATH**" of unknown cause. At baseline, this patient grew 3 bacteria from the baseline sputum sample: *S. pneumoniae*, *E. aerogenes*, and *P. mirabilis* - all were susceptible to ceftibuten. At the time of death, a repeat sputum sample was not obtained. It is possible that this progression was associated with *S. pneumoniae*.

The combined clinical/bacteriologic cumulative responses at posttherapy follow-up were looked at for *S. pneumoniae*. For ceftibuten, of the 6 isolated, all 4 persisters were associated with clinical failure while the 2 eradicated were associated with clinical cure. For cefaclor, a 3 eradicated were associated with clinical cures.

CONCLUSIONS:

With regard to clinical efficacy for the **clinical test-of-cure** population, success rates beyond day +3 were 17/39 (44%) vs. 24/41 (59%), respectively. The corrected 95% CI = {-39, 9%}. There is a trend that ceftibuten 200 mg b.i.d. was less effective than both cefaclor 250 t.i.d. and 500 t.i.d. combined.

For bacteriologic responses, ceftibuten appeared to be more effective than cefaclor in the eradication of β-lactamase (+) pathogens (2/3 vs. 3/7, respectively), while it was less effective in the eradication of *S. pneumoniae*, albeit small numbers.

CONCLUSIONS:

In general, both secondary bacterial infection of acute bronchitis and acute bacterial exacerbations of chronic bronchitis are empirically treated infections by the medical community. The clinician infrequently cultures the sputum but initiates antimicrobial therapy based on clinical signs & symptoms including character and amount of sputum. If cultures are obtained, their influence on decision-making in the management of these patients is often small; unless the patient is not responding to the empirically chosen regimen. Thus, for the purpose of reviewing these two indications, the reviewer placed the greatest emphasis on drug efficacy based on the clinical population in contrast with the bacteriologic efficacy; hence, the **clinical test-of-cure population**.

From a recently published textbook, Sanford Chodosh, M.D., in his chapter, *"Bronchitis and Asthma" from Gorbach, Bartlett, and Blacklow, (eds.) Infectious Diseases. Saunders, 1992, pp. 476-485*, states, "...failure of therapy within the treatment period or recrudescence of infection within 2 weeks of stopping therapy occurs in 12 to 28 per cent of patients treated with optimal antimicrobial therapy - and reportedly in as many as 70 per cent with suboptimal therapy." Furthermore, in this same chapter, concerning the treatment of AECB with cefaclor, 250 mg p.o., t.i.d., approximately 29% failed to respond during treatment, and 71% either failed to respond during treatment or rebounded within 2 weeks after completing therapy. With regard to a recommended appropriate duration of therapy, Dr. Chodosh further states, "..the minimal duration of therapy should be 10 to 14 days."

In the MO's approach to the overall evaluation of the studies for critical review of the AECB indication, the comparative trials were grouped as follows: **C88044 *et al***, the only study that employed the ceftibuten 400 mg q.d. dosing, was divided into **C88044**, the domestic study, as **study #1**. The remaining international studies, **I88111, I30217, and I88327**, were grouped as **study #2**.

From these studies, it was determined that ceftibuten 400 mg p.o. q.d. appeared to be less effective than cefaclor in the treatment of secondary bacterial infection of acute bronchitis. Based on this, it was decided that further review of acute bacterial bronchitis experience from other studies at other dosing regimens would be unproductive (i.e., ceftibuten 200 mg b.i.d). As no other ceftibuten 400 mg q.d. AECB experience was submitted with this application, it was decided to critically review the ceftibuten 200 mg b.i.d. AECB experience from the remaining studies; namely **C87001 *et al*** and **I88230**. Although many assumptions are made in combining these studies, the ceftibuten

200 mg b.i.d. and cefaclor 250 t.i.d. and 500 t.i.d. was considered, as a whole, a **supportive** study.

Thus, for the reviewer's **clinical test-of-cure** population, if the experience from studies #1 and #2 are combined, the cumulative posttherapy clinical outcomes for **acute bacterial bronchitis** demonstrated successful responses in 62/92 (67%) of ceftibuten and 23/29 (79%) of cefaclor patients. Using the 95% confidence interval approach corrected for continuity, this was {-30%, 5%}. Using the 95% CI, it appears that a trend exists that ceftibuten has worse efficacy compared to cefaclor. However, from 2-tailed hypothesis testing, the p-value = 0.2 which doesn't support this being a trend. (Usually a p-value between 0.05-0.1 denotes a trend.)

For the **AECB** patients, respective combined success rates were 62/110 (56%) and 32/54 (59%); the corrected 95% CI approach = {-20%, 15%}. Uncorrected, {-19%, 13%}. Therefore, after combining these studies, the sample size is large enough for ceftibuten to meet the 95% CI approach.

> *Medical Officer's Comment:* The MO believes it is reasonable to combine these studies as there were a greater number of hospitalized patients from the international study. Presumably these patients were more ill, which would make it appropriate that they be supportive of the domestic study. (Although success rates were higher in the international study.)

As previously shown, when the ceftibuten 200 mg b.i.d AECB experience is combined from C87001 *et al* and I88320, the respective cumulative success rates for the clinical test-of-cure population were 17/39 (44%) vs. 24/41 (59%), respectively. The corrected 95% CI = {-39%, 9%}. Clearly, this pooled analysis does not support the findings from the pooled analysis of C88044 *et al*. Indeed, it appears that a trend exists that ceftibuten 200 mg b.i.d. was less efficacious than cefaclor 250/500 mg t.i.d. However, again, using 2-tailed hypothesis testing, the p=0.18, which does not support a trend.

As discussed elsewhere, the applicant believes that the ceftibuten 200-300 mg b.i.d. pneumonia data should be considered supportive of ceftibuten 400 mg q.d. bronchitis. The MO does not believe that ceftibuten 300 mg b.i.d. pneumonia could be used to support ceftibuten 400 mg q.d. bronchitis. However, it was decided to look at the pooled ceftibuten 200 mg b.i.d. pneumonia patients compared with cefaclor 500 mg t.i.d. for valid patients. The following is seen:

Clinical Responses for the Applicant's Valid Pneumonia Patients Who Received Either Ceftibuten 200 mg B.I.D. or Cefaclor 500 mg T.I.D. (All studies)*
(According to applicant)

Clinical Response	No. of Patients (%) Ceftibuten		Cefaclor	
At End-of-Therapy	(n=95)		(n=64)	
Positive response	85	(89)	59	(92)
Cure	70	(74)	46	(72)
Improvement	15	(16)	13	(20)
Failure	10	(11)	5	(8)
Not specified	0		1	
At Follow-up	(n=56)		(n=43)	
Positive response	41	(73)	36	(84)
Cure	37	(66)	31	(72)
Improvement	4	(7)	5	(12)
Negative response	15	(27)	7	(16)
Early Failure*	10	(18)	5	(12)
Relapse	5	(9)	2	(5)

* Failures at end-of-therapy carried forward as the extended follow-up visit response.

Using the 95% CI approach for the cumulative posttherapy follow-up clinical outcomes, corrected, it is {-29%, 8%}. Uncorrected, {-27%, 6%}. Thus, using the applicant's assessments, the MO having not reviewed the patients critically, again a trend is seen, that ceftibuten is less efficacious than the comparable dose of cefaclor. This too cannot be considered supportive of ceftibuten 400 mg q.d. AECB.

> ***Medical Officer's Comment:*** The data above represents the applicant's assessments provided in the original NDA. Of interest, during the review of this indication, once the applicant was aware that the Division was having "difficulties" with this indication, the applicant submitted "revised" clinical assessments and revised evaluabilities. In that revised data base, at EOT, for ceftibuten, successes increased by 1 and failures **decreased** by 2. In contrast, for the cefaclor arm, successes increased by 1 and failures **increased** by 2. By F/U, for ceftibuten, cumulative successes had increased by 3 and failures **decreased** by 3. For cefaclor, successes had increased by 1, while failures **increased** by 3. Respective "revised" cumulative F/U success rates are 43/55 (78%) vs. 37/47 (79%). The uncorrected 95% CI = {-17%, 15%}. The MO finds this concerning that these changes appear to be biased in favor of the applicant's drug.

With regard to bacteriologic efficacy in bronchitis patients, in

the U.S. study, ceftibuten appeared to be reasonably efficacious against all "pathogens." However, in the international studies for C88044 *et al*, eradication rates were much lower overall. Moreover, eradication rates appeared to be significantly lower for *S. pneumoniae*. This was reconfirmed in the ceftibuten 200 mg b.i.d. AECB experience, where 2/6 *S. pneumoniae* were eradicated. From a bacteriologic standpoint, based on this data, it would appear that ceftibuten has *in vivo* efficacy problems against *S. pneumoniae* - at least with international isolates. Ceftibuten did not appear to have problems with β-lactamase (+) pathogens. However, evaluable numbers are small.

Based on the review of the data submitted, the treatment indications
acute bacterial exacerbations of chronic bronchitis should NOT be approved.

(See Final Conclusions for suggestions on how to proceed at this time with this indication.)

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NA Indication

INTEGRATED SAFETY SUMMARY:

PHASE I TRIALS:

According to the applicant, during Phase 1, ceftibuten was administered to 456 subjects, ages ranging between 18-83 years-old. This number includes patients studied by both Schering-Plough

(1) PHASE 1 STUDIES:

42 subjects were studied with ages ranging between 20-48 years-old. Drug exposure ranged from single-dose 25-200 mg to multiple-dose 100 mg b.i.d. x 14 days or 200 mg b.i.d. x 7 days. No clinical or laboratory adverse experiences were reported.

> *Medical Officer's Comment:* On March 31, 1992, the applicant submitted a study report for C91238-01, "Multiple-dose GI tolerance study of **300 and 400 mg b.i.d.** doses of SCH 39720 in normal male volunteers," to IND In this double-blind, placebo-controlled, parallel-group study, 54 patients were enrolled in one of the three study arms. Treatment lasted 14 days. All patients completed the study. No clinical or laboratory adverse experiences were noted for any subjects.

(2) SCHERING-PLOUGH PHASE 1 STUDIES:

Clinical AE's:
414/456 subjects were enrolled in Schering-Plough trials while the remainder participated in trials conducted by (See below.) Dosing varied between 200-800 mg single-doses to 200-400 mg b.i.d.

No pattern of occurrence for clinical adverse experiences relative to dose was seen.

Laboratory AE's:
5/67 (7%) **300 mg single-dose** subjects developed significant laboratory AE's. One patient developed mild elevation of AST/ALT. This resolved within one week.

The remaining 3 subjects took part in the chronic renal insufficiency study, C87091-01. One individual experienced mild elevations of AST/ALT, another a mild decrease in the total WBC count, and two developed elevations of per cent eosinophils (14% and 30%, respectively [normal upper limit = 6%]).

In a **400 mg single-dose** study, C90-420-01, 2/18 developed mild

elevations of SGPT and SGOT, respectively.

Ceftibuten Pts. Discontinued From Phase 1 Studies Due to the Development of an AE:

C90875Q1014: (Ceftibuten 400 mg single-dose; 3-way crossover study) Approximately 2-3 days following administration of a single dose of ceftibuten 400 mg to a 27-year-old black male, a flu-like syndrome developed with mild headache, fever, fatigue, neck stiffness, sore throat, and lymphadenopathy. Approximately, 3 days later, elevations of SGOT, SGPT, and alkaline phosphatase were noted, 60 IU/L, 105 IU/L, and 160 IU/L, respectively. These values were within normal limits (WNL) at baseline and subsequently returned to normal. According to the investigator, the association with ceftibuten was considered "unrelated."

DEATHS:

C8710001003: This 59-year-old white male with lung adenocarcinoma and COPD was enrolled in a ceftibuten 200 mg single-dose pharmacokinetic trial. He was admitted to the hospital with pneumonia due to *K. pneumoniae* and a pleural effusion. He died approximately 1 week after receipt of study drug due to progression of pleural effusion secondary to lung CA.

C8710001020: This 72-year-old white male had squamous cell CA of the lung. He was enrolled in the same trial. On 8/31/90, the patient received a single-dose of ceftibuten and underwent bronchoscopy. During the procedure, the patient became hypotensive "secondary to demerol" and died two days later. No additional information is provided.

COMBINED PHASE 2/3 CLINICAL AE EXPERIENCE:

(1) CLINICAL STUDIES:

According to the applicant, in conducted clinical trials, 1,345 patients received ceftibuten capsules. Doses ranged from 50-600 mg/day. 40 gastrointestinal AE's were reported in 30 (2.2%) patients. Otherwise, most AE's were mild-moderate in severity. Only 8 were considered severe: one each of skin eruption, vomiting, stomach ache, diarrhea, dizziness, "heavy feeling in head," "discomfort," and tachycardia. The AE's were considered, "similar to those seen with cephems."

(2) SCHERING-PLOUGH CLINICAL STUDIES:

According to the applicant, 1587 patients received ceftibuten in Phase 2/3 clinical trials (where studies were completed and the blind was broken). (See Table 1.) Of these, 1041 (66%) received ceftibuten 400 mg q.d., 359 (23%) ceftibuten 200 mg b.i.d. and 187 (12%) ceftibuten 300 mg b.i.d. The respective mean durations of therapy were 8.7, 9.6, and 8.7 days. The treatment durations for the majority of patients ranged from 1-16 days.

Ceftibuten studies were conducted in the U.S. as well as in several foreign countries. According to the applicant, the mean age of patients was 52.6 years-old. Approximately 65% were male, 35% females who received either ceftibuten 200 mg b.i.d or 300 mg t.i.d. Of the ceftibuten 400 mg q.d. recipients, 43% were male and 57% were female. Approximately 85-90% of all subjects were caucasian. Twenty-six per cent (26%) of ceftibuten 200 mg b.i.d. patients were hospitalized compared with 20% for those were administered ceftibuten 400 mg q.d. (The hospitalization status for ceftibuten 300 mg b.i.d. patients was not known.)

> ***Medical Officer's comment:*** Among the comparators, 33% of cefaclor 250 mg t.i.d. patients were inpatients compared with 17% of cefaclor 500 mg t.i.d. recipients.

At least one clinical AE, independent of relatedness to the study drug, was noted in 37/359 (10%) ceftibuten 200 mg b.i.d., 30/187 (16%) ceftibuten 300 mg b.i.d. recipients, and 212/1041 (20%) ceftibuten 400 mg q.d., . (See Table 1.)

Gastrointestinal complaints had the highest reporting rates. These complaints were noted for 22/359 (6%), 18/187 (10%), and 116/1041 (11%) of respective ceftibuten dosing groups.

Headache incidence differed between ceftibuten treatment groups: 2/359 (<1%), 3/187 (2%), and 41/1041 (4%), respectively. Similarly for nausea: 5/359 (1%), 5/187 (3%), and 44/1041 (4%).

Diarrhea was noted in 6/359 (2%), 4/187 (2%), and 37/1041 (4%) of respective ceftibuten dosing groups. Gastritis was more common among ceftibuten 300 mg b.i.d. recipients; 5/187 (3%) vs. 5/359 (1%) for ceftibuten 200 mg b.i.d. and 2/1041 (<1%) of ceftibuten 400 mg q.d. recipients.

Other than gastritis, for those differences noted above, there appeared to be a direct correlation between incidence of AE's and milligrams of ceftibuten administered at each dose. (i.e., the higher the milligrams administered/dose, the greater the incidence of AE's reported.)

Table 1.
Summary of All Adverse Experiences Occurring During Treatment with Ceftibuten BID, Ceftibuten 300 mg BID, and Ceftibuten 400 mg QD.*
(According to applicant)

	Ceftibuten 200 mg BID (n=359)	Ceftibuten 300 mg BID (n=187)	Ceftibuten 400 mg QD (n=1041)
Body System	Total	Total	Total
Any Adverse Experience	37 (10%)	30 (16%)	212 (20%)
Autonomic Nervous System Disorders	2 (<1%)	1 (<1%)	7 (<1%)
Flushing	0	1 (<1%)	1 (<1%)
Hypotension	1 (<1%)	0	1 (<1%)
Lacrimation	0	0	1 (<1%)
Miosis	0	0	1 (<1%)
Mouth, Dry	1 (<1%)	0	2 (<1%)
Sweating, Increased	0	0	2 (<1%)
Body as a Whole - General Disorders	4 (1%)	7 (4%)	59 (6%)
Allergy	0	0	1 (<1%)
Asthenia	0	0	1 (<1%)
Back Pain	0	0	1 (<1%)
Chest Pain	0	0	2 (<1%)
Cramps, Legs	0	0	1 (<1%)
Fatigue	0	1 (<1%)	5 (<1%)
Fever	1 (<1%)	0	0
Headache	2 (<1%)	3 (2%)	41 (4%)
Malaise	0	1 (<1%)	2 (<1%)
Pain	0	2 (1%)	6 (<1%)
Rigors	1 (<1%)	0	1 (<1%)
Skeletal Pain	0	0	1 (<1%)
Overdosage	0	0	2 (<1%)
Cardiovascular Disorders, General	1 (<1%)	0	2 (<1%)
Cardiac Failure	1 (<1%)	0	0
Hypertension	0	0	1 (<1%)
Syncope	0	0	1 (<1%)
Central & Peripheral Nervous System Disorder	3 (<1%)	3 (2%)	17 (2%)
Convulsions	0	0	1 (<1%)
Dizziness	3 (<1%)	2 (1%)	13 (1%)
Hypertonia	0	0	1 (<1%)
Paresthesia	0	0	2 (<1%)
Respiratory Depression	0	1 (<1%)	0

* Number of patients reporting an adverse experience at least once during the study. Some patients reported more than one adverse experience, therefore the total number of patients reporting adverse experiences may be less than the total number of adverse experiences listed in sub-categories for a particular body system. Includes Protocols LRTI C87-001, C88-044, 187-107, 187-223, 187-233, 187-234, 187-236, 187-325, 188-111, 188-217, 188-230, 188-327; Sinusitis C89-135; UTI C87-069, C88-081, 187-128, 187-232, 187-247, 187-326, and 189-054.

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Table 1 (Con't).*

Body System	Ceftibuten 200 mg BID (n=359) Total	Ceftibuten 300 mg BID (n=187) Total	Ceftibuten 400 mg QD (n=1041) Total
Gastrointestinal System Disorders	22 (6%)	18 (10%)	116 (11%)
Abdominal Pain	2 (<1%)	3 (2%)	11 (1%)
Anorexia	2 (<1%)	2 (1%)	0
Colitis	0	0	1 (<1%)
Constipation	0	1 (<1%)	4 (<1%)
Diarrhea	6 (2%)	4 (2%)	37 (4%)
Dyspepsia	1 (<1%)	1 (<1%)	19 (2%)
Eructation	0	0	1 (<1%)
Flatulence	0	1 (<1%)	1 (<1%)
Gastritis	5 (1%)	5 (3%)	2 (<1%)
Gingival Bleeding	0	0	1 (<1%)
Hemorrhoids	0	1 (<1%)	1 (<1%)
Hiccup	0	1 (<1%)	0
Loose Stools	1 (<1%)	0	4 (<1%)
Nausea	5 (1%)	5 (3%)	44 (4%)
Vomiting	3 (<1%)	1 (<1%)	17 (2%)
Hearing & Vestibular Disorders	0	1 (<1%)	1 (<1%)
Tinnitus	0	1 (<1%)	1 (<1%)
Heart Rate & Rhythm Disorders	2 (<1%)	0	2 (<1%)
Fibrillation, Atrial	1 (<1%)	0	1 (<1%)
Palpitation	0	0	1 (<1%)
Tachycardia	1 (<1%)	0	0
Liver & Biliary System Disorders	0	1 (<1%)	2 (<1%)
SGOT Increased	0	1 (<1%)	1 (<1%)
SGPT Increased	0	1 (<1%)	2 (<1%)
Metabolic & Nutritional Disorders	0	0	1 (<1%)
LDH Increased	0	0	1 (<1%)
Musculo-Skeletal System Disorders	0	0	; (<1%)
Myalgia	0	0	3 (<1%)
Myocardial, Endocardial, Pericardial, & Valve Disorders	0	0	1 (<1%)
Myocardial Infarction	0	0	1 (<1%)
Platelet, Bleeding & Clotting	0	1 (<1%)	0
Thrombocythemia	0	1 (<1%)	0

* Number of patients reporting an adverse experience at least once during the study. Some patients reported more than one adverse experience, therefore the total number of patients reporting adverse experiences may be less than the total number of adverse experiences listed in sub-categories for a particular body system. Includes Protocols C87-001, C88-044, 187-107, 187-223, 187-233, 187-234, 187-236, 187-325, 188-111, 188-217, 188-230, 188-327; C89-135; C87-069, C88-081, 187-128, 187-232, 187-247, 187-326, and 189-054.

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Table 1 (Con't).*

Body System	Ceftibuten 200 mg BID (n=359) Total	Ceftibuten 300 mg BID (n=187) Total	Ceftibuten 400 mg QD (n=1041) Total
Psychiatric Disorders	1 (<1%)	2 (<1%)	9 (<1%)
Agitation	0	1 (1%)	2 (<1%)
Depression	0	0	1 (<1%)
Insomnia	0	0	2 (<1%)
Nervousness	0	0	2 (<1%)
Paroniria	1 (<1%)	0	0
Somnolence	0	1 (1%)	3 (<1%)
Reproductive Disorders, Female	0	0	3 (<1%)
Leukorrhoea	0	0	1 (<1%)
Vaginitis	0	0	2 (<1%)
Resistance Mechanism Disorders	2 (<1%)	1 (<1%)	3 (<1%)
Infection, Fungal	0	0	1 (<1%)
Moniliasis	1 (<1%)	1 (<1%)	1 (<1%)
Moniliasis, Genital	0	0	1 (<1%)
Sepsis	1 (<1%)	0	0
Respiratory System Disorders	0	2 (1%)	20 (2%)
Bronchospasm	0	1 (<1%)	0
Coughing	0	0	1 (<1%)
Dyspnea	0	1 (<1%)	0
Epistaxis	0	0	3 (<1%)
Hemoptysis	0	0	1 (<1%)
Nasal Congestion	0	0	2 (<1%)
Nasal Irritation	0	0	1 (<1%)
Pharyngitis	0	0	5 (<1%)
Pneumothorax	0	0	1 (<1%)
Respiratory Insufficiency	0	0	1 (<1%)
Rhinitis	0	0	5 (<1%)
Sneezing	0	0	2 (<1%)
Upper Respiratory Tract Infection	0	0	1 (<1%)
Skin & Appendages Disorders	3 (<1%)	1 (<1%)	17 (2%)
Photosensitive Allergy	0	0	1 (<1%)
Pruritus	0	1 (<1%)	9 (<1%)
Rash	1 (<1%)	0	4 (<1%)
Rash Erythematous	1 (<1%)	0	0
Urticaria	1 (<1%)	0	3 (<1%)
Special Senses Other, Disorders	0	0	2 (<1%)
Taste Perversion	0	0	2 (<1%)

* Number of patients reporting an adverse experience at least once during the study. Some patients reported more than one adverse experience, therefore the total number of patients reporting adverse experiences may be less than the total number of adverse experiences listed in sub-categories for a particular body system. Includes Protocols C87-001, C88-044, I87-107, I87-223, I87-233, I87-234, I87-236, I87-325, I88-111, I88-217, I88-230, I88-327; C89-135; C87-069, C88-081, I87-128, I87-232, I87-247, I87-326, and I89-054.

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Table 1 (Con't).*

Body System	Ceftibuten 200 mg BID (n=359) Total	Ceftibuten 300 mg BID (n=187) Total	Ceftibuten 400 mg QD (n=1041) Total
Urinary System Disorders	0	1 (<1%)	1 (<1%)
Dysuria	0	1 (<1%)	0
Renal Failure, Acute	0	0	1 (<1%)
Vision Disorders	0	0	3 (<1%)
Eye Abnormality	0	0	1 (<1%)
Vision Abnormal	0	0	2 (<1%)
White Cell & RES	1 (<1%)	0	2 (<1%)
Disorders	1 (<1%)	0	1 (<1%)
Granulocytopenia	0	0	1 (<1%)
Leukopenia	0	0	1 (<1%)
WBC Abnormal, NOS			

* Number of patients reporting an adverse experience at least once during the study. Some patients reported more than one adverse experience, therefore the total number of patients reporting adverse experiences may be less than the total number of adverse experiences listed in sub-categories for a particular body system. Includes Protocols C87-001, C88-044, 187-107, 187-223, 187-233, 187-234, 187-236, 187-325, 188-111, 188-217, 188-230, 188-327; C89-135; 187-069, C88-081, 187-128, 187-232, 187-247, 187-326, and 189-054.

The proportions of clinical AE's considered "related" to ceftibuten were 31/37 (84%) of ceftibuten 200 mg b.i.d., 25/30 (83%) of ceftibuten 300 mg b.i.d., and 154/212 (73%) ceftibuten 400 mg q.d. recipients.

According to the applicant, the majority of clinical AE's reported were mild-moderate in severity. Severe or life-threatening AE's were reported in 4/359 (1%) of ceftibuten 200 mg b.i.d., 7/187 (4%) ceftibuten 300 mg b.i.d., and 31/1041 (3%) of ceftibuten 400 mg q.d. recipients.

OVERALL CLINICAL AE EXPERIENCE:

According to the applicant, for patients who reported at least one clinical AE independent of relatedness to drug, the highest rate was in the ceftibuten 400 mg q.d. group. (See Table 2.) Furthermore, ceftibuten 400 mg q.d. patients experienced the highest headache rate, 15/413 (4%), compared to other ceftibuten or cefaclor dosings. Gastrointestinal complaints were somewhat higher in the ceftibuten 400 mg q.d. group compared to cefaclor 250 t.i.d. or ceftibuten 200 mg b.i.d. However, they were comparable for ceftibuten 300 mg b.i.d. or cefaclor 500 mg t.i.d.

Using the applicant's electronic data base, the MO identified patients in the trials who experienced either a severe or life-threatening AE considered to be at least possibly-related to the study drug. (See Table 3.) No clear differences were noted between treatment groups.

Table 2.
Number and Percentages of Patients with Adverse Experiences for Ceftibuten 200 mg BID, Ceftibuten 300 mg BID, Ceftibuten 400 mg QD, Cefaclor 250 mg TID, or Cefaclor 500 mg TID.*
(According to applicant)

	Ceftibuten 200 mg BID (n=359)	Ceftibuten 300 mg BID (n=187)	Ceftibuten 400 mg QD (n=413)	Cefaclor 250 mg TID (n=216)	Cefaclor 500 mg TID (n=241)
	Total	Total	Total	Total	Total
Any Adverse Experience	37 (10%)	30 (16%)	78 (19%)	35 (16%)	36 (15%)
Autonomic Nervous System Disorders	2 (<1%)	1 (<1%)	2 (<1%)	0	0
Flushing	0	1 (<1%)	0	0	0
Hypotension	1 (<1%)	0	0	0	0
Miosis	0	0	1 (<1%)	0	0
Mouth dry	1 (<1%)	0	1 (<1%)	0	0
Body as a Whole - General Disorders	4 (1%)	7 (4%)	22 (5%)	6 (3%)	8 (3%)
Allergy	0	0	0	0	1 (<1%)
Asthenia	0	0	1 (<1%)	1 (<1%)	0
Back pain	0	0	1 (<1%)	1 (<1%)	0
Chest pain	0	0	1 (<1%)	2 (<1%)	0
Erythema	0	0	0	1 (<1%)	0
Fatigue	0	1 (<1%)	2 (<1%)	0	0
Fever	1 (<1%)	0	0	0	0
Headache	2 (<1%)	3 (2%)	15 (4%)	2 (<1%)	6 (2%)
Malaise	0	1 (<1%)	0	0	0
Pain	0	2 (1%)	1 (<1%)	0	2 (<1%)
Rigors	1 (<1%)	0	1 (<1%)	0	0
Therapeutic response increased	0	0	1 (<1%)	0	0
Cardiovascular Disorders - General	1 (<1%)	0	0	2 (<1%)	0
Cardiac failure	1 (<1%)	0	0	1 (<1%)	0
Syncope	0	0	0	1 (<1%)	0
Central & Peripheral Nervous System Disorders	3 (<1%)	3 (2%)	3 (<1%)	5 (2%)	4 (2%)
Convulsions	0	0	1 (<1%)	0	0
Dizziness	3 (<1%)	2 (1%)	1 (<1%)	4 (2%)	3 (1%)
Paresthesia	0	0	1 (<1%)	0	1 (<1%)
Respiratory depression	0	1 (<1%)	0	0	0
Vertigo	0	0	0	1 (<1%)	0

* Includes Protocols C87-001, C88-044, 187-107, 187-223, 187-233, 187-234, 187-236, 187-325, 188-111, 188-217, 188-230, and 188-327.

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Table 2 (Con't).*

	Ceftibuten 200 mg BID (n=359)	Ceftibuten 300 mg BID (n=187)	Ceftibuten 400 mg QD (n=413)	Cefaclor 250 mg TID (n=216)	Cefaclor 500 mg TID (n=241)
	Total	Total	Total	Total	Total
Gastrointestinal System Disorders	22 (6%)	18 (10%)	36 (9%)	14 (6%)	22 (9%)
Abdominal pain	2 (<1%)	3 (2%)	2 (<1%)	2 (<1%)	0
Anorexia	2 (<1%)	2 (1%)	0	0	2 (<1%)
Colitis	0	0	1 (<1%)	0	0
Constipation	0	1 (<1%)	1 (<1%)	0	1 (<1%)
Diarrhea	6 (2%)	4 (2%)	9 (2%)	3 (1%))	6 (2%)
Dyspepsia	1 (<1%)	1 (<1%)	4 (<1%)	0	1 (<1%)
Flatulence	0	1 (<1%)	1 (<1%)	0	0
Gastritis	5 (1%)	5 (3%)	0	0	4 (2%)
Gingival bleeding	0	0	1 (<1%)	0	0
Hemorrhage rectum	0	0	0	1 (<1%)	0
Hemorrhoids	0	0	1 (<1%)	0	0
Hiccups	0	1 (<1%)	0	0	0
Loose stools	1 (<1%)	0	1 (<1%)	1 (<1%)	0
Melena	0	0	0	0	1 (<1%)
Nausea	5 (1%)	5 (3%)	16 (4%)	8 (4%)	11 (5%)
Vomiting	3 (<1%)	1 (<1%)	7 (2%)	3 (1%)	1 (<1%)
Hearing & Vestibular Disorders	0	1 (<1%)	0	0	0
Tinnitus	0	1 (<1%)	0	0	0
Heart & Rhythm Disorders	2 (<1%)	0	1 (<1%)	2 (<1%)	1 (<1%)
Cardiac arrest	0	0	0	1 (<1%)	0
Fibrillation, atrial	1 (<1%)	0	0	0	0
Palpitation	0	0	1 (<1%)	0	1 (<1%)
Tachycardia	1 (<1%)	0	0	1 (<1%)	0
Liver & Biliary System Disorders	0	1 (<1%)	2 (<1%)	0	1 (<1%)
SGOT increased	0	1 (<1%)	1 (<1%)	0	1 (<1%)
SGPT increased	0	1 (<1%)	2 (<1%)	0	1 (<1%)

* Includes Protocols C87-001, C88-044, 187-107, 187-223, 187-233, 187-234, 187-236, 187-325, 188-111, 188-217, 188-230, and 188-327.

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Table 2 (Con't).*

	Ceftibuten 200 mg BID (n=359)	Ceftibuten 300 mg BID (n=187)	Ceftibuten 400 mg QD (n=413)	Cefaclor 250 mg TID (n=216)	Cefaclor 500 mg BID (n=241)
	Total	Total	Total	Total	Total
Metabolic & Nutritional Disorders	0	0	0	0	1 (<1%)
Phosphatase alkaline increased	0	0	0	0	1 (<1%)
Musculo-Skeletal System Disorders	0	0	1 (<1%)	1 (<1%)	0
Myalgia	0	0	1 (<1%)	0	0
Musculo-skeletal pain	0	0	0	1 (<1%)	0
Myo Endo Pericardial & Valve Disorders	0	0	1 (<1%)	0	0
Myocardial infarction	0	0	1 (<1%)	0	0
Platelet Bleeding & Clotting Disorders	0	1 (<1%)	0	0	0
Thrombocythemia	0	1 (<1%)	0	0	0
Psychiatric Disorders	1 (<1%)	2 (<1%)	7 (2%)	2 (<1%)	0
Agitation	0	1 (<1%)	1 (<1%)	1 (<1%)	0
Insomnia	0	0	2 (<1%)	1 (<1%)	0
Nervousness	0	0	2 (<1%)	0	0
Paroniria	1 (<1%)	0	0	0	0
Somnolence	0	1 (<1%)	3 (<1%)	0	0
Reproductive Disorders, Female	0	0	1 (<1%)	1 (<1%)	0
Leukorrhoea	0	0	1 (<1%)	0	0
Vaginitis	0	0	0	1 (<1%)	0
Resistance Mechanism Disorders	2 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
Infection, funga	0	0	0	2 (<1%)	0
Moniliasis	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
Sepsis	1 (<1%)	0	0	0	0

* Includes Protocols C87-001, C88-044, 187-107, 187-223, 187-233, 187-234, 187-236, 187-325, 188-111, 188-217, 188-230, and 188-327.

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Table 2 (Con't).*

	Ceftibuten 200 mg BID (n=359)	Ceftibuten 300 mg BID (n=187)	Ceftibuten 400 mg QD (n=413)	Cefaclor 250 mg TID (n=216)	Cefaclor 500 mg TID (n=241)
	Total	Total	Total	Total	Total
Respiratory System Disorders	0	2 (<1%)	9 (2%)	5 (2%)	3 (1%)
Bronchospasm	0	1 (<1%)	0	0	0
Coughing	0	0	1 (<1%)	1 (<1%)	0
Dyspnea	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Epistaxis	0	0	1 (<1%)	0	0
Hemoptysis	0	0	1 (<1%)	0	1 (<1%)
Nasal congestion	0	0	0	1 (<1%)	0
Pharyngitis	0	0	2 (<1%)	0	0
Pleural pain	0	0	0	1 (<1%)	0
Pneumonia lobar	0	0	0	1 (<1%)	0
Pneumothorax	0	0	1 (<1%)	0	0
Respiratory insufficiency	0	0	1 (<1%)	0	1 (<1%)
Rhinitis	0	0	2 (<1%)	0	0
Sneezing	0	0	1 (<1%)	0	0
Skin & Appendages Disorders	3 (<1%)	1 (<1%)	7 (2%)	5 (2%)	4 (2%)
Pruritus	0	1 (<1%)	3 (<1%)	2 (<1%)	2 (<1%)
Pruritus, genital	0	0	0	2 (<1%)	0
Rash	2 (<1%)	0	2 (<1%)	1 (<1%)	1 (<1%)
Rash erythematous	1 (<1%)	0	0	0	0
Urticaria	1 (<1%)	0	2 (<1%)	0	1 (<1%)
Special Senses Disorders	0	0	2 (<1%)	0	0
Taste perversion	0	0	2 (<1%)	0	0
Urinary System Disorders	0	1 (<1%)	1 (<1%)	0	0
Dysuria	0	1 (<1%)	0	0	0
Renal failure acute	0	0	1 (<1%)	0	0
Vision Disorders	0	0	0	2 (<1%)	1 (<1%)
Conjunctivitis	0	0	0	1 (<1%)	0
Eye pain	0	0	0	0	1 (<1%)
Vision abnormal				1 (<1%)	0
White Cell & RES Disorders	1 (<1%)	0	1 (<1%)	0	0
Granulocytopenia	1 (<1%)	0	0	0	0
WBC abnormal NOS	0	0	1 (<1%)	0	0

* Includes Protocols C87-001, C88-044, 187-107, 187-223, 187-233, 187-234, 187-236, 187-325, 188-111, 188-217, 188-230, and 188-327.

Table 3
Clinical AE's in Trials Considered Severe and Either Possibly, Probably, or Definitely Related to the Study Drug
(According to the applicant)

CLINICAL AE'S	CEFTIBUTEN			CEFACLOR	
	400 mg qd† (n=411)	200 mg bid (n=367)	400 mg bid (n=186)	250 mg tid (n=216)	500 mg tid (n=241)
Chest pain	0	0	0	1[C]	0
Convulsions	1	0	0	0	0
Coughing	0	0	0	1	0
Diarrhea	1	2	0	1	0
Dizziness	0	0	1	0	0
Dyspepsia	1	0	0	0	1
Headache	2	0	1	0	0
Inc. Alk. phosphatase‡	0	0	0	0	1[D]
Infection, fungal	0	0	0	1	0
Malaise	0	0	1	0	0
Nausea	1[A]	0	0	1[B]	1
Pain	0	0	1	0	0
Pruritus	1	0	0	1[C]	0
Pruritus, genital	0	0	0	1	0
SGOT increased‡	0	0	0	0	1[D]
SGPT increased‡	0	0	0	0	1[D]
Vomiting	1[A]	0	0	1[B]	0
TOTAL PATIENTS WITH AE'S	7 (2%)	2 (<1%)	4 (2%)	6 (3%)	3 (1)
TOTAL AE'S	8	2	4	8	5

* No AE's considered at least possibly due to the study drug were also life-threatening.
‡ Although these actually represent laboratory AE's, they were included in the applicant's clinical AE's.
† Includes patients who received other ceftibuten dosings (i.e., 200 mg q.d.)
NB: Superscript letters represent AE's occurring in the same patient.

Medical Officer's Comment: The total "N" in this table differs from table 2. The N's in this table were generated by the MO using the applicant's electronic data base.

OVERALL CLINICAL AE EXPERIENCE:

According to the applicant, for the studies, ceftibuten 400 mg q.d. recipients experienced the largest incidence of at least one AE independent of relatedness (21%), only slightly higher than TMP/SMX (18%). (See Table 4.) As with the studies, ceftibuten recipients experience ≈4% headache, higher than the other treatment arms. Abdominal pain and diarrhea were also seen more frequently in the ceftibuten arm.

Again, the MO looked at the applicant's electronic data base for severe AE's at least possibly-related to the study drug. Both ceftibuten and TMP/SMX patients experienced more severe AE's than norfloxacin. (See Table 5.) Two ceftibuten patients experienced severe diarrhea. (See *C. difficile* Diarrhea section below.)

Table 4.
Number and Percentage of Patients with Adverse Experiences by Investigator-Determined Relationship for Ceftibuten 400 mg QD, Ofloxacin 200 mg BID, Norfloxacin or TMP/SMX 160/800 mg QD.*
(According to applicant)

	Ceftibuten 400 mg QD (n=511)	Ofloxacin 200 mg BID (n=20)	Norfloxacin 400 mg BID (n=50)	TMP/SMX 160/800 mg QD (n=136)
Any Adverse Experiences	106 (21%)	1 (5%)	3 (6%)	24 (18%)
Autonomic Nervous System Disorders	4 (<1%)	0	0	0
Flushing	1 (<1%)	0	0	0
Hypotension	1 (<1%)	0	0	0
Mouth Dry	1 (<1%)	0	0	0
Sweating, Increased	2 (<1%)	0	0	0
Body as a Whole - General Disorders	26 (5%)	0	2 (4%)	3 (2%)
Allergy	1 (<1%)	0	0	0
Asthenia	0	0	2 (4%)	0
Chest Pain	1 (<1%)	0	0	0
Cramps, Legs	1 (<1%)	0	0	0
Fatigue	3 (<1%)	0	0	1 (<1%)
Fever	0	0	0	1 (<1%)
Headache	22 (4%)	0	1 (2%)	1 (<1%)
Malaise	1 (<1%)	0	0	0
Cardio ascular Disorders - General	2 (<1%)	0	0	1 (<1%)
Hypertension	1 (<1%)	0	0	0
Syncope	1 (<1%)	0	0	1 (<1%)
Central & Peripheral Nervous System Disorders	11 (2%)	0	1 (2%)	3 (2%)
Dizziness	10 (2%)	0	0	3 (2%)
Paresthesia	1 (<1%)	0	0	0
Vertigo	0	0	1 (2%)	0
Gastrointestinal System Disorders	63 (13%)	1 (5%)	2 (4%)	12 (9%)
Abdominal Pain	9 (2%)	0	0	0
Constipation	2 (<1%)	0	0	2 (1%)
Diarrhea	25 (5%)	0	0	0
Dyspepsia	13 (3%)	1 (5%)	1 (2%)	1 (<1%)
Eructation	1 (<1%)	0	0	0
Gastritis	2 (<1%)	0	0	0
GI Hemorrhage	0	0	0	1 (<1%)
Loose Stools	2 (<1%)	0	0	0
Nausea	23 (5%)	0	0	8 (6%)
Tongue Ulceration	0	0	0	1 (<1%)
Vomiting	9 (2%)	0	1 (2%)	1 (<1%)
Hearing & Vestibular Disorders	0	0	1 (2%)	0
Tinnitus	0	0	1 (2%)	0
Heart Rate & Rhythm Disorders	1 (<1%)	0	0	0
Fibrillation	1 (<1%)	0	0	0
Musculo-Skeletal System Disorders	2 (<1%)	0	0	0
Myalgia	2 (<1%)	0	0	0

* Includes Protocols C87-069, C88-081, 187-128, 187-232, 187-247, 187-326, and 189-054.

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Table 4 (Con't).*

	Ceftibuten 400 mg QD (n=511)	Ofloxacin 200 mg BID (n=20)	Norfloxacin 400 mg BID (n=50)	TMP/SMX 160/800 mg QD (n=136)
Psychiatric Disorders	2 (<1%)	0	0	3 (2%)
Agitation	1 (<1%)	0	0	0
Appetite Increased	0	0	0	1 (<1%)
Depression	1 (<1%)	0	0	1 (<1%)
Somnolence	0	0	0	1 (<1%)
Reproductive Disorders, Female	2 (<1%)	0	0	0
Vaginitis	2 (<1%)	0	0	0
Resistance Mechanism Disorders	1 (<1%)	0	0	1 (<1%)
Moniliasis	0	0	0	1 (<1%)
Moniliasis, Genital	1 (<1%)	0	0	0
Respiratory System Disorder	5 (<1%)	0	0	1 (<1%)
Epistaxis	0	0	0	1 (<1%)
Nasal Congestion	2 (<1%)	0	0	0
Pharyngitis	2 (<1%)	0	0	0
Upper Respiratory	1 (<1%)	0	0	0
Skin & Appendage Disorders	10 (2%)	0	0	5 (4%)
Photosensitivity Allergy	1 (<1%)	0	0	0
Pigmentation Abnormal	0	0	0	1 (<1%)
Pruritus	6 (1%)	0	0	3 (2%)
Rash	2 (<1%)	0	0	3 (2%)
Urticaria	1 (<1%)	0	0	0
Special Senses Other Disorders	0	0	0	1 (<1%)
Taste Perversion	0	0	0	1 (<1%)
Vision Disorders	2 (<1%)	0	0	0
Eye Abnormality	1 (<1%)	0	0	0
Vision Abnormal	1 (<1%)	0	0	0

* Includes Protocols C87-069, C88-081, 187-128, 187-232, 187-247, 187-326, and 189-054.

Table 5
Clinical AE's in Trials Considered Severe and Either Possibly, Probably, or Definitely Related to the Study Drug
(According to the applicant)

CLINICAL AE'S	Ceftibuten 400 mg qd (n=512)	TMP-SMX 160/800 bid (n=135)	Norfloxacin 400 mg bid (n=135)
Abdominal pain	1	0	0
Asthenia	0	0	1[B]
Constipation	0	1	0
Diarrhea	2	0	0
GI hemorrhage	0	1	0
Headache	3	0	0
Nausea	2	0	0
Periorbital swelling	1[A]	0	0
Pruritus	1	1	0
Rhinorrhea	1[A]	0	0
Tongue ulceration	0	1	0
Urticaria	1[A]	0	0
Vomiting	1	0	1[B]
TOTAL PATIENTS WITH AE'S	11 (2%)	4 (3%)	1 (<1%)
TOTAL AE'S	13	4	2

* No AE's considered at least possibly due to the study drug were also life-threatening.

NB: No ofloxacin recipients experienced severe AE's considered possibly, probably, or definitely related to the study drug. Superscript letters represent AE's occurring in the same patient.

Medical Officer's Comment: The total "N" in this table differs from table 4. The N's in this table were generated by the MO using the applicant's electronic data base.

CLINICAL AE EXPERIENCE:

According to the applicant, from on-going trials, Augmentin® patients experienced twice as many clinical AE's compared to the ceftibuten arm. (See Table 6.) These differences were especially seen in the gastrointestinal system (nausea, vomiting, diarrhea, and loose stools). Headache was also higher in the Augmentin® arm. However, headache is typically seen with sinusitis and may be difficult to attribute to the drug.

Table 6.
Number and Percentage of Patients with Adverse Experiences for Ceftibuten 400 mg QD, or Augmentin® 500 mg TID*
(According to applicant)

	Ceftibuten 400 mg QD (n=117)	Augmentin® 500 mg TID (n=62)
	Total	Total
Any Adverse Experience	28 (24%)	27 (44%)
Application Site Disorders	0	1 (2%)
Injection Site Pain	0	1 (2%)
Autonomic Nervous System Disorders	1 (<1%)	1 (2%)
Lacrimation	1 (<1%)	0
Sweating Increased	0	1 (2%)
Body as a Whole - General Disorders	11 (9%)	8 (13%)
Headache	4 (3%)	7 (11%)
Malaise	1 (<1%)	0
Pain	5 (4%)	1 (2%)
Skeletal Pain	1 (<1%)	0
Therapeutic Response Increased	1 (<1%)	0
Central & Peripheral Nervous System Disorders	3 (3%)	1 (2%)
Dizziness	2 (2%)	1 (2%)
Hypertonia	1 (<1%)	0
Gastrointestinal System Disorders	12 (10%)	15 (24%)
Abdominal Pain	0	1 (2%)
Constipation	1 (<1%)	0
Diarrhea	3 (3%)	8 (13%)
Dyspepsia	2 (2%)	1 (2%)
Loose Stools	1 (<1%)	1 (2%)
Nausea	5 (4%)	5 (8%)
Vomiting	1 (<1%)	1 (2%)
Hearing & Vestibular Disorders	1 (<1%)	1 (2%)
Earache	0	1 (2%)
Tinnitus	1 (<1%)	0
Metabolic & Nutritional Disorders	1 (<1%)	0
LDH Increased	1 (<1%)	0
Reproductive Disorders Female	0	3 (5%)**
Vaginal Hemorrhage	0	1 (2%)**
Vaginitis	0	2 (3%)**

* Includes Protocol C89-135.

** According to the applicant, percentages calculated on total patients (n=62). If calculated on the number of female patients, (n=43), percentages would be 7% for total Reproductive Disorder, 2% for total Vaginal Hemorrhage, and 5% for Vaginitis.

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Table 6 (Con't).*

	Ceftibuten 400 mg QD (n=117)	Augmentin® 500 mg TID (n=62)
	Total	Total
Resistance Mechanism Disorders	1 (<1%)	1 (2%)
Infection Fungal	1 (<1%)	1 (2%)
Respiratory System Disorders	6 (5%)	1 (2%)
Epistaxis	2 (2%)	1 (2%)
Nasal Irritation	1 (<1%)	0
Pharyngitis	1 (<1%)	0
Rhinitis	3 (3%)	0
Sneezing	1 (<1%)	0
Vision Disorders	1 (<1%)	0
Vision Abnormal	1 (<1%)	0
White Cell and RES Disorders	1 (<1%)	0
Granulocytopenia	1 (<1%)	0
Leukopenia	1 (<1%)	0

* Includes Protocol C89-135.

ADDITIONAL CEFTIBUTEN PATIENTS DISCONTINUED FROM PHASE 2/3 STUDIES DUE TO THE DEVELOPMENT OF AN AE: (The reader is referred to the specific study evaluations above for a discussion of discontinued patients in the respective studies.)

According to the applicant, ceftibuten patients not discussed elsewhere in this review, were discontinued from the study drug due to the development of an AE. The specifics follow. In addition, CRF's were included for three patients where drug assignment was not provided as the patient remained blinded (rash x 2 and bleeding from a gastric ulcer).

LRTI:

C8700104011: (Ceftibuten 300 mg q12h x 6 days; actually AECB) On day 3 moderate diarrhea developed. According to the investigator, the association with ceftibuten was considered "probable."

C8700104012: (Ceftibuten 300 mg q12h x 2 days; AECB) On day 2 of therapy, moderate flushing and moderate pruritus developed. According to the investigator, the association for both AE's with ceftibuten were considered "probable." In the comment section of the CRF, the investigator stated that, "itching believed due to anxiety." However, the patient had a history of penicillin allergy.

C8700104021: (Ceftibuten 300 mg q12h x 4 days; On day 4 of therapy, severe respiratory depression ensued following aspiration of barium. The patient was intubated. According to the investigator, the association with ceftibuten was considered "unrelated."

C8804404002: (Ceftibuten 200 mg q12h x 2 days; On day 1 of therapy, moderate nausea, vomiting, and rigors developed. According to the investigator, the association for these AE's with ceftibuten were considered "related." The patient had NIDDM and polymyositis.

C8804404164: (This patient was not included in the efficacy data base; ceftibuten (dose not provided) x 2 day; "bronchitis.") On day 2, the patient developed moderate nausea and epigastric pain. According to the investigator, the association with ceftibuten was considered "probable."

C8804411007: (Ceftibuten 200 mg q12h x 4 days; On day 3 of therapy, mild dizziness and hypotension developed due to dehydration. According to the investigator, the association of ceftibuten with these AE's were considered "unrelated." The following day, mild "granulocytopenia" was noted. At baseline, the WBC was 15,400/mm^3 with 14% bands and 68% PMN's. By day 4, the WBC had dropped to 3700/mm^3 with 0% bands and 42% PMN's. The association with ceftibuten was considered "probable." In light of the "granulocytopenia," ceftibuten was discontinued. This patient had a history of IVDA and ETOH abuse. No follow-up labs are reported.

> ***Medical Officer's Comment:*** "Granulocytopenia" is typically defined as an absolute neutrophil count (ANC) of <1000/mm^3. According to this definition, this patient had not developed granulocytopenia at the time the drug was discontinued.

C8804434001: (Ceftibuten 200 mg q12h x 3 days; On day 2 of therapy, fever developed. This was followed on day 3 with sepsis. According to the investigator, the association with ceftibuten was considered "unrelated." At

baseline, this patient grew *Neisseria spp.* and *α-hemolytic streptococci*. *Staphylococcus spp.* grew from the blood. On day 3, the two organisms isolated from the sputum persisted.

> ***Medical Officer's Comment:*** This patient was a clinical failure. However, the applicant did not assign this response. Instead, the patient was discontinued owing to an "adverse experience."

I8722304005: (Ceftibuten 300 mg q12h x 9 days; On day 7 of therapy this 37-year-old women developed "adverse experiences" of moderate anorexia and severe malaise. According to the investigator, the association with ceftibuten was considered "possible." On day 2 of therapy, the patient was placed on acyclovir ointment for a "herpetic oral rash."

> ***Medical Officer's Comment:*** Although not described as an "adverse experience," on day +2 of therapy, "hepatitis" was noted as a "concurrent illness" requiring hospitalization. On day 3 of therapy, SGPT and SGOT were only slightly elevated (31 and 49 IU, respectively; upper limit of normal range for both are 30 IU and 37 IU). By day 8 these had increased to 70 IU and 79 IU, respectively. Alkaline phosphatase had also increased to 191 IU (upper limit of normal is 92 IU.) By day +2, the SGOT and SGPT were returning to baseline while the alkaline phosphatase remained elevated at 227 IU. Based on this, the applicant should have classified "hepatitis" as an adverse event, NOT a concurrent illness.

I8723302002: (Ceftibuten 300 mg q12h x 4 days; , On day 4 of therapy, mild fatigue and headache developed. According to the investigator, the association with ceftibuten was considered "possible."

I8732509002: (Ceftibuten 300 mg q12h x 11 days; On day 11, moderate dizziness and tinnitus was noted. According to the investigator, the association with ceftibuten was considered "probable."

I8732509032: (Ceftibuten 300 mg q12h x 3 days; AECB) On day 3, moderate abdominal pain developed. According to the investigator, the association with ceftibuten was considered "probable." The patient was receiving ranitidine at the time of this episode; the patient had been receiving this drug for the last 3-4 months for "stomach pain."

I8732509035: (Ceftibuten 300 mg q12h x 4 days; AECB) On day 3 of therapy, moderate dyspepsia, dyspnea, and flatulence developed. According to the CRF, "ARDS" developed and the patient underwent an open lung biopsy. No pathogen was isolated from the biopsy. According to the investigator, the association for all three "adverse experiences" with ceftibuten was "probable."

I8823001108: (Ceftibuten 200 mg q12h x 11 days; AECB) On day 11 of therapy, severe diarrhea developed; it lasted for 2 weeks and required treatment with loperamide. According to the investigator, the association with ceftibuten was considered "possible." The patient had a history of diverticulitis and was s/p "colon resection."

All patients who were discontinued from ceftibuten due to the development of an AE are discussed in the respective section of the NDA review above.

There were three ceftibuten patients enrolled in trials whose CRF's were submitted with the original NDA as these patients were discontinued from ceftibuten therapy owing to the development of AE's.

I8823402004: (Ceftibuten 400 mg q.d. x 7-8 days;
On day 4 of therapy, patient developed moderate diarrhea and abdominal pain. The study drug was discontinued owing to the development of diarrhea. "The patient refused laboratory tests." According to the investigator, the association with ceftibuten was considered "related."

C8913505011: (Ceftibuten 400 mg q.d. x 2 days;
Following 3 capsules of study drug, the patient complained of mild headache. According to the investigator, the association with ceftibuten was considered "unrelated."

C8913516002: (Ceftibuten 400 mg q.d. x 3 days; On day 2 of therapy, the patient experienced severe diarrhea. Loperamide was given. According to the investigator, the association with ceftibuten was considered "probable."

ADDITIONAL DEATHS IN PHASE 2/3 TRIALS: (The reader is referred to the specific study evaluations in this MOR for a discussion of deaths that occurred in those studies. Overall, there were 24 deaths reported for ceftibuten recipients in the NDA. No deaths were considered due to ceftibuten.)

C8700110007: (Ceftibuten 300 mg q12h x 3 days; AECB) This 74-year-old white male with squamous cell cancer of the lung, COPD, and a history of TB, died on day 3 of therapy. The lung cancer eroded into the patient's pulmonary artery. *S. aureus*, ceftibuten-resistant, grew from the baseline sputum. According to the investigator, an association with the study drug is "doubtful."

I8722301014: (Ceftibuten 200 mg q12h x 5 days; This 66-year-old white female with aortic/mitral disease died on day 5 of therapy of multiple pulmonary emboli. This patient grew *H. influenzae* at baseline. According to the investigator, an association with the study drug is "unrelated."

I8722304012: (Ceftibuten 300 mg q12h x 4 days; AECB) This 64-year-old white male with severe COPD died on day +1 of therapy of "disease progression." The patient was switched to cefotaxime being a clinical failure. At baseline, the patient grew *H. influenzae* (ceftibuten "S") and *S. pneumoniae* (ceftibuten "I"; zone = 18 mm). No follow-up cultures were obtained. According to the investigator, an association with the study drug is "unrelated."

I8732501002: (Ceftibuten 300 mg q12h x 1 day; AECB) This 81-year-old white male with Parkinson's disease died on day +1 of therapy due to a "CVA and dehydration." The CVA occurred on the day of admission. The patient received 2 doses and was switched to parenteral flucloxacillin. No cultures were obtained. According to the investigator, an association with the study drug is "unrelated."

I8823002002: (Ceftibuten 200 mg q12h x 2 days; This 78-year-old white male with COPD died on day +4 of therapy due to "disease progression." The patient's infiltrate progressed and respiratory failure ensued. No autopsy was obtained. At baseline, the following organisms grew from the sputum: *S. pneumoniae* ("S" to ceftibuten), *P. maltophilia* ("S"), *K. pneumoniae* ("S"), and *Enterobacter spp.* (no suscept.). A blood culture was negative. According to the investigator, an association with the study drug is "doubtful."

Medical Officer's Comment: According to the applicant, at the time of NDA submission, there were 9 deaths from various other clinical studies where the blind remained intact.

(The following patient was not submitted with the efficacy analysis.)

I8732603029: (Ceftibuten 400 mg q.d. x 12 days; . This 70-year-old white male with NIDDM, chronic atrial fibrillation, and CRF grew ≥10^5 CFU/mL *K. oxytoca* from the baseline urine. Approximately 11 days posttherapy, the patient died of "CHF complicated by decreased renal function and pulmonary edema." The investigator considered this "unrelated" to ceftibuten. The baseline pathogen was eradicated from the urine 5 days posttherapy.

OVERALL PHASE 2/3 LABORATORY AE EXPERIENCE:

(SCHERING-PLOUGH STUDIES:)

Using the applicant's criteria to determine abnormal findings, comparing various ceftibuten, cefaclor, TMP/SMX, and quinolone dosings, TMP/SMX recipients experienced the greatest increases in serum BUN and serum creatinine (See Tables 7-10.) As previously stated, serum creatinine could be falsely elevated due to interference with the assay. However, this reasoning could not be used to explain the applicant's finding of a greater proportion of elevated serum BUN.

No other differences in laboratory AE's stand-out for the MO as significant.

Table 7
Overall Number of Patients* and Percent Incidence of Abnormal§ Clinical Chemistry Laboratory Value in Ceftibuten Capsules and Cefaclor Treatment Groups Stratified by Dose Regimen
(According to applicant)

	Ceftibuten 200 mg BID		Ceftibuten 300 mg BID		Ceftibuten 400 mg QD		Cefaclor 250 mg TID		Cefaclor 500 mg TID	
Eosinophils	19/289	(7%)	6/152	(4%)	23/846	(3%)	8/171	(5%)	7/196	(4%)
Hemoglobin	21/323	(7%)	21/168	(13%)	42/927	(5%)	6/185	(3%)	19/215	(9%)
Platelets (above 700)	10/309	(3%)	6/163	(4%)	1/873	(<1%)	0/178		2/211	(<1%)
Platelets (below 100)	0/309		0/163		2/873	(<1%)	1/178	(<1%)	3/211	(1%)
WBC	0/323		0/168		4/926	(<1%)	0/184		0/217	
BUN	34/306	(11%)	19/164	(12%)	44/800	(6%)	18/170	(11%)	21/208	(10%)
Creatinine	30/318	(9%)	9/171	(5%)	43/852	(5%)	10/184	(5%)	7/217	(3%)
SGOT (AST)	10/305	(3%)	6/165	(4%)	3/801	(<1%)	2/174	(1%)	4/210	(2%)
SGPT (ALT)	8/289	(3%)	2/152	(1%)	9/820	(1%)	1/168	(<1%)	9/199	(5%)
Total Bilirubin	5/284	(2%)	2/148	(1%)	13/816	(2%)	6/170	(4%)	8/198	(4%)
Alkaline Phosphatase	8/305	(3%)	4/165	(2%)	6/826	(<1%)	0/173		2/209	(1%)

* The denominator reflects the total number of patients that had a baseline laboratory assessment with subsequent assessment(s) during treatment.

§ **Applicant's criteria for abnormal findings:**
BUN, Total bilirubin - 25% increase above baseline value and above the upper limit of normal range.
SGOT, SGPT - 3 times the upper limit of normal range.
Alkaline phosphatase - above 1.5 times the upper limit of normal range if baseline value is within normal range, otherwise 50% increase above baseline value.
Creatinine - 0.5 mg/dL increase from baseline value and above the upper limit of normal range.
Eosinophils - above 700/mm^3 if baseline value is < 700/mm^3.
Hemoglobin - 2g/dL decrease from baseline.
WBC - below $2.5x10^3/mm^3$.
Platelets - below $100x10^3$ and more than 50% change from baseline value.
Platelets - above $700x10^3$ and more than 50% change from baseline value.

Table 8.
Overall Number of Patients* and Percent Incidence of Abnormal§ Clinical Chemistry Laboratory Values in TMP-SMX, Augmentin®, Ofloxacin, and Norfloxacin Treatment Groups 400 mg QD
(According to applicant)

	Ceftibuten 400 mg QD	TMP-SMX 1600 mg/800 mg BID	Augmentin® 500 mg TID	Ofloxacin 200 mg BID	Norfloxacin 400 mg BID
Eosinophils	23/846 (3%)	2/102 (2%)	2/50 (4%)	1/14 (7%)	0/47
Hemoglobin	42/927 (5%)	12/122 (10%)	0/52	2/20 (10%)	5/49(10%)
Platelets (above 700)	1/873 (<1%)	1/118 (<1%)	0/49	0/20	0/47
Platelets (below 100)	2/873 (<1%)	2/118 (2%)	0/49	0/20	1/47(2%)
WBC	4/926 (<1%)	1/121 (<1%)	1/52 (2%)	0/20	0/49
BUN	44/800 (6%)	13/84 (15%)	0/52	2/20 (10%)	1/48(2%)
Creatinine	43/852 (5%)	11/86 (13%)	1/52 (2%)	1/20 (5%)	1/49(2%)
SGOT (AST)	3/801 (1%)	1/75 (1%)	0/52	0/20	0/49
SGPT (ALT)	9/820 (1%)	3/80 (4%)	0/51	0/20	0/49
Total Bilirubin	13/816 (2%)	3/83 (4%)	0/52	2/20 (10%)	1/48(2%)
Alkaline Phosphatase	6/826 (<1%)	0/84	0/52	1/20 (5%)	1/48(2%)

* The denominator reflects the total number of patients that had a baseline laboratory assessment with subsequent assessment(s) during treatment.

§ **Applicant's criteria for abnormal findings:**
BUN, Total bilirubin - 25% increase above baseline value and above the upper limit of normal range.
SGOT, SGPT - 3 times the upper limit of normal range.
Alkaline phosphatase - above 1.5 times the upper limit of normal range if baseline value is within normal range, otherwise 50% increase above baseline value.
Creatinine - 0.5 mg/dl increase from baseline value and above the upper limit of normal range.
Eosinophils - above 700/mm^3 if baseline value is < 700/mm^3.
Hemoglobin - 2 G decrease from baseline.
WBC - below 2.5/mm^3.
Platelets - below 100 and more than 50% change from baseline value.
Platelets - above 700 and more than 50% change from baseline value.

Table 9.
Overall Number of Patients* and Percent Incidence of Abnormal§ Clinical Urinalysis Laboratory Value in Ceftibuten Capsules, and Cefaclor Treatment Groups Stratified by Dose Regimen.
(According to applicant)

	Ceftibuten 200 mg BID		Ceftibuten 300 mg BID		Ceftibuten 400 mg BID		Cefaclor 250 mg TID		Cefaclor 500 mg TID	
Specific Gravity	3/284	(1%)	3/154	(2%)	49/850	(6%)	17/158	(11%)	3/199	(2%)
pH	46/280	(16%)	26/165	(16%)	124/824	(15%)	17/136	(13%)	32/201	(16%)
Glucose	8/284	(3%)	4/170	(2%)	30/824	(4%)	8/137	(6%)	5/207	(2%)
Protein	18/284	(6%)	8/170	(5%)	54/844	(6%)	2/137	(2%)	11/208	(5%)
Hemoglobin	18/283	(6%)	9/170	(5%)	59/819	(7%)	7/137	(5%)	10/207	(5%)
Red Blood Cells	23/280	(8%)	12/163	(7%)	122/842	(15%)	16/136	(12%)	21/205	(10%)
White Blood Cells	34/279	(12%)	21/164	(13%)	105/845	(12%)	20/135	(15%)	24/205	(12%)
Epithelial Cells	34/279	(12%)	26/162	(16%)	162/827	(20%)	24/136	(18%)	24/205	(12%)
Bacteria	24/277	(9%)	12/163	(7%)	64/831	(8%)	11/136	(8%)	15/205	(7%)
Crystals	17/276	(6%)	6/159	(4%)	67/825	(8%)	17/136	(13%)	17/205	(8%)
Casts	3/165	(2%)	7/160	(4%)	16/345	(5%)	0/2		1/157	(<1%)

* The denominator reflects the total number of patients that had a baseline laboratory assessment with subsequent assessment(s) during treatment.

§ **Applicant's criteria for abnormal findings:**
Specific gravity - ≤1.00 or ≥1.075.
pH - ±2.0 units from baseline.
Glucose - if baseline value is within normal range and value is >1+. Otherwise if value is above the baseline value.
Hemoglobin - if baseline value is within normal range and value is >1+. Otherwise if the value is above the baseline value.
Protein - if baseline value is within normal range and value is >1+. Otherwise if value is above the baseline value.
Microbiology -
WBC - if baseline value is within normal range and value is 6-20/high power field (HPF). Otherwise if value is above the baseline value.
RBC - if baseline value is within normal range and value is 6-20/HPF. Otherwise if value is above the baseline value.
Epithelial Cells - If baseline is within normal range and value is 6-20/HPF. Otherwise if value is above the baseline value.
Bacteria - if baseline value is within normal range and value is 6-20/HPF. Otherwise if value is above the baseline value.
Crystals - if baseline value is within normal range and value is 6-20/HPF. Otherwise if value is above the baseline value.

¶ Ceftibuten capsules (200 mg BID, 300 mg BID, and 400 mg QD); Cefaclor (250 mg TID, 500 mg TID)

Table 10.
Overall Number of Patients* and Percent Incidence of Abnormal§ Clinical Urinalysis Laboratory Values in TMP-SMX, Augmentin, Ofloxacin, and Norfloxacin Treatment Groups Compared to Ceftibuten 400 mg QD
(According to applicant)

	Ceftibuten 400 mg QD	TMP-SMX 1600 mg/800 mg BID	Augmentin® 500 mg TID	Ofloxacin 200 mg BID	Norfloxacin 400 mg BID
Specific Gravity	49/850 (6%)	1/112 (<1%)	1/58 (2%)	1/14 (7%)	0/42
pH	124/824 (15%)	28/124 (23%)	4/52 (8%)	1/17 (6%)	12/48 (25%)
Glucose	30/824 (4%)	1/125 (<1%)	0/53	6/20 (30%)	2/47 (4%)
Protein	54/844 (6%)	12/133 (9%)	1/53 (2%)	9/20 (45%)	2/48 (4%)
Hemoglobin	59/819 (7%)	10/127 (8%)	8/53 (15%)	6/16 (38%)	7/48 (15%)
Red Blood Cells	122/842 (15%)	22/131 (17%)	5/52 (10%)	5/20 (25%)	5/47 (11%)
White Blood Cells	105/845 (12%)	14/131 (11%)	4/52 (8%)	1/20 (5%)	2/48 (4%)
Epithelial Cells	162/827 (20%)	36/130 (28%)	8/52 (15%)	1/16 (6%)	2/47 (4%)
Bacteria	64/831 (8%)	15/131 (12%)	6/52 (12%)	1/16 (6%)	1/48 (2%)
Crystals	67/825 (6%)	11/128 (9%)	7/51 (14%)	0/16	1/47 (2%)
Casts	16/345 (5%)	7/121 (6%)		0/16	0/37

* The denominator reflects the total number of patients that had a baseline laboratory assessment with subsequent assessment(s) during treatment.

§ **Applicant's criteria for abnormal findings:**
Specific gravity - ≤1.00 or ≥1.075.
pH - ±2.0 units from baseline.
Glucose - if baseline value is within normal range and value is >1+.
Hemoglobin - if baseline value is within normal range and value is >1+.
Protein - if baseline value is within normal range and value is >1+.
Microbiology -
WBC - if baseline value is within normal range and value is >20.
RBC - if baseline value is within normal range and value is >20.
Epithelial Cells - If baseline is within normal range and value is >20.
Bacteria - if baseline value is within normal range and value is >20.
Crystals - if baseline value is within normal range and value is >20.

OVERDOSAGE IN PHASE 2/3 TRIALS:

C8804432107: (ceftibuten 400 mg q.d. x 6 days; AECB) This 36-year-old white male patient (56.4 kg) self-administered 20-200 mg ceftibuten capsules over the first 4 days (on average, 1000 mg/d = 18 mg/kg/d). In the adverse reaction section of the data base, the patient developed a "concomitant illness" of "severe nervousness" on the first day. According to the laboratory data, on day 6, the only laboratory abnormalities were "many" urine crystals and 1+ blood in the urine. Otherwise, no other changes were seen; a "toxicology screen" was performed and was negative. In addition, from the reviewer's assessment, the patient was a clinical failure.

Clostridium difficile DIARRHEA:

According to the applicant, of the 1587 ceftibuten recipients, 6 (<1%) experienced diarrhea, of varying severities, due to *C. difficile*. 5/6 patients were enrolled in trials; 3/5 came from study C88081, the open noncomparative uncomplicated UTI trial. These patients were C8808101033, C8808101050, C8808101054, C8700104011, I8724704016, and I8732607019. 4/6 were discontinued early from therapy owing to the diarrhea.

The MO identified one additional ceftibuten patient, C8706905018, who, according to the CRF comment pages, developed severe diarrhea on day 8 of ceftibuten therapy requiring treatment with metronidazole.

No patients who received any of the comparator drugs experienced *C. difficile* diarrhea.

OVERVIEW OF SAFETY UPDATE:

On July 1, 1993, the applicant submitted a safety update which included safety information for all subjects (n=493) and patients (n=1870) who received ceftibuten capsules in completed trials up through December 1, 1991 as well as "serious" AE's from on-going trials up through March 31, 1992. The original NDA ISS included safety data accumulated through June 15, 1991.

The rate of adverse experiences, clinical and laboratory, was not significantly different from those reported in the NDA ISS. No additional cases of *C. difficile* diarrhea were noted in the safety update.

> ***Medical Officer's Comment:*** Of interest, approximately 3 years ago, the MO noted that Schering IND protocols did not include prothrombin (PT) and partial thromboplastin time (PTT) determinations. When this point was raised with Dr. Kammer during a telecon, he responded that Schering had coagulation experience with over 2000 patients and that no abnormalities had been seen. Based on this information, the reviewer agreed that it would be unnecessary that routine PT/PTT's be obtained in subsequent studies.
>
> The MO can find only a handful of patients in the entire NDA who had PT/PTT's obtained. However, the reviewer is not overly concerned as this cephem does not contain the NMTT side group which other cephalosporins possess. The NMTT group has been associated with coagulopathy.

In the safety update, "drug-demographic" AE's were examined. For the ceftibuten recipients, independent of dose, 22% of patients ≤40-years-old compared to 13% of patients >65-years-old, experienced AE's. A higher incidence of AE's were seen for women than for men (21% vs. 13%). According to the applicant, a higher incidence of AE's were observed in U.S. versus international studies (23% vs. 13%), which they attributed possibly due to different reporting practices.

Ceftibuten patients discontinued from phase 2/3 studies due to the development of an AE subsequent to NDA submission:
According to the applicant, there were 7 ceftibuten recipients experienced 8 AE's and were subsequently discontinued from therapy. These included abdominal pain (2), skin rash (2), joint pain (1), diarrhea (2), and inc. liver enzymes (1). Both diarrhea patients received ceftibuten 400 mg q.d.

Ceftibuten patients who died subsequent to NDA submission:
Short death summaries for 10 additional ceftibuten recipients, not reported in the original NDA, were provided in the safety

update. All but 2 patients received ceftibuten 400 mg q.d. None were considered related to ceftibuten toxicity.

These 10 cases consisted of: MI (1), MI or PE (1); respiratory failure due to underlying COPD (1), "hemorrhagic abdominal syndrome" (1); septic shock in a pneumonia patient due to *S. pneumoniae* - ceftibuten 200 mg b.i.d. (1); progression of underlying cancer (2); pneumonia not responsive to ceftibuten therapy due to *E. coli* and *H. influenzae* (1); cardiorespiratory failure (1); development of sepsis 2-3 weeks following ceftibuten for a UTI (pathogen not provided) (1).

SAFETY CONCLUSIONS:

In general, ceftibuten appeared to be relatively safe compared with the other drugs studied. There appeared to be a direct relationship between mg of ceftibuten received at each dosing and the incidence of clinical AE's - 400 mg recipients tended to experience more AE's than 200 mg recipients. In general, this relationship was not seen with laboratory AE's. Gastrointestinal AE's and headache tended to be the most pronounced clinical AE's.

There were a total of 7 cases of *C. difficile* diarrhea. As previously stated, of interest, 3/7 cases were seen in the small open study.

OVERALL CONCLUSIONS:

As discussed in the conclusions, as bronchitis is an empirically-treated infection where the initiation of anti-infective drug therapy is based on clinical findings, greatest emphasis was placed on the clinical efficacy population. Using this strategy, neither acute bacterial bronchitis nor AECB met the 95% confidence interval approach.

The applicant studied 1452 patients. Yet, many of the patients had other diagnoses and received dosing regimens (200 mg b.i.d. or 300 mg b.i.d.) which differed from treatment indications and dosing regimens requested in their proposed labeling. From these 1452 patients, across all studies, 187 ceftibuten 400 mg q.d. and 87 cefaclor 250 mg t.i.d. recipients were enrolled with, what the reviewer could determine, to have acute bacterial bronchitis. Similarly, for AECB, respective enrolled numbers were 216 and 130. The total number of enrolled patients who were treated with the appropriate dose and had a suitable diagnosis was 620/1452 (43%).

Looking at the **clinical test-of-cure** population, for acute bacterial bronchitis, evaluable numbers for the two treatment groups were 158 and 63, respectively. For AECB, 174 and 98. Now the total number of clinically evaluable patients is decreased to 493/1452 (34%). It is clear from the dosing regimens employed in the protocols, that these were Phase 2/3 dose-finding studies. None of the protocols employed a single ceftibuten dosing schedule for the appropriate diagnosis.

With regard to combining all ceftibuten 400 mg q.d. studies, the 95% CI was not met. Larger numbers might have shown ceftibuten to be LESS efficacious than cefaclor 250 mg t.i.d.

For **AECB**, combining all ceftibuten 400 mg q.d. studies, although low clinical cure rates were realized for both arms, the 95% CI interval was barely met. However, in the search for a "second" corroborative AECB study, neither the ceftibuten 200 mg b.i.d. AECB experience from C87001 *et al* nor the ceftibuten 200 mg b.i.d. pneumonia experience (using applicant's assessments) met the 95% CI approach. Hence, no second study.

As discussed in the pharmacokinetics portion of this review, the applicant contends that in their clinical LRTI studies, the 200 mg b.i.d. ceftibuten experience should be considered supportive of their 400 mg q.d. results. From pharmacokinetic studies, the extrapolated 24 hr. AUC for ceftibuten 200 mg b.i.d. administration was ≈110 hr•μg/mL compared to 80 hr•μg/mL for the

400 mg q.d. dosing. These 24 hr. AUC's differ significantly, although extreme pharmacokinetic variability existed between studies. From a pharmacokinetic standpoint, it is difficult to agree with the applicant.

From a bacteriologic standpoint, as previously discussed, the MO has concerns about ceftibuten's *in vivo* activity against *S. pneumoniae*. As one might expect from the *in vitro* data, it appears to be efficacious against *H. influenzae*, including β-lactamase-producing pathogens. However, as bronchitis, in general, is an empirically-treated disease, it is concerning that ceftibuten has problems with one of the major pathogens involved in bronchitis infections due to bacterial pathogens.

The applicant submitted data for 724 enrolled patients. As the applicant requested approval of complicated in general, more difficult infections to treat, the MO focused the review on this population. 462/724 had . Of these patients, 185 ceftibuten, 64 TMP/SMX, 35 norfloxacin, and 9 ofloxacin patients were bacteriologically evaluable. Thus, 293/724 (40%) were evaluable for this indication. In contrast to the studies, all protocols solely employed 400 mg q.d. dosing for ceftibuten. However, again, the 2:1 randomizations were used.

In these studies, a bacteriologically evaluable population was most important. However, from a bacteriologic standpoint, evaluable patient numbers were again a problem. Only when the U.S. and international ceftibuten-TMP/SMX studies were combined was the uncorrected 95% CI approach barely met. As with the search for the "second" confirmatory study was fruitless. This second study, the quinolone-controlled international trials, showed ceftibuten to be less efficacious to the quinolones WITHOUT a safety advantage. Furthermore, there are some unresolved concerns with regard to ceftibuten's efficacy against *E. coli*, the primary pathogen

****

In the NDA review, the MO acknowledges that many changes were made to infectious diagnoses, patient evaluability (using different evaluation criteria from those set-up in the protocols), and changes in bacteriologic and clinical responses. The reviewer addresses each of these points below:

(1) One might argue that it is unreasonable for the reviewer to reassign diagnoses. In response I would say that the

same approach was taken by the applicant on a *post hoc* basis. Acute bacterial bronchitis and AECB were not distinguished in the case report forms. Indeed, the reviewer believes that the MO's "corrected" diagnoses better represent the population studied than the applicant's *post hoc* reassignment of infectious diagnoses.

(2) The protocols were originally designed such that only bacteriologic AND clinical patients were evaluable. As stated above, since bronchitis is typically an empirically-treated infection, the MO believes that it was appropriate to dispense with this requirement. Indeed, if more strict evaluability criteria were maintained, the 95% CI approach would be more difficult to meet.

(3) The MO was more strict relative to assignment of clinical and bacteriologic responses. For example, as previously described, if a patient's illness showed insignificant clinical improvement within a proscribed time, even though the applicant considered the patient "improved" by the end of therapy, the MO changed the applicant's final response from "improvement" to "fail." The MO made every attempt to treat all drug arms similarly.

Certainly, as the cure rates decrease, the per cent difference around the lower limit of the 95% CI accepted by the division becomes increased. For example, with cure rates of 90%, a maximum 10% difference is acceptable. However, for a cure rate of 70% or less, a 20% difference is used. Thus, reestablishing the applicant's higher cure rates with the same number of clinically evaluable patients again would make the 95% CI more difficult to meet.

Based on the previous discussion, the reviewer believes that the application has been fairly reviewed. Indeed, the criteria described above are less strict than those set-up in the protocols. Yet, the MO believes that the veracity of the data is not compromised by this approach.

From a safety standpoint, the reviewer does not have significant concerns about ceftibuten. It appears, from a safety standpoint, to behave similarly to other cephalosporins. The major clinical adverse events appeared to be gastrointestinal and hypersensitivity reactions. There appeared to be a higher incidence of headache associated with ceftibuten 400 mg q.d. administration.

In summary, the number of evaluable patients is the major issue in the nonapprovability of this indication; especially the problem of the 2:1 randomization of ceftibuten to comparators. This explains why the 95% confidence interval approach is not

met. Indeed, the applicant acknowledges in the NDA that they did not meet the evaluability rates they had projected. In addition to the evaluability number problems, concerns with ceftibuten efficacy against *S. pneumoniae* in and *E. coli* in remain.

THIS NDA IS NOT APPROVABLE.

RECOMMENDATIONS:

Where might the applicant *go from* here in light of this NDA being nonapprovable? In the reviewer's opinion, the following strategy might be used by the applicant in order to garner the indications requested in this application. In all future studies, it is important that adequate follow-up be obtained, that investigator's efficacy assessments be corroborated by the specific signs & symptoms recorded in the case report form including comments, and that a 1:1 drug randomization be employed.

AECB: Following combination of all studies, the 95% confidence interval approach was not met. In contrast, for AECB, this was just barely met. In order for the applicant to garner either indication, this would require new studies with special attention to the *in vivo* activity against *S. pneumoniae*.

For larger evaluable numbers might demonstrate that ceftibuten 400 mg q.d. is less effective than a chosen approved comparator in the treatment of The applicant might consider a different dosing regimen.

For **AECB**, one additional well-controlled clinical trial would be sufficient.

For both bronchitis infections, future protocols should include **double-blind** studies, good documentation of baseline sputum Gram's stains, and adequate posttherapy follow-up (as previously discussed with the applicant at the End-of-Phase 2 meeting).

It is conceivable that following additional studies, ceftibuten could be approved for either bronchitis indication with restricted labeling for *S. pneumoniae*. Namely, approval for β-lactamase (+) and (-) strains of *H. influenzae* and *M. catarrhalis* WITHOUT approval of *S. pneumoniae*; however, such depends on future studies.

The applicant should be required to perform one additional adequate well-controlled blinded trial with special attention to ceftibuten's efficacy against *E. coli*. As previously discussed, the applicant might consider conducting clinical studies which employ different ceftibuten dosing.

Brad Leissa, M.D.
Medical Officer / HFD-520

Concurrence Only:
HFD-520/DivDir/Lumpkin
HFD-520/SMO/Albrecht

cc: Orig. NDA
HFD-340
HFD-520
HFD-520/DepDir/Gavrilovich
HFD-520/MO/Leissa
HFD-520/Pharm/Buko
HFD-520/Micro/Dionne
HFD-520/Chem/
HFD-520/CSO/DeBellas
WP51\FILES\CEDAX\NDA\FINAL.FDA
2/2/93

2/16/93

APPENDIX:

Clinically Relevant Laboratory Adverse Experiences:

Not all laboratory values flagged as "out of the normal range" were considered significant by the reviewer. Therefore, for laboratory abnormalities to be considered clinically relevant, the following criteria were developed by the reviewer and used for all patients. The MO only accepted laboratory values that were obtained either during therapy or up to 2 weeks posttherapy as possibly being associated with the study drug. For a patient to have "evaluable" laboratory tests, they were required to have a specific baseline laboratory value followed by a subsequent determination either on therapy or posttherapy. Patients were excluded as the laboratory abnormality being possibly associated with the study drug if they either had an underlying diagnosis or received a concomitant medication that was likely to be associated with these changes. (i.e., low WBC count while receiving concurrent chemotherapy.)

HEMATOLOGY:

Hemoglobin (Hgb.): To be considered clinically relevant, follow-up hgbs. in **males** needed to be $\leq$11 mg/dL and in **females** $\leq$9 gm/dL AND there had to be a decrease of 3.0 mg/dL from baseline.

Leukocyte count (WBC): $\leq 3500/mm^3$ including a decrease of $1000/mm^3$ compared to a baseline $>3500/mm^3$. The Absolute Neutrophil Count (ANC) (ANC = [band forms + PMN's]) was considered significant if, following a normal baseline value, the subsequent value was <1000/. .

Eosinophils: $>500/mm^3$ including 2x baseline. Baseline value $\leq 500/mm^3$.

Platelet count: $\leq 150,000/mm^3$ including a change of $100,000/mm^3$ compared to baseline **OR** $\geq 600,000/mm^3$ with a result 1.5x greater than the baseline value.

CHEMISTRY:

Alkaline phosphatase (ALP): $\geq$2x ULN. If pretreatment >ULN, >2x baseline.

Bilirubin (total): $\geq$1.5x ULN or an inc. of 1 mg/dL IF baseline WNL.

Blood urea nitrogen (BUN): ≥2x ULN and ≥2x baseline and baseline WNL.

Creatinine: The follow-up value had to be abnormal including an increase of 25% over baseline.

Glucose: <60 mg% or >100 g/dL. If baseline >ULN, then ≥2x increase. (Diabetics are excluded unless hypoglycemia noted.)

SGOT (AST) or SGPT (ALT): ≥3x ULN. If pretreatment above ULN, ≥3x baseline.

COAGULATION:

Prothrombin time (PT): ≥33% inc. from baseline and "flagged" as abnormal. In these study, controls were not consistently reported.

URINALYSIS:

NOTE: Urine blood, protein, and glucose were assessed using the following scale: 0, trace, 1+, 2+, 3+, 4+, or 5+.

Urine RBC's and WBC's were assigned the following by the applicant (numbers reflect count/LPF):

A = None, negative, within normal limits.
B = 1-5, trace, present, slight, rare, occasional.
C = 6-15, moderate
D = 16-50, many, frequent
E = >50, too numerous to count, innumerable.

Blood: ≥1+ with normal urine (0 or trace) at baseline.

Protein: ≥1+ with normal urine (0 or trace) at baseline.

Glucose: ≥2+ with normal urine (0, trace, or 1+) at baseline.

WBC's: C,D, or E with normal baseline (A or B).

RBC's: C,D, or E with normal baseline (A or B).

Urinary RBC's and WBC's were not evaluated in the studies, as changes often were associated with the individual's underlying infection.

Medical Officer's Review of Amendment to Original NDA
Ceftibuten Tablets- NDA 50-685

Applicant: Schering-Plough Incorporated
Date of Submission: November 5, 1993
Review Assigned: January 18, 1994
Review Completed: July 5, 1994; revised August 23, 1994; revised December 2, 1994

Material Reviewed: Medical Officer's Review by Dr. Brad Leissa, dated February 2, 1993, of original 300 volume submission, dated December 20, 1991.

Major clinical amendment for the indication of acute bacterial exacerbation of chronic bronchitis (AECB), dated November, 1993, consisting of 16 volumes with clinical data for 373 patients and 23 volumes of case record forms;

Applicant's Clinical Data Management Plan (CDMP) discussed with this Medical Officer February 18, 1994;

Amendments and Correspondence (including facsimiles and diskettes containing electronic data):
4/8/94; 4/12/94; 4/8/94; 6/6/93; and 6/8/94.

Meetings: February 18, 1994; March 16 and 18, 1994; and May 12, 1994

Name of Drug:

Generic: Ceftibuten

Trade: CEDAX® Capsules

Code Name: 7432-S; SCH 39720

Chemical Name: (+)-(6R,&R)-7-[(Z)-2-(2-amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo [4.2.0.] oct-2-ene-2-carboxylic acid, dihydrate

Molecular Formula: $C_{15}H_{14}N_4O_6S_2 \cdot 2H_2O$

Chemical Structure:

Pharmacologic Category:

Ceftibuten is an oral semisynthetic cephalosporin whose chemical structure is similar to 3 other cephalosporins: cefixime (Suprax®), ceftriaxone (Rocephin®) and ceftazidime (Fortaz®). Ceftibuten incorporates a new side chain, carboxyethilidene, which is respon ble for oral absorption as well as stability against -lactamases.

Background

The new drug application for Ceftibuten (CEDAX®) Capsules consisted of 300 volumes and was submitted December 20, 1991. The applicant sought approval for the indications of secondary bacterial infections of acute bronchitis and acute bacterial exacerbations of chronic bronchitis, and urinary tract infections including pyelonephritis, recurrent cystitis, and complicated urinary tract infections. The original NDA was reviewed by Dr. Brad Leissa and resulted in a non-approvable letter in March, 1993. (See Medical Officer's Review of NDA 50-685, dated February 2, 1993 and the action letter of March 22, 1993.)

Regarding the indication of secondary bacterial infections of acute bronchitis and acute bacterial exacerbations of chronic bronchitis (AECB), Dr. Leissa wrote in his "Recommendations":

> _____ _____AECB: Following combination of all studies, the 95% confidence interval approach was not met. In contrast, for AECB, this was just barely met. In order for the applicant to garner either indication, this would require new studies with special attention to the *in vivo* activity against *S. pneumoniae*.
>
> For , larger evaluable numbers might demonstrate that ceftibuten 400 mg q.d. is less effective than a chosen approved comparator in the treatment of acute bacterial bronchitis. The applicant might consider a different dosing regimen.
>
> For AECB, one additional well-controlled trial would be sufficient.
>
> For both bronchitis infections, future protocols should include **double-blind** studies, good documentation of baseline sputum Gram's stains, and adequate posttherapy follow-up..."

In November, 1993, the applicant filed a major clinical amendment again seeking approval for the indication of **acute exacerbation of chronic bronchitis (AECB)**. The amendment consists of 16 volumes of clinical data and 23 volumes of case record forms for 373 patients diagnosed with an acute exacerbation of chronic bronchitis. Electronic files of the data were provided to this reviewer in March, 1994.

PROPOSED PACKAGE CIRCULAR (pertinent to AECB)

INDICATIONS AND USAGE

CEDAX® (Ceftibuten) is indicated for the treatment of the following infection when caused by susceptible strains of the designated organisms:

Acute Bacterial Exacerbation of Chronic Bronchitis

caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (beta-lactamase positive and negative strains), and *Streptococcus pneumoniae*. Culture and susceptibility testing of the causative pathogen to determine its susceptibility to ceftibuten is recommended.

Therapy may be started, however, while awaiting the results of these studies. If necessary, antibiotic therapy should be adjusted appropriately once susceptibility has been established.

Medical Officer's Comment: The proposed labeling for AECB submitted with this amendment differs from the labeling last requested in the Ceftibuten Capsule NDA reviewed by Dr. Leissa in the specific organisms requested. Previously, the applicant sought to include Haemophilus parainfluenzae and Klebsiella pneumoniae, in addition to the organisms named in the current proposed package insert. Regarding this change, the applicant explained that "...the etiologic role of H. parainfluenzae and K. pneumoniae is not yet fully recognized..."

DOSAGE AND ADMINISTRATION

Infection	Description	Unit Dose	Frequency	Duration	Daily Dose
Acute Bacterial Exacerbation of Chronic Bronchitis	–	400 mg	q24 hours	5-14 days	400 mg

Study C90-045 Protocol Outline

- *Study design*

  Assessor-blind, Controlled Trial

- *Inclusion criteria*

  [See detailed Inclusion Criteria on page 6 of this review.]

  Signs and symptoms of acute exacerbation of chronic bronchitis
  Chest X-Ray
  Satisfactory Gram-stain
  Microbiologic culture (Optional)

- *Treatment*

  Cedax 400 mg QD for 5 to 14 days
  Suprax 400 mg QD for 5 to 14 days[1]

- *Assessment Visits*

  Visit 1 - Baseline
  Visit 2 - During Treatment
  Visit 3 - Post-Treatment (0-6 days)
  Visit 4 - Follow-up (7-21 days)

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[1] The package insert for Suprax® (cefixime) reads:
ACUTE BRONCHITIS AND ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS, caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (beta-lactamase positive and negative strains).
DOSAGE AND ADMINISTRATION:
ADULTS: The recommended dose of SUPRAX is 400 mg daily.

[*MO Comment: No specific treatment duration is given other than in the treatment of infections due to S. pyogenes, in which a therapeutic dosage of Suprax is recommended for at least 10 days.*]

Protocol: **C90-045**

Title: Comparison of the Efficacy, Safety, and Tolerance of Ceftibuten (SCH 39720) Capsules with that of Cefixime (Suprax®) in the Treatment of Acute Exacerbations of Chronic Bronchitis in Adults

Design: This was a multicenter, evaluator-blind, randomized, controlled clinical trial in adults in the United States. Patients with acute exacerbations of chronic bronchitis were randomized in a 1:1 ratio, to receive 5-14 days of treatment with ceftibuten 400 mg given once daily (QD) or cefixime (Suprax®) 400 mg QD. Evaluation of the signs and symptoms of acute exacerbations of chronic bronchitis, Gram stain of sputum, sputum culture and susceptibility testing and spirometry evaluations were performed at baseline and at each visit. Chest x-rays were performed at baseline and were required posttreatment only for patients who were failures.

The primary evaluation of efficacy was the overall clinical assessment for the clinical efficacy population based on the clinical response at Visit 3 (0-6 day end-of-treatment visit) and Visit 4 (7-21 day extended follow-up visit). The investigator evaluated change from baseline in signs and symptoms of acute exacerbation of chronic bronchitis at Visit 3 and Visit 4.

The secondary evaluation of efficacy was the overall microbiologic assessment. The microbiologic efficacy population was comprised of patients in the clinical efficacy population who were considered microbiologically evaluable. Evaluation of efficacy for the microbiologic efficacy population was overall microbiologic assessment based on microbiologic response for patients at Visit 3 and Visit 4. A microbiologic response also was assigned to each pathogen at Visits 3 and 4.

Evaluation of safety was based on the incidence of adverse events and laboratory abnormalities.

Inclusion Criteria:

Male or female adults, who were at least 18 years of age, were eligible for enrollment if they met the following criteria:

- diagnosis of acute exacerbation of chronic bronchitis; i.e., chronic cough and sputum production for longer than two consecutive years, and on most days for three consecutive months;

- evidence of acute exacerbation of chronic bronchitis as indicated by the following signs and symptoms of disease:

  - increased cough and/or dyspnea;
  - increased sputum production; and
  - increased sputum purulence

  ***Medical Officer's Comments on Inclusion Criteria**: The protocol called for documentation of the evidence of exacerbation of patients' chronic bronchitis. Investigators fulfilled this criterion by recording the presence and severity of such parameters as cough and/or dyspnea, sputum production and purulence. However, there is no record of a patient's baseline pre-infection state, which made it difficult for the MO to assess independently whether the patient returned to baseline. (See the case record form [CRF] in appendix A of this review.) This prompted the MO to ask the applicant how investigators determined if patients returned to their baseline pre-infection state. The applicant responded in correspondence dated June 6, 1994:*

  "The source of information on the patient's baseline state was not specifically collected. In many cases, the investigator had knowledge of the patient's baseline state. In other cases, the patient was the source of information. For this study we could not use a completely well state as an endpoint for the definition of cure, since the patients are all chronically ill. Therefore the clinical response of "Cure" was defined as the resolution of acute symptoms and signs with return to pre-infection baseline level with regard to the degree of dyspnea, frequency of cough, sputum production and absence of fever.'

  The MO agrees with this definition. However, a study design in which pre-infection baseline clinical status was queried at entry for all patients would have been preferable.

- evidence of purulent sputum as defined by the presence on Gram stain of > 25 polymorphonuclear leukocytes and < 10 squamous epithelial cells per low power magnification field;

- no evidence of pneumonia on chest x-ray performed within 48 hours before the start of treatment;

- the infection had to be considered appropriate, in the judgment of the investigator, for treatment with cefixime dosed once daily for five to 14 days;

- women of childbearing potential must have had a negative urine or serum gonadotropin pregnancy test at entry;

- written informed consent had to be obtained.

Exclusion Criteria:

- a history of immediate-type hypersensitivity or serum sickness reactions to a penicillin, cephalosporin, or any other beta-lactam antibiotic;
- patients with any immunodeficiency, including those with malignancy or immunodeficiency syndromes;
- patients with infections known before enrollment to be caused by bacteria resistant to either ceftibuten or cefixime;
- patients in whom it is well-known on the basis of past experience, that causative pathogens persist at the end of antibiotic therapy (such as all patients with cystic fibrosis or IgA deficiency and some patients with bronchiectasis);
- patients who must begin corticosteroid treatment or who must have their existing level of corticosteroids increased for relief of the respiratory symptoms of this acute exacerbation;
- patients with any known or suspected renal impairment (serum creatinine >2 mg/dL), severe hepatic dysfunction (SGOT or SGPT more than three times the upper normal limit, or bilirubin 4 mg/dL) or neutropenia ($\leq$1000 neutrophils/mm^3);

  Medical Officer's Comment: The results of pre-treatment laboratory tests were not usually known at study entry. Consequently, 12/373 (3%) patients with a laboratory abnormality (mild anemia, elevated liver-associated enzymes, or elevated creatinine) were inadvertently entered into the trial. Of these patients, 11/12 (92%) were otherwise appropriately entered into the trial, took the prescribed course of therapy (on average, 10 days treatment) and completed both the end of therapy (9-6 days) and extended follow-up (7-21 days) visits. Hence, the Medical Officer considered these patients evaluable.

- patients with infection at enrollment that suggests a need for parenteral antibiotic therapy, or more than 14 days of therapy;
- treatment within 72 hours prior to enrollment with an antibiotic(s) which, in the judgment of the investigator, (based on in-vitro activity, dose and route of administration) is potentially effective in the patient's infection;
- pregnant or nursing women;
- treatment with any other systemic antibiotic agent at any time during the course of treatment with study drug; [*MO Comment: Patients who were failures, and thus treated with another antibiotic, were not excluded]*;
- patients with chronic diarrhea, or patients having diarrhea for greater than five days duration prior to enrollment;
- patients with a high probability of death within 48 hours of study entry;
- previous treatment in this study with ceftibuten or cefixime whether treatment was completed or prematurely discontinued;
- use of any other investigational drug within 30 days prior to enrollment;
- any other condition, which in the opinion of the investigator, would make the patient unsuitable for enrollment or make evaluation of the study drug impossible.

Entry Procedures

In order to establish the diagnosis and determine the suitability of the patient for the study, screening evaluations were conducted. These evaluations were to be completed within 48 hours prior to the initiation of therapy, and included the following:

medical history and physical examination;

- evaluation of the signs and symptoms of AECB;
- chest x-ray;
- Gram stain of sputum;
- laboratory studies; (See table below for the lab tests specified by protocol.)
- sputum culture and susceptibility testing (optional); and
- spirometry evaluations (optional).

Table: Clinical Laboratory Tests at Study Entry

Hematology
- hemoglobin or hematocrit
- total white blood cell count with differential

Blood Chemistries
- SGOT (AST)
- SGPT (ALT)
- alkaline phosphatase
- total bilirubin (direct if total increased)
- creatinine

Urinalysis
- pH
- specific gravity
- protein
- glucose
- hemoglobin
- microscopic examination of sediment, including presence of cells (type), casts (type) and bacteria

Randomization and Treatment

Patients meeting entry criteria were randomized on a 1:1 basis to one of the following treatment groups:

- ceftibuten 400 mg in a single dose QD (one 400-mg capsule)
- cefixime (Suprax®) 400 mg in a single dose QD (one 400-mg tablet)

All patients were to be treated for a minimum of five consecutive days, but not more than 14 days. Patients were to be followed for seven to 21 days after the end of treatment. The random code was to be held by a third party (eg, the study pharmacist) who was not involved in the treatment or evaluation of the patient in order to maintain the blind of the investigator and study staff. *(N.B. The Medical Officer reviewed the case summaries and case record forms of all enrolled blinded as to treatment arm.)* For all patients, a bottle of study drug containing sufficient capsules for 10 days of treatment was to be dispensed at the beginning of therapy. Drug was to be administered without regard to meals.[2] At every visit, the patient was to have the bottle containing the remaining capsules available to the third party for counting to verify patient compliance.

Medical Officer's Comment: While the protocol stipulated a treatment duration range of 5-14 days, the average length of treatment for patients, excluding failures, was 10 days. This is discussed in greater detail under the "Clinical Efficacy Results" section of this review.

Regarding patients who received greater than 10 days of treatment (42/269 or 16% of the MO's evaluable dataset with a successful outcome, balanced in the two treatment arms), the MO asked the applicant how investigators decided therapy duration for a given patient. Was it decided at entry that one patient would get 2 bottles dispensed (and take only 14 pills) and another get 1 bottle (and take 7-10 pills)? Was severity of presenting signs and symptoms, and their resolution during therapy, taken into account? How was this documented? The applicant responded in correspondence dated June 6, 1994:

"The protocol was designed to reflect common medical practice of the treatment of acute exacerbation of chronic bronchitis... the protocol reads:

> Patients will be treated for a minimum of 5 consecutive days but not more than 14 days. Treatment should continue for at least 48 to 72 hours after the patient becomes asymptomatic, or until a confirmed clinical cure or improvement is demonstrated, or until there is no source to culture.'

"For all patients, a bottle of study drug containing sufficient capsules for 10 days of

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[2] The package insert for Suprax® (cefixime) reads:

ACTIONS/CLINICAL PHARMACOLOGY:

SUPRAX, given orally, is about 40% to 50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food.

treatment was to be dispensed at the beginning of therapy. Investigator's decision to dispense additional drug to patients was made on a case by case basis and was based on the investigator's medical judgement. Even though severity of signs and symptoms was reported during the study, no specific documentation about the investigator's rationale for the decision about the length of therapy was collected."

Assessments During Study Visits

Patients were to be evaluated at Visit 2 (3-5 days during treatment or more often if considered appropriate), at Visit 3 (0-6 days after end-of-treatment), and at Visit 4 (7-21 days following the completion of therapy). A flow chart summa izing the study assessment schedule is provided in the table below.

> ***Medical Officer's Comment:*** *In the original protocol, Visit 3 was to occur 1-3 days post therapy; Visit 4, 7-14 days post therapy. However, in the November, 1993 submission, the applicant analyzed the data with expanded ranges: 0-6 days after the end of therapy for Visit 3, and 7 to 21 days after the end of therapy for Visit 4, with an interval of at least four days between Visits 3 and 4. The Medical Officer asked the applicant to submit as well an analysis of the data using the follow-up time-frames originally defined in the protocol. This analysis according to the original protocol, received June 7, 1994, differed from the analysis with expanded ranges only in that the number of evaluable patients was slightly smaller. There was no significant change in patient demographics, disease characteristics, or overall clinical or microbiologic outcome. As such, the analysis will not be reproduced here.*

At each evaluation, signs and symptoms of infection were to be evaluated. Gram stain, culture and susceptibility testing of sputum specimen (if appropriate source was available and clinically indicated), chest x-rays (in patients who were considered treatment failures), and pulmonary function tests (if clinically indicated) also were to be performed at all visits. At Visit 3 (0-6 day end-of-treatment visit) and Visit 4 (7-21 day extended follow-up visit), clinical response was to be determined. In addition, at Visit 3, the routine urine and blood tests that were conducted during screening, were to be repeated. If a patient could not or did not return for Visit 4 (7-21 day extended follow-up visit), the investigator was to attempt to contact the patient. In cases where the patient could be reached, but could not return for the evaluation, the investigator was to ascertain by telephone or letter whether or not the patient remained asymptomatic.

If there were any abnormal laboratory values at any time during the study, laboratory tests were to be repeated until the results returned to within the normal range or were attributed to other causes.

SCHEDULE OF EVENTS

ACTION STEPS	Pretreatment Day 1	During Treatment Days 3-14	Post-Tx Days 0 - 6 Days 7 - 21
Consent Obtained	X		
Pregnancy Test	X§		
Medical History	X		
Complete Physical Examination	X		
Evaluation of Signs and Symptoms	X	X¶	X
Pulmonary Function Tests	X	X¶	X
Randomization of Patient	X		
Gram Stain, Culture and Susceptibility Testing of Sputum Specimen	X§	X*	X*
Clinical Laboratory Tests (CBC, Chem-panel, Urinalysis)	X§		XA
Chest X-rays	X§	XB	XB
Adverse Events	X	X	X
Clinical Evaluation of Response to Therapy			X

§ Within 48 hours before starting treatment.

¶ Every 3-5 days, or more often if appropriate, during treatment.

* If appropriate source is available and as clinically indicated.

A 0-6 days posttreatment. In addition, any clinically significant abnormal laboratory tests were to be repeated at appropriate intervals either during or posttreatment until they had returned to normal or had been judged to be due to other causes.

B For patients who were considered treatment failures.

Evaluation of Efficacy

The applicant performed efficacy analyses on three patient populations: the clinical efficacy population, the microbiologic efficacy population, and the intent-to-treat population.

Medical Officer's Comment: The MO will present only the clinical efficacy and microbiologic efficacy populations in this review.

To be included in the evaluation of drug effectiveness for the **clinical efficacy population**, patients were required to have:

- a Gram stain of sputum that was strongly suggestive (both qualitatively and quantitatively) of bacterial infection (i.e., Gram stain of >25 polymorphonuclear leukocytes and < 10 squamous epithelial cells per low power magnification field);
- a minimum of five and no more than 14 consecutive days of treatment with the assigned study drug or a minimum of three consecutive days in the event of clinical failure or superinfection; [***MO Comment: A single patient on Ceftibuten appeared to have received 15 days of therapy. Since it was not clear if the patient missed one dose, thus receiving 14 days of therapy, the reviewer opted to consider this patient evaluable.***]
- no more than two days of missed treatment and no consecutive days of missed treatment;
- investigator's assessment of clinical response at Visit 3 (0-6 day end-of-treatment visit) and Visit 4 (7-21 day extended follow-up visit);
- an interval of at least four days between Visit 3 and Visit 4; and
- no other antibiotic or systemic corticosteroid treatment at any time during the study except for patients with treatment failure or relapse.

To be included in the evaluation of drug effectiveness in the **microbiologic efficacy population (a sub-population of the clinical efficacy population)**, patients were to fulfill these additional requirements:

- Have a valid baseline pathogen isolated in the pretreatment culture of sputum. A microorganism isolated in the pretreatment culture was considered a valid pathogen if:
  - the culture was performed within 48 hours before the start of treatment;
  - the microorganism was susceptible to both study drugs and valid zone sizes have been reported;

- the microorganism was one of the following pathogens considered valid for acute exacerbation of chronic bronchitis;
  - *Haemophilus influenzae;*
  - *Moraxella catarrhalis;* or
  - *Streptococcus pneumoniae.*

A microbiologic response also was to be assigned to the following organisms. However, these two organisms were not to be included in the microbiologic evaluation of the patient.

- *Haemophilus parainfluenzae*
- *Klebsiella pneumoniae*

Medical Officer's Comment: Since the applicant is not seeking to include these organisms in the proposed package insert, the MO considered evaluable patients whose sputum grew Haemophilus parainfluenzae or Klebsiella pneumoniae in the clinical efficacy population only.

Evaluation of Clinical Response

The primary efficacy parameter was the overall clinical assessment. Evaluation of clinical efficacy at Visit 3 and Visit 4 was to be based on the investigator's assessment of the patient's clinical response to treatment. The signs and symptoms associated with acute exacerbation of chronic bronchitis (cough, dyspnea, sputum production, chills, cyanosis and rales/rhonchi) were to be included in the investigator's assessment of clinical response. The intensity of each sign and symptom of infection was to be graded as follows:

- 0 = absent or none;
- 1 = slight or mild;
- 2 = moderate;
- 3 = severe or marked.

In addition, a mean symptom severity score for each sign and symptom and a global symptom severity score were to be determined at baseline.

There were two time points during the study at which the investigator was to assess the patient's clinical response to treatment:

- Visit 3 (0-6 day end-of-treatment visit), and
- Visit 4 (7-21 day extended follow-up visit).

Medical Officer's Comment: *The MO agrees with using the clinical response as the primary efficacy parameter. For patients who comprised the clinical efficacy population, the average time for the end-of therapy visit, Visit 3 (V3), was 1.7 days after the last dose of ceftibuten; 1.8 days after the last dose of cefixime. Visit 4, designated the "extended follow-up visit" by the applicant, took place an average of 10 days after completion of therapy with either drug. The MO based her overall clinical assessment of patients on visit 4 (with failures at visit 3 carried forward).*

Visit 3 (0-6 Day End-of-Treatment Visit)

At Visit 3 (0-6 day end-of-treatment visit), the investigator was to indicate clinical status by assigning patients to one of the following categories:

Cure: Resolution of acute signs and symptoms with return to pre-infection baseline level with regard to the degree of dyspnea, frequency of cough, 24-hour sputum volume, and absence of fever and chills.

Improvement: Subjective improvement in dyspnea, with reduction in frequency of cough, 24-hour sputum volume, and resolution of fever if initially febrile, but without return to pre-infection baseline.

Failure: Complete lack of response in the above parameters.

Unassessable: The patient was to be considered unassessable if:

- an unallowed drug has been administered before the clinical assessment for treatment of an indication other than acute exacerbation of chronic bronchitis;
- study drug has been administered for less than 72 hours; or
- the patient did not return.

Medical Officer's Comment: *The MO agrees with the applicant's definitions for clinical response at the end of therapy.*

Visit 4 (7-21 Day Extended Follow-up Visit)

At Visit 4 (7-21 day extended follow-up visit), the investigator was to assess the patient's clinical response to treatment according to the following definitions:

Sustained Cure:	Continued resolution of signs and symptoms of infection.
Sustained Improvement:	Continued decrease of signs and symptoms of infection.
Relapse:	Reappearance of signs and symptoms of acute disease (at any time between Visit 3 and Visit 4) in a patient with a clinical cure or improvement at Visit 3.
Unassessable:	The patient was to be considered unassessable if: · an unallowed drug has been administered for an indication other than acute exacerbation of chronic bronchitis ; or · the patient did not return.

Supportive evidence of clinical improvement included:

- improvement in arterial blood gases,
- improvement in pulmonary function tests,
- diminished sputum purulence on Gram stain, and
- decreased WBC count if elevated at baseline.

Medical Officer's Comment: *To simplify the assessment terms at V4, the test-of-cure visit, the MO used "Cure", "Improvement", and "Relapse".*

"Improvement" was maintained as a category of clinical outcome given two factors: 1) the nature of the infection: acute exacerbation of chronic bronchitis, which leaves many patients symptomatic at their best; and, 2) the lack of a very clear picture, from the reviewer's standpoint, of what a patient's chronic bronchitis clinical status was prior to the acute exacerbation.

Clinical parameters were evaluated to determine a patient's progress (sputum production, cough, dyspnea, etc.). With regard to optional pulmonary function tests (PFTs), only a minority of patients enrolled (69/373 or 18%) had any PFTs performed (only 52/69 had both pre- and post-therapy PFTs), and the MO did not use them in assessing clinical outcome. In general, patients with a successful clinical outcome (cure or improvement) had improved PFTs post-therapy. No arterial blood gases were drawn on any patient.

Evaluation of Microbiological Response

Microbiologic response for the patient and by pathogen was to be assessed by the investigator at two time points during the study:

- Visit 3 (0-6 day end-of-treatment visit); and
- Visit 4 (7-21 day extended follow-up visit)

In addition, an overall microbiologic assessment was to be assigned to the patients based on microbiologic response evaluations at Visit 3 and Visit 4.

Microbiologic response was to be assigned to patients who had valid baseline pathogens (i.e., *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pneumoniae*). Microbiologic response by pathogen was to be assigned for the valid baseline pathogens as well as for *Haemophilus parainfluenzae* and *Klebsiella pneumoniae*.

Regardless of whether or not a repeat sputum culture was performed (some patients had no sputum to culture), the microbiologic response for each patient and for each pathogen or organism was to be classified as follows.

Visit 3 (0-6 Day End-of-Treatment Visit)

Eradication

Documented: absence of all pathogen(s) or organism(s) from sputum culture.

Presumed: signs and symptoms of AECB were resolved or improved; a repeat sputum culture was not performed or not able to be performed.

Persistence

Documented: continued presence in sputum culture of the same pathogen(s) or organism(s) isolated at baseline.

Presumed: continued presence of signs and symptoms of AECB; a repeat sputum culture was not performed.

Eradication with Colonization[3]: isolation of a new pathogen(s) or organism(s) other than the original pathogen(s) or organism(s) with improvement or cure of clinical signs and symptoms of infection.

Superinfection: isolation of a new pathogen(s) or organism(s) other than the original pathogen(s) or organism(s) with persistence or worsening of signs and symptoms of infection.

Medical Officer's Comment: *The MO did not assign a microbiologic response at the end of treatment (unless the patient was a failure) since the average time at which the Visit 3 culture was taken for patients in the microbiologic efficacy population was 1.6 days after the last dose of ceftibuten; 1.5 days after the last dose of cefixime.*

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[3] Response was colonization for microbiologic response by pathogen.

Visit 4 (7-21 Day Extended Follow-up Visit)

Eradication

Documented: absence of all pathogen(s) or organism(s) from sputum culture.

Presumed: signs and symptoms of acute exacerbation of chronic bronchitis were resolved or improved; a repeat sputum culture was not performed or not able to be performed.

Persistence

Documented: the same pathogen(s) or organism(s) isolated from sputum cultures at baseline and at Visit 3 also was isolated in the sputum culture performed at Visit 4.

Presumed: continued presence of signs and symptoms of acute exacerbation of chronic bronchitis; a repeat sputum culture was not performed.

Relapse:

Documented: absence of both the pathogen(s) or organism(s) and of clinical signs and symptoms at Visit 3, but isolation of the Baseline pathogen(s) or organism(s) from any sputum culture performed during the interval from Visit 3 to Visit 4 accompanied by signs and symptoms of infection.

Presumed: absence of both the pathogen(s) or organism(s) and of clinical signs and symptoms at Visit 3, but recurrence of signs and symptoms during the interval from Visit 3 to Visit 4; a repeat sputum culture was not performed.

Medical Officer's Comment: *The Medical Officer did not use a microbiologic response of "relapse" at Visit 4. If a patient clinically relapsed by V4, the microbiologic assessment was "eradication, documented" if a sputum culture at Visit 4 was negative; "persistence, documented" if the Visit 4 sputum culture was positive; or "persistence, presumed" if a Visit 4 sputum culture was not done. Of the applicant-designated visit 4 "Relapses" in the microbiologic efficacy population, a total of 11 patients (5 in the ceftibuten arm, 6 in cefixime arm), 2/5 patients on ceftibuten had no culture done at V4 vs 1/6 patients on cefixime.*

Reinfection:	absence of both the pathogen(s) or organism(s) and symptoms at Visit 3, but presence of a different (documented) pathogen(s) or organism(s) in any sputum culture performed during the interval from Visit 3 to Visit 4, accompanied by signs and symptoms of infection.
Eradication with Colonization:	isolation of new pathogen(s) or organism(s) other than the original pathogen(s) or organism(s) with improvement or cure of clinical signs and symptoms of infection.
Unassessable	a valid pathogen or organism was isolated at baseline, but the patient did not have a clinical response at Visit 3 or 4.

Overall Microbiologic Assessment

An overall microbiologic assessment was to be derived for each patient from the microbiologic responses at Visit 3 and/or Visit 4. The overall microbiologic assessment was to be based on the microbiologic response at Visit 4. **However, if the patient received concomitant antimicrobial treatment between Visit 3 and Visit 4, or the patient did not return for Visit 4, the overall microbiologic assessment was to be the same as that at Visit 3** [*emphasis mine*]. If colonization was observed at Visit 3 or Visit 4, the overall microbiologic assessment was to be "eradication with colonization". In addition, if no valid pathogen was isolated at baseline, the assessment was to be "unknown".

Medical Officer's Comment: *The Medical Officer did not agree with the determination of an overall microbiologic response based upon Visit 3. As stated previously, patients in the microbiologic efficacy population were seen on average at Visit 3 just one-and-a-half days after the last dose of either study drug. In study C88-058-01, a human pK study, the half-life values for ceftibuten ranged from 1.9 to 17.7 hours. With potentially long half-lives, then, for both ceftibuten and cefixime, the Medical Officer did not consider a "presumptive eradication"or "documented eradication" microbiologic response at this time to be valid since patients may still have significant levels of drug on board. Thus, the MO considered the test-of-cure culture to be that taken at Visit 4 (unless the patient failed earlier). If patients were unable to produce sputum at this visit, the microbiologic response was based upon the clinical outcome, where cure or improvement = presumptive eradication, and failure or relapse = presumptive persistence. Visit 4 took place on average 11 days after the last dose of either study drug [range 7-18 days, median 11 days].*

Evaluation of Safety

The evaluation of safety was performed on the safety population, a sub-population of the intent-to-treat population that includes patients who had documented receipt of at least one dose of study medication.

Patients were to be monitored for adverse effects of treatment. The evaluation of safety included changes from baseline in laboratory tests and all reports of adverse events. Adverse events, including those related to concurrent illnesses, were to be recorded on the case report form along with the date of onset, duration, and intensity of each event. The following scale was used to grade the intensity of adverse events:

mild:	awareness of a sign or symptom but easily tolerated;
moderate:	discomfort enough to cause interference with usual activity or to affect clinical status;
severe:	incapacitating with inability to do usual activity or to significantly affect clinical status;
life-threatening:	adverse event threatened the patient's life.

The investigator also was to determine the relationship of each adverse event or laboratory abnormality to the study medication (unrelated, possibly related, probably related, or related). The outcome of, treatment for, or change in study drug dosage required also was to be recorded for every adverse event. If a severe or life-threatening adverse event occurred, study drug treatment was to be discontinued. The investigator also was to determine if laboratory abnormalities were clinically significant.

As specified in the protocol, the proportion of patients in each treatment group in the safety population with at least one adverse event related to the gastrointestinal system were to be compared. *Clostridium difficile* studies (stool smear and toxin) were to be performed on any patient who had persistent diarrhea during study drug administration or during the posttreatment follow-up period.

STUDY RESULTS

Investigators

C90-045-01
Barry McLean, MD
Internal Medicine Specialist
Suite 101
Professional Office Building
2018 Brookwood Medical Center
Birmingham, AL 35209

C90-045-02
Michael McCarthy, MD
1130 U.S. Highway 202
Raritan, NJ 08869

C90-045-03
Arthur Eskew, MD
President, Clinical Research Associates, Inc.
Suite 612
186 Lincoln Street
Boston, MA 02111

C90-045-04
Zev Munk, MD
Allergy and Clinical Immunology
902 Frostwood No. 223
Houston, TX 77024

C90-045-06
Robert Chiulli, MD
Anthony D. Puopolo, MD
High Street Medical Center
270 High Street
Clinton, MA 01510

C90-045-07
Robert E. McCabe, MD
VA Medical Center
150 Muir Road
Martinez, CA 94553

C90-045-09
Sanford Chodosh, MD
Chief of Pulmonary Medicine
VA Outpatient Clinic
Pulmonary Research-111C
251 Causeway Street
Boston, MA 02114

C90-045-10
Peter Costantini, Pharm.D, DO
c/o Jersey Research Foundation, Inc.
2021 New Road
Suite 19
Linwood, NJ 08221

Investigators designated C90-045-05 and C90-045-08 did not enroll any patients.

C90-045-11
C. Andrew DeAbate, MD
Medical Research Center
3655 Veterans Memorial Boulevard
Metairie, LA 70002

C90-045-12
John Gezon, MD
1388 Arlington Drive
Salt Lake City, UT 84103

C90-045-13
Kirk Jacobson, MD
Oregon Research Group
1200 Hilyard Street
Suite 200
Eugene, OR 97401

C90-045-14
Richard B. Berry, MD
VA Medical Center
Pulmonary Section (111P)
Long Beach, CA 90822

C90-045-15
Thomas Nolen, MD
Columbiana Clinic
200 Mildred Street
Columbiana, AL 35051

C90-045-16
Felix A. Sarubbi, MD
Internal Medicine
PO Box 70622 ETSU
Quillen College of Medicine
Johnson City, TN 37614

C90-045-17
Fredric Jackson, MD
Three Tree Medical Arts Building
16259 Sylvester Road SW
Suite 401
Seattle, WA 98166

C90-045-18
Richard Finley, MD
Department of Infectious Disease
University Hospital
2500 N. State Street
Jackson, MS 39216

C90-045-19
Michael A. Mcadoo, MD
6041 Telcom Drive
Milan, TN 38358

C90-045-20
David Ginsberg, DO
Harleysville Medical Associates
176 Main Street
Harleysville, PA 19438

C90-045-21
George Bensch, MD
4628 Georgetown Place
Stockton, CA 95207

C90-045-22
Thomas Littlejohn, MD
Piedmont Research Associates
1901 S. Hawthorne Road
Suite 306
Winston-Salem, NC 27107

C90-045-23
James D. Blake, MD
Hoover Family Practice
1575 Montgomery Highway
Birmingham, AL 35216

C90-045-24
Melvin D. Russell, MD
Community Medical Arts Center
1013 Friendship Road
Tallassee, AL 36078

C90-045-25
James M. Abroms, MD
1817 Oxmoor Road
Homewood, AL 35209

A total of 373 patients were enrolled by 23 investigators as listed below. Minor differences in the evaluable number of patients as determined by the applicant and the Medical Officer are highlighted.

Table Distribution of Patient Population (Study No. C90-045)

	Number of Patients					
	Intent-to-Treat		Clinical Efficacy		Microbiologic Efficacy	
Investigator/ Center	Ceftibuten 400 mg QD	Cefixime 400 mg QD	Ceftibuten 400 mg QD	Cefixime 400 mg QD	Ceftibuten 400 mg QD	Cefixime 400 mg QD
			SP/MO*	SP/MO	SP/MO	SP/MO
McLean/01	21	21	16/16	17/19	3/3	0/0
McCarthy/02	2	1	2/2	1/1	0/0	0/0
Eskew/03	2	2	2/2	1/1	1/1	1/1
Munk/04	6	8	6/6	7/7	0/0	0/0
Chiulli/06	9	10	7/7	8/8	2/2	3/3
McCabe/07	22	22	15/16	20/19	4/4	5/5
Chodosh/09	12	12	12/12	9/9	8/8	8/8
Costantini/10	3	3	3/3	3/3	1/1	0/0
DeAbate/11	41	40	34/39	36/37	10/14	14/14
Gezon/12	4	5	2/3	1/4	1/2	0/1
Jacobson/13	5	4	4/4	4/4	2/2	2/2
Berry/14	6	7	5/5	7/7	3/3	0/0
Nolen/15	11	11	9/10	9/9	3/3	2/3
Sarubbi/16	12	11	9/9	10/11	8/8	4/5
Jackson/17	6	6	2/3	3/4	1/2	1/1
Finley/18	5	5	5/5	4/4	0/0	0/0
McAdoo/19	7	7	6/7	5/5	2/2	0/0
Ginsberg/20	3	0	2/2	0/0	1/1	0/0
Bensch/21	2	1	2/2	1/1	1/1	0/0
Littlejohn/22	1	1	1/1	1/1	1/1	1/1
Blake/23	1	0	0/1	0/0	0/0	0/0
Russell/24	5	5	4/4	5/5	0/0	0/0
Abroms/25	2	3	2/2	3/3	0/0	0/0
Total	188	185	150/161	155/167	52/58	41/44

* SP = Schering-Plough; number of patients in the specific efficacy population according to the applicant.
MO = Medical Officer; number of patients in the specific efficacy population according to the MO.

Number of Patients Excluded From Patient Populations and Reasons for Exclusion
(Differences between the applicant and medical officer are highlighted.)

Reason for Exclusion	Ceftibuten 400 mg QD (N=188) SP/MO	Cefixime 400 mg QD (N=185) SP/MO	Total (N=373) SP/MO
Excluded from Safety Population	**3/3**	**0/0**	**3/3**
Immediate drop-out	2/2	0/0	2/2
Never received medication	1/1	0/0	1/1
Excluded from Clinical Efficacy Population Included in Safety Population	**35/24**	**31/24**	**66/48**
Did not meet entrance criteria	17/7	11/5	28/12
Insufficient duration of disease (< 2 years)	4/2	2/0	6/2
Unacceptable Baseline laboratory value	9/1	3/0	12/1
Unacceptable Baseline X-ray	2/2	3/2	5/4
Unsatisfactory Baseline Gram Stain	2/2	3/3	5/5
Improper visit spacing	3/3	3/3	6/6
Insufficient efficacy data	7/6	12/10	19/16
Drop-out/Adverse event	5/3	10/8	15/11
No further exclusion reason	2/3	2/2	4/5
Other antibiotic within 72 hrs of study entry	1/1	1/1	2/2
Misrandomized	2/2	0/0	2/2
Noncompliance w/dosing regimen	1/1	0/0	1/1
Unacceptable concomitant therapy	4/4	4/5	8/9
Excluded from Microbiologic Efficacy Population Included in Clinical Efficacy Population	**98/103**	**114/118**	**212/221**
Did not meet microbiologic criteria	98/103	114/118	212/221
Missing zone/source	2/2	1/1	3/3
No pathogen isolated pretherapy	95/101	112/117	207/218
Pathogen not susceptible	0/0	1/0	1/0
Pathogen resistant Schering Rx	1/0	0/0	1/0

Clinical Response of CEFTIBUTEN Patients *Reclassified by the Medical Officer*

PATIENT	SP VALIDITY	SP OVERALL CLINICAL ASSESSMENT	MO VALIDITY	MO CLINICAL ASSESSMENT
	SAFETY	RELAPSE; BUT INSUFFICIENT DURATION OF DISEASE	CLIN/MICRO	RELAPSE: SYMPTOMS AECB ≥ 2 YEARS
	CLIN/MICRO	IMPROVEMENT	SAFETY	UNASSESSABLE: INADEQUATE INFO
	SAFETY	CURE; UNACCEPTABLE BASELINE LAB	CLINICAL	CURE: LAB UNKNOWN AT STUDY ENTRY
	CLINICAL	CURE; PATHOGEN RESISTANT SCHERING RX	CLIN/MICRO	CURE: INVESTIGATOR KEPT ON DRUG
	SAFETY	CURE; UNACCEPTABLE BASELINE LAB	CLINICAL	CURE: LAB UNKNOWN AT STUDY ENTRY
	SAFETY	CURE; UNACCEPTABLE BASELINE LAB	CLINICAL	CURE: LAB UNKNOWN AT STUDY ENTRY
	SAFETY	CURE; UNACCEPTABLE BASELINE LAB	CLIN/MICRO	CURE: LAB UNKNOWN AT STUDY ENTRY
	SAFETY	CURE; UNACCEPTABLE BASELINE LAB	CLIN/MICRO	CURE: LAB UNKNOWN AT STUDY ENTRY
	SAFETY	CURE; UNACCEPTABLE BASELINE LAB	CLIN/MICRO	CURE: LAB UNKNOWN AT STUDY ENTRY
	SAFETY	NOT ASSESSED;UNACCEPTABLE BASELINE LAB	CLIN/MICRO	FAILURE: LAB UNKNOWN AT STUDY ENTRY
	SAFETY	IMPROVEMENT;INSUFFICIENT DURATION OF DISEASE	CLINICAL	IMPROVEMENT;SYMPTOMS AECB ≥ 2 YEARS
	SAFETY	CURE; UNACCEPTABLE BASELINE LAB	CLIN/MICRO	CURE: LAB UNKNOWN AT STUDY ENTRY
	SAFETY	NOT ASSESSED;DROP-OUT/ADVERSE EVENT	CLINICAL	FAILURE
	SAFETY	NOT ASSESSED;DROP-OUT/ADVERSE EVENT	CLINICAL	FAILURE
	CLINICAL	IMPROVEMENT	CLINICAL	FAILURE
	CLINICAL	CURE	CLINICAL	FAILURE
	CLINICAL	CURE	CLINICAL	FAILURE

Clinical Response of CEFIXIME Patients *Reclassified by the Medical Officer*

PATIENT	SP VALIDITY	SP OVERALL CLINICAL ASSESSMENT	MO VALIDITY	MO CLINICAL ASSESSMENT
	SAFETY	NOT ASSESSED;INSUFFICIENT DURATION OF DISEASE	CLINICAL	FAILURE: SYMPTOMS AECB ≥ 2 YEARS
	SAFETY	NOT ASSESSED;DROP-OUT/ADVERSE EVENT	CLINICAL	FAILURE
	CLINICAL	CURE	SAFETY	CURE-STEROID STARTED 72 HR PRIOR
	SAFETY	CURE; UNACCEPTABLE BASELINE LAB	CLINICAL	CURE;LAB UNKNOWN AT STUDY ENTRY
	SAFETY	CURE; INSUFFICIENT DURATION OF DISEASE	CLIN/MICRO	CURE: SYMPTOMS AECB ≥ 2 YEARS
	SAFETY	CURE; UNACCEPTABLE BASELINE LAB	CLINICAL	CURE;LAB UNKNOWN AT STUDY ENTRY
	SAFETY	IMPROVEMENT; UNACCEPTABLE BASELINE LAB	CLINICAL	IMPROVED;LAB UNKNOWN AT STUDY ENTRY
	CLINICAL	CURE; PATHOGEN NOT SUSCEPTIBLE	CLIN/MICRO	CURE: INVESTIGATOR KEPT ON DRUG
	SAFETY	NOT ASSESSED; DROP-OUT/ADVERSE EVENT	CLIN/MICRO	FAILURE
	SAFETY	IMPROVEMENT; UNACCEPTABLE BASELINE X-RAY	CLINICAL	IMPROVEMENT: CXR WITHOUT PNEUMONIA
	CLINICAL	IMPROVEMENT	CLINICAL	FAILURE;NOT IMPROVED BY STUDY DAY 6

Demographic Data and Disease Characteristics

Baseline demographic data of the Medical Officer's clinical efficacy population appear below. The applicant's demographic summary table was very similar, and for the sake of brevity, is not reproduced here.

Demographic Data for the Clinical Efficacy Population

	Ceftibuten	Cefixime
Number of Patients	161	162
Sex		
Male	100 (62%)	102 (63%)
Female	61 (38%)	60 (37%)
Race		
White	130 (81%)	139 (86%)
Black	30 (19%)	16 (10%)
Other	1 (<1%)	7 (4%)
Age (yrs)		
Mean	55	55
Median	57	55
Range (min-max)		
Weight (kg)		
Mean	78	79
Median	77	78
Range (min-max)		
Summary of Smoking History		
Current	79 (49%)	95 (59%)
Former	61 (38%)	48 (30%)
Never	21 (13%)	19 (12%)
Years Smoked Mean	30	31
Median	30	30
Range		
CXR on Entry		
Abnormality/Chronic*	71	80
Normal	90	82

**Medical Officer's Comment: The majority of chronic changes were read as "COPD", "emphysema", "increased interstitial markings", "fibrosis", and "chronic bronchitis".*

CLINICAL EFFICACY RESULTS

APPLICANT'S ASSESSMENT of Clinical Response for Patients in the Clinical Efficacy Population at Visit 3: End-of-Treatment Visit

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=150)	Cefixime 400 mg QD (N=155)
Cure/Improvement	125 (83%)[§]	136 (88%)
Cure	106 (71%)	116 (75%)
Improvement	19 (13%)	20 (13%)
Failure	25 (17%)	19 (12%)

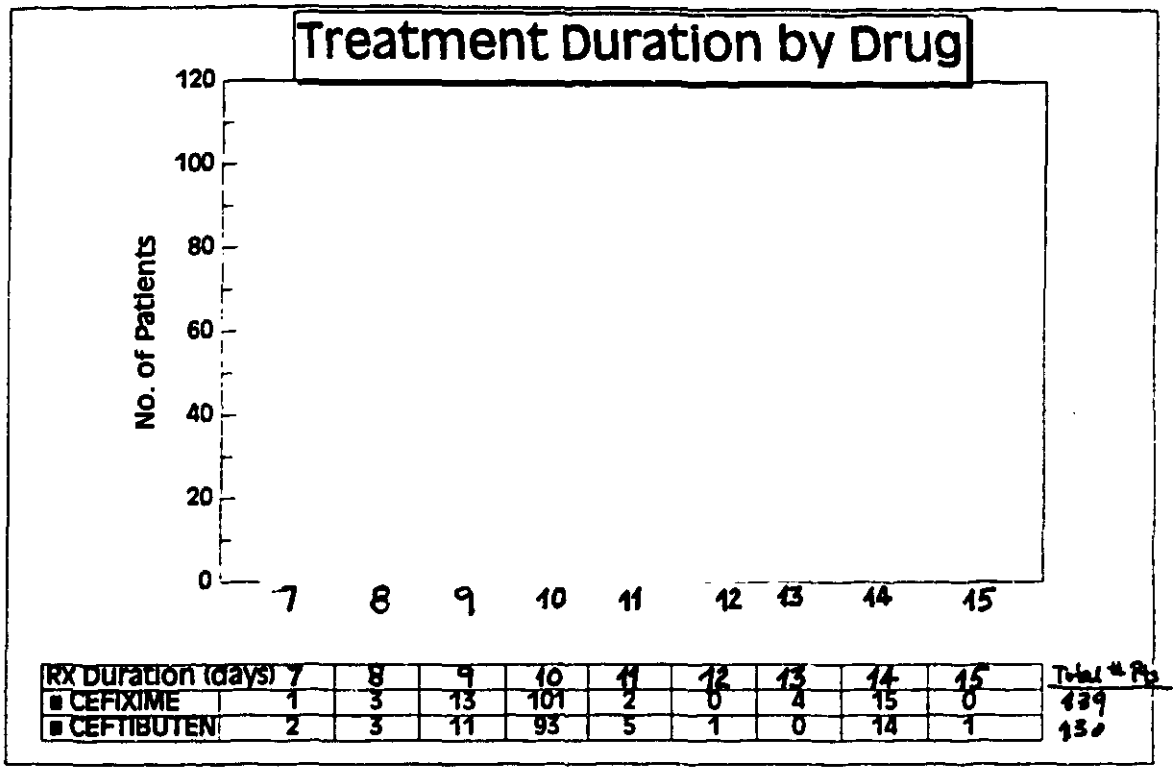
* Clinical response sorted by treatment and clinical response sorted by investigator at Visit 3 (end-of-treatment visit) for the clinical efficacy population are provided in Appendices C-5 and C-6, respectively.
§ Percentages may not add up to 100% due to rounding of values.

MEDICAL OFFICER'S ASSESSMENT of Clinical Response for Patients in the Clinical Efficacy Population at Visit 3: End-of-Treatment Visit

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=161)	Cefixime 400 mg QD (N=162)
Cure/Improvement	130 (81%)*	139 (86%)
Cure	112 (70%)	114 (70%)
Improvement	18 (11%)	25 (15%)
Failure	31 (19%)	23 (14%)

* Percentages may not add up to 100% due to rounding of values.

Medical Officer's Comment: It should be noted that no evaluable patient in the clinical efficacy population with a successful outcome (a total of 130 ceftibuten patients and 139 cefixime patients, according to the reviewer) at the end of treatment was treated with less than a week of either study medication. While the protocol stipulated a treatment duration range of 5-14 days, the graph below illustrates that the mean number of days of treatment with either drug was 10. (Similar results are obtained with the applicant's evaluable dataset.)



RX Duration (days)	7	8	9	10	11	12	13	14	15	Total # Pts
CEFIXIME	1	3	13	101	2	0	4	15	0	139
CEFTIBUTEN	2	3	11	93	5	1	0	14	1	130

Medical Officer's Comment: *The majority of patients with a successful outcome by visit 3, in either study arm, received 10 days of drug treatment. The population used to generate this graph is the reviewer's clinical efficacy population at visit 3 (excluding failures).*

APPLICANT'S ASSESSMENT of Clinical Response for Patients in the Clinical Efficacy Population at Visit 4: "Extended" Follow-up Visit

	Number (%) of Patients[§]	
	Ceftibuten 400 mg QD (N=150)	Cefixime 400 mg QD (N=155)
Sustained Cure/Improvement	117/125 (94%)	128/136 (94%)
Sustained Cure	101/125 (81%)	112/136 (82%)
Sustained Improvement	16/125 (13%)	16/136 (12%)
Relapse	8/125 (6%)	8/136 (6%)
Unassessable	25	19
95% Confidence Interval	(-0.065, 0.065)	

* Clinical response sorted by treatment and clinical response sorted by investigator at Visit 4 (extended follow-up visit) for the clinical efficacy population can be found in Appendices C-7 and C-8, respectively.
§ Percentages are based on the number of patients with a response at Visit 4 (extended follow-up visit).

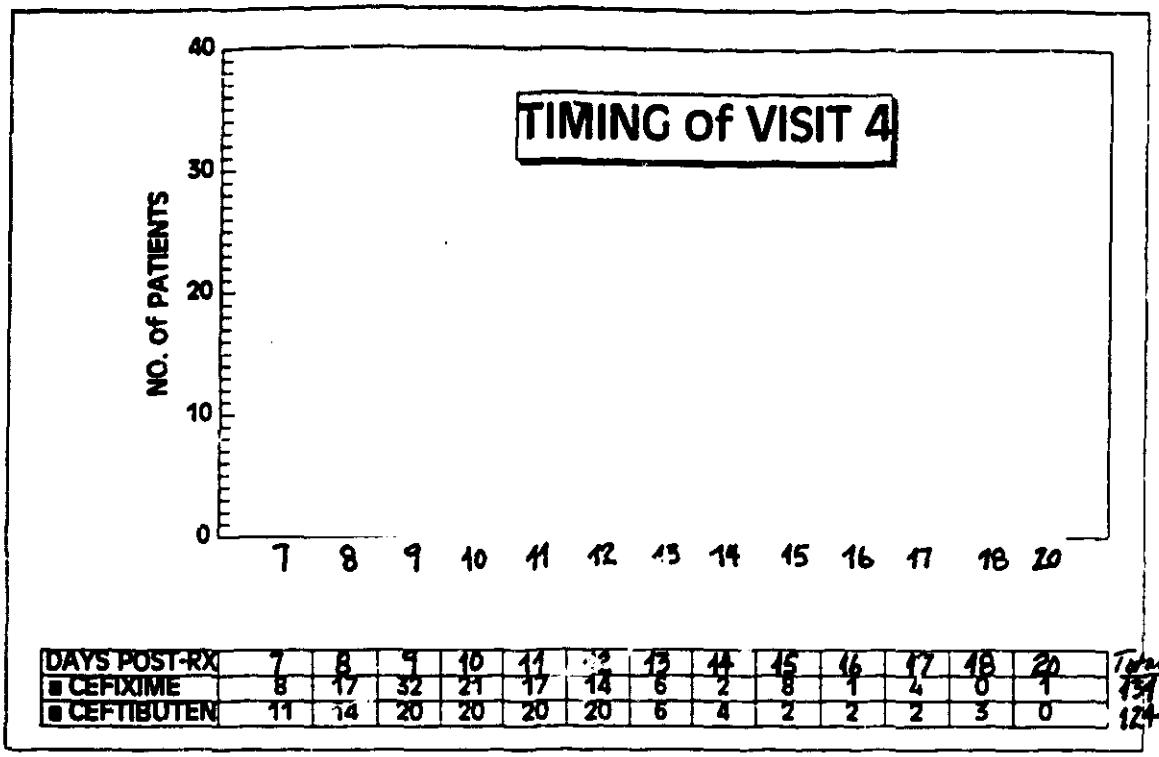
Medical Officer's Comment: *In the above table showing the applicant's assessment at Visit 4 (on average, 11 days post-therapy), the applicant has not carried forward patients who were failures at the end of treatment. Instead, these patients have been labeled "unassessable". The MO presents her results below, carrying forward those patients who were failures at the end of treatment (V3) as "failures" at V4, for the overall evaluation of efficacy.*

MEDICAL OFFICER'S ASSESSMENT of Clinical Response for Patients in the Clinical Efficacy Population at Visit 4: Test-of-Cure

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=161)	Cefixime 400 mg QD (N=162)
Cure/Improvement	124 (77%)	131 (81%)
Cure	109 (68%)	115 (71%)
Improvement	15 (9%)	16 (10%)
Relapse	6 (4%)	8 (5%)
Failure	31 (19%)	23 (14%)
95% Confidence Interval*	(-0.135, 0.055)	

*95% Confidence Interval around the difference in successful outcomes.

Medical Officer's Comment: *For patients in the clinical efficacy population, clinical response is similar for the two treatment arms. More failures are seen with ceftibuten, but the $CI_{95\%}$ is met. It is also of interest to note the timing of Visit 4 for patients in the clinical efficacy population with a successful outcome according to the reviewer.* ***(See the graph on the following page.)***



DAYS POST-RX	7	8	9	10	11	12	13	14	15	16	17	18	20	Total # Pts
■ CEFIXIME	8	17	32	21	17	14	6	2	8	1	4	0	1	131
■ CEFTIBUTEN	11	14	20	20	20	20	6	4	2	2	2	3	0	124

Medical Officer's Comment: *As illustrated in the graph above, Visit 4 took place, on average, 11 days after the last dose of either study drug [range 7-20 days post-therapy, median 11 days]. Thus, the MO considered the "test-of-cure" visit 4 (unless the patient failed earlier). The population used to generate this graph was the reviewer's clinical efficacy population at visit 4 (excluding failures).*

APPLICANT'S ASSESSMENT of Clinical Response for Patients in the Microbiologic Efficacy Population at Visit 3: End-of-Treatment Visit

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=52)	Cefixime 400 mg QD (N=41)
Cure/Improvement	38 (73%)[§]	38 (93%)
Cure	33 (63%)	31 (76%)
Improvement	5 (10%)	7 (17%)
Failure	14 (27%)	3 (7%)
95% Confidence Interval	(-0.345, -0.026)	

* Clinical response by sorted treatment and clinical response sorted by investigator at Visit 3 (end-of-treatment visit) for the microbiologic efficacy population are provided in Appendices C-15 and C-16, respectively.

§ Percentage may not add up to 100% due to rounding of values.

MEDICAL OFFICER'S ASSESSMENT of Clinical Response for Patients in the Microbiologic Efficacy Population at Visit 3: End-of-Treatment Visit

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=58)	Cefixime 400 mg QD (N=44)
Cure/Improvement	43 (74%)	40 (91%)
Cure	39 (67%)	32 (73%)
Improvement	4 (7%)	8 (18%)
Failure	15 (26%)	4 (9%)
95% Confidence Interval	(-0.331, -0.009)	

Medical Officer's Comment: *It is of great interest that the disparity in successful clinical outcome between the two treatment arms is seen in the microbiological efficacy population, that subset of the clinical efficacy population who have definitive acute bacterial exacerbations of chronic bronchitis. Why ceftibuten performed less-well in this population is better understood with analysis of the microbiologic response by pathogen which* *begins on page 34.*

APPLICANT'S ASSESSMENT of Clinical Response for Patients in the Microbiologic Efficacy Population at Visit 4: "Extended" Follow-up

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=52)§	Cefixime 400 mg QD (N=41)§
Sustained Cure/Improvement	33/38 (87%)	32/38 (85%)¶
Sustained Cure	29/38 (76%)	28/38 (74%)
Sustained Improvement	4/38 (11%)	4/38 (11%)
Relapse	5/38 (13%)	6/38 (16%)
Unassessable	14	3
95% Confidence Interval	(-0.144, 0.184)	

* Clinical response sorted by treatment and clinical response sorted by investigator at Visit 4 (extended follow-up visit) for the microbiologic efficacy population can be found in Appendices C-17 and C-18, respectively.

§ Percentages are based on the number of patients with a response at Visit 4 (extended follow-up visit).

¶ Percentages may not add up to 100% due to rounding of values.

Medical Officer's Comment: *In the above table showing the applicant's clinical response for patients in the microbiologic efficacy population at Visit 4 (on average, 11 days post-therapy for each study drug), the applicant has again not carried forward patients who were failures at the end of treatment. Instead, these patients have been labeled "unassessable". The MO presents her results below, carrying forward end-of-treatment failures. Clearly, when failures are added to the relapses at Visit 4, the* $CI_{95\%}$ *is not met.*

MEDICAL OFFICER'S ASSESSMENT of Clinical Response for Patients in the Microbiologic Efficacy Population at Visit 4: "Test of Cure" Visit

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=58)§	Cefixime 400 mg QD (N=44)§
Cure/Improvement	39 (67%)	34 (77%)
Cure	36 (62%)	30 (68%)
Improvement	3 (5%)	4 (9%)
Relapse	4 (7%)	6 (14%)
Failure	15 (26%)	4 (9%)
95% Confidence Interval	(-0.293, 0.093)	

Applicant's Assessment of Overall Microbiologic Response* for Patients in the Microbiologic Efficacy Population

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=52)	Cefixime 400 mg QD (N=41)
Overall Eradication[1]	40 (77%)	34 (83%)
Eradication	40 (77%)	32 (78%)
(w colonization)	0	2 (5%)
Persistence	9 (17%)	3 (7%)
Relapse	3 (6%)	4 (10%)
95% Confidence Interval#	(-0.220, 0.125)	

* Overall microbiologic assessment is derived from microbiologic response evaluations observed at Visit 3 (end-of-treatment visit) and/or Visit 4 (extended follow-up visit).
§ Overall microbiologic assessment sorted by treatment and overall microbiologic assessment sorted by investigator are provided in Appendices C-20 and C-21, respectively.
¶ Includes eradication or eradication with colonization.
\# Confidence interval for the difference in eradication rates between the two treatment groups.

MEDICAL OFFICER'S ASSESSMENT of Microbiologic Response for Patients in the Microbiologic Efficacy Population at Visit 4: "Test of Cure" Visit

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=58)*	Cefixime 400 mg QD (N=44)*
Eradication [documented/presumed]	46 (71%) [3/43]	38 (82%) [7/31]
Persistence	19 (29%)	8 (18%)
Persistence by Visit 3 [documented/presumed]	15 (23%) [5/10]	5 (13%) [3/2]
Persistence by Visit 4 [documented/presumed]	4 (6%) [1/3]	3 (9%) [2/1]
95% Confidence Interval	(-0.285, 0.065)	

* Six ceftibuten and two cefixime patients had multiple pathogens at entry, sometimes with a mixed micro response (e.g., one eradicated isolate, one persistent) by Visit 4. Percentages are calculated on the basis of a total N=65 for ceftibuten, N=46 for cefixime, though there are technically only 58 ceftibuten patients and 44 cefixime patients in the microbiologic efficacy patient population.

Medical Officer's Comment: The reason for the applicant's lower number of patients with persistent pathogens is illustrated by patient C9004507005. At 1-day post-treatment, the patient was assessed by the investigator as a clinical failure. On that same day, within 24 hours after the last dose of ceftibuten, a sputum culture was taken and grew no pathogen. The patient was prescribed Septra DS for 10 days, scored as a clinical failure, but assessed as a microbiologic success with eradication of Moraxella catarrhalis. The MO considers this approach invalid for patients whose cultures were taken 1 day after finishing study drug; the MO assessed such patients as clinical failures with presumed microbiologic persistence. Since many patients did not have a V4 sputum culture taken, and the V3 culture was often taken just 1-1.5 days after the last dose of drug, the MO's microbiologic responses closely parallel the clinical responses in the micro efficacy population. This is in contrast to the applicant's analysis.

MEDICAL OFFICER'S ASSESSMENT OF
Microbiologic Response by Pathogen for the Microbiologic Efficacy Population
Treatment Arm- Cefibuten

Pathogen Total Isolates	Overall Eradication Rate	No. of Isolates/ -lactamase Status	Micro Assessment* (% Eradication)
		18 -lac (-)	15 E (83%)
			2 Pv3
			1 Pv4
[redacted]	[redacted]		5 E (83%)
		6 -lac (+)	1 Pv3
			3 E (43%)
		7 not tested	2 Pv3
			2 Pv4
		1 -lac (-)	1 E (100%)
[redacted]	[redacted]		9 E (60%)
		15 -lac (+)	5 Pv3
			1 Pv4
		2 not tested	1 E (50%)
			1 Pv3
[redacted]	[redacted]	—	12 E (75%)
16 isolates		—	4 Pv3

*Key E=Eradication Pv3=Persistence at visit 3 Pv4=Persistence at visit 4

MEDICAL OFFICER'S ASSESSMENT OF
Microbiologic Response by Pathogen for the Microbiologic Efficacy Population
Treatment Arm- Cefixime

Pathogen Total Isolates	Overall Eradication Rate	No. of Isolates/ -lactamase Status	Micro Assessment* (% Eradication)
		12 -lac (-)	11 E (92%)
			0 Pv3
			1Pv4
[redacted]	[redacted]		2 E (40%)
		5 -lac (+)	1 Pv3
			2 Pv4
		3 Not Tested	3 E (100%)
		3 -lac (-)	3 E (100%)
[redacted]	[redacted]		
		9 -lac (+)	9 E (100%)
		3 Not tested	3 E (100%)
[redacted]		---	7 E (64%)
		---	4 Pv3

*Key E=Eradication Pv3=Persistence at visit 3 Pv4=Persistence at visit 4

Applicant's Assessment of Microbiologic Response by Pathogen at Visit 3 (0-6 Day End-of-Treatment Visit)

Prior to treatment, a total of 100 valid Baseline pathogens (i.e., Haemophilus influenzae, *Moraxella [Branhamella] catarrhalis* or *Streptococcus pneumoniae*) were isolated from 93[4] patients. Fifty-eight of these valid pathogens were isolated at Baseline from 52 ceftibuten patients. The remaining 42 valid pathogens were isolated at Baseline from 41 cefixime patients.

Medical Officer's Comment: One must bear in mind the timing of cultures taken at visit 3 for patients in the applicant's microbiologic efficacy population who had a successful clinical outcome (cure or improvement, totalling 38 ceftibuten and 38 cefixime patients as noted on page 31). As shown below, only 7 total patients had a visit 3 culture taken beyond 3 days post-therapy.

Visit 3 Culture Taken (Days Post-Therapy)	No. Ceftibuten Patients	No. Cefixime Patients
0	1	3
1	19	19
2	6	9
3	8	4
4	2	3
5	2	0
	38	38

According to the applicant, at Visit 3, the two treatment groups were similar with regard to total[5] eradication rates for all pathogens. Total eradication of all pathogens was 81% (47/58) in the ceftibuten group compared with 86% (36/42) of patients in the cefixime group. (See applicant's Table 28 immediately below.) With regard to individual isolates, total[6] eradication of both *Haemophilus influenzae* and *Streptococcus pneumoniae* was similar for both treatment groups. Total eradication of *Haemophilus influenzae* was 89% (24/27) for the ceftibuten group and 85% (17/20) for the cefixime group. For *Streptococcus pneumoniae*, total eradication was 79% (11/14) in the ceftibuten group compared with 78% (7/9) in the cefixime group. For *Moraxella catarrhalis*, the total eradication rate was unexpectedly lower in the ceftibuten group (71% [12/17]) than in the cefixime group (92% [12/13]).

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[4] More than one pathogen may have been isolated from a single patient.

[5] Includes total ("presumed" and "documented" microbiologic responses) for all pathogens.

[6] Includes both "presumed" and "documented" microbiologic response for individual pathogens.

Table 28. APPLICANT'S Microbiologic Response for Individual Isolates: Eradication Rates For Microbiologic Efficacy Population at Visit 3: End-of-Treatment Visit (Study No. C90-045).*

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefixime 400 mg QD
Haemophilus influenzae		
Total§	24/27 (89%)	17/20 (85%)
Presumed	20/20 (100%)	13/14 (93%)
Documented	4/7 (57%)	4/6 (67%)
Moraxella (Branhamella) catarrhalis		
Total§	12/17 (71%)	12/13 (92%)
Presumed	9/10 (90%)	9/9 (100%)
Documented	3/7 (43%)	3/4 (75%)
Streptococcus pneumoniae		
Total§	11/14 (79%)	7/9 (78%)
Presumed	7/8 (88%)	5/5 (100%)
Documented	4/6 (67%)	2/4 (50%)
Grand Total¶	47/58 (81%)	36/42 (86%)
Presumed	36/38 (95%)	27/28 (96%)
Documented	11/20 (55%)	9/14 (64%)

* Microbiologic response by pathogen at Visit 3 (end-of-treatment visit) for the microbiologic efficacy population is provided in Appendix C-26.

§ Includes both "presumed" and "documented" microbiologic response at Visit 3 (end-of-treatment visit).

¶ Includes total ("presumed" and "documented") microbiologic responses for all pathogens.

Applicant's Assessment of Microbiologic Response by Pathogen at Visit 4 (7-21 Day End-of-Treatment Visit)

At Visit 4 (7-21 day extended follow-up visit), microbiologic response results were available for a total of 83 valid pathogens isolated at Baseline from 76 patients[7] (44 pathogens were isolated from 38 patients in the ceftibuten group and 39 pathogens were isolated from 38 patients in the cefixime group).

> *Medical Officer's Comment: The reader is reminded that the applicant did not carry forward the assessments of "persistence" at Visit 3.*

At Visit 4, the two treatment groups were similar with regard to preventing relapse for all pathogens. The total[8] relapse rate for all pathogens was 7% (3/44) for the ceftibuten group compared with 13% (5/39) for cefixime group. In the ceftibuten group, relapse occurred with two *Haemophilus influenzae* and one *Moraxella catarrhalis* isolate. Relapse was observed in the cefixime group with two *Haemophilus influenzae* isolates and two *Streptococcus pneumoniae* isolates.

In patients who had continued eradication of their pathogen, total[8] eradication of all pathogens was 93% (41/44) in the ceftibuten group compared with 87% (34/39) in the cefixime group. With regard to individual isolates, ceftibuten was more effective than cefixime in the eradication of *Streptococcus pneumoniae*; 100% (10/10) and 71% (5/7) in the ceftibuten and cefixime groups, respectively. Total[9] eradication of *Haemophilus influenzae* and *Moraxella catarrhalis* was similar for both treatment groups. Total eradication of *Haemophilus influenzae* was 91% (21/23) for the ceftibuten group and 84% (16/19) for the cefixime group. Total eradication of *Moraxella catarrhalis* was 91% (10/11) and 100% (13/13) for the ceftibuten and cefixime groups, respectively.

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[7] More than one pathogen may have been isolated from a single patient.

[8] Includes total ("presumed" and "documented") microbiologic response for all pathogens.

[9] Includes both "presumed" and "documented" microbiologic response for individual isolates.

Table 29. APPLICANT'S Microbiologic Response for Individual Isolates: Eradication Rates for Microbiologic Efficacy Population at Visit 4: Extended Follow-up Visit (Study No. C90-045).*

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefixime 400 mg QD
Haemophilus influenzae		
Total¶	21/23 (91%)	16/19 (84%)
Presumed	19/21 (91%)	13/14 (93%)
Documented	2/2 (100%)	3/5 (60%)
Moraxella (Branhamella) catarrhalis		
Total¶	10/11 (91%)	13/13 (100%)
Presumed	10/10 (100%)	9/9 (100%)
Documented	0/1 (0%)	4/4 (100%)
Streptococcus pneumoniae		
Total¶	10/10 (100%)	5/7 (71%)
Presumed	9/9 (100%)	4/4 (100%)
Documented	1/1 (100%)	1/3 (33%)
Grand Total¶	41/44 (93%)	34/39 (87%)
Presumed	38/40 (95%)	26/27 (96%)
Documented	3/4 (75%)	8/12 (67%)

* Microbiologic response by pathogen at Visit 4 (extended follow-up visit) for the microbiologic efficacy population is provided in Appendix C-27.

§ Includes both "presumed" and "documented" microbiologic response at Visit 4 (extended follow-up visit).

¶ Includes total ("presumed" and "documented") microbiologic responses for all pathogens.

***Medical Officer's Comment:** If one looks at the data in the micro efficacy population, excluding those patients with Moraxella catarrhalis isolated pre-therapy, the following results are obtained:*

MEDICAL OFFICER'S ASSESSMENT of Clinical Response for Patients in the Microbiologic Efficacy Population at Visit 4:Test-of-Cure Visit

	Number (%) of Patients	
	Ceftibuten 400 mg QD (N=40)	Cefixime 400 mg QD (N=29)
Cure/Improvement	28 (70%)	20 (69%)
Cure	28 (70%)	17 (59%)
Improvement	0	3 (10%)
Failure	9 (23%)	4 (14%)
Relapse	3 (7%)	5 (17%)
95% Confidence Interval	(-0.240, 0.260)	

Similar clinical response in the microbiologic efficacy population is obtained, then, in both treatment arms when patients with M. catarrhalis are excluded. With this exclusion, however, the number of evaluable patients/pathogens in the microbio ogic efficacy population becomes much smaller, and the 95% confidence interval around the difference in successful outcomes is not met. If one looks at the in vitro data for ceftibuten submitted to the original NDA. specifically the MIC_{90} values for Haemophilus influenzae, Streptococcus pneumoniae and *Moraxella catarrhalis, together with the human pharmacokinetic data, one might predict relative eradication rates that match the pattern found in this study.*

In the proposed package insert, the applicant writes that the average plasma concentration in adults after oral administration of a 400 mg capsule is 3.2 mcg/ mL at 8 hours post dose. Furthermore, studies conducted in patients undergoing bronchoscopy and lung surgery demonstrated penetration (approximately 50% of the plasma concentration) into respiratory fluids and pulmonary tissue. Theoretically, then, patients with B-lactamase positive strains of M. catarrhalis (MIC_{90} 4 mcg/ mL), as well as certain strains of Streptococcus pneumoniae (MIC_{90}, 2-8), might not have adequate blood/tissue levels through two-thirds of the dosing interval.

In Dr. Brad Leissa's review of the original NDA, the number of isolates in the domestic trial (C88044) is small. In this study, a total of 5 Moraxella catarrhalis isolates were cultured. (See Table 35 reproduced below). For B-lactamase producing strains of M. catarrhalis, 2/4 (50%) were eradicated. There were only 3 S. pneumoniae isolates, and all 3 were eradicated. For H. influenzae, 10/13 (77%) B-lactamase negative strains were eradicated. Trends are difficult to discern and firm conclusions impossible to draw with these small numbers. If one combines the microbiologic data across the domestic and international studies reviewed by Dr. Leissa, together with the domestic study C90045 reviewed here, the following eradication rates are obtained:

Study No./ *Isolate* (β-lac status)		C88044	I88111, I88217, I88324	C90045	TOTAL
M catarrhalis	(-)*	1/1	3/3	~~1/2~~ 2/3	~~9/16~~ (86%)
	(+)	2/4	1/2	9/15 (60%)	12/21 (57%)
H. influenzae	(-)*	10/13 (77%)	12/17 (71%)	18/25 (72%)	40/55 (73%)
	(+)	0/1	0	5/6 (83%)	5/7 (71%)
S. pneumoniae		3/3	8/16 (50%)	12/16 (75%)	23/35 (66%)

*Includes isolates not tested for β-lactamase activity.

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CEFTIBUTEN

Study No./ *Isolate* (-lac status)		C88044	I88111, I88217, I88324	C90045	TOTAL
M catarrhalis	(-)*	1/1	3/3	2/3	6/7 (86%)
	(+)	2/4	1/2	9/15	12/21 (57%)
					18/28 (64%)
H. influenzae	(-)*	10/13	12/17	18/25	40/55 (73%)
	(+)	0/1	0	5/6	5/7 (71%)
					45/62 (73%)
S. pneumoniae		3/3	3/16	12/16	23/35 (66%)

*Includes isolates not tested for -lactamase activity.

CONTROL DRUGS

Study No./ Control *Isolate* (-lac status)		C88044/ Ceclor	I88111, I88217, I88324/ Ceclor	C90045/ Cefixime	TOTAL
M catarrhalis	(-)*	1/1	1/2	6/6	8/9
	(+)	1/1	-	9/9	10/10
					18/19 (95%)
H. influenzae	(-)*	3/6	7/10	14/15	24/31
	(+)	0	0	2/5	2/5
					26/36 (72%)
S. pneumoniae		4/4	3/5	7/11	14/20 (70%)

***IN VITRO* CEFTIBUTEN SUSCEPTIBILITIES BY ASCENDING MIC**
(According to applicant)

	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
GRAM NEGATIVE		
Proteus mirabilis	≤0.015	0.03
Proteus vulgaris	0.03	0.03
Providencia	<0.03	0.03
Neisseria	<0.06	0.06
Haemophilus influenzae		
β-lactamase (-)	<0.06	0.06
β-lactamase (+)	<0.06	0.06
Amp-R; β-lactamase (-) (7 strains)	3.84	7.68
Haemophilus parainfluenzae	0.06	0.06
Salmonella	0.03	0.5
Klebsiella pneumoniae	0.03	0.12
Shigella	0.06	0.25
Citrobacter diversus	0.06	0.25
Escherichia coli	0.12	0.25†
Moraxella catarrhalis		
β-lactamase (-)	0.12	2.0
β-lactamase (+)	2.0	4.0
Mixed population	1.0	4.0
Serratia	0.5	8.0*
Morganella morganii	0.25	16.0*
Citrobacter freundii	2.0	>32*
Enterobacter cloacae	1.0	>32*
Pseudomonas	>32	>32
GRAM POSITIVE		
Streptococcus pyogenes	0.5	1.0
Streptococcus pneumoniae		
PCN-susceptible	1.0	2.0**
PCN-resistant	>16	>16
Mixed population	3.0	8.0‡
Enterococci	>32	>32
Streptococcus agalactiae	16	>32
Staphylococci	>32	>32*
OBLIGATE ANAEROBES		
Various anaerobes	>32	>32

* Strains known to contain chromosomal cephalosporinases that hydrolyze ceftibuten.

† Two studies in Europe demonstrated MIC_{90}'s of 16 µg/mL.

‡ Two studies in U.S. demonstrated MIC_{90}'s of >16 µg/mL.

** The majority of pathogens (n=543) came from a Canadian study. However, there were 3 additional studies from the U.S. with penicillin-susceptible *S. pneumoniae* whose MIC_{90}'s ranged between 4-8 µg/mL

Medical Officer's Comment: Combining all *in vitro* studies, the respective weighted MIC_{50}'s and MIC_{90}'s for *S. pneumoniae* are µg/mL.

Table 35
Cumulative "Pathogen" Eradication Rates for MO's
Valid Bronchitis Pathogens at F/U (C88044)
(According to reviewer)

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis		
Moraxella (Branhamella) catarrhalis		
β-lactamase (-)†	1/1 (100)	0
β-lactamase (+)	1/2 (50)	0
Haemophilus influenzae		
β-lactamase (-)	6/7 (86)	2/2 (100)
β-lactamase (+)	1/1 (100)	1/1 (100)
Haemophilus parainfluenzae		
β-lactamase (-)	2/2 (100)	1/1 (100)
β-lactamase (+)	-	0
Klebsiella pneumoniae	1/1 (100)	0
Streptococcus pneumoniae	1/1 (100)	0
Total	13/15 (87)	4/4 (100)
AECB		
Moraxella (Branhamella) catarrhalis		
β-lactamase (-)	1/1 (100)	1/1 (100)
β-lactamase (+)	2/4 (50)	1/1 (100)
Haemophilus influenzae		
β-lactamase (-)	10/13 (77)	3/6* (50)
β-lactamase (+)	0/1 (0)	0
Haemophilus parainfluenzae		
β-lactamase (-)	6/6 (100)	2/2 (100)
β-lactamase (+)	1/1 (100)	0
Klebsiella pneumoniae	2/2 (100)	1/1 (100)
Streptococcus pneumoniae	3/3 (100)	4/4 (100)
Total	25/31 (81)	12/15 (80)

* Eradication is the absence of the causative organism(s) at or immediately after termination of therapy (documented), or the complete disappearance of the culture source (e.g., sputum) so that follow-up culture is impossible (presumptive).
† Includes pathogens not tested for β-lactamase activity.
* = Designates pathogens with bacteriologic relapse.

Bacteriologic Superinfections/Reinfections:
The reviewer identified 1 bacteriologic superinfection (due to one of the five pathogens) which occurred in the U.S. study - a cefaclor patient. There were no bacteriologic reinfections documented. Details follow:

C88044291O8 (cefaclor, AECB): On day +3, this individual became infected with *H. influenzae*, β-lactamase negative. (cefaclor zone 30mm; susceptible pathogen). This patient was a clinical failure.

Table 35
Cumulative "Pathogen" Eradication Rates for MO's
Valid Bronchitis Pathogens at F/U (International)
(According to reviewer)

	Number (%) of Isolates	
	Ceftibuten 400 mg QD	Cefaclor 250 mg TID
Acute Bacterial Bronchitis		
Moraxella (Branhamella) catarrhalis		
β-lactamase (-)†	2/2 (100)	0
β-lactamase (+)	0	0
Haemophilus influenzae		
β-lactamase (-)	9/10 (90)	0
β-lactamase (+)	2/2 (100)	0
Haemophilus parainfluenzae		
β-lactamase (-)	1/1 (100)	0
β-lactamase (+)	0	0
Klebsiella pneumoniae	1/1 (100)	1/1 (100)
Streptococcus pneumoniae	2/5 (40)	4/6 (67)
Total	**17/21 (81)**	**5/7 (71)**
AECB		
Moraxella (Branhamella) catarrhalis		
β-lactamase (-)	3/3 (100)‡	1/2 (50)
β-lactamase (+)	1/2 (50)	0
Haemophilus influenzae		
β-lactamase (-)	12/17 (71)••	7/10 (70)‡
β-lactamase (+)	0	0
Haemophilus parainfluenzae		
β-lactamase (-)	3/3 (100)	2/4 (50)
β-lactamase (+)	0	0
Klebsiella pneumoniae	3/4 (75)	0
Streptococcus pneumoniae	8/16 (50)	3/5 (60)‡
Total	**30/45 (67)**	**13/21 (62)**

* Eradication is the absence of the causative organism(s) at or immediately after termination of therapy (documented), or the complete disappearance of the culture source (e.g., sputum) so that follow-up culture is impossible (presumptive).

† Includes pathogens not tested for β-lactamase activity.

• Designates pathogens with documented relapse.

Adverse Events

All Adverse Events

Overall, there was a similar incidence of adverse events in the two treatment groups. (See the table below.) Adverse events occurred in 37% (68/185) of ceftibuten patients compared with 44% (81/185) of cefixime patients. Adverse events of the gastrointestinal system were the most frequent, occurring in 14% (26/185) of patients in the ceftibuten group compared with 18% (34/185) of patients in the cefixime group. The most commonly reported gastrointestinal event was diarrhea; 3% (6/185) and 8% (14/185) for ceftibuten and cefixime, respectively.

Most adverse events were mild or moderate in severity (Grade 1 or Grade 2, respectively). However, nine of 370 patients reported severe (Grade 3) adverse events; six of these patients were in the cefixime group (3%, 6/185) and three of these patients were in the ceftibuten group (2%, 3/185). The only severe adverse event reported by more than one patient was diarrhea; this was reported as severe by two patients in the cefixime group.

Life-threatening (Grade 4) adverse events were reported for only two patients.[a] One ceftibuten-treated patient (Patient Center C90-045-23) had life-threatening dyspnea, and one cefixime-treated patient (Patient Center C90-045-18) had a life-threatening ventricular arrhythmia and died. Both life-threatening adverse events were considered by the investigator as unrelated to treatment.

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a: Clinical summaries for patients who had life-threatening adverse events are provided in **Appendix D-2.**

Number (%) of Patients in the Safety Population Reporting Adverse Events (Study No. C90-045).*

	Number of (%) of Patients			
	Ceftibuten 400 mg QD (N=185)		Cefixime 400 mg QD (N=185)	
	All Grades	Grade** 3 or 4	All Grades	Grade 3 or 4
PATIENTS WITH ANY ADVERSE EVENT§	68 (37%)	4 (2%)	81 (44%)	7 (4%)
Autonomic Nervous System Disorders	4 (2%)	0	0	0
Mouth dry	4 (2%)	0	0	0
Sweating increased	1 (<1%)	0	0	0
Body as a Whole - General	19 (10%)	1 (<1%)	20 (11%)	1 (<1%)
Asthenia	0	0	1 (<1%)	0
Back pain	3 (2%)	0	1 (<1%)	1 (<1%)
Chest pain	1 (<1%)	0	0	0
Cramps, legs	1 (<1%)	0	2 (1%)	0
Fatigue	2 (1%)	0	0	0
Fever	0	0	1 (<1%)	0
Headache	12 (6%)	1 (<1%)	15 (8%)	0
Pain	2 (1%)	0	0	0
Weight decrease	0	0	1 (<1%)	0
Cardiovascular Disorders, General	1 (<1%)	0	1 (<1%)	0
Hypertension	0	0	1 (<1%)	0
Syncope	1 (<1%)	0	0	0
Central and Peripheral Nervous System Disorders	7 (4%)	0	5 (3%)	0
Confusion	1 (<1%)	0	0	0
Dizziness	5 (3%)	0	2 (1%)	0
Dysphonia	0	0	1 (<1%)	0
Paresthesia	1 (<1%)	0	1 (<1%)	0
Tongue paralysis	0	0	1 (<1%)	0
Vertigo	1 (<1%)	0	0	0
Gastrointestinal System Disorders	26 (14%)	0	34 (18%)	2 (1%)
Abdominal pain	4 (2%)	0	3 (2%)	1 (<1%)
Anorexia	1 (<1%)	0	2 (1%)	0
Constipation	1 (<1%)	0	4 (2%)	0
Dehydration	0	0	1 (<1%)	0
Diarrhea	6 (3%)	0	14 (8%)	2 (1%)

Cont'd

* A summary of all adverse events during treatment and all adverse events by severity are provided in Appendices D-3 and D-4, respectively. A listing of all adverse events by treatment group and investigator can be found in Appendix D-5, and by adverse event, treatment group and investigator in Appendix D-6.

§ Number of patients reporting adverse events at least once during the study. Some patients may have reported more than one adverse event.

** Grade 1 = mild; 2 = moderate; 3 = severe; and 4 = life-threatening.

(Cont'd). Number (%) of Patients in the Safety Population Reporting Adverse Events (Study No. C90-045).*

	Number of (%) of Patients			
	Ceftibuten 400 mg QD (N=185)		Cefixime 400 mg QD (N=185)	
	All Grades	Grade** 3 or 4	All Grades	Grade** 3 or 4
Gastrointestinal System Disorders Cont'd				
Dyspepsia	5 (3%)	0	2 (1%)	0
Dysphagia	0	0	2 (1%)	0
Gastritis	0	0	1 (<1%)	0
Gastrointestinal Disorder, Nos	0	0	2 (1%)	0
Gastroenteritis	1 (<1%)	0	0	0
Hemorrhoids	1 (<1%)	0	0	0
Loose Stools	3 (2%)	0	8 (4%)	0
Melena	0	0	1 (<1%)	1 (<1%)
Nausea	7 (4%)	0	8 (4%)	0
Stomatitis	0	0	1 (<1%)	0
Stool abnormal	0	0	1 (<1%)	1 (<1%)
Tongue discoloration	0	0	1 (<1%)	0
Vomiting	1 (<1%)	0	3 (2%)	0
Hearing & Vestibular Disorders	1 (<1%)	0	0	0
Ear disorder, Nos	1 (<1%)	0	0	0
Heart Rate and Rhythm Disorders	0	0	1 (<1%)	1 (<1%)
Arrhythmia ventricular	0	0	1 (<1%)	1 (<1%)
Metabolic and Nutritional Disorders	1 (<1%)	0	1 (<1%)	0
Gout	0	0	1 (<1%)	0
Hypokalemia	1 (<1%)	0	0	0
Musculoskeletal System Disorders	4 (2%)	0	3 (2%)	0
Arthralgia	1 (<1%)	0	1 (<1%)	0
Arthritis aggravated	1 (<1%)	0	0	0
Muscle disorder	0	0	2 (1%)	0
Myalgia	2 (1%)	0	1 (<1%)	0
Platelet, Bleeding and Clotting Disorders	0	0	2 (1%)	0
Hematoma	0	0	2 (1%)	0

Cont'd

* A summary of all adverse events during treatment and all adverse events by severity are provided in Appendices D-3 and D-4, respectively. A listing of all adverse events by treatment group and investigator can be found in Appendix D-5, and by adverse event, treatment group and investigator in Appendix D-6.

** Grade 1 = mild; 2 = moderate; 3 = severe; and 4 = life-threatening.

(Cont'd). Number (%) of Patients in the Safety Population Reporting Adverse Events (Study No. C90-045).*

	Number of (%) of Patients			
	Ceftibuten 400 mg QD (N=185)		Cefixime 400 mg QD (N=185)	
	All Grades	Grade** 3 or 4	All Grades	Grade** 3 or 4
Psychiatric Disorders	5 (3%)	1 (<1%)	6 (3%)	1 (<1%)
Anxiety	0	0	2 (1%)	0
Depersonalization	0	0	1 (<1%)	0
Depression	2 (1%)	1 (<1%)	0	0
Insomnia	3 (2%)	0	0	0
Nervousness	0	0	2 (1%)	1 (<1%)
Somnolence	0	0	2 (1%)	0
Reproductive Disorders, Female	2 (1%)	0	3 (2%)	0
Dysmenorrhea	0	0	1 (<1%)	0
Leukorrhoea	0	0	1 (<1%)	0
Vaginitis	2 (1%)	0	1 (<1%)	0
Resistance Mechanism Disorders	5 (3%)	0	2 (1%)	0
Abscess	2 (1%)	0	0	0
Herpes Simplex	1 (<1%)	0	0	0
Infection, fungal	1 (<1%)	0	0	0
Infection, viral	1 (<1%)	0	1 (<1%)	0
Moniliasis	0	0	1 (<1%)	0
Respiratory System Disorders	15 (8%)	2 (1%)	12 (6%)	2 (1%)
Bronchospasm	2 (1%)	1 (<1%)	4 (2%)	1 (<1%)
Dyspnea	3 (2%)	1 (<1%)	1 (<1%)	1 (<1%)
Epistaxis	0	0	2 (1%)	0
Hemoptysis	1 (<1%)	0	0	0
Hyperventilation	1 (<1%)	0	0	0
Laryngitis	1 (<1%)	0	0	0
Nasal Congestion	2 (1%)	0	0	0
Pharyngitis	1 (<1%)	0	0	0
Rhinitis	2 (1%)	0	3 (2%)	0
Sinusitis	4 (2%)	0	3 (2%)	0
Skin & Appendages Disorders	4 (2%)	0	8 (4%)	0
Dermatitis	0	0	1 (<1%)	0
Dermatitis contact	1 (<1%)	0	0	0
Parasite skin	1 (<1%)	0	0	0
Pruritus	1 (<1%)	0	1 (<1%)	0
Rash	1 (<1%)	0	5 (3%)	0
Rash, maculopapular	0	0	1 (<1%)	0
Skin disorder	0	0	1 (<1%)	0

Cont'd

* A summary of all adverse events during treatment and all adverse events by severity are provided in Appendices D-3 and D-4, respectively. A listing of all adverse events by treatment group and investigator can be found in Appendix D-5, and by adverse event, treatment group and investigator in Appendix D-6.

** Grade 1 = mild; 2 = moderate; 3 = severe; and 4 = life-threatening.

Table 47 (Cont'd). Number (%) of Patients in the Safety Population Reporting Adverse Events (Study No. C90-045).*

	Number of (%) of Patients			
	Ceftibuten 400 mg QD (N=185)		Cefixime 400 mg QD (N=185)	
	All Grades	Grade** 3 or 4	All Grades	Grade** 3 or 4
Special Senses, Other Disorders	2 (1%)	0	0	0
Taste perversion	2 (1%)	0	0	0
Urinary System Disorders	1 (<1%)	0	1 (<1%)	0
Dysuria	0	0	1 (<1%)	0
Polyuria	1 (<1%)	0	0	0
Vascular (Extracardiac) Disorders	2 (1%)	0	0	0
Purpura	2 (1%)	0	0	0
Vision Disorders	0	0	1 (<1%)	0
Vision, blurred	0	0	1 (<1%)	0

* A summary of all adverse events during treatment and all adverse events by severity are provided in Appendices D-3 and D-4, respectively. A listing of all adverse events by treatment group and investigator can be found in Appendix D-5, and by adverse event, treatment group and investigator in Appendix D-6.

** Grade 1 = mild; 2 = moderate; 3 = severe; and 4 = life-threatening.

Two cefixime-treated patients (Patient Center C90-045-09) had *Clostridium difficile* isolated during treatment. Three cefixime patients (Patient , Center C90-045-06; Patients Center C90-045-09; and Patient , Center C90-045-15) had testing for *C. difficile* toxin performed. Results for all three patients were negative.

Treatment-Related Adverse Events

Treatment-related adverse events were those considered by the investigator to be possibly or probably related to treatment. Overall, there was a similar incidence of treatment-related adverse events in the two groups. Treatment-related adverse events occurred in 14% (26/185) of ceftibuten-treated patients compared with 19% (36/185) of cefixime-treated patients. Adverse events of the gastrointestinal system again were the most frequent, occurring in 9% (16/185) of patients in the ceftibuten group compared to 12% (23/185) of patients in the cefixime group. In the ceftibuten group, with the exception of severe headache reported by one patient, all treatment-related adverse events were mild or moderate in severity. In the cefixime group, three patients reported severe adverse events considered related to treatment. There were no life-threatening treatment-related adverse events

Patients with at Least One Gastrointestinal Disorder

As specified in the protocol, an additional analysis of the number of patients with at least one gastrointestinal event was performed. The gastrointestinal events included in this analysis were restricted to abdominal pain, constipation, diarrhea, dyspepsia, gastritis, gastroenteritis, melena, vomiting, loose stools, gastrointestinal disorder (nos[a]), and stool abnormal. The number of patients who reported at least one of these gastrointestinal adverse events (all or treatment-related) was not different for both treatment groups ($p=0.163$ for all gastrointestinal events; $p=0.104$ for treatment-related gastrointestinal events). Eleven percent (19/185) of ceftibuten patients reported at least one of these gastrointestinal adverse events compared with 16% (29/185) of patients in the cefixime group. At least one of these treatment-related gastrointestinal event was reported by 7% (12/185) and 12% (22/185) of ceftibuten and cefixime patients, respectively.

a: Not otherwise specified.

Number (%) of Patients in the Safety Population Reporting Treatment-Related Adverse Events (Study No. C90-045).*

	Number of (%) of Patients			
	Ceftibuten 400 mg QD (N=185)		Cefixime 400 mg QD (N=185)	
	All Grades	Grade** 3 or 4	All Grades	Grade** 3 or 4
PATIENTS WITH ANY TREATMENT-RELATED ADVERSE EVENT§	26 (14%)	1 (<1%)	36 (19%)	3 (2%)
Autonomic Nervous System Disorders	3 (2%)	0	0	0
Mouth dry	3 (2%)	0	0	0
Sweating increased	1 (<1%)	0	0	0
Body as a Whole - General	5 (3%)	1 (<1%)	4 (2%)	0
Headache	5 (3%)	1 (<1%)	4 (2%)	0
Central and Peripheral Nervous System Disorders	4 (2%)	0	3 (2%)	0
Confusion	1 (<1%)	0	0	0
Dizziness	3 (2%)	0	2 (1%)	0
Paresthesia	1 (<1%)	0	0	0
Tongue paralysis	0	0	1 (<1%)	0
Gastrointestinal System Disorders	16 (9%)	0	23 (12%)	2 (1%)
Abdominal pain	3 (2%)	0	3 (2%)	1 (<1%)
Anorexia	1 (<1%)	0	2 (1%)	0
Constipation	1 (<1%)	0	3 (2%)	0
Diarrhea	3 (2%)	0	11 (6%)	2 (1%)
Dyspepsia	3 (2%)	0	1 (<1%)	0
Dysphagia	0	0	1 (<1%)	0
Gastritis	0	0	1 (<1%)	0
Gastrointestinal Disorder, Nos	0	0	1 (<1%)	0
Loose stools	3 (2%)	0	7 (4%)	0
Melena	0	0	1 (<1%)	1 (<1%)
Nausea	4 (2%)	0	3 (2%)	0
Stomatitis	0	0	1 (<1%)	0
Stool abnormal	0	0	1 (<1%)	1 (<1%)
Tongue disorder	0	0	1 (<1%)	0
Vomiting	1 (<1%)	0	1 (<1%)	0
Musculoskeletal System Disorders	0	0	1 (<1%)	0
Arthralgia	0	0	1 (<1%)	0

Cont'd

* A summary of treatment-related adverse events and treatment-related adverse events by severity are provided in Appendices 0-8 and 7-9, respectively.
§ Number of patients reporting adverse events at least once during the study. Some patients may have reported more than one adverse event.
** Grade 1 = mild; 2 = moderate; 3 = severe; and 4 = life-threatening.

(Cont'd). Number (%) of Patients in the Safety Population Reporting Treatment-Related Adverse Events (Study No. C90-045).*

	Number of (%) of Patients			
	Ceftibuten 400 mg QD (N=185)		Cefixime 400 mg QD (N=185)	
	All Grades	Grade** 3 or 4	All Grades	Grade** 3 or 4
Psychiatric Disorders	0	0	3 (2%)	1 (<1%)
Depersonalization	0	0	1 (<1%)	0
Nervousness	0	0	1 (<1%)	1 (<1%)
Somnolence	0	0	1 (<1%)	0
Reproductive Disorders, Female	2 (1%)	0	2 (1%)	0
Leukorrhoea	0	0	1 (<1%)	0
Vaginitis	2 (1%)	0	1 (<1%)	0
Resistance Mechanism Disorders	0	0	1 (<1%)	0
Moniliasis	0	0	1 (<1%)	0
Respiratory System Disorders	0	0	1 (<1%)	0
Bronchospasm	0	0	1 (<1%)	0
Skin & Appendages Disorders	0	0	4 (2%)	0
Dermatitis	0	0	1 (<1%)	0
Rash	0	0	2 (1%)	0
Rash, maculopapular	0	0	1 (<1%)	0
Special Senses Other, Disorders	2 (1%)	0	0	0
Taste Perversion	2 (1%)	0	0	0
Vascular (Extracardiac) Disorders	1 (<1%)	0	0	0
Purpura	1 (<1%)	0	0	0

* A summary of treatment-related adverse events and treatment-related adverse events by severity are provided in Appendices D-8 and D-9, respectively.

** Grade 1 = mild; 2 = moderate; 3 = severe; and 4 = life-threatening.

Deaths and Other Serious Adverse Events

Two deaths occurred during treatment or within 30 days of the last dose of study medication (**Table 50**). One ceftibuten-treated patient (Patient , Center C90-045-06) died due to the underlying disease. One cefixime patient (Patient Center C90-045-18) died due to a ventricular arrhythmia.

Table 50. Summary of Patients Who Died (Study No. C90-45).

Control No.	Study No./ Patient No.	Age/Sex	Study Med/ Dose/ Duration	Severe Adverse Events	Cause of Death	Relationship to Study Medication
93-02-091	C90-045-06/	53/M	Ceftibuten 400 mg QD/ 10 days	None	Underlying Disease (Lobectomy)	Unrelated
93-03-1281	C90-045-18/	55/F	Cefixime 400 mg QD/ 1 day	Cardio-vascular Event (ventricular arrhythmia)	Adverse Event	Unrelated

Serious adverse events are defined as those that are life-threatening, or have an outcome of hospitalization, permanent disability, or death; they include such conditions as cancer, congenital anomalies, and overdose.

Eight patients (three treated with ceftibuten and five treated with cefixime) had adverse events assessed by the investigator or the sponsor as serious (See the table below). The most common serious adverse event reported was dyspnea which was reported by four patients (one ceftibuten-treated and three cefixime-treated patients), and was considered unrelated to treatment.

Patients with Serious* Adverse Events (Study No. C90-045).

Control No.	Treatment	Center/ Patient No.	Duration of Treatment	Adverse Event	Relationship to Study Drug
93-02-091	Ceftibuten	C90-045-06	10 days	Encephalopathy	Unrelated
				Pulmonary hemorrhage	Unrelated
				Fibrillation, ventricular	Unrelated
				Hemoptysis	Unrelated
				Fibrillation, atrial	Unrelated
				Syncope	Unrelated
				Chest pain	Unrelated
				Coughing	Unrelated
93-02-5301§	Ceftibuten	C90-045-16	3 days	Drug abuse	Unrelated
				Speech disorder	Unrelated
				Gait abnormal	Unrelated
				Hematuria	Not provided
				Urine abnormal	Not provided
93-06-501	Ceftibuten	C90-045-23	3 days	Bronchitis	Not provided
				Bronchospasm	Not provided
				Dyspnea	Not provided
93-07-181	Cefixime	C90-045-04	10 days	Conditions aggravated	Possible
				Dyspnea	Possible
				Bronchospasm	Possible
				Coughing	Possible
					Possible
93-08-2141	Cefixime	C90-045-09	14 days	Diarrhea (C. difficile)	Possible
				Loose stools	Possible
				Vomiting	Possible
				Nausea	Possible
				Anorexia	Possible
93-07-171	Cefixime	C90-045-09	9 days	Colitis	Probable
				Diarrhea (C. difficile)	Probable
				Weight decrease	Probable
				Abdominal pain	Probable
				Anorexia	Probable
				Flatulence	Probable
				Fever	Probable
				Moniliases	Probable
				Constipation	Probable
92-07-521	Cefixime	C90-045-17	10 days	Dyspnea	Unrelated
				Hypertension	Unrelated
				Respiratory disorder	Unrelated
				Disease progression	Unrelated
93-03-1281	Cefixime	C90-045-18	1 day	Cerebrovascular disorder	Unrelated
				Circulatory failure	Unrelated
				Fibrillation, ventricular	Unrelated
				Cardiac failure	Unrelated
				Bronchitis	Unrelated
				Apnea	Unrelated
				Dyspnea	Unrelated
				Edema peripheral	Unrelated
				Fever	Unrelated
				Vomiting	Unrelated

* Reported to Schering-Plough Drug Safety Surveillance. Patient summaries appear in Appendix D-2.
§ These adverse events were not included in the safety database.

Laboratory Test Results

Shift Table of Clinical Laboratory Results

Examination of shift table results showed that the majority of patients had normal laboratory parameters at Baseline that remained normal after treatment with ceftibuten or cefixime. Other results, particularly from normal to low for most hematologic parameters, and from normal to high for serum chemistries and enzyme activity, revealed no other notable findings. The majority of patients had normal laboratory parameters before and after treatment with ceftibuten. However, as expected in these patients with bacterial infections, many had elevated WBC counts at Baseline, the majority of which decreased to within the normal range at the end of treatment and was accompanied by resolution of disease. In patients with normal values at Baseline, the proportion of ceftibuten patients who had decreases to values below normal in hemoglobin levels, and WBC counts was similar to those seen with cefixime. Likewise, the proportion of ceftibuten patients with increases or decreases in alkaline phosphatase, creatinine, SGOT and SGPT levels was similar to those seen with cefixime.

Clinical Chemistry, Hematology and Urinalysis Results

With the exception of patients with eosinophils $>700/mm^3$ at baseline, the number and percent of patients with abnormal laboratory test results following treatment was similar for the two treatment groups. The most common abnormality in both treatment groups was an increase in eosinophils. Although the number and percent of patients with Baseline eosinophil counts $>700/mm^3$ at baseline that remained $>700/mm^3$ after treatment was greater for the ceftibuten group (43% [3/7] compared with the cefixime group (12% [1/8]); this difference is not considered clinically relevant. Changes in the laboratory tests results are consistent with the observations from previous studies with ceftibuten and with findings described for other cephalosporins.

Results of urinalysis tests were unremarkable; there are no clinically relevant differences between the two groups. The most common observed abnormal laboratory parameters in both treatment groups were changes in urine pH and the presence of protein, epithelial cells, white blood cells and crystals in the urine.

Incidence of Abnormal Laboratory Values for Clinical Chemistry and Hematology:* Safety Population (Study No. C90-045).§

	Number (%) of Patients	
	Ceftibuten 400 mg QD	Cefixime 400 mg QD
Clinical Chemistry†		
Alkaline Phosphatase	0/173	0/174
BUN	0/6	0/7
Creatinine	0/172	1/174 (<1%)
SGOT	2/173 (1%)	0/174
SGPT	2/172 (1%)	1/172 (<1%)
Total Bilirubin	0/171	2/174 (1%)
Hematology†		
Eosinophils		
Baseline >700/mm³	3/7 (43%)	1/8 (13%)
Baseline 700/mm³	4/162 (3%)	4/163 (3%)
Hemoglobin	2/173 (1%)	3/175 (2%)
Platelets		
<100,000	0/7	0/6
>700,000	0/7	0/6
WBC	1/171 (<1%)	0/174

* A summary of patients with abnormal hematology or blood chemistry values can be found in Appendix D-16. See Appendix D-17 for a listing of patients with abnormal laboratory values. A listing of all laboratory values is provided in Appendix D-18. A summary of patients with abnormal hematology or blood chemistry values considered related to treatment can be found in Appendix D-19. A listing of patients with abnormal laboratory values considered treatment-related is provided in Appendix D-20.

§ Criteria for abnormal findings -
Alkaline phosphatase - above 1.5 times the upper limit of normal range if Baseline value is within normal range, otherwise 50% increase above Baseline value.
Creatinine - 0.5 mg/dL increase from Baseline value and above the upper limit of normal range.
SGOT and SGPT - 3 times the upper limit of normal range.
Total bilirubin, BUN - 25% increase above Baseline value and above the upper limit of normal range.
Eosinophils
(Baseline 700/mm³) - Baseline eosinophil value 700/mm³ and increasing to greater than 700/mm³
(Baseline >700/mm³) - Baseline eosinophil value >700/mm³ and remaining greater than 700/mm³.
Hemoglobin - 2 g decrease from Baseline.
WBC - below 2.5 mm³.
Platelet - below 100 or above 700 and more than 50% change from Baseline value.

Incidence of Abnormal Laboratory Values for Urinalysis:*
Safety Population (Study No. C90-045).§

	Number (%) of Patients	
	Ceftibuten 400 mg QD	Cefixime 400 mg QD
Bacteria	13/136 (10%)	15/141 (11%)
Crystals	14/136 (10%)	11/141 (8%)
Epithelial	13/136 (10%)	9/142 (6%)
Glucose	5/137 (4%)	3/143 (2%)
Gran. Casts	1/136 (<1%)	0/141
Hyaline Casts	3/136 (2%)	2/141 (1%)
Hemoglobin	2/137 (2%)	5/143 (4%)
pH	13/138 (9%)	5/143 (4%)
Protein	5/137 (4%)	4/143 (3%)
RBC	3/136 (2%)	2/142 (1%)
Specific Gravity	0/152	0/150
WBC	11/136 (8%)	5/143 (4%)

* A summary of patients with abnormal urinalysis can be found in Appendix D-21. See Appendix D-17 for a listing of patients with abnormal laboratory values. A listing of all laboratory values is provided in Appendix D-18. See Appendix D-22 for a summary of patients with abnormal urinalysis considered related to treatment.

§ Criteria for abnormal findings -
Bacteria, Crystals, Epithelium, Gran. Casts, Hyaline Casts, RBC and WBC - if Baseline value is within normal range and value >6-15; otherwise, if value > Baseline value.
Glucose, Hemoglobin, Protein - if Baseline value is within normal range and value >1+; otherwise, if value > Baseline value.
Ph - ±2.0 units from Baseline.
Specific gravity - ≤1.00 or ≥1.075.

Patients with Clinically Noteworthy Laboratory Values

Two patients (one ceftibuten and one cefixime) had clinically noteworthy laboratory values. The ceftibuten-treated patient (Patient Center C90-045-07) had eosinophil levels that were normal at Baseline (400/mm^3), and elevated at the end-of-treatment (5400/mm^3). The cefixime-treated patient (Patient Center C90-045-11) had WBC counts which were considered normal at Baseline (8000/mm^3), but decreased at the end-of-treatment (2,100/mm^3).

Discontinuations Due to Adverse Events

Twelve patients were withdrawn early from the study because of clinical adverse events. Three patients were in the ceftibuten treatment group and the remaining 9 patients were in the cefixime group. An additional two cefixime-treated patients (Patient . Center C90-045-09 and Patient Center C90-045-12) discontinued treatment due to an adverse event with study drug, but did not discontinue from the study. The clinical events and relationship to treatment are shown below. The most common reason for discontinuation of treatment or the study was diarrhea.

Patients Who Discontinued From the Study Because of Adverse Events or Laboratory Abnormalities*: Safety Population (Study No. C90-045).

Center/ Patient No.	Adverse Event	Relationship to Treatment	Days on Study Drug
CEFTIBUTEN 400 MG QD			
C90-045-13	Bronchospasm	Unrelated	9
C90-045-19	Loose stools	Possible	9
	Sinusitis	Unrelated	9
C90-045-23§	Increased shortness of breath - acute exacerbation of COPD	Unrelated	3
CEFIXIME 400 MG QD			
C90-045-01	Rash	Possible	3
C90-045-01	Sinusitis	Unrelated	9
C90-045-04	Pressure headache	Possible	2
C90-045-06	Abdominal cramps	Probable	6
	Diarrhea	Probable	6
C90-045-09	Stomach cramps	Probable	9
	Decreased appetite	Probable	9
	Diarrhea	Probable	9
	Bloated feeling	Probable	9
C90-045-12§	Asthma attack	Unrelated	2
C90-045-14	Diarrhea	Related	11
C90-045-15	Dysphagia	Probable	5
	Gastritis	Probable	5
C90-045-16	Anxiety	Unrelated	8
	Nervousness	Unrelated	8
C90-045-18	Cardiovascular event (ventricular arrhythmia)	Unrelated	1
C90-045-19	Nervousness	Possible	2

* A listing of patients who discontinued due to clinical adverse events or laboratory abnormalities is provided in Appendix D-23.
§ Patient discontinued treatment due to an adverse event, but did not discontinue the study. Neither patient was evaluable for efficacy.

Discussion

The approach to treatment of patients with acute exacerbation of chronic bronchitis (AECB) is largely empiric. Physicians do not usually order a sputum Gram stain or culture on such patients, but instead decide the need for antimicrobial therapy based on such parameters as a change in volume and/or color of sputum, increase in cough and/or shortness of breath, and presence of fever. Only when patients given such treatment do not fare well, do clinicians usually consider sputum Gram stain and culture to guide therapy further.

With this empiric approach in mind, then, one can understand the emphasis placed on the clinical outcome in an acute exacerbation of chronic bronchitis trial. Whether or not the patient grows the same bacteria at the study's conclusion, as at entry, is not so important as the clinical assessment of the patient's sputum production, cough and dyspnea . In the setting of a patient who has returned to his pre-infection baseline status, yet has a positive post therapy culture, a clinician usually treats the patient, not the culture, recognizing that such patients are frequently colonized with bacteria. Conversely, a patient who fails to improve his symptoms, whether or not a post-therapy culture is positive, frequently is prescribed a second round of antimicrobial therapy.

Whenever an empiric approach is taken with patients who appear to have an infectious disease, it is recognized that not every patient will have a bacteriologic etiology (some may be viral, others allergic in nature, etc.). Thus, patients with appropriate symptoms enter an AECB trial, but only a fraction of them will actually have an acute bacteriologic exacerbation of their recurrent bronchitis. How a drug treatment fares in this latter patient population is perhaps more telling than in the general patient population of clinically evaluable patients.

In the analysis of clinical response of patients in the clinical efficacy population of this review, ceftibuten performed equally well as cefixime. In the subset of patients with proven bacteriologic etiology, however, ceftibuten had significantly more clinical failures than cefixime. When the data are analyzed by response by pathogen, the reason for the disparity in outcome in study C90-045 between the clinical efficacy and microbiologic efficacy populations becomes evident: ceftibuten clearly demonstrated problems in effecting a successful clinical outcome in patients with underlying *Moraxella catarrhalis* in their sputum. A variable half-life and C_{max} for ceftibuten, the dosing interval chosen (once daily), and the MIC_{90} of -lactamase positive Moraxella catarrhalis isolates likely influenced the outcome.

When one combines eradication rates from all ceftibuten studies involving patients with AECB, the cumulative eradication rate for *S. pneumoniae* isolates is 23/35 (66%). (See page 38a of this review.) At this time, when resistance to *S. pneumoniae* is a concern in many places worldwide, including the United States, the reviewer can not recommend this drug for approval for treatment of AECB due to *S. pneumoniae* because this rate of eradication in this disease is not clinically acceptable today.

Medical Officer's Conclusions and Recommendations

Based on the performance of ceftibuten (Cedax®) in the clinical efficacy population of protocol C90045, the drug appears equivalent to another marketed product (cefixime, Suprax®) for acute exacerbation of chronic bronchitis. This information corroborates the first domestic study reviewed by Dr. Brad Leissa, C88044, wherein ceftibuten was shown to be equivalent to cefaclor in the treatment of patients with AECB. As such, the Medical Officer recommends approval of the ceftibuten for AECB.

However, the number of bacteriologic isolates in the domestic study, C88044, reviewed by Dr. Leissa was small and did not reveal much of a trend about ceftibuten's performance in the microbiologic efficacy population. The AECB trial reviewed here, C90045, together with the domestic and international studies reviewed by Dr. Leissa, presents a large enough database of patients with proven acute bacteriologic exacerbations of chronic bronchitis to reveal trends. With regard to patients whose sputum grew *Moraxella catarrhalis and Streptococcus pneumoniae*, the trends are disturbing in the setting of empiric treatment.

If an antimicrobial is to be used well empirically, it must be expected to cover adequately the likely pathogens in a given infection. When some pathogens are well-covered while others are not, the empiric use of that drug is then highly questionable. This is the scenario with ceftibuten.

In conclusion, the Medical Officer recommends approval of ceftibuten capsules for the treatment of acute exacerbation of chronic bronchitis, **but not as first-line therapy.** Adequate information should be included in the label to tell prescribing physicians that the drug should not be used in patients with acute bacteriologic exacerbation of chronic bronchitis due to *Moraxella catarrhalis or Streptococcus pneumoniae*.

Medical Officer's PROPOSED PACKAGE CIRCULAR (pertinent to AECB)

INDICATIONS AND USAGE

CEDAX® (Ceftibuten) is indicated for the treatment of the following infection when caused by susceptible strains of the designated organisms:

Acute Bacterial Exacerbation of Chronic Bronchitis
caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains) only.

NOTE: CEDAX® IS NOT INDICATED FOR THE EMPIRIC TREATMENT OF CHRONIC BRONCHITIS WHEN IT IS PROBABLE THAT MORAXELLA CATARRHALIS OR STREPTOCOCCUS PNEUMONIAE IS A CAUSATIVE PATHOGEN.

Janice Soreth, MD
Janice Soreth, M.D. 7/5/94
Medical Officer
Revised 8/23/94

Concurrence only:

HFD-520/DivDir/Lumpkin
HFD-520/SMO/Albrecht

ja 8/25/94
per SMO addendum
12/14/94

cc:
Orig. NDA
HFD-340
HFD-520
HFD-520/DepDir/Gavrilovich
HFD-520/Pharm-Buko
HFD-520/Micro-Dionne
HFD-520/Stat-Turney
HFD-520/Chem
HFD-520/Debellas

12/26/94

NDA 50-685

DRAFT

Medical Officer's Review of Amendment to Original NDA
Ceftibuten Capsules

Applicant:	Schering-Plough Incorporated
Date of Submission:	May 31, 1993
Review Completed:	September 1, 1995
Material Reviewed:	16-volume submission of a clinical study report designated C90-038; 5-volume submission of a clinical study report designated P92-020. Both were studies of patients with acute exacerbation of chronic bronchitis (AECB). Applicant Position Paper, dated April 27, 1995, consisting of 2 volumes.
Purpose of Submission:	To provide new data to support the applicant's claim that Ceftibuten is indicated for *empiric* treatment of patients with acute exacerbation of chronic bronchitis (AECB) due to *S. pneumoniae, H. influenzae, and M. catarrhalis*. In an approvable letter issued December, 1994, the Division proposed that ceftibuten not be indicated for empiric treatment of AECB since eradication rates of *M. catarrhalis* were inadequate both clinically and statistically.
Name of Drug:	
Generic:	Ceftibuten
Trade:	CEDAX® Capsules
Code Name:	7432-S; SCH 39720
Chemical Name:	(+)-(6R,&R)-7-[(Z)-2-(2-amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo [4.2.0.] oct-2-ene-2-carboxylic acid, dihydrate
Molecular Formula:	$C_{15}H_{14}N_4O_6S_2 \cdot 2H_2O$
Chemical Structure:	

Pharmacologic Category:

Ceftibuten is an oral semisynthetic cephalosporin whose chemical structure is similar to 3 other cephalosporins: cefixime (Suprax®), ceftriaxone (Rocephin®) and ceftazidime (Fortaz®). Ceftibuten incorporates a new side chain, carboxyethilidene, which is responsible for oral absorption as well as stability against β-lactamases.

History of the NDA Submission

The new drug application for Ceftibuten (CEDAX®) Capsules consisted of 300 volumes and was submitted December 20, 1991. The applicant sought approval for the indications of secondary bacterial infections of acute bronchitis and acute bacterial exacerbations of chronic bronchitis, and urinary tract infections including pyelonephritis, recurrent cystitis, and complicated urinary tract infections. The original NDA was reviewed by Dr. Brad Leissa and resulted in a non-approvable letter in March, 1993. (See Medical Officer's Review of NDA 50-685, dated February 2, 1993 and the action letter of March 22, 1993.)

Regarding the indication of secondary bacterial infections of acute bronchitis and acute bacterial exacerbations of chronic bronchitis (AECB), Dr. Leissa wrote in his "Recommendations":

> "Acute bacterial bronchitis and AECB: Following combination of all acute bacterial bronchitis studies, the 95% confidence interval approach was not met. In contrast, for AECB, this was just barely met. In order for the applicant to garner either indication, this would require new studies with special attention to the *in vivo* activity against *S. pneumoniae*.
>
> For larger evaluable numbers might demonstrate that ceftibuten 400 mg q.d. is less effective than a chosen approved comparator in the treatment of acute bacterial bronchitis. The applicant might consider a different dosing regimen.
>
> For AECB, one additional well-controlled trial would be sufficient..."

In November, 1993, the applicant filed a major clinical amendment seeking approval for acute exacerbation of chronic bronchitis (AECB). The amendment included a single study report, C90-045, and provided clinical data for 373 patients diagnosed with AECB. I reviewed these data and recommended approval of ceftibuten capsules for the treatment of AECB, but not for empiric use. In my analysis of patients with a proven bacteriologic etiology for their acute exacerbation episode, ceftibuten had significantly more clinical failures than cefixime. When data were analyzed by response by pathogen, it became evident that ceftibuten had problems in effecting a successful clinical outcome in patients with underlying *Moraxella catarrhalis* in their sputum. Similarly, the cumulative eradication rate for *S. pneumoniae* isolates in patients with AECB was only 66% (23/35),

which paralleled Dr. Brad Leissa's findings in children with acute otitis media due to *S. pneumoniae*. At a time when resistance to *S. pneumoniae* is a concern in many countries, including the United States, this rate of eradication for *S. pneumoniae* did not seem clinically acceptable, however equivalent to cefixime. My recommendation, then, for approval of ceftibuten capsules for the treatment of AECB was limited to *H. influenzae* only.

In December, 1994, the Division issued an approvable letter for Ceftibuten Capsules and Ceftibuten for Oral Suspension with the restriction *not for empiric use* in both the AECB (capsules) and acute otitis media (suspension) indications. In May, 1995, representatives from Schering-Plough met with the Division to maintain that restricted labeling was not warranted. In a position paper of April 27, 1995, they asserted that Ceftibuten Capsules are effective in patients with AECB due to *M. catarrhalis* and presented additional data from two studies filed previously to the IND only: P92-020 and C90-038. This review will examine the data in these two studies and their impact on the overall eradication rates for *M. catarrhalis*.

Applicant's Study Synopsis for C90-038

TITLE A Comparison of the Efficacy, Safety, and Tolerance of Ceftibuten (SCH 39720) Capsules in the Fed and Fasted State with that of Amoxicillin/Clavulanate (Augmentin®) in the Treatment of Acute Exacerbations of Chronic Bronchitis in Adults.

STUDY DESIGN This was a multicenter, evaluator-blind, randomized, controlled clinical trial in adults. Patients of at least 18 years of age with acute exacerbations of chronic bronchitis were randomized in a 1:1:1 ratio, to receive 5-15 days of treatment with ceftibuten 400 mg given once daily (QD) fed (instructed to be taken with meals), ceftibuten 400 mg QD fasted (instructed to be taken 1 hour before meals) or amoxicillin/clavulanate (Augmentin) 500 mg given three times daily (TID) fed.

However, for this clinical study report, fed and fasted ceftibuten results were pooled and compared with results obtained with Augmentin. Before the study blind was broken, it was decided by the Sponsor that if the two ceftibuten groups were poolable, the most valid comparison for the study would be ceftibuten pooled (fed and fasted) versus Augmentin.

The poolability was examined by testing the equality in the two ceftibuten groups of 1) the overall clinical assessment in the clinical efficacy population for efficacy analyses and 2) the proportion of patients in the safety population with at least one adverse event related to the gastrointestinal system (ie, abdominal pain, constipation, diarrhea, dyspepsia, gastritis, gastroenteritis, melena, vomiting, loose stools, gastrointestinal disorder [nos] and stool abnormal) for safety analyses. Since no statistically significance difference was found between the ceftibuten fed and ceftibuten fasted groups, all subsequent analyses were done comparing the pooled ceftibuten group with the Augmentin group. Results for the ceftibuten fed and ceftibuten fasted treatment groups are provided in the appropriate Appendices for completeness.

Evaluation of the signs and symptoms of chronic bronchitis, Gram stain of sputum, sputum culture and susceptibility testing and spirometry evaluations were performed at Baseline and at each visit. Chest x-rays were performed at Baseline and were required posttreatment only for patients who were a clinical failure.

The primary evaluation of efficacy was the overall clinical assessment for the clinical efficacy population. Overall clinical assessment was classified as either "success" or "non-success" based on the clinical response at Visit 3 (0-6 day end-of-treatment visit) and Visit 4 (7-21 day extended follow-up visit). At Visit 3, the patient's clinical response to treatment was categorized as either "cure", "improvement", or "failure". At Visit 4, clinical response was categorized as "sustained cure", "sustained improvement" or "relapse" in the case of patients who had worsening or reappearance of signs and symptoms after an initial positive response. The investigator evaluated change from Baseline in signs and symptoms of acute exacerbation of chronic bronchitis at Visit 3 and Visit 4. The microbiologic efficacy population was comprised of patients in the clinical efficacy population who were considered microbiologically evaluable. Evaluation of efficacy for the microbiologic efficacy population was overall microbiologic assessment based on microbiologic response for patients at Visit 3 and Visit 4. Overall microbiologic assessment was classified as either "eradication", "eradication with colonization", "persistence","relapse", "reinfection", "superinfection", or "unassessable". A microbiologic response also was assigned to each pathogen at Visits 3 and 4. The evaluation of safety was based on the incidence of adverse events and laboratory abnormalities.

STUDY POPULATIONS Four hundred sixty-nine patients (316 ceftibuten and 153 Augmentin) were enrolled in the study and included in the intent-to-treat population. One Augmentin patient never received drug and was excluded from the safety population. Therefore, 468 patients (316 ceftibuten and 152 Augmentin) were included in the safety population. Three hundred sixty-nine patients (252 ceftibuten and 117 Augmentin) were included in the clinical efficacy population. The main reasons for exclusion were failure to meet entrance criteria and insufficient efficacy data. Fifty-five patients (40 ceftibuten and 15 Augmentin patients) were included in the microbiologic efficacy population. The main reason for exclusion from the microbiologic efficacy population was failure to isolate a pathogen pretherapy.

For the clinical efficacy population, the treatment groups were comparable with regard to demographic characteristics. Mean age of patients was 55.3 years for ceftibuten and 53.8 years for Augmentin. The two groups were similar at Baseline for signs and symptoms of acute exacerbations of chronic bronchitis. For the microbiologic efficacy population, with the exception of smoking history (58%, 23/40 of ceftibuten-treated patients were currently smoking vs 33%, 5/15 of Augmentin-treated patients), the two treatment groups were similar in demographic characteristics. For the intent-to treat and safety populations, the two treatment groups also were comparable with regard to demographic characteristics.

RESULTS

Efficacy For the clinical efficacy population, overall clinical success rates were equivalent for the two treatments; 84% (211/252) for ceftibuten-treated patients compared with 80% (93/117) for Augmentin-treated patients, (95% confidence interval for the difference between treatments: (-4.5%, +13.6%). At Visit 3, clinical response was similar for the two treatment groups. Cure or improvement in the signs and symptoms of chronic bronchitis occurred in 90% (227/252) of ceftibuten-treated vs. 84% (98/117) of Augmentin-treated patients. At Visit 4, clinical relapse (reappearance of signs and symptoms during the 7-21 day extended follow-up period), occurred in 7% (16/227) and 5% (5/98) of patients in the ceftibuten and Augmentin groups, respectively.

For the microbiologic efficacy population, overall eradication rates (eradication or eradication with colonization) also were equivalent for the two treatments; 98% (36/37) for ceftibuten-treated patients and 86% (12/14) for Augmentin-treated patients (95% confidence interval for the difference between treatment: -5.2, +21.2). For microbiologic response of individual pathogens at Visit 3, total eradication rates for all pathogens and total eradication rates for Haemophilus influenzae (96% [26/27] for the ceftibuten group and 88% [7/8] for the Augmentin group, Streptococcus pneumoniae (100% [12/12] in the ceftibuten group and 83% [5/6] in the Augmentin group, and Moraxella catarrhalis (80% [4/5] and 100% [2/2] for the ceftibuten and Augmentin groups, respectively, were adequate and similar for the two treatment groups. At Visit 4, the treatment groups were similar with regard to total eradication of all pathogens and total eradication of the individual isolates. In addition, relapse rates were similar for the two treatment groups at this visit.

For the microbiologic efficacy population, results for the clinical efficacy parameters were similar to those observed in the clinical efficacy population.

For the intent-to-treat population, clinical and microbiologic response results were similar and confirm those observed with the clinical and microbiologic efficacy populations.

Safety Overall, there was a similar incidence of adverse events in the two treatment groups (41%, 131/316 for ceftibuten compared with 57%, 77/152 for Augmentin). Adverse events of the gastrointestinal system were the most frequent, occurring in 19% (60/316) of patients in the ceftibuten group compared with 29% (44/152) of Augmentin patients. The most commonly reported gastrointestinal events were nausea (reported in 6% [20/316] of ceftibuten-treated patients and 12% [18/152] of Augmentin-treated patients) and diarrhea (reported in 6% [20/316] and 9% [14/152] of ceftibuten and Augmentin patients, respectively). Most adverse events were mild or moderate in severity. There were no life-threatening adverse events reported. Eighteen patients (13 treated with ceftibuten and five treated with Augmentin) had adverse events assessed by the investigator or the sponsor as serious. Serious adverse events considered possibly related to treatment occurred in one ceftibuten patient and one Augmentin patient. With the exception an additional two patients (one ceftibuten patient and one Augmentin patient) who had serious adverse events whose relatedness to treatment was not provided, all other serious adverse events were considered unrelated to treatment.

Few abnormal laboratory test results were reported; the most common abnormality in both treatment groups was an increase in eosinophils consistent with the observations from previous studies with ceftibuten and with findings described for other cephalosporins.

Nineteen patients (10 ceftibuten and 9 Augmentin patients) were withdrawn early from the study because of clinical adverse events. The most common reason for discontinuation of treatment or the study was diarrhea in the ceftibuten group and nausea in the Augmentin group. An additional two patients (one ceftibuten-treated patient and one Augmentin-treated patient discontinued treatment due to an adverse event with study drug, but did not discontinue from the study. Furthermore, one Augmentin patient discontinued the treatment due to an adverse event, but discontinued the study due to treatment failure. Four deaths (four ceftibuten patients) which were considered unrelated to treatment occurred during treatment or within 30 days of the last dose of study medication.

CONCLUSIONS The following conclusions can be drawn from this study in adults:

- Ceftibuten 400 mg once daily for 5-15 days, was effective in the treatment of acute exacerbations of chronic bronchitis;
- Ceftibuten 400 mg QD was as effective as Augmentin 500 mg TID in the treatment of acute exacerbations of chronic bronchitis;
- Ceftibuten 400 mg QD was safe and well tolerated, and had a frequency of adverse events similar to that observed with Augmentin 500 mg TID.
- No effect was observed with ceftibuten 400 mg QD when patients were instructed to take ceftibuten with a meal or one hour prior to a meal; both treatment groups were effective in the treatment of acute exacerbations of chronic bronchitis.

Applicant's Study Synopsis for C92-020

Title	Evaluation of the Safety and Efficacy of Cedax™ Capsules, 400 mg q.d., Compared to Cipro® Tablets, 500 mg b.i.d. in the Treatment of Acute Exacerbation of Chronic Bronchitis
Study Sites	Multicenter study (20 centers) performed in U.S.A.
Study Dates/Clinical Phase	October 30, 1992 to June 30, 1993 / Phase IV
Study Objectives	To evaluate the safety and efficacy of Cedax™ (ceftibuten; Schering-Plough) 400 mg q.d. vs Cipro® (ciprofloxacin HCl; Miles) 500 mg b.i.d. in the treatment of acute exacerbation of chronic bronchitis (such as bronchitis that accompanies, emphysema, asthma, and asthmatic bronchitis) in an adult population. The primary endpoint to be evaluated was the overall clinical assessment as measured by the success rate of the patients; secondary endpoints to be evaluated were microbiologic response, the safety and tolerability of the treatments.
Study Design	Multicenter, evaluator blind, randomized parallel-group comparison. Patients who met the study entry criteria were to be randomized to receive oral doses of either Cedax™ 400 mg q.d. or Cipro® 500 mg b.i.d. for 7 to 14 days on an outpatient basis.

Study Medication and Dosage

Formulation, route, Duration of Treatment	Study drug was provided as capsules or tablets for oral administration in opaque bottles with child-proof caps. Each bottle contained 14 Cedax capsules or 28 Cipro tablets. These were dispensed at the site in sufficient quantities to provide for a minimum of 7 days and a maximum of 14 days of treatment.
Dosage and frequency	Cedax™ (ceftibuten/Scherin, Plough): 400 mg q.d. (1 x 400 mg capsule administered once daily) Cipro® (ciprofloxacin hydrochloride/Miles): 500 mg b.i.d. (1 x 500 mg tablet administered twice daily [q 12 hours])

Study Procedures

The clinical assessment of patient's response was evaluated on post-treatment day 0-6 (Visit 3) and post-treatment day 7-21 (Visit 4). Clinical response was rated as clinical cure, clinical improvement, clinical failure and unassessable on Visit 3 and as sustained cure, sustained improvement, clinical relapse and unassessable on Visit 4. Microbiologic response of causative organisms susceptible to both study drugs was rated on Visit 3 and Visit 4 as eradication (elimination), persistence, colonization, superinfection, and indeterminate (unassessable) on Visit 3 and as eradication (elimination), persistence, relapse, reinfection,

colonization and indeterminate (unassessable) on Visit 4. Microbiologic response by patient was rated as eradication (elimination), persistence, eradication with colonization, superinfection and indeterminate (unassessable) on Visit 3 and as eradication (elimination), persistence, relapse, reinfection, eradication with colonization and indeterminate (unassessable) on Visit 4. An overall microbiologic assessment by patient was rated as eradication (elimination), persistence, relapse, reinfection, eradication with colonization, superinfection and indeterminate (unassessable). Patient ratings of the severity of their signs and symptoms were recorded at baseline (pre-treatment) and daily on a diary from treatment day 1 through the last day of treatment. Safety and treatment tolerability were evaluated for all patients by recording clinical adverse events and results of laboratory tests (hematology, blood chemistry and urinalysis). Chest x-rays were performed at baseline and again if clinically indicated for treatment failure.

Statistical Methods

Analyses were carried out on four populations: intent-to-treat population (303 patients), safety population (299 patients), clinical efficacy population (225 patients) and microbiologic efficacy population (72 patients). Continuous variables were analyzed using analysis of variance; discrete variables (including clinical and microbiologic response rates) were analyzed by the Fisher's Exact test or the Cochran-Mantel-Haenszel test. Time to disappearance of signs and symptoms was tested using Wilcoxon test. To test the equivalence between the Cedax™ and Cipro® groups, the lower limit of the 95% confidence interval for the difference in the overall clinical success rates was used.

Total enrollment by June 30, 1993 303

Total included in this study report: 303

Patient Population

	Cedax™ 400 mg q.d.	Cipro® 500 mg b.i.d.
Enrolled	150	153
Not treated	3	1
Intent-to-treat	150	153
Evaluable for:		
Safety	147	152
Clinical Efficacy	112	113
Microbiologic Efficacy	38	34

Patient Demography (Intent-to-treat)

Cedax™ 400 mg q.d. - 71 males, 79 females, mean age 51.7 years (range 18-84 years);
Cipro® 500 mg b.i.d. - 68 males, 85 females, mean age 51.9 years (range 18-85 years);

Applicant's Study Synopsis for C92-020

Results - Intent-to-Treat Population

The primary efficacy variable for the intent-to-treat population was the overall clinical assessment (success rate). The success rates were observed in 79.3% (119/150) of Cedax™-treated group and in 83.7% (128/153) of Cipro®-treated group. The 95% confidence interval for the difference in success rate was (-13.7%, +5.1%). The two treatment groups were therapeutically equivalent. The proportion of patients clinically cured or improved was similar for both groups – 95.5% (127/133) of Cedax™-treated patients vs 93.5% (128/137) of Cipro®-treated patients at Visit 3; at Visit 4, 90.7% (108/119) of Cedax™-treated patients vs 96.6% (116/120) of Cipro®-treated patients had similar sustained cure or improvement. The clinical response to treatment in the intent-to-treat population is summarized below:

Clinical Response	Cedax™ 400 mg q.d.	Cipro® 500 mg b.i.d.
Overall Assessment		
% Success	79.3% (119/150)	83.7% (128/153)
95% C.I. (Cedax™-Cipro®)	-13.7% to +5.1%	
Days 0 - 6 Post-Treatment		
% Cured or Improved	95.5% (127/133)	93.5% (128/137)
Days 7 - 21 Post-Treatment		
% Sustained Cured or Improved	90.7% (108/119)	96.6% (116/120)

Results - Population Evaluable for Clinical Efficacy

The results of treatment in the patients evaluable for clinical efficacy are summarized below. The overall clinical response showed success rates of 87.5% (98/112) for Cedax™ and 89.4% (101/113) for Cipro® which were therapeutically equivalent. The proportion of patients clinically cured or improved was similar for both groups – 94.6% (106/112) in Cedax™-treated patients vs 92.9% (105/113) in Cipro®-treated patients at Visit 3; at Visit 4, 92.5% (98/106) Cedax™-treated patients vs 96.2% (101/105) Cipro®-treated patients had similar sustained cure or improvement.

Clinical Response	Cedax™ 400 mg q.d.	Cipro® 500 mg b.i.d.
Overall Assessment		
% Success	87.5% (98/112)	89.4% (101/113)
95% C.I. (Cedax™-Cipro®)	-11.1% to +7.4%	
Days 0 - 6 Post-Treatment		
% Cured or Improved	94.6% (106/112)	92.9% (105/113)
Days 7 - 21 Post-Treatment		
% Sustained Cured or Improved	92.5% (98/106)	96.2% (101/105)

Results - Population Evaluable for Microbiologic Efficacy

The proportion of patients whose pre-treatment target pathogens were eliminated (total microbiologic elimination rate) were comparable between the two treatment groups with 92.1% (35/38) for Cedax™ and 97.1% (33/34) for Cipro® at Visit 3 and 91.4% (32/35) for Cedax™ vs 93.9% (31/33) for Cipro® at Visit 4.

Microbiological Response

By Pathogen	Percent of Patients With Eradication	
	Cedax™ 400 mg q.d.	Cipro® 500 mg b.i.d.
Days 0 - 6 Post-Treatment		
M. Catarrhalis	100.0% (9/9)	100.0% (11/11)
H. Influenzae	92.0% (23/25)	95.8% (23/24)
S. Pneumoniae	88.9% (8/9)	100.0% (1/1)
H. Parainfluenzae	100.0% (7/7)	100.0% (3/3)
K. Pneumoniae	–	0.0% (0/1)
Days 7 - 21 Post-Treatment	Percent of Patients With Eradication	
M. Catarrhalis	100.0% (8/8)	90.9% (10/11)
H. Influenzae	91.3% (21/23)	100.0% (23/23)
S. Pneumoniae	88.9% (8/9)	0.0% (0/1)
H. Parainfluenzae	100.0% (7/7)	100.0% (3/3)
K. Pneumoniae	–	100.0% (1/1)
By Patient and by visit	Percent of Patients With Total Eradication	
Days 0 - 6 Post-Treatment	92.1% (35/38)	97.1% (33/34)
Days 7 - 21 Post-Treatment	91.4 % (32/35)	93.9% (31/33)
Overall Assessment by Patient	Percent of Patients With Total Eradication	
	89.5% (34/38)	91.2% (31/34)

Results - safety

The number (%) of patients with at least one adverse event during the study were: 77/147 (52.4%) with Cedax™ 400 mg q.d. and 74/152 (48.7%) with Cipro® 500 mg b.i.d. The most common adverse events are summarized below:

Number (%) of Patients	Cedax™ 400 mg q.d.	Cipro® 500 mg b.i.d.
Headache	39 (26.5%)	30 (19.7%)
Nausea	11 (7.5%)	8 (5.3%)
Musculoskeletal Pain	6 (4.1%)	11 (7.2%)
Diarrhea	9 (6.1%)	7 (4.6%)
Rhinitis	9 (6.1%)	6 (4.0%)
Fatigue	7 (4.8%)	4 (2.6%)
Dyspepsia	6 (4.1%)	5 (3.3%)
Nasal Congestion	4 (2.7%)	6 (4.0%)
Fever	4 (2.7%)	5 (3.3%)
Pruritus	2 (1.4%)	6 (4.0%)
Pharyngitis	3 (2.0%)	4 (2.6%)
Loose Stool	4 (2.7%)	3 (2.0%)
Myalgia	3 (2.0%)	3 (2.0%)

Four patients (2 on Cedax™, 2 on Cipro®) discontinued treatment due to adverse events: one patient) on Cedax™ developed skin ulceration (exacerbation of stasis ulcers) on day 14, one patient , on Cedax™ had sinusitis on day 14, one patient on Cipro® on day 15 developed bronchospasm, and one patient on Cipro® complained of fatigue on day 5. The majority of adverse events were considered by the investigators to be either mild or moderate in severity. No patient died during the study.

Analysis of the laboratory test results at the end of the study revealed that 15 patients (4 on Cedax™, 11 on Cipro®) had elevated SGPT values, 11 patients (5 on Cedax™, 6 on Cipro®) had elevated SGOT values and 3 patients (1 on Cedax™, 2 on Cipro®) developed eosinophilia. No patient was removed from the study because of abnormal laboratory test results.

Conclusion

Treatment for a period of 14 days (range 2 - 17 days) with Cedax™ administered once daily at a dose of 400 mg was as effective and as well tolerated as 500 mg of Cipro® twice daily in the treatment of acute exacerbation of chronic bronchitis.

***Medical Officer's Comment:** In the best case scenario, every additional patient with AECB due to M. catarrhalis identified by the applicant in studies P92-020 and C90-038 with documented or presumed eradication would be added to the previous NDA tables of microbiologic eradication generated by the Medical Officer in the December, 1994 review.*

Table Study C88-044 et al., Study C90-045, Study C90-038 and Study P92-020. Eradication Rates in Patients with *M. catarrhalis* at Baseline

	Eradication/Total	
	Ceftibuten 400 mg QD	Controls*
NDA trials		
Study C88-044 et al (vs cefaclor)	7/10 (70%)	3/4 (75%)
Study C90-045 (vs cefixime)	11/18 (61%)	15/15 (100%)
Additional trials		
Study C90-038 (vs co-amoxiclav)	7/9 (78%)	4/4 (100%)
Study P92-020 (vs ciprofloxacin)	8/9 (89%)	10/11 (91%)
Total:	33/46 (72%)	32/34 (94%)

* Cefaclor 250 mg TID; cefixime 400 mg QD, co-amoxiclav 500 mg TID; ciprofloxacin 500 mg BID.

***Medical Officer's Comment:** There is still more than a 20% difference in the overall eradication rate of M. catarrhalis in AECB patients treated with ceftibuten from all protocols combined compared to patients treated with comparator agents.*

The Medical Officer then combined all the "additional trials" patients with M. catarrhalis eradicated, as noted above, with the microbiologic efficacy results for patients with AECB due to other pathogens (S. pneumoniae or H. influenzae). (See Medical Officer's Review, December 1994, page 38.)

Ceftibuten	C88-044	I88-111 I88-217 I88-324	C90-045	C90-038	C92-020	Total
M. catarrhalis	3/5	4/5	11/18	7/9	8/9	33/46 (72%)
H. influenzae	10/14	12/17	23/31	---	---	45/62 (73%)
S. pneumoniae	3/3	8/16	12/16	---	---	23/35 (66%)
Total Isolates						**101/143 (71%)**

Controls	C88-044	I88-111 I88-217 I88-324	C90-045	C90-038	C92-020	Total
M. catarrhalis	2/2	1/2	15/15	4/4	10/11	32/34 (94%)
H. influenzae	3/6	7/10	16/20	---	---	26/36 (72%)
S. pneumoniae	4/4	3/5	7/11	---	---	14/20 (70%)
Total Isolates						**72/90 (80%)**

Medical Officer's Comment: *The 95% CI for the difference in successful outcomes between ceftibuten and comparator agents with regard to <u>all isolates</u>, assuming the best case scenario of including every additional M. catarrhalis isolate identified by the applicant as eradicated, is (-0.22, 0.04), showing inferiority of ceftibuten.*

MO Comments on Safety/C90-038

There were four deaths in this study. All 4 patients had received treatment with ceftibuten. No deaths were reported with the comparator, Augmentin.

Patient C90-038-19 was an 84 year-old female with COPD, hypertension, and atrial fibrillation, treated with ceftibuten for AECB for 10 days (sputum culture grew no pathogen). Five days after her last dose of ceftibuten the patient was hospitalized with severe respiratory insufficiency, right heart failure and electrolyte imbalance. The applicant provided no information on CXR, laboratory findings, or further medication administered during the hospitalization. The patient died 11 days after the last dose of ceftibuten. The applicant considered the patient a "sustained cure" and her death unrelated to study drug.

Patient C90-038-20 was a 77 year-old male with prior history of diabetes and Alzheimer's disease. The patient received one dose of ceftibuten and was hospitalized 24 hours later with acute renal failure. He died 14 days after entry into the study of sepsis, perforated gall bladder, and multiple organ failure. The patient's death was considered unrelated to study drug.

Patient 90-038-24 was a 58 year-old male with emphysema, coronary artery disease with bypass surgery and cerebrovascular accident. The patient was admitted to the hospital 4 days after starting ceftibuten due to increasing shortness of breath and atrial fibrillation. The patient was removed from the study, recorded to be improving (no details provided), and discharged 5 days later. Three-weeks after the last dose of ceftibuten, the patient dies due to respiratory insufficiency, pulmonary carcinoma, and fungal infection. Adverse events were considered unrelated to study medication.

Patient 90-038-39 was a 69-year old male with emphysema, prior TB, hypertension, transient ischemic attacks and left hip replacement. The patient did not return after taking the first 5 days of ceftibuten. Attempts to contact the patient were unsuccessful. The investigator was eventually notified that the patient died 18 days after entry into the study. Cause of death was reported as pulmonary hemorrhage secondary to pulmonary carcinoma.

Serious adverse events were reported in 14 ceftibuten and 5 Augmentin patients (see table below).

Table 51. Patients with Serious* Adverse Events (Study No. C90-038).

Control No.	Treatment	Center/ Patient No.	Duration of Treatment	Adverse Event	Relationship to Study Drug
92-05-741	Ceftibuten	C90-038-19	7 days	Cardiac failure, right	Unrelated
				Respiratory insufficiency	Unrelated
				Disease progression	Unrelated
				Electrolyte abnormality	Unrelated
92-05-751	Ceftibuten	C90-038-20	1 day	Multiple organ failure	Unrelated
				Gall bladder disorder	Unrelated
				Disease progression	Unrelated
92-04-341	Ceftibuten	C90-038-24,	7 days	Dyspnea	Unrelated
94-08-531				Cardiac arrest	Unrelated
				Respiratory arrest	Unrelated
				Pulmonary carcinoma	Unrelated
				Infection, fungal	Unrelated
93-06-641	Ceftibuten	C90-038-29,	3 days	Condition aggravated	Unrelated
				Bronchospasm	Unrelated
				Dyspnea	Unrelated
92-12-761	Ceftibuten	C90-038-30,	13 days	Condition aggravated	Possible
				Dyspnea	Possible
93-11-621	Ceftibuten	C90-038-39,	5 days	Pulmonary hemorrhage	Unrelated
				Pulmonary carcinoma	Unrelated
93-07-551	Ceftibuten	C90-038-41,	10 days	No adverse event[a]	Unrelated
93-07-541	Ceftibuten	C90-038-41,	10 days	Myocardial infarction	Unrelated
92-12-151	Ceftibuten	C90-038-44,	3 days	Pneumonia	Unrelated
				Dyspnea	Unrelated
				Chest pain	Unrelated
				Coughing	Unrelated
				Heart disorder	Not provided
				Hypertension	Not provided
92-11-771	Ceftibuten	C90-038-44,	5 days	No adverse reaction[a]	Unrelated
93-08-2171	Ceftibuten	C90-038-44,	6 days	Abdominal pain	Unrelated
93-03-361	Ceftibuten	C90-038-46,	3 days	Disease progression	Unrelated
93-10-1651	Ceftibuten	C90-038-46,	10 days	Condition aggravated	Unrelated
				Respiratory disorder	Unrelated
92-11-651	Augmentin	C90-038-11	12 days	No adverse reaction[a]	Unrelated
94-08-801	Augmentin	C90-038-20	0 days	Condition aggravated	Not provided
				Emphysema	Not provided
				Drug level altered[f]	Possible
94-08-541	Augmentin	C90-038-23	6 days	Disease progression	Unrelated
92-05-711	Augmentin	C90-038-24	3 days	Dyspnea	Unrelated
				Coughing	Unrelated
				Hypoxia	Unrelated
				Dizziness	Possible
				Nausea	Possible
				Fever	Unrelated
93-10-951	Augmentin	C90-038-46,	5 days	Condition aggravated	Unrelated

a: Reported to Schering-Plough Drug Safety Surveillance. Patient summaries appear in Appendix D-3.
b: Patient had two distinct Drug Safety Surveillance reports of serious adverse events, and therefore, was assigned two seperate Drug Safety Surveillance control numbers.
c: Patient felt no improvement and requested hospitalization.
d: Patient inadvertently took 2 ceftibuten capsules daily instead of one capsule daily, therefore, the outcome is classified as an overdose.
e: Patient had a history of psychiatric problems and suicide attempts, the patient was hospitalized after completion of the study for repair of a lacerated right arm tendon and adult psychiatric care.
f: Patient's theophylline level was altered.

Medical Officer's Summary and Conclusion

The applicant has submitted additional data from two studies of patients with acute exacerbation of chronic bronchitis (AECB). Patients with *Moraxella catarrhalis* isolated from their sputum at entry were highlighted, to try to demonstrate that ceftibuten is equivalent to other marketed anti-infectives in treating AECB due to the three major pathogens (*S. pneumoniae, H. influenzae, and M. catarrhalis*). The data from these additional patients, together with the pivotal trials reviewed previously in the NDA, demonstrate that ceftibuten is clinically and statistically inferior to comparator agents in treating patients with acute *bacterial* exacerbation of chronic bronchitis.

Medical Officer's Recommendations

1. The restricted label sent to the applicant with the action letter of December, 1994, should stand. A clinical studies section highlighting the eradication rates for *S. pneumoniae, H. influenzae, and M. catarrhalis* should be included. Such labeling is consistent with that recently approved for dirythromycin

2. Package inserts for other marketed anti-infectives which do not adequately cover the 3 major pathogens in AECB should be revised to include both restrictive labeling ("not for empiric use" or "not first-line therapy") as well as clinical studies sections which detail the differences in clinical outcome and eradication rates noted in adequate and controlled clinical trials.

Janice Soreth, M.D. 9/1/95
Medical Officer

NDA 50-685 December 19, 1994

Medical Officer's Review of A Safety Update

Sponsor: Schering Corporation

Name of Drug: Ceftibuten (SCH 39720)
Cedax® Capsules

Submission Dates: October 19, 1994
December 1, 1993

Material Submitted:

The sponsor submitted a safety update on December 1, 1993 which includes additional safety data regarding ceftibuten capsules obtained since the safety update submitted in June 1992 (reviewed by Dr. Brad Leissa). It consists of a single volume.

In a May 20, 1994 fax to the sponsor, the medical officer requested another safety update. On May 20, 1994, the sponsor explained that the database for the capsules studies had not been closed. In lieu of a complete safety update, the sponsor would submit a list of deaths and dropouts. On October 19, 1994, then, the sponsor submitted a list of serious adverse events reported since November 1993.

Sponsor's Synopsis for the December 1, 1993 Safety Update for Cedax Capsules

Safety data presented in this submission were obtained between the cut-off dates for the June 1992 Safety Update and the following dates:

- August 9, 1993 for patients in clinical trials sponsored by Schering-Plough and for which data were available for inclusion in the computer database.
- August 31, 1993 for reports of serious adverse events from ongoing Schering-Plough sponsored studies or locally-sponsored studies (protocols written by a local subsidiary or a local investigator and not by Schering Plough personnel in the USA).

Safety data from 2,054 patients who received ceftibuten capsules in clinical safety and efficacy studies sponsored by Schering-Plough are included in the computer database for complete evaluation in this update. Data from 1,870 (of the 2,054) patients were included in the June 1992 Safety Update. Since that update, safety data from an additional 185 patients who received ceftibuten in a randomized trial of ceftibuten 400 mg QD versus cefixime 400 mg QD in the treatment of acute exacerbations of chronic bronchitis in adults have been obtained and have been incorporated.[1]

Medical Officer's Comment: In this safety update, the reviewer will focus on any new clinical or laboratory safety data from these 185 patients.

Deaths

Capsule summaries for two patients in Schering-Plough sponsored clinical trials who died since the June 1992 Safety Update (C90-045-06/020 and C90-045-18/006) are given below:

Patient: C90-045-06
Treatment: Ceftibuten 400 mg QD
This 71 year old male patient was a former smoker with a 56 year smoking history and a 17 year history of chronic bronchitis. Past medical history was significant for emphysema, hypertension, and a partial pulmonary lobectomy over ten years previous for malignancy. The patient entered the study with acute exacerbation of seven days duration. Sputum culture at entry was negative. The patient completed dosing and was considered a cure. The only adverse event noted while on therapy was a persistent mild headache which was designated as possibly related to study drug. Thirteen days after the end of treatment, the patient developed hemoptysis and collapsed at home. He was found to be in ventricular fibrillation and was resuscitated. He was brought to a local emergency room. Bronchoscopy revealed a left lower lung bleed which resulted in patient death four days after admission. Autopsy demonstrated recurrent lung malignancy. The investigator indicated that he did not believe the patient's death was related to study drug.

Patient: C90-045-18
Treatment: Cefixime 400 mg QD
This 55 year old female patient with no smoking history had a 3 year history of chronic bronchitis. Past medical history was significant for diabetes mellitus, congestive heart failure, and cerebrovascular accident. The patient entered the study with an acute exacerbation of 26 days' duration. She was randomized to cefixime but received only one day of therapy. In fact, on the day of study entry, the patient collapsed outside the hospital due to ventricular arrhythmia. The patient was hospitalized for treatment and died due to hemodynamic collapse. The blind was broken and the patient was found to be on cefixime. The investigator did not think that the event was related to study drug.

As of the cut-off date for this submission (August 9, 1993), 27 of 2,054 patients (1.3%) who received ceftibuten in Schering-Plough sponsored trials died during the study or within 30 days post-treatment. Death occurred in 13 of 1,085 patients (1.3%) who were randomized to comparative agents. Twenty-six additional deaths (14 ceftibuten, 11 comparative agents, and 1 unblinded medication) occurred in other studies (pharmacokinetic, locally sponsored, or ongoing clinical). No death was attributed to treatment with either ceftibuten or comparator agents.

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1 The total population of patients receiving ceftibuten (2,054) does not equal 1,870 plus 185 because of the exclusion of one patient (patient I87-325-09/054; previously included) who received ceftibuten 300 mg BID and off-study antibiotic concomitantly. This patient had no adverse events.

Discontinuations

Clinical capsule summaries for patients treated with ceftibuten or comparative who discontinued because of adverse events or laboratory abnormalities subsequent to the June 1992 Safety Update are given below. A total of 14 patients discontinued treatment (3 ceftibuten-treated patients and 11 cefixime-treated patients):

Patient: C90-045-01
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Event: rash
This 35 year old male patient was a current smoker with a 16 year smoking history and a 2 1/2 year history of chronic bronchitis. The medical history was unremarkable. The patient entered the study with an acute exacerbation of 15 days duration. He was randomized to cefixime. Sputum culture at entry showed no growth. He received three doses of study medication. On the second day of study medication the patient developed a rash of moderate severity that was considered by the Investigator as "possibly" related to study drug. The patient was discontinued and switched to Biaxin.

Patient: C90-045-01
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Event: sinusitis
This 32 year old female patient was a current smoker with a 17 year smoking history and a ten year history of chronic bronchitis. The medical history was unremarkable. The patient entered the study with an acute exacerbation of 9 days duration. She was randomized to cefixime. No sputum culture was obtained at entry. After nine days of therapy the patient was discontinued from the study due to development of sinusitis and switched to erythromycin.

Patient: C90-045-04
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Event: pressure headache
This 55 year old female patient with no smoking history had a ten year history of chronic bronchitis. The patient's medical history was significant for hypothyroidism and hypertension. The patient entered the study with an acute exacerbation of two months duration. She was randomized to cefixime. Sputum culture at entry was positive for *M. catarrhalis*. The patient was discontinued from the study after two doses of study medication due to a development of "pressure headache" and she was switched to cefaclor. The investigator listed the adverse event as "possibly" related to study drug.

Patient: C90-045-06
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Events: abdominal cramps, diarrhea

This 63 year old female patient was a current smoker with a forty year smoking history and a seven year history of chronic bronchitis. Medical history was unremarkable. The patient entered the study with acute exacerbation of 3 days duration. She was randomized to cefixime. Sputum culture at entry was negative. Six days after beginning study medication, the patient was discontinued from the study due to a development of diarrhea and abdominal cramping, both of moderate severity. Although *Clostridium difficile* testing was not done, treatment with metronidazole was started. The patient's symptoms resolved once off study. The investigator designated these adverse events as "probably" related to study medication.

Patient: C90-045-09
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Events: stomach cramps, decreased appetite, diarrhea, bloated feeling
This 77 year old male patient was a former smoker with a 25 year smoking history and a 53 year history of chronic bronchitis. The patient's medical history was significant for asthma, hypertension, and prostate cancer. The patient entered the study on 3/8/93 with an acute exacerbation of seven days duration and he was randomized to cefixime. Sputum culture at entry grew *Pseudomonas aeruginosa* resistant to both ceftibuten and cefixime; a subsequent culture grew normal flora. The patient was designated as a sustained cure at study completion. The therapy was discontinued after 9 days due to the development of acute colitis with explosive diarrhea. He was prescribed Flagyl. Stool culture was not performed. The diarrhea lasted for about 10 days until 3/25/93. On 3/26/93 the patient was seen by the Investigator, the diarrhea and associated GI symptoms had resolved, but the patient was found to have oral moniliasis and was started on Nystatin. Five days after this visit he reported by phone the recurrence of diarrhea but declined to visit the emergency room. Diarrhea continued until the next visit on 4/5/93. At that time, a stool sample was obtained and sent for culture, however, the lab failed to perform *C. difficile* testing. The patient subsequently underwent proctologic exam and was hospitalized with a diagnosis of acute colitis which resolved while he was inpatient. The investigator identified the early GI adverse events as probably related and the later ones as possibly related.

Patient: C90-045-012
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Event: asthma attack
This 36 year old female patient was a former smoker with a 17 year smoking history and a three year history of chronic bronchitis. The patient's medical history was significant for childhood-onset asthma. The patient entered the study with an acute exacerbation of 6 days duration. She was randomized to cefixime. Sputum culture at entry grew *H. influenzae* sensitive to both ceftibuten and cefixime. The patient was discontinued after two days of therapy due to an acute asthma attack of moderate severity requiring a visit to the emergency room where IV steroids and albuterol aerosol treatment was started. The investigator did not believe the event was related to treatment with study medication.

Patient: C90-045-013
Treatment: Ceftibuten 400 mg QD
Discontinuation due to Adverse Event: bronchospasm
This 48 year old female patient was a former smoker with a 35 year smoking history and a six year history of chronic bronchitis. The patient's medical history was significant for emphysema and reactive airway disease. The patient entered the study with an acute exacerbation of 2 days duration. She was randomized to ceftibuten. Sputum culture at entry was positive for *H. influenzae* (intermediate sensitive to ceftibuten, sensitive to cefixime), *H. parainfluenzae* (same sensitivities), α-Streptococcus, Neisseria, and *H. parahemolyticus*. The patient suffered an episode of moderately severe bronchospasm on the fourth day of dosing. This was treated with metaproterenol inhaler and albuterol nebulizer. The next day the patient experienced a recurrence of symptoms and at this time she was treated with oral steroids. On day 9, the patient was discontinued due to the above adverse event. The investigator evaluated the events as unrelated to study drug administration.

Patient: C90-045-014
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Event: diarrhea
This 48 year old male patient with no smoking history had a six year history of chronic bronchitis. The patient's medical history was significant for inflammatory bowel disease stable for several months on sulfasalazine therapy. The patient entered the study with an acute exacerbation of one month duration. He was randomized to cefixime. Sputum culture at entry grew *H. parainfluenzae* (no sensitivities done). Later culture demonstrated normal flora. The patient received eleven doses of study drug. On the eleventh day of the study, the patient developed severe diarrhea requiring study discontinuation. The investigator described this event as "related" to study drug administration. The patient was treated with hydrocortisone per rectum and Lomotil. The patient was also given metronidazole for a presumptive diagnosis of *C. difficile* colitis (testing for *C. difficile* was attempted but was not successfully performed). Symptoms resolved and then relapsed off of metronidazole. The patient was given a second course of metronidazole with resolution of diarrhea.

Patient: C90-045-015
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Events: dysphagia, gastritis
This 56 year old female patient was a current smoker with a 40 year smoking history and a three year history of chronic bronchitis. Medical history was unremarkable. The patient entered the study with an acute exacerbation of three days duration. She was randomized to cefixime. Sputum culture at entry showed no growth. The patient received five doses of study medication. On the fourth study day, the patient developed gastritis and dysphagia of moderate severity requiring discontinuation. The investigator believed the event was "probably" related to treatment with study medication.

Patient: C90-045-016
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Events: anxiety, nervousness
This 77 year old female patient was a current smoker with a 48 year smoking history and a more than ten year history of chronic bronchitis. The patient's medical history was significant for anxiety, childhood-onset asthma/reactive airway disease, emphysema, and coronary artery disease. The patient entered the study with an acute exacerbation of one day duration. She was randomized to cefixime. Sputum culture at entry grew *S. pneumoniae* sensitive to cefixime and resistant to ceftibuten. Repeat culture during treatment demonstrated only normal flora. The patient was discontinued from the study after 8 days of therapy due to anxiety/nervousness of moderate severity. The patient also complained of an irregular heart rate while on study drug; cardiology evaluation was negative. Following discontinuation from the study the patient was started on cefuroxime and oral steroids. She remained anxious despite discontinuation. The investigator did not believe the event was related to treatment with study medication.

Patient: C90-045-18
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Event: cardiovascular event (ventricular arrythmia)
This 55 year old female patient with no smoking history had a 3 year history of chronic bronchitis. The patient's medical history was significant for diabetes mellitus, congestive heart failure, and cerebrovascular accident. The patient entered the study with an acute exacerbation of 25 days of duration. She was randomized to cefixime but she received only one day of therapy. In fact, on the day of study entry, the patient collapsed outside the hospital due to ventricular arrhythmia. The patient was hospitalized for treatment and died due to hemodynamic collapse. The blind was broken and the patient was found to be on cefixime. The investigator did not think that the event was related to study drug.

Patient: C90-045-019
Treatment: Ceftibuten 400 mg QD
Discontinuation due to Adverse Events: loose stools, sinusitis
This 60 year old female patient was a current smoker with a 40 year smoking history and a 10 year history of chronic bronchitis. The patient's medical history was significant for hypertension. The patient entered the study with an acute exacerbation of three days duration. She was randomized to ceftibuten. Sputum culture at entry showed heavy growth of normal flora. The patient completed the treatment receiving 9 doses of study medication and she was considered improved. On the eighth day after entry to the study, the patient experienced mild "loose stools" which resolved spontaneously. The investigator deemed this event as "possibly" related to study medication. At the post-treatment visit, the patient was found to have evidence of sinusitis and was placed on ceftrozil and discontinued from the study. The investigator did not believe the event was related to treatment with study medication.

Patient: C90-045-019
Treatment: Cefixime 400 mg QD
Discontinuation due to Adverse Event: nervousness
This 51 year old female patient was a current smoker with a 35 year smoking history and a 41 year history of chronic bronchitis. The patient's medical history was significant for anxiety, hypertension, peripheral vascular disease, and irritable bowel syndrome. The patient entered the study with an acute exacerbation of 3 days

duration. She was randomized to cefixime. Sputum culture at entry grew normal flora. The patient developed severe "nervousness" on the day of entry which required discontinuation on the third day of the study. The investigator designated the event as "possibly" related to treatment with study medication.

Patient: C90-045-23
Treatment: Ceftibuten 400 mg QD
Discontinuation due to Adverse Events: increased shortness of breath, acute exacerbation of COPD
This 61 year old male patient was a current smoker with a 45 year smoking history and a 20 year history of chronic bronchitis. The patient's medical history was significant for emphysema, hypertension, and peptic ulcer disease. The patient entered the study with an acute exacerbation of seven days of duration. Sputum culture was not done at entry. The patient was hospitalized for increased shortness of breath and acute exacerbation of COPD after three doses of study drug and he was discontinued from the study. The investigator did not believe the event was related to study drug.

One percent (6 of 456) of patients who received ceftibuten 200 mg BID, 5% (9 of 186) of patients who received ceftibuten 300 mg BID, and 3% (40 of 1,412) of patients who received ceftibuten 400 mg QD were withdrawn from clinical trials for either adverse events or laboratory abnormalities. These overall incidences are similar to those reported previously in the June 1992 Safety Update (1% [6 of 455] of patients who received ceftibuten 200 mg BID, 4% [8 of 187] of patients who received ceftibuten 300 mg BID, and 3% [35 of 1,228] of patients who received ceftibuten 400 mg QD).

The percentages of patients randomized to comparative agents and discontinued from clinical trials for adverse events or laboratory abnormalities are as follows: 4% (9 of 242) of patients who received cefaclor 250 mg TID; 2% (4 of 250) of patients who received cefaclor 500 mg TID; 6% (11 of 185) of patients who received cefixime 400 mg QD; 7% (12 of 161) of patients who received TMP/SMX 160/800 mg BID; 3% (2 of 65) of patients who received Augmentin® 500 mg TID, and 2% (1 of 52) of patients who received norfloxacin 400 mg BID. None of the patients who received ofloxacin 200 mg BID (n=29), ceftriaxone 1g IM (n=73), cefatrizine 500 mg TID (n=14), or cefuroxime axetil® 500 mg BID (n=1) discontinued prematurely from the studies because of adverse events or laboratory abnormalities.

NDA 50-685

Cedax Capsules Safety Update

Serious Adverse Events

The following is a list of serious adverse reactions for ceftibuten or comparator agents reported since the December 1993 safety update:

Table 1. Serious Adverse Events Occurring with Ceftibuten Capsule or Comparator Drugs in Ongoing and Locally Sponsored Clinical Studies.

Study Center	Patient	Treatment	Dosage	Duration of Treatment (Days)*	Event(s)	Relationship to Study Drug§	Cause of Death for Events Resulting in Death
C90-038-39		Blinded Study (Ceftibuten vs Augmentin)	unknown	5	Pulmonary Hemorrhage Pulmonary Carcinoma	Unlikely	Pulmonary exsanguination due to bronchogenic carcinoma.
C90-038-46		Blinded Study (Ceftibuten vs Augmentin)	unknown	10	Condition Aggravated Respiratory Disorder	Unlikely Unlikely	Not applicable
C90-038-46		Blinded Study (Ceftibuten vs Augmentin)	unknown	5	Condition Aggravated	Unlikely	Not applicable
C92-125-05		Ceftibuten	400 mg	10	Taste Perversion	Probable	Not applicable
C92-125-43		Ceftibuten Cipro	400 mg 500 mg	8 2	Colitis Pseudomembranous Diarrhea, *Clostridium difficile* Diarrhea Abdominal Pain Fever Myalgia Rigors Headache SGOT Increased SGPT Increased	Unlikely Unlikely Not Provided Not Provided Unlikely Unlikely Unlikely Not Provided Not Provided Not Provided	Not applicable
C92-125-43		Ceftibuten	400 mg	4	Taste Perversion	Probable	Not applicable
#90-039-62		Ceftibuten	400 mg	11	Condition Aggravated Respiratory Disorder Hepatic function abnormal	Unlikely Unlikely Unlikely	Not applicable
191-257-50¶		Ceftibuten	400 mg	5	Leukocytosis Diarrhea Headache Fever	Unlikely Unlikely Unlikely Unlikely	Not Applicable
189-380-51		Ceftibuten	400 mg	3	Intestinal Disorder	Unlikely	Not applicable

* Total duration of treatment.
§ As determined by the Sponsor's Drug Safety Surveillance group or by the investigator.
¶ This reportwas received during May 1993; however, it was not included in the 11/30/93 Ceftibuten Capsule Safety Update

Table 1. (Cont'd) Serious Adverse Events Occurring with Ceftibuten Capsule or Comparator Drugs in Ongoing and Locally Sponsored Clinical Studies.

Study Center	Patient	Treatment	Dosage	Duration of Treatment (Days)*	Event(s)	Relationship to Study Drug§	Cause of Death for Events Resulting in Death
L00-359-2		Ceftibuten	400 mg	5	Cardiac Failure Left Sepsis	Unlikely Unlikely	Not applicable
L00-359-2		Ceftibuten	400 mg	10	Breast Neoplasm Malignant Female	Unlikely	Not applicable
L00359208301		Ceftibuten	800 mg	10	Hernia	Unlikely	Not applicable
L00359208301		Ceftibuten	800 mg	10	Bradycardia	Unlikely	Not applicable
L00359208301		Ceftibuten	800 mg	11	Dysphagia Asthenia Anorexia	Not Provided Not Provided Not Provided	Not applicable
M90-835-54¶		Ceftriaxone	2000 mg	11	Hepatic Enzymes Increased	Possible	Not applicable
M90-835-55		Ceftibuten	400 mg	5	Cardiac Failure Aortic Stenosis Disease Progression	Unrelated Unrelated Unrelated	Cardiac decompensation
M90-839		Augmentin	500 mg TID	10	Condition Aggravated Bronchospasm	Unlikely Unlikely	Not applicable
M91-265-71		Ceftibuten	800 mg	2	Cardiac Failure Disease Progression Respiratory Insufficiency	Unlikely Unlikely Unlikely	Acute respiratory failure
M91-265-78		Cefpodoxime Proxetil	400 mg	5	Ketosis	Unlikely	Not applicable
M93-134-01		Blinded Study (Ceftibuten vs Augmentin)	400 mg	10	Dyspnea	Unlikely	Not applicable
P92-019-06		Biaxin	1000 mg	Unknown	SGOT Increased SGPT Increased	Unlikely Unlikely	Not applicable

* Total duration of treatment.
§ As determined by the Sponsor's Drug Safety Surveillance group or by the investigator.
¶ This report was received during June 1993; however, it was not included in the 11/30/93 Ceftibuten Capsule Safety Update.

Potentially Important Abnormal Clinical Laboratory Test Results

A clinical summary for one ceftibuten-treated patient with an abnormal lab test which occurred in completed clinical studies subsequent to the June 1992 Safety Update appears below:

> **Patient: C90-045-011**
> **Treatment: Ceftibuten 400 mg QD**
> **Abnormality: Decreased neutrophil count**
> This 34 year old female patient was a current smoker with an 18 year smoking history and a ten year history of chronic bronchitis. The patient entered the study with an acute exacerbation of 14 days duration. She was randomized to ceftibuten. Sputum culture at entry showed no growth. The patient completed the treatment receiving ten doses of study medication and was assessed as a "cure." At the post-treatment visit, the patient was found to have a decreased leukocyte count from 8,000 to 2,100/mm^3. This drop of the leukocyte count was due to a decrease in the neutrophil count that dropped from 6,700/mm^3 (84%) to 210/mm^3 (10%). The investigator assessed this laboratory abnormality as "possibly" related to study medication. At the next follow-up visit, the patient was found to have clinically relapsed and was placed on erythromicin. No further lab tests are available. [*Medical Officer's Comment: The investigator should have repeated a complete blood count with differential in this relapsed patient who would qualify as having severe neutropenia if the count of 210/mm^3 was real.*]

The frequency of clinical laboratory abnormalities associated with ceftibuten treatment appeared similar to that observed following treatment with comparator agents. Elevations of BUN and serum creatinine were the most frequent laboratory abnormalities associated with treatment with ceftibuten (both occurring in 6% of the 2,054 patients), and occurred in similar frequencies with the comparator agents. Other reported laboratory abnormalities for both ceftibuten and comparators were decreases in hemoglobin, increased levels of eosinophils (absolute counts), and, to a lesser degree, increases in results of liver function tests (SGOT, SGPT, total bilirubin, and alkaline phosphatase). Trends for slight decreases in neutrophil and total white blood cell counts, and for increases in platelet count, were also observed. These findings were not considered clinically important. The most common urinary laboratory abnormalities were the presence of epithelial cells, red blood cells, white blood cells, and trivial changes in urinary pH.

The June 1992 Safety Update summarized results for 468 subjects who received ceftibuten capsules in Phase I clinical pharmacology studies sponsored by Schering-Plough. No additional data have been obtained.

A summary of results from 2,279 patients and 42 healthy volunteers who participated in studies sponsored by was included in the NDA and the previous Update. No new data have been reported by

Schering-Plough-sponsored clinical trials with ceftibuten capsules were conducted in 21 countries. In the total patient population, there was an approximately equal distribution of males and females enrolled in the studies. The mean age of patients was 53.0 years and the majority of patients were white (87%). Adverse events occurred in 19% (388 of 2,054) of patients who received ceftibuten capsules in Schering-Plough sponsored trials. The most frequently reported individual adverse events were diarrhea, nausea, and headache; each occurred in 3% of the 2,054 patients who received ceftibuten.

As a group, gastrointestinal disorders were the most frequently reported type of adverse events, and include diarrhea, nausea, dyspepsia, vomiting, and abdominal pain. The incidence of gastrointestinal disorders was 6% (27 of 456) with ceftibuten 200 mg BID[2], 10% (19 of 186) with ceftibuten 300 mg BID, and 11% (157 of 1,412) with ceftibuten 400 mg QD.[3]

The overall incidence of clinical adverse events, the types of adverse events (e.g., gastrointestinal), and the incidence of the most frequently occurring adverse events (i.e., diarrhea, nausea, and headache) associated with ceftibuten appear to be related to the individual dose (i.e., 200 mg, 300 mg, or 400 mg) rather than the total daily dose.

Drug-demographic interaction data show that the incidence of adverse events in patients treated with ceftibuten capsules 200 mg BID, 300 mg BID, or 400 mg QD ranged from 23% in patients ≤40 years of age to 16% in patients >65 years of age. A higher incidence of adverse events was generally observed for women than for men (22% vs 16%). Race only slightly affected the incidence of adverse events (19% for whites; 15% for non-whites). A higher incidence of adverse events observed in patients enrolled in US versus international studies (26% versus 14%) may be related to reporting practices. When only drug-related event rates are evaluated, differences between site location are removed, and the differences in adverse event rates across the dosages are less striking. [*Medical Officer's Comment: Nevertheless, there is still a trend in U.S. patients of increasing drug-related adverse event rate with increasing ceftibuten dose, as seen in the table below.*]

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2 BID = twice daily

3 QD = once daily.

Table 8.1 Number (%) of Patients with Adverse Events, (Total and Drug-Related) for Ceftibuten 200 mg BID, Ceftibuten 300 mg BID, and Ceftibuten 400 mg QD, Stratified by Study Location

All Adverse Events	U.S.	International	Total
200 mg BID	9 (11%) (n=79)	37 (10%) (n=377)	46 (10%) (n=456)
300 mg BID	8 (19%) (n=43)	22 (15%) (n=143)	30 (16%) (n=186)
400 mg QD	214 (28%) (n=776)	98 (15%) (n=636)	312 (22%) (n=1,412)
Total	231 (26%) (n=898)	157 (14%) (n=1,156)	388 (19%) (n=2,054)
Drug-Related	**U.S.**	**International**	**Total**
200 mg BID	7 (9%) (n=79)	33 (9%) (n=377)	40 (9%) (n=456)
300 mg BID	5 (12%) (n=43)	21 (15%) (n=143)	26 (14%) (n=186)
400 mg QD	121 (16%) (n=776)	84 (13%) (n=636)	205 (15%) (n=1,412)
Total	133 (15%) (n=898)	138 (12%) (n=1,156)	271 (13%) (n=2,054)

Drug-disease interaction data suggest that in patients with renal insufficiency, the dose or frequency of dosing should be adjusted based on creatinine clearance.

All available safety data collected from worldwide clinical trials and submitted previously in this update demonstrate that ceftibuten is well tolerated and appears to have a safety profile similar to that of other oral cephalosporins.

Medical Officer's Conclusions

The safety information presented in December, 1993 Safety Update and the October, 1994 submission do not present new clinical or laboratory adverse event information on ceftibuten capsules. The most common drug-related adverse events for patients, as determined by the investigator, are gastrointestinal side effects, including diarrhea and nausea.

The precise incidence rates for a given adverse event are different for US and non-US patient populations. For labeling purposes, incidence rates from US patients presented in the cumulative safety data of the December, 1993 Safety Update should be used.

Janice Soreth MD 12/19/94

Janice Soreth, M.D.
Medical Officer

Concurrence only:
HFD-520/DivDir/Lumpkin
HFD-520/SMO/Albrecht

12/21/94

cc:
Orig. NDA
HFD-340
HFD-520
HFD-520/DepDir/Gavrilovich
HFD-520/Pharm-Buko
HFD-520/Micro-Dionne
HFD-520/Stat-Turney
HFD-520/Chem
HFD-520/Debelias

12/20/94

EXCLUSIVITY SUMMARY FOR NDA # 50-585 SUPPL #_____

Trade Name Cedax® Capsules Generic Name Ceftibuten

Applicant Name Schering-Plough Research Institute HFD # 520

Approval Date If Known _____

Regulated under Section 507 of the Act and is therefore ineligible for exclusivity

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /___/

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

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

YES /___/ NO /___/

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

_____

_____

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

_____

_____

Revised 5-90

cc: Original NDA Division File HFD-84

d) Did the applicant request exclusivity?

YES /___/ NO /___/

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

_____

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

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

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 de-sterification 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# _____ _____

NDA# _____ _____

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 6. 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?

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, 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: _____

Regulated under 507 of the "Act" and is ineligible for exclusivity

[signature] 12/4/92
Signature Date
Title: Legal Manager

[signature] 1/16/92
Signature of Date
Division Director

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 50-585 Trade (generic) names Cedax® (Ceftibuten) Capsules

Check any of the following that apply and explain, as necessary, on the next page:

yes 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

✓ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

___ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

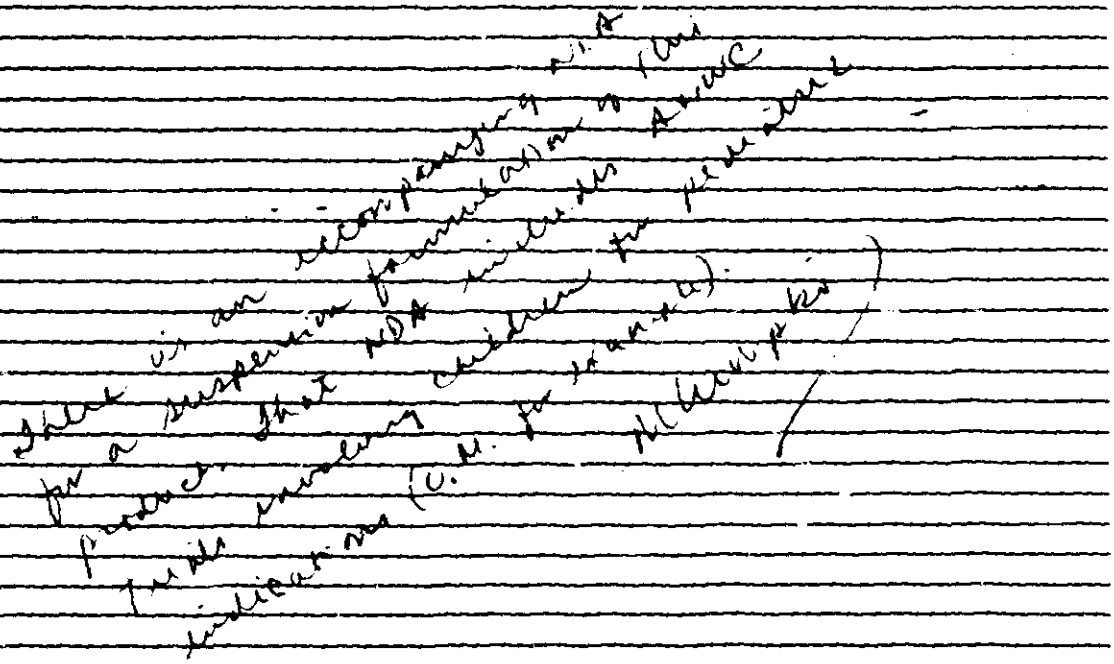
___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. 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 do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____



Carmen DeBellas
Signature of Preparer

12/9/92
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

Pharm

Review and Evaluation of Pharmacology And Toxicology Data
Division of Anti-Infective Drug Products
HFD-520

NDA 50-685 (original submission dated December 20,1991)

Drug: CEDAX$_R$ (brand of ceftibuten) Capsules

Category: Cephalosporin antibiotic

Sponsor: Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0350
Telephone (908) 298-4000

Number of Vols.: 1.1 to 1.23

Date CDER Received: Dec. 20,1991

Date Assigned: 1/10/92

Date Review Started: 3/10/92

Date 1st Draft Completed: September 14, 1992

Date Review Accepted by Supervisor: December 10,1992

Review Objectives: To establish the safety of the drug to humans based on animal studies.

Dosage Form & Route of Administration: 200mg and 400mg capsules; oral
Related Submissions: IND IND
NDA 50-686 (Powder for Oral Suspension).
For Code Names, Chemical Name, Name of Manufacturer, Chemical Structure see the "REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA of Dec. 14,1987; IND IND

According to the "NDA Specifications for Ceftibuten 200 and 400mg Capsules" the concentration of the "Total Related Compounds" is equal or less than 6.0% from which 1% is the trans isomer.

CEFTIBUTEN FORMULATIONS USED IN NONCLINICAL STUDIES

A 14C-Ceftibuten.HCl solution in 0.1 M phosphate buffer, pH=8 (10mg ceftibuten equ/ml)

B Ceftibuten aqueous solution (5mg/ml)

Ceftibuten aqueous suspension (300 mg/ml for rat studies); 200mg/ml for dog studies)

D Ceftibuten pediatric suspension (36 mg/ml)

E Ceftibuten solution in physiological saline

F Ceftibuten packed in gelatin capsules

G Ceftibuten 25% suspension in 5% aqueous acacia solution

PHARMACOLOGY

1) 8. General Pharmacology of the Oral Cephem Antibiotic 7432-S and its Metabolite 7432-S-Trans.

Abstract: " General pharmacological activities of 7432-S were studied in various species of animals and compared with those of cefaclor (CCL). In addition, 7432-S-trans as a metabolite of 7432-S was studied and compared with its mother compound. 7432-S-and CCL were administered orally, while 7234-S-trans as well as 7432-S was prepared iuto its 25% Na salt solution and administered I.V. at a rate of 1 or 5 ml/min.
7432-S produced no marked influence on gross behavior of mice when administered in days (at 1,000mg/kg and lower dosage levels). However, slight hypoactivity was noted at 600mg/kg and higher dosage levels and slight hypothrermia, anesthesia potentiation and loose stool, at 2000 mg/kg and higher dosage levels. In dogs, this drug elicited vomiting in a few animals when administered in a single dose at a dosage level of 1,000mg/kg and vomiting, mild loose stool and loose stool with mucous and blood when administered at a dosage level of 1,000mg/kg twice daily for five consecutive days. However, it produced no effect on any other behavior, various central nervous system parameters or rat neuromuscular junction. No noticeable effect was produced on respiration, blood pressure or ECG in conscious dogs and anesthetized cats or on isolated Guinea pig right atrium. The passage of charcoal meal in mouse small intestine was slightly enhanced at 500mg/kg and higher dosage levels and spontaneous motility of rabbit stomach in situ, isolated rabbit and Guinea pig ileum and rat uterus showed no drug-related change.
This drug produced no influence on parameters reflecting the function of rat kidneys with the exception of slightly decreased urine volume when administered in a single dose at a dosage

level of 1,000mg/kg.
When it was administered at a dosage level of 1,000mg/kg twice daily for five consecutive days, urine volume and urinary excretion of electrolytes were decreased and urinary pH was slightly lowered. This drug decreased the secretion of gastric juice and total acid output in rats,but produced no influence on plasma glucose levels in rabbits. Since this drug influenced a part of d4eterminations and observations only when administered determinations and observations only when administered in larger doses, especially by successive administration, it is apparent that its general pharmacological effects are in general extremely mild and as mild as, or milder than, those of CCL. Further, general pharmacological effects of 7432-S-trans-rich Na are mild as, or slightly milder than, those of 7432-S Na with the exception of vomiting induction in dogs.
Drugs Used in the Above Studies: 1) 7432-S= The to be marketed subject drug, 2) 7432-S Na (cis/trans ratio= 98.44/1.56, 3) 7432-S-trans-rich Na (trans/cis ratio= 78.55/211.45). Other Cephalosporin Reference Drug= Cefaclor (CCL) ."

Reviewer's Remarks: I agree with the Applicant's view that since the general pharmacological effects of ceftibuten are just as mild or milder than those of Ceclor(R) (Cefaclor, USP, Lilly), I considered the drug to be safe.
The vomition induction of ceftibuten in dogs is worse than that of cefaclor. The canine species is particularly sensitive non-specifically to the vomition inducing effects of any substance which irritates the gastric mucosa in humans only so mildly that it results in no vomition; I am not concerned about the emetic effect of the drug either.

PHARMACOKINETICS

The list of pharamcokinetic studies presented in Vol. 1.12 is not completely identical with the list given in Vol. 1.1 under "REFERENCES FOR APPLICATION SUMMARY". Since except the Reproduction Studies there was no useful review done in the IND phase of the submission, there is no time for detailed reviews, ~~are for~~ a condensed summary of the results is presented. (Ruthie)

writing up a

1) Ceftibuten, given orally, is well absorbed in the rat, mouse and dog, based on urinary excretion data, but appears to be slightly absorbed in the rabbit and cynomolgus monkey as only about 20% of the dose was recovered in their urine. In both rats and dogs, most of the drug-derived material in plasma is unchanged ceftibuten indicating that

MMC 2/19/93 after talk w/ K.C.

presystemic elimination ("first pass metabolism") is negligible.
Ceftibuten-trans, the major conversion product of ceftibuten, is present in plasma in low concentrations.

2) In mice, ceftibuten absorption is dose proportional for low to moderately low doses, but less than dose proportional at high doses. In rats and dogs, ceftibuten absorption appears to be dose-proportional for the dose used in the pharmacokinetic studies (20 mg/kg) and the lowest toxicokinetic dose (300 mg/kg for the rat and 200mg/kg for the dog),but less than dose-proportional for the higher toxicokinetic doses. In monkeys, less than dose proportional absorption already occurrs at relatively low doses.

3) The presence of food decreases the rate and extent of ceftibuten absorption in rats, mice and cynomolgus monkeys.

4) The absolute bioavailability of ceftibuten after an oral dose of 20 mg/kg is 66% in the rat and 64% in the dog.

5) There is no drug accumulation in rats following multiple oral administration of 20mg/kg doses or hepatic drug metabolizing enzyme induction upon repeated oral administration of 20 mg/kg doses or hepatic metabolizing enzyme induction upon repeated oral administration of 200 mg/kg doses. Likewise, no drug accumulation occurs in rats and dogs upon multiple administration of toxicological doses (27 to 216 mg/kg/day for one month in rats and 200 to 800 mg/kg/day for one or three months or or 150 to 600 mg/kg/day for six months in dogs).

6) Ceftibuten is poorly to moderately bound to serum/plasma proteins of mice, rats, rabbitts, dogs (all less than 40%) and cynomolgus monkeys (55-80%) as well as humans (60-64%).

7) In rats, ceftibuten is widely distributed throughout the tissues. However, high concentrations occur only in the kidneys, the primary organ of ceftibuten excretion. In all other tissues, the concentrations of total radioactivity and unchanged ceftibuten are lower than those in plasma. The radioactivity in all tissues declines rapidly with time and no tissue accumulation or change in the tissue distri-

bution pattern of ceftibuten in mice is similar to that observed in rats. In both species, the concentrations of ceftibuten in some major tissues after a 20 mg/kg oral dose are above the minimum inhibitory concentrations (MICs) (1ug/ml or g) for at least a two hour interval.

8) Small amounts of ceftibuten and/or ceftibuten-derived material cross the rat placenta, reaching concentrations in fetal tissues considerably lower than those in maternal tissues. Small amounts of ceftibuten and or ceftibuten-derived material also pass into rat milk.

9) The drug penetrates into rat inflammatory exudate and cerebrospinal fluid but the concentrations attained in these fluids are lower than those in plasma.

10) Ceftibuten is not readily metabolized in the rat and dog. Most of the drug-derived material excreted into the urine is unchanged ceftibuten. In addition, the urine contains small amounts of ceftibuten-trans and very small amounts of two minor metabolites.

11) The total body clearance and terminal phase half life (t1/2) are similar in rats and mice indicating that these two animal species do not differ from each other with respect to ceftibuten pharmacokinetics.

In dogs, ceftibuten is eliminated more slowly than in rats and mice as indicated by the lower total body clearance and longer t1/2.

12) Ceftibuten is excreted primarily into the urine by the rat, mouse and dog and possibly by the rabbit and monkey The renal clearance in the dog is about 30% of that in the rat and mouse. Biliary excretion (as determined in rats) is minimal.

In summary, ceftibuten is well absorbed in the rat, mouse and dog. Absorption is less than dose-proportional when administered at toxicological doses. The presence of food decreases the rate and extent of ceftibuten absorption. The drug is not an enzyme inducer and does not accumulate upon multiple dosing. The binding to plasma prroteins is low to moderate. Ceftibuten is not readily metabolized. It is rapidly eliminated from the body through the kidneys and does not accumulate in any tissue. The

drug appears to undergo some isomerization to its trans form in the stomach.
Thus, based on the metabolic disposition and pharmacokinetics in laboratory animals, ceftibuten does not appear to present any safety concern.

Reviewer's Remarks: What we have here is a thorough excersise in comparative pharmacokinetics and metabolic disposition.

Since the various animal sprecies used in the study showed various patterns lacking consistency, for each parameter, the selection of the proper animal model or models happened after parameters were studied in all species involved in the study. The next chapter will give the final answer to this complex question.

Comparison of Human and Animal Disposition/Pharmacokinetics

Ceftibuten bioavailability in man is 70% or higher, based upon urinary excretion of unchanged drug. As in the laboratory animals, presystemic biotransformation ("first pass metabolism") is negligible. In man, as in animals, the absorption of ceftibuten at high doses appears to be dose dependent. In humans at lower doses, the absorption of ceftibuten is nearly complete. Food decreases the rate and extent of ceftibuten absorption in both man and the laboratory species.

Plasma concentrations of ceftibuten are dose proportional in man with doses between 200 and 400 mg (therapeutic doses), but are lees than dose proportional at an 800mg/kg dose.

In man after a 400 mg oral dose (therapeutic dose) and in animals after a 20 mg/kg oral dose, the plasma concentrations of ceftibuten are above the MICs (1 ug/ml) of most organisms from approximately 2 hr (mice) to 12 hr (man).

Ceftibuten is moderately bound to human plasma proteins. In this respect, man is more similar to the monkey than to other animal species.

Ceftibuten is not readily metabolized in either man, rat or dog. Only one major (unchanged ceftibuten))

and three minor (ceftibuten-trans, B-1 and B-2) components are found in the urine of rats, dogs and humans.

Ceftibuten is excreted primarily via the kidneys by both man and laboratory species. In man, however, the total body clearance and the renal clesarance are lower and the terminal phase half life is longer than those in animals. With respect to these pharmacokinetic parameters, man apprears to be closer to the dog than the rat or mouse.

In summary, the metabolic disposition and pharmacokinetic profile of ceftibuten in laboratory animals is similar to those in man. The dog appears to be the animal species most closely resembling man with respect to the pharmacokinetic disposition of ceftibuten.

Reviewer's Remarks: The Applicant's summary is acceptable.

PHARMACOKINETICS OF CEFTIBUTEN IN LABORATORY ANIMALS AND MAN FOLLOWING SINGLE ORAL DOSES

The table gives an excellent comparison of the animal and human pharmacokinetic data.
[A xeroxed page from the submission (05 0440)] should be inserted here.

TOXICOKINETICS

The toxicokinetics of ceftibuten were determined in rats and dogs following single oral doses so as to relate dose (mg/kg) administered with "exposure". The doses evaluated in rats (300, 1,000 and 3000mg/kg) were 52.6 to 526 times the therapeutic dose level of 400 mg (5.71 mg/kg) in man (aasuming an average human body weight of 70 kg). Similarly, the doses evaluated in dogs (200, 400 and 800mg/kg) were 35 to 140 times the therapeutic dose. In both rats and dogs , the maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve [AUC (0-24 hr)] were dose-related.

The plasma Cmax and AUC attained in these toxicokinetic studies were compared to the values observed in man following administration of the therapeutic dose of 400mg. In rats, after an oral dose of 3000mg/kg, the Cmax and AUC values were about 10 and 14 times the respective values in man. In dogs, after an

E. Summary of Data

The pharmacokinetic data obtained in laboratory animals after a single oral dose of ceftibuten are summarized in Table 4 along with pertinent human data and the plasma concentration-time curves for animal species and man are presented in Figure 1.

TABLE 4

PHARMACOKINETICS OF CEFTIBUTEN IN LABORATORY ANIMALS AND MAN FOLLOWING SINGLE ORAL DOSES

Species	Dose (mg/kg)	Cmax (µg/ml)	Tmax (hr)	AUC(I) (µg·hr/ml)	t½ (hr)	Cl/F (ml/min/kg)	Vdarea/F (L/kg)	F (%)	Ae (% of dose)	Clr (ml/min/kg)	Ref.
Rat	20							51	50.1	7.63	1,4
Mouse	20							56	55.7	7.23	4
Rabbit	20							21	20.8	-	3
Dog	20							80	39.8	2.23	11
Cynomolgus Monkey	20							20	20.0	-	3
Man	2.9[c]	10.8	2.1	49.4	2.15	0.89	0.16	90	70.4	0.50	28

Cmax : Maximum plasma concentration
Tmax : Time to reach Cmax
AUC(tf) : Area under the plasma concentration-time curve from time zero to the last evaluable time interval
AUC(I) : Area under the plasma concentration-time curve from time zero to infinity
t½ : Terminal phase half-life
Cl/F : Total body clearance
Vdarea : Apparent volume of distribution
Ae : Urinary excretion
Clr : Renal clearance
F : Extent of absorption, based on urinary excretion (it represents minimum absorption)

[a]AUC(tf)
[b]Not determined
[c]Based on 70 kg body weight

oral dose dose of 800mg/kg, the Cmax and AUC values were about 9 and 19 times the respective values in man.

The data in the following table clearly show that the rats and dogs were exposed to concentrations of ceftibuten well above the concentrations attained in man following administration of the therapeutic dose of 400mg.

Insert between this page and the following page the table: RELATIONSHIP BETWEEN RAT AND DOG EXPOSURE TO CEFTIBUTEN AFTER TOXICOKINETIC DOSES AND HUMAN EXPOSURE AFTER A THERAPEUTIC DOSE. (The table makes the understanding of the above paragraph much easier.)
A xeroxed page from the submission (05 0449).
Numbering of the table: Number of the previous page/a.

A C U T E T O X I C I T Y S T U D I E S .

NDA Review Number: 27, Submissions Number: 34.
Page No.: 05 0770
Acute Toxicity Study of 7432-S and 7432-S-trans in Rats.

Breed of Rats: Sprague Dawley

Compounds Used in the Study and Route of Administration:

1) 7432-S by a single oral administration.

2) Sodium salt of the trans isomer-rich 7432-S (7432-S-trans- Na) and of 7432-S (7432-S-Na) by oral and I.V.-administrations were studied for comparison.

Results:

1) No death attributable to intoxication occurred after oral administration of 10g/kg. Signs of toxicity: Inactivity, weakness, loose stools, watery stools and abdominal distention due to cecal dilation.
Applicant's Conclusions: "There were no findings suggesting visceral disorder and 7432-S was classified as "practically non-toxic".

2) No deaths from the oral administration of 7432-S-trans-Na at a dose of 10g/kg, and the rats recovered from loose or watery stools quickly.
The oral LD_{50} OF 7432-S-Na for male rats : 10 g/kg
for female rats: 8.3g/kg

~~18~~

TABLE 5

RELATIONSHIP BETWEEN RAT AND DOG EXPOSURE TO CEFTIBUTEN AFTER TOXICOKINETIC DOSES AND HUMAN EXPOSURE AFTER A THERAPEUTIC DOSE

Species (Ref.)	Dose (mg/kg)	Multiple of Human Therapeutic Dose (400 mg)*	Cmax (μg/ml)	AUC (μg·hr/ml)	Multiple of Human Therapeutic Dose Cmax (15.0 μg·hr/ml)*	Multiple of Human Therapeutic Dose AUC (73.74 μg·hr/ml)*
CD® Rat (5)	300	52.6				
	1000	175				
	3000	526				
Beagle dog (5)	200	35				
	400	70				
	800	140				

*Ref.29 (first dose)

3) "The findings of the intravenous administration of 7432-S-trans-Na and 7432-S-Na included toxic signs considered attributable to acute circulatory disturbances and shock such as tonic convulsions immediately after adminsitration, bleeding in various organs and tissues, increased hydrothorax and ascites, pale kidney accompanying histological changes such as renal tubular dilation, and centrilobular hepatocyte necrosis. Large volume hypertonic solution is considered mainly responsible for these changes. The deaths occurred within 60 minutes after dosing, and LD_{50} value for 7432-S-trans.Na was 4.0 g/kg for males and 4.5 g/kg for females, and that for 7432-S-Na 3.3 g/kg for males and 3.6 g/kg for females."

R.Rs.: The above ~~above~~ explanation of the toxic signs is not in agreement with solid, well established scientific facts available in standard textbooks. However, this is not important at this late stage of the research. It is more important to explain the reason for testing 7432-S-trans-rich-Na in spite of the fact that the to be marketed drug substance (7432-S) consists of 94% cis isomer and 6% related compounds. One % (1%,absolute) of the 6% related compounds is the trans isomer. This low percentage of trans isomer contamination is not alarming, however, since the trans isomer of 7234-S increases in the blood and urine after oral administration, the investigation of the toxicity of the trans-isomer became mandatory.
Since the preparation of the strictly trans isomer of 7234-S is very difficult, a compound which contained a large amount of the trans isomer (trans:cis= 78.55:21.45) was used in this study (7432-S-trans).
"As 7234-S-trans is hardly absorbed from the intestine, it was intravenously administered as a sodium salt of (7432-S-trans.Na.). For comparison, sodium salt of 7432-S (7432-S.Na) was synthesized and intrasvenously adminsitered. In addition to the intravenous injection, acute toxicity of 7432-S-trans-Na and 7432-S-Na was also tested by oral adminsitration, and compared with that of 7432-S.

Final Evaluation of the Study by the Applicant:"Acute toxicity of 7432-S-trans Na is essentially not different from that of 3274-S, and toxicity induced by oral administration was very slight as in the case of 7432-S. Since 7432-S-trans which is generated after 7432-S-trans administration is limited in quantity, it does not seem likely to modify the toxicity of 7432-S.
R.Rs.: I agree.

NDA Review No. 28, Submission No.35, Page No. 05 1156
Acute Toxicity Study in Dogs by Oral Adminisatration of after 7432-s. (D-20866)

Animals: Four male and four female Beagle dogs
Age:
8-9 months.

Test Compound: 7432-S was suspended in the 5% aqueous acacia solution to obtain 25 W/V% suspension for dosing.

Dosing: Gr.# 1, consisting of two males and two females received by gavage a single dose of 2,500mg/kg (10 A.M.).
Gr.II, consisting of two males and females reveived by gavage a single dose of 5,000mg/kg (10 A.M.)

RESULTS:

. Body Weight and Food Consumption: No change in any of the animals.

Auditory Examination: No abnormalities in Preyer reflex were observed in any of the animals.

Preyer's Reflex: Involuntary movements of the ears produced by auditory stimulation.(Dorland's 27th Ed.)

Ophthalmoscopy: No abnormalities

Hematology: Examnination on day 3 and 13 revealed no abnormalities

Blood Biochemistry: Examinatiom on day 3 and 13 revealed no abnormalities

Blood Levels: The blood levels of of 7432-S at 1,3 and 24 hrs. after dosing of 2500 and 5000mg/kg showed the peak 1-3 hours after administration, and dose dependent blood levels became apparent 24 hours after administration.

Organ Weights: Both absolute and relative organ weights remained normal.

Histopathology: Cystistaxis, acinar atrophy of submandibular gland, hemorrhage or congestion of mucous mambranes in the digestive tract, retinal degeneration. Since these changes were all mild, sporadically noted in a few animals , not dose-related, and the same as those observed in untreated animals, they were considered not related to 7432-S treatment.

NDA Review No.: 29, Submission No.: 36.

Acute Toxicity of Degradation Products of 7432-S (Ceftibuten) in Rats. (I) (D24026).

Compounds to be Tested:

1) 7432-S-$N_{(1)}$ decarboxylated product from 7432-S by heating
2) 7432-S-SDP[2] decomposition productof 7432-S stored under accelerated conditions (50°C,RH90% for 50 days period) in solid state.

Objectives of the Study: To investigate the sigle dose acute toxiciy of the above #1 and #2 compounds, when given by the oral route. (No chemical structure of the above contaminants is shown in the "Toxicity Studies"- portion of the submission.)
Groups of Rats(SD): 6/group/sex.
Formula Used for Treatment: Aqueous suspensuion of compound # 1 and # 2 in 5% (W/V) acacia solution.

Doses: 2000mg/kg of both compounds.

Fasting Periods: 16 to 18 hrs. prior to dosing and 2 hrs. post dosing.

Clinical Observation Period: A 14-day period.
Post Mortem Observatrions.: At termination all the rats were examined for gross lesions, and 3 representratives from each group undervent histological examination.

In vivo observations and measurements were such as one expects from non-treated normal animals.

Clinical Signs: The only sign found was the loose stools during the first six days of the study in both groups.
Gross Necropsy Findings: Slight Enlargement of the Cecum in the rats of # 1 group .
Histopathology: The cecum and other main organs did not reveal any changes.

Applicant's Conclusions: Both compounds exerted a very low degree of toxicity. - I agree.

NDA-Review No: 30, Submission No: 37.

Acute Toxicity Study of the Degradation Products of 7432-S (Ceftibuten) in Rats. (II) (D-24026)

Abstract & Summary of the Study

The oral acute toxicities of 7432-S-I_1, an impurity of 7432-S, and 78234-S-L_2,-L_3, and -N_2, the degradation products of 7432-S, were studied in six week old male and female SD rats. 7234-S-I_1, -L_2, and L_3, were adminsitered once orally to the rats by gavage at a dose of 2000mg/kg, and 7432-S-N_2, was administered in the same fashion, at five single doses of 125, 250, 500, 1000 and 2000mg/kg.
In the 7432-S-N_2, 2000mg/kg group, 1/6 males and 2/6 females died. These animals showed decreased spontaneous motor activities, abdominal writhing and depressed respiration from about three hours post-dosing, and , at about four hours post dosing, they developed clonic or tonic convulsion, dyspnea, and cyanosis and died of respiratory arrest. Necropsy of these dead animals disclosed retention of viscous fluid containing test compound-like white crystals in the gut lumen, erosion in the glandular portion of the stomach, petechiae in the thymus, and of the spleen. These findings suggest that the cause of death may be suffocation by the refluxing of administered suspension given in excess of the technically applicable amount (as estimated from its physical properties.)
R.Rs.: The sponsor's words, " the cause of death may be suffocation by the refluxing of administered suspension" are supported by the pathology report, i.e., "localized intraalveolar hemorrhages" in the lungs of rats died spontaneously.

In the 7432-S-L_3 group, the animals passed watery mucous stools on the dosing day and slightly soft stools from day 1 (dosing day: day 0) until about day 4. Soft stools were also observed in the 7432-S-I_1, group, but changes in the 7432-S-L_2, 2000mg/kg group, and 7432-N_2, 1000mg/kg or lower groups were unremarkable. Among the survivors, body weight gain was normal in all groups, and histopathological findings were also unremarkable.

The acute toxicities of 7432-S-I_1,, -L_2, -L_3, were very weak in rats, and the lethal dose was 2000mg/kg or higher for all these three compounds. 7432-S-N_2 produced no toxic changes at 1000mg/kg.

R.Rs: I agree with the applicant's conclusion and this is good for practical purposes. However, true scientific evaluation cannot be made without taking the actual concentration of the contaminants of the drug substance into consideration. By consulting the assigned microbiologist, Dr.Dionne, I learned that the applicant established set limits for all the six contaminants and that the concentration of the six contaminants in the new drug product is under the set limits. -

NDA 50-685-6 **CEFTIBUTEN CAPSULES**

Related Compounds				
Group X	Total NMT	%		HPLC Gel filtration
HPLC Related Compounds				HPLC
Total	NMT	%		
Any Individual Peak Unkowns and I1	NMT	%		
(RRT 0.12 to 0.50) N1	NMT	%	Total	
(RRT 0.50 to 0.60) N2, L2, L3	NMT	%		
(RRT 0.60 to 0.74) Trans	NMT	%	Total	
(RRT 0.75 to 0.85) L4, L5 and Unkowns	NMT	%		
(RRT 0.86 to 1.5)	NMT	%	Total	
Total Related Compound	NMT	%		

RRT = Relative Retention Time

The table showing the set limits of the contaminants (Related Compunds) should be inserted after this page. (#12/a)
Note: In the "REFERENCES FOR APPLICATION SUMMARY"of Vol.1.1, the following study is listed: 38. Acute oral Toxicity Studies of SCH 39720 in Neonatal (8-day Old), Juvenile (28-Day old), and Adult (8-Week Old) Rats. I cannot locate this study in this NDA or in NDA 50-586.
The assigend CSO should request an answer for the whereabouts of Study # 38.
NDA-Review No.:32; Submission No.:39.

Sh 39720 (Ceftibuten) Acute Inhalation Toxicity and Primary Irritancy Studies. (D-24759)

Test:	Dermal Irritation	Eye Irritation
	Irritation: 4-hr,	Rabbit (abraded) Rabbit
Dose:	0.5g	80mg (0.1ml)
Vehicle:	distilled water	none

Amount of Vehicle: 0.4 ml
Test: Acute Inhalation Toxicity,Rat
Chamber Size: 120 liters
Generation Method: auger dust feed
Mean Chamber Dust Concentration: 3.94mg/l
Mass Median Aerodynamic Diameter: 3.6 microns

R E S U L T S

Inhalation Toxicity (rat)

Males: 4 hours exposure
Females: 4 hours exposure

Gross Signs of Toxicity: Animals covered with a yellow dust (test material), blepharospasm, slight weight loss in two females.

Dermal Irritation (Rabbit): SCH 39720 produced no erythema, edema or other reactions on any of four rabbits.

Eye Irritation (Rabbit): SCH 39720 produced no corneal injury, iritis or conjunctival irritation in any of 3 rabbits.

NDA-Review No. 33; Submission No. 40.
Acute Oral Toxicity Studies off Sch 39270 (with Related Compounds) in Juvenile (One Month Old) and Adult (8 week Old) Mice.

Objectives of the Study: To determine the acute effects of high doses of SCH 39270, a cephalosporin antibiotic with approximately 16% related compounds, when given as a single

oral dose to fasted juvenile and adult CR-1:CD-1 (ICR)BR VAF/Plus mice.

Vehicle: 0.45% aqueous methylcellulose,which was also serving as the substance given to the animals of the control group. One group consisted of five males and five females. Several drug treated groups were used for the study, the highest being 5,000mg/kg. The mice were observed for 14 days after dosing. The study was evaluated by determining the LD_{50} value, the Maximum Asymptomatic Dose and the Maximum Nonlethal Dose. The highest dose groups remained free of compound- related changes in physical appearance, behavior, body weight or post mortem findings. The Applicant's Cconclusion: "Based on the results of this study, it can be concluded that SCH 39720 with approximately 16% related compounds has a low degree of toxicity when adminsitered as a single oral dose to juvenile (one-month old) or adult (8-week old) mice.

NDA-Review No.34; Submission No. 41.

Acute Oral Toxicity Study of SCH 39720 (with Related Compounds) in Neonatal (4-Day Old) Rats.

Objectives of the Study: To determine the acute toxicity of SCH 39720 (with related compounds) when given as a single oral (PO) dose to four-day old Crl: CD (SD) BR VAF/Plus rats.
Except for the doses this study is almost identical with the mouse study (40).

The Applicant's Suymmary & Evaluation of the Study
SCH 39720 with approximately 16% related compounds was well tolerated at doses up to 620mg/kg, or approximately 70 times the proposed clinical dose of 9 mg/kg/day (Clinical Program Projections for SCH 39720, January 8,1987, when administered as a single oral dose to neonatal (four day old) rats. The target organ identified in this study was the thymus gland, as indicated by a reduction in size observed at doses of 1260mg/kg and above. Mortality was observed only after doses of 2500mg/kg (males) and 5000 mg/kg (males and females).

NDA-Review No. 35; Submission No. 42.

Acute Oral Toxicity Studies of SCH 39720 (with Related Compounds) in Juvenile (One-Month Old) and Adult (8-Week Old) Rats.

The Objectives of the Study: To determine the acute effects of high doses of SCH 39720, a cephalosporin antibiotic with

approximately 16% related compounds, when given as a single oral dose to fasted juvenile and adult CR1:CD- (SD)BR VAF/Plus rats.

The details of this study, except the doses (LD_{50}, Maximum Asymptomatic Dose, Maximum Nonlethal Dose) are practically identical with those of the former study.

The LD_{50} Values in both age groups and both sexes are >5,000mg/kg.
The Maximum Asymptomatic Dose is 2,000mg/kg in both age groups and both sexes.The Maximum Nonlethal Dose is 5,000mg/kg in both age groups and both sexes.

Summary and Conclusion of the Applicant:

All rats completed the dosing regimen in good health. The only clinical signs observed were loose stools containing compound-like material in both adult and juvenile rats dosed with 5,000mg/kg. This was most likely an effect of the large volume of test article administered. No changes in behaviour or body weight were observed.
There were no test article-related gross necropsy findings. The findings observed in one 2000mg/kg-dosed 8-week old male (small testicles) and in one 5000 mg/kg-dosed 8-week old male (marbled kidney) are considered incidental and unrelated to dosing.

Based on the results of this study, it can be concluded that SCH 39720 with approximately 16% related compounds has a low degree of toxicity when adminsitered as a single oral dose to juvenile (one month old) or adult (8 week old),rats.

R.Rs.: I agree.

MULTIDOSE STUDIES

NDA-Review No. 36, Submission No. 43.

One-Month Subcute Toxicity Study of 7432-S in Rats.(35 consecutive days).

Animals: Sprague-Dawley rats [(Jcl:SD strain), 6 weeks of age.
Groups & Dosing: Control: 20(10*) M + 20(10) F, treatment: None; GR.7432-S low dose: 10 M + 10 F, treatment: 300mg/kg/day; Gr.7432-S mid-dose: 10 M + 10 F, treatment: 1,000mg/kg/day; Gr.7432-S high dose: 20(10) F + 20(10) M, trreatment: 3,000mg/kg/day; Gr.CCL one dose level: 20(10)M, 20(10)F, treatment: 3,000mg/kg.
(*) : No. of rats used for recovery study

RESULTS AND EVALUATION

No-Effect Dose Level (except cecal enlargement): 300mg/kg
Death Rate and Clinical Signs: No death in any group. Soft stools and abdominal dilation due to cecal enlargement were the only signs observed.
Body Weight: There was some body weight gain in both 1,000mg/kg and 3,000mg/kg groups. Interestingly the applicant found the weight gain almost equal to the weight gain of the cecum (enlargement).
In testing antibacterials or antibiotics this is the predictably always present lesion, without peculiar significance.
Food Consumption (F.C.) & Its Relation to Plasma Ingredients: These parameters changed slightly in the mid and high dose groups and in the control CCL group, though not in the same direction. The F.C. moved upwards, the plasma protein, triglyceride and potassium levels moved downwards.
For these phenomena the applicant gives the following explanation: "The same changes were observed in CCL group and are considered attributable mainly to to changes in enterobacterial flora caused by antibacterial activity of 7432-S and CCL accompanied by drecreased potentials of digestion and absorption". R.Rs.: This explanation is unacceptable and it is not needed.
If this would be the answer than the same changes in plasma ingredients should be observed during the testing of each and every antinbac-terial or antibiotic. My experience does not prove this. Furthermore, changes in the enterobacterial flora cannot decrease the potentials of digestion and absorption. The colon and the cecum does not have any digestive activity, andthe only thing which could be absorbed from the lg. intestine is water.

Various urine changes such as decrease of urine volume, higher protein content than normal (I think the applicant means higher than traces) occurred in the mid and high dose groups and in the CCL group but no confirming lesions were observable during the histopathologic examinations. Therefore the results of the urinalysis are not significant.

The elevated plasma creatinine and urea levels in the high dose females are not significant, since the results of the renal histopathological examination have no confirming value. However, in the CCL group the kidney weight was slightly increased and regeneration of the tubular epithelium was evident during microscopic studies.

Hemorrhages, bacterial masses occurred in the lamina propria of the cecal mucosa in the 7432-S, CCL treated and control groups, therefore, their significance is nil.

Conclusion: Even the mid and high dose levels appeared

only minimally toxic. The "no effect dose level" is alerady spelled out in the introductory portion of this review.

NDA-Review No. 37; Submission No. 44.

a) One-Month Subacute Toxicity Study of 7432-S in Dogs. (Study report in the submission.)

b) Subacute Toxicity of 7432-S in Dogs. (Publication from the material of the study report a).
Kobayashi, F., et al.,1989, Chemotherapy 37, S-1, 833-857.
For the review of the study the summary of the publication will be presented here.

The subacute toxicity of 7432-S was studied by administering the compound orally to beagle dogs for 35 days at daily dose levels of 200, 400, and 800mg/kg, and its effect compared to that of a reference drug, cefaclor (CCL).

1) In 7432-S 800mg/kg group, vomiting and diarrhea, were observed but the frequency was far less than in the case of CCL.
2) No changes attributable to adminsitration of 7432-S were observed in body weight, food consumption, ophthalmoscopy, auditory examination, hematological examination, urinalysis, bone marrow tests blood & liver biochemistry, organ weight and histopathological examination.
3) The serum levels of 7432-S after administration indicate that it does nor accumulate in nthe body even when adminsitered orally for a consecutive period.

4) There were no indications of marked toxicity produced by 7432-S in the present study. and it is anticipated that the maxiumum no-eff ect dose in dogs is 800 mg/kg/day. R.Rs: I agree.

NDA-Review No. 38; Submission No. 45.

Four-Week Toxicity Study of 7432-S-Trans-Rich-Na in Rats.

SUMMARY AND EVALUATION OF THE STUDY

To detect the differences in toxicities of 7432-S (cis rich) and its trans form, 7432-S-trans-Na was intravenously adminisitered to Jcl:SD strain male and female rats once a day for 28 days at the dose levels of 12.5, 50 or 200mg/kg/day.

1) No notable changes were observed in general

conditions of the 7432-S-trans-Na and the 7432-S-Na intravencus administration (I.V.) groups. In the 7432-S-trans-Na oral administration (p.o.) group soft stool and abdominal distention (caused by the dilated cecumy) were observed. The body weight gain was satisfactory in all groups, and no marked changes were observed in food consumption or water intake.

2) Urinalysis revealed slightly acidified urine in males given 50 mg/kg or more, and females given 200 mg/kg of 7432-S-trans-Na i.v. and males and females of the 7432-S-Na i.v. group and the 7432-S-trans-Na p.o. group. Acidic urine disappeared upon withdrawal.

3) No notable autopsy findings or changes in organ weight were observed in the 7432-S-trans-Na and the 7432-S-Na i.v. groups. In the 7432-S-trans-Na p.o. group, the cecum weight increased pronouncedly and the spleen weight decreased slightly. The cecum contents were voluminous and slightly soft.

4) No notable changes were found in hematological examination, biochemical examination of blood and the liver, and histopathological examination of any of the treated groups.

No findings suggesting toxicity were obtained by intravenous administration of 7432-S-trans-Na even at 200 mg/kg nor any qualitative differences observed from the 7432-S-Na i.v. group a the same dose. Oral administration of 7432-S-trans-Na produced only soft stool and abdominal distention attributable to the dilated cecum.

Consequently, it was concluded that toxicity different from that of 7432-S in nature would not be manifested even if trans-isomer increased gradually after administration of 7432-S.

Reviewer's Remarks: The applicant's conclusions are acceptable.

NDA-Review No.: 39; Submission No.: 46.

One-Month Oral Toxicity Study of Sch 39720 (Pediatric Suspension) in Young Dogs.

(The Pediatric Suspension contains approximately 20% related compounds at the end of its shelf life.) The purpose of the study is to see whether or not such a high rate of contamination (20% related compounds) will increase the toxicity of the drug.

Groups & Dosing: Three groups consisting 14 M and 14 F infant CD(R)VAF/PlusTM rats; each received single daily oral doses of 36, 72 or 282 mg/kg of SCH 39720 with related compounds in a pediatric suspension by esophageal intubation for one month. The fourth group served as the control receiving the pediatric formula only.
At the start of dosing, the rats were 4 days old.

Methods to Assess the Toxicity of the Formula:

1) Observation for mortality and changes in physical appearance and behaviour.
2) Recording of body weight twice weekly.
3) Recording of the eye opening and incisor eruption.
4) Righting reflex and the startle response to a Galton whistle, used to assess vestibular and auditory function, respectively, were determined during Week 4 of dosing.
5) An opthalmoscopic examination wAs conducted during Week 4.
6) Blood Samples: Collected for determination of the concentration of the subject drug from six additional rats/sex/group during Week 4.
7) The determination of serum chemistry and hematology parameters were obtained from blood collected from 9-10 rats/sex/group at the Week 5 necropsy.
8) All tissues from the control and the high dose rats as well as all gross lesions, were processed and examined for histopathologic changes.

"Evaluation: SCH 39720 with related compounds as a pediatric suspension was well tolerated when given to infant rats for one month at single daily oral doses up to 282mg/kg. At this dose level, the pediatric suspension contained 20 times the amount of related compounds that would be given based on a proposed pediatric clinical dose of 9 mg/kg/day of ceftibuten at the end of its shelflife. During Week 4, increases in plasma concentrations of SCH 39720 at one hour

postdose were not dose proportional, but increased in a dose related manner, although some overlap in individual values between adjacent

groups was observed. No consistent sex-dependent differences in plasma levels of SCH 39720 were noted. The no-effect dose level in this study was 282 mg/kg. No target organs of toxicity were identified in this study. The results of this study do not preclude further development of this pediatric suspension of SCH 39720 with related compounds."

NDA-Review No. 40, Submission No. 47.

One Month Oral Toxicity Study of Sch 39720 (Pediatric Suspension) in Young Rats.
Objectives of the Study: To assess the systemic toxicity of SCH 39720, a cephalosporin antibiotic when given orally as a pediatric suspension to young rats for approximately one month.
Groups: Three; 10 male and 10 female CD(R) VAF/PLUS TM rats for drug treatemnt, and one group (10/sex) for control.

Dosing: Each drug treated group was administered SCH 39720 aqueous suspension, via esophageal intubation, once daily at doses of 27, 54, or 256mg/kg.
Control Group: They received daily the SCH-39720 vehicle only.
Determination of the Plasma Level of SCH-39728 occurred in additional groups of rats (six/six) from each SCH 39720 dosed group.

Age & Weight of Rats at Start: 28 days and 59-75(M), and 56-75(F).

Results & Evaluation of the Study:" SCH 39720, when given as an oral suspension to young rats at doses up to 216mg/kg or 24 times the clinical dose (the higest practical dose), was well tolerated. Lower mean neutrophil counts, which have been reported for other cephalosporins (Browning et al.: Handbook of Exp[erimental Pharmacology, 1983, pp.371-379), were observed in the males only, but were not noted in a one-month dog study. The results of this study do not preclude further development of this compound.
Reviewer's Remarks: The sponsor's evaluation is acceptable.

NDA-Review 41; Submission No. 48

One Month Oral Toxicity Study of SCH 39720 Pediatric Suspension) in Infant Dogs.
Objectives of the Study: To assess the sytemic toxicity of SCH 39720, a cephalosporin antibiotic, when given orally as a pediatric suspension to infant dogs for one month.

Animals, Groups & Dosing: Three groups of infant beagle dogs (3/sex). Each received single oral doses of 45, 90 Or 360mg/kg of SCH 39720 in a Pediatric Suspension by esophageal intubation for one month. An additional group of three male & female dog served as a control receiving daily the Pediatric Suspension Vehicle. Age of the animals at start: Two weeks. Weight of the animals at start: 0.5 - 1.0 kg (males); 0.4 to 0.8kg (females).

Daily Observations: Each once daily for changes in physical appearance and behavior.
Body Weights: Recorded twice weekly.
Ophthalmoscopic Examinations: During week 4.
Physical Examinations(EKG, body temp., BP, respiratory and heart rates) during week 4.

Blood Samples for Hematology and Clinical Chemistry Measurements: Collected during were collected during Week 4.
Blood samples for SCH 39720 levels from treated and control dogs collected: During week 4.
Necropsy, body and organ weight measurements and processing for histopathological examination followed standard procedures.
Survival Rate: All
Body Weight, general condition, behavior, ophthalmologic or physical examination data: No compound related changes.

"During Week Four (day 25), plasma concentrations at one hour postdose appeared to increase in a dose-related manner, although overlap in individual values between adjacent groups was observed. No consistent, sex dependent differences in plasma levels of SCH 39720 were noted in any of the one-hour postdose samples on Day 25 (Week 4) of the study.

No SCH 39720-related changes occurred in hematology or clinical chemistry parameters. There were no organ weight, necropsy or histopathologic findings associated with SCH 39720.

Sponsor's Evaluation: SCH 39720 Pediatric Suspension was well tolerated when given by esophageal intubation to infant beagle dogs for one month at a single daily dose up to 360mg/kg or 40 times the proposed pediatric clinical dose at 9mg/kg/day (Clinical Programs Projections for SCH 3972, January 8, 1987). The no-effect dose level in this study was 360mg/kg. No target organs of toxicity were identified.

The results of this study support further development of this SCH 39720 Pediatric Suspension."
NDA Review No.: 42; Submission No.: 49.

One-Month Oral Toxicity Study of SCH 39720 (Pediatric Suspension) in Infant Rats.

Objectives of the Study: To assess the systemic toxicity of SCH 39720, a cephalosporin antibiotic, when given orally as a pediatric suspension to infant rats for one month.

Animals, Groups & Doses: Three groups 14/sex each, infant Crl: CD(R) (SD)BR VAF/Plus(TM) rats, each treated with a single daily oral dose of 27, 54 or 216mg/kg of SCH 39720 in a Pediatric Suspension by esophageal intubation for one month.

The number of the females in the 27mg/kg group was only 13 due to a technical error.
Control Gr.: An additional group (14/sex) was dosed with the vehicle only. A special group (6/sex) was added for the determination of the subject compound in the plasma.

Housing: Seven/sex pups/dose group with foster dams until weaning at 21 days of age, after which time they were separated by sex and housed in pairs.
Age & Weight at the Start of Dosing: 4 days old; Males: 6.7-12.1 g, Females: 6.5 to 12.7 g.
Daily Observations: Mortality & changes in physical appearance and behavior.
Body Weight: Recorded twice weekly.
Other Developmental Parameters Recorded: Dates of eye opening and incisor eruption.
Assessment of Vestibular & Auditory Function: Righting reflex and startle response to a Galton Whistle, respectively, were determined during Week 4 of dosing.
Ophthalmscopic Examination: During week 4.
Blood Samples For Determination of Plasma Levels of the Drug: Collected during Week 4

(special group).
Hematology & Serum Chemistry Parameters: Determined

on blood samples collected from 10 rats/sex/group at the terminal necropsy.
All animals (died or sacrificed) were necropsied.
Organ-to-body weight ratios calculated of selected organs.
All the animals were posted (scheduled and non-scheduled necropsies), all gross lesions were processed for histopathology.

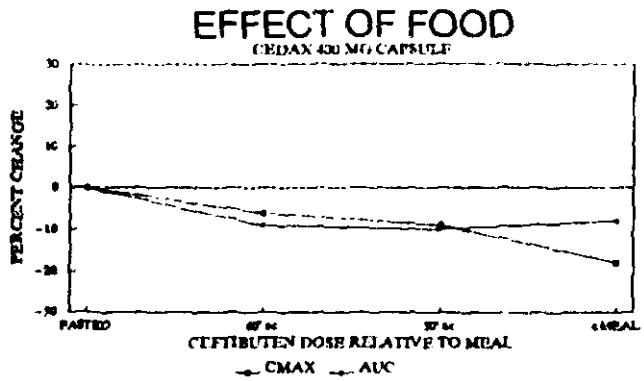
Sponsor's Evaluation: SCH 39720 Pediatric Suspension was well tolerated when given by esophageal intubation to infant rats for one month at a single daily dose up to 216mg/kg or 24 times the proposed pediatric clinical dose of 9mg/kg/day (Clinical Program Projections for SCH 39720, January 8, 1987). The "no effect" dose level in this study was 216 mg/kg. No target organs of toxicity were identified.
Increases in plasma concentrations at one hour postdose were not dose proportional but increased in a dose-related manner, although some overlap in individual values between adjacent groups was observed. No consistent, sex-dependent differences in plasma levels of SCH 39720 were noted in the one-hour samples on Day 25 (Week 4) of the study.
The results of this study support further development [redacted] of this SCH 39720 Pediatric Suspension.

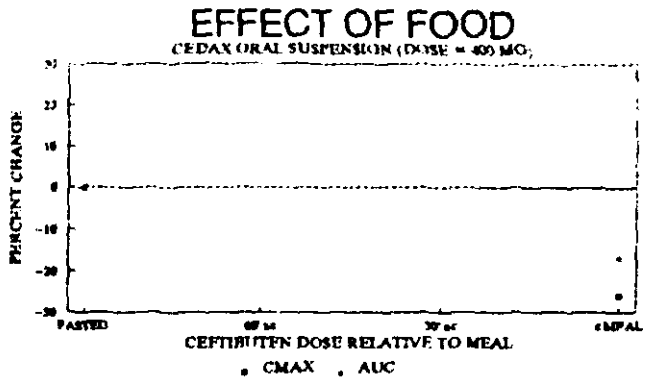
NDA-Review No.43. Submission No. 50.

One-Month Oral Toxicity Study of SCH 39720 (Pediatric Suspension with Related Compoundws) in Infant Rats.

Objectives of the Study: To assess the systemic toxicity of SCH 39720 (ceftibuten), a cephalosporin antibiotic with related compounds, when given orally as a pediatrtic suspension to infant rats for one month. This pediatric suspension contains approximarely 20% related compounds at the end of shelf life.
Animals: CD(R)VAF/Plus(TM) infant rats
Groups: Four groups (three treated and one control), 14/sex each.
Doses: 72, 82 or 282mg/kg of SCH 39720 with related compounds in a pediatric suspension by esophageal intubation for one month.
Control Group: The vehicle only.

Bio





I have looked at the information provided by Schering via fax on 12/20/95 regarding the effect of food on the bioavailability of CEDAX Capsules and CEDAX Oral Suspension. The applicant submitted the information to support their claim that the ceftibuten products should be administered one hour before or two hours after meals.

The plots above illustrate the changes that occurred in ceftibuten bioavailability when the products were administered with a high fat meal. The plot on the left shows that food does have some effect on the bioavavilability of ceftibuten from CEDAX Capsules when administered as early as 60 minutes before a high fat meal. However, using a 20% criterion for the difference in mean parameter values, the effect of food on capsule bioavailability is not significant for any condition studied. Theferefore, it is appropriate to say in the lable that food does not affect the bioavailability of CEDAX Capsules.

The plot on the right shows that the effect of food on bioavailability is formulation–dependent. Bioavailability from Cedax Oral Suspension was affected by food more than bioavailability from CEDAX Capsules. Since we have no data for drug administration 30 minutes before and 60 minutes before meals, we have no idea where the percent decrease in CMAX (or AUC) might be 20%. For CEDAX Oral Suspension , the information is not sufficient for us to change our recommendation for the label, i.e. two hours before and one hour after meals.

F Pelsor 12/20/95
Dir Pharm. Eval III

DEC 1 1 1992

NDA 50-685 & 50-686 SUBMISSION DATE: 12/20/1991
CEDAX Capsules & Suspension REVIEWER: Emil Samara, Ph.D.
Ceftibuten 200 mg & 400 mg Capsule and 90 mg/5 ml & 180 mg/5 ml Suspension.
Schering-Plough Corporation, 2000 Galloping Hill Road, Kenilworth, NJ 07033.

REVIEW OF NEW DRUG APPLICATION

BACKGROUND:

CEDAX (Ceftibuten) is a new, semisynthetic, third generation cephalosporin antibiotic with a carboxyethylidene side chain, for oral administration. Ceftibuten exhibited antibacterial activity when evaluated against a wide range of gram-negative and certain gram-positive microorganisms. The bacterial activity of ceftibuten results from inhibition of bacterial cell wall synthesis. Ceftibuten was stable in the presence of broad spectrum plasmid-mediated beta-lactamases. At concentrations of $\leq$ 1 μg/ml, most sensitive strains of organisms were susceptible to ceftibuten. The molecular weight of ceftibuten dihydrate is 446.43 and the structural formula is:

CEDAX capsule contain ceftibuten dihydrate equivalent to 200 mg and 400 mg ceftibuten. CEDAX powder for oral suspension after reconstitution contains ceftibuten dihydrate equivalent to either 90 mg ceftibuten per 5 ml or 180 mg ceftibuten per 5 ml.

The recommended dose of CEDAX, for adults, is one 400 mg capsule or two 200 mg capsules taken once daily. And for children, is 9 mg/kg/day of the reconstituted powder in a suspension, given as a single daily dose. Children weighing more than 45 kg or older than 12 years should receive the recommended adult dose.

The drug substance, ceftibuten dihydrate, is manufactured by for use by Schering Corporation of New Jersey to manufacture, package and label drug product. Trans-ceftibuten, a metabolite of (cis) ceftibuten, exhibits one-eight of the antibacterial activity of ceftibuten.

SYNOPSIS:

The sponsor has studied the pharmacokinetics (single and multiple dose), metabolism and excretion of ceftibuten. The pharmacokinetics of ceftibuten was tested also in geriatric subjects and liver and renal impairment patients. Drug interaction with theophylline, Mylanta®, and ranitidine was studied. The sponsor conducted one bioequivalency study showing that the capsule formulation is bioequivalent to the suspension formulation. Additional bioequivalency studies were conducted to demonstrate the bioequivalency of the different investigational capsule formulations and strengths.

RECOMMENDATION:

The studies submitted for CEDAX capsules and suspension (NDA 50-685 & 50-686) are acceptable for meeting the biopharmaceutics requirements, provided Comments 4 to 14 are addressed satisfactorily by the sponsor.

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SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS

I. BIOAVAILABILITY/BIOEQUIVALENCY:

A. Bioavailability: The bioavailability of the to be marketed capsule formulation was found to be bioequivalent to the suspension formulation.

B. Food Effect: The food effect was studied on the capsule and suspension formulation in four different studies. It could be concluded that in both dosage forms the ingestion of food, within one hour of drug administration, decrease the rate and extent of absorption.

II. Pharmacokinetics:

A single 400 mg capsule of ceftibuten produces an average peak plasma concentration of 15 μg/ml at 2 to 3 hours after administration. The elimination half-life in subjects with normal renal function is approximately 2.5 hours. No significant accumulation occurred, following multiple oral administration of 400 mg ceftibuten q 24 h for 7 days. Urinary excretion is the major route of elimination, with more than 50% of the dose appearing unchanged in the urine within 24 hours. Approximately 63% of ceftibuten is bound to plasma proteins (COMMENT 7).

III. Metabolism:

Following single dose administration of radiolabeled ceftibuten, 95% of the dose was recovered in urine and feces (56% and 39% respectively). Based on the HPLC assay, 48% of the administered dose was recovered in urine as ceftibuten and 11% as trans-ceftibuten. In addition to trans-ceftibuten two minor metabolites were detected in the plasma and urine.

IV. Special Population:

A. Elderly Subjects: The pharmacokinetics of ceftibuten in elderly subjects was studied under multiple 200 mg bid dosing. The accumulation ratio calculated on day 3 and 4 were 1.27 and 1.30, respectively. The half-life was found to be 3.2 hours. However, following a 400 mg QD it is assumable that no accumulation will occur. (COMMENT 6)

B. Renal Impairment: The AUC (from 66 to 472 μg.hr/ml) and the half-life (from 2.7 to 22.3 hrs) values increased linearly with declining renal function, whereas the renal clearance (from 51.7 to 2.1 ml/min) values decreased with declining renal function (COMMENT 13). About 39% of the dose was eliminated by hemodialysis.

C. Hepatic Impairment: The study results, in comparison to normal subjects from another study, show that the AUC increased by 40% and the half-life increased by 60% (from 2.5 to 4.1 hr). However, the sponsor indicated that these changes in the pharmacokinetics of ceftibuten were attributed to differences in renal function rather than liver function. ? Do they agree? (BP).

V. Drug Interaction:

The pharmacokinetics of single intravenous dose of theophylline was not altered by multiple-dose ceftibuten administration (COMMENT 2). Concurrent administration of

ceftibuten with Mylanta did not affect ceftibuten bioavailability. Multiple dose administration of Ranitidine did not significantly affect the single dose administration of ceftibuten; the Cmax was not changed while the AUC increased by 15%. (COMMENT 12)

VI. PHARMACODYNAMICS:

Several studies were undertaken to assess the penetration of ceftibuten in various body fluids and tissues including inflammatory fluid, nasal secretion, tracheal secretion, bronchial secretion, lung tissue, and middle ear fluid. The concentration of ceftibuten in most tested tissues and fluids were less than the corresponding plasma concentrations (COMMENT 11).

VII. Formulation:

One suspension formulation was used in all the studies. Two capsule formulations were used in the pivotal studies the 200 mg formulation (Schering formule # 2136)

Both formulation were found to be bioequivalent to the to be marketed formulations. (COMMENTS 9 & 10)

VIII. Dissolution:

The proposed dissolution methods for ceftibuten capsules (using USP apparatus 1 at 100 rpm in 1000 ml 0.05 M phosphate buffer, pH 7) and suspension (using USP apparatus 2, at 50 rpm, in 1000 ml 0.05 M phosphate buffer, pH 7) is not accepted. (COMMENTS 8)

IX ASSAY: Four HPLC assays were used, three for the plasma levels and one for the urinary levels. In some of the tissue distribution studies a microbiological assay was used. (COMMENTS 4 & 5).

COMMENTS

(Comments 1-3 are for the attention of the reviewing medical officer and chemist)

1. There was dose proportionality in AUC and urinary excretion of ceftibuten at the 200 mg and 400 mg single-doses with deviation from dose proportionality at the 800 mg dose.

2. Neither the effect of theophylline on ceftibuten pharmacokinetics nor the effect of multiple dosing of ceftibuten in theophylline pharmacokinetics was tested.

3. The manufacturing site mentioned in the cover letter (NJ) is different than the site mentioned in the chemistry section (Florida) of the summary volume.

4. In the prestudy assay validation plasma samples were either directly injected to the HPLC or a solid phase clean up procedure was used. However, in at least two studies the analytical method was modified by adding a and/or using In most of the other studies the analytical method procedure was not mentioned. Accordingly, the sponsor is requested to provide the analytical method used in each study and revalidate the method (were) the and/or was used.

5. The sponsor is requested to provide stability data for ceftibuten in plasma and urine during sample collection, storage and processing. Furthermore, the sponsor is requested to provide the individual recovery results (from Schering Plough plasma method) and recovery information for the other methods.

6. The sponsor indicated that compared to healthy volunteers (receiving the same dosage regimen as in study C88-098-01), the geriatric volunteers yielded higher Cmax and higher AUC values and longer half-life. Age and/or renal function may be responsible for these changes in the pharmacokinetic parameters. In order to determine if these changes are age related the renal function of the geriatric patients need to be evaluated.

7. For the protein binding, the sponsor is requested to submit the following:
   a) The effect of ceftibuten on the binding of the other tested drugs if available,
   b) How many replicates were used to evaluate the in vitro protein binding and
   c) Description and validation of the analytical method used.

8. For the dissolution specification the sponsor is requested to provide the following
   a) The analytical method used in the dissolution tests should be validated for specificity accuracy and linearity,
   b) Since more than 90% of the capsule content was dissolved using the method with rotation speed of rpm. The sponsor is recommended to consider using the paddle method with a rotation speed of rpm. this rotation speed, as previously tested, is more sensitive to batch to batch differences, and
   c) The sponsor is recommended to test the dissolution of the suspension formulation with rpm as rotation speed rather the proposed rpm.

9. For studies C90-420-01 and C90-375-01 the sponsor is requested to submit the SAS output used to analyze and calculate the 90% confidence intervals.

10. For study C88-058-01 the sponsor is requested to provide or explain the following:
   a) The variability in the half-life values (ranged from hrs) in this study were unreasonably high. This variability was not observed in any of the other reviewed studies.
   b) Compared to other studies, where a 200 mg dose of ceftibuten was administered, The individual and mean Cmax and AUC values obtained in this study were relatively higher. These values were comparable to values obtained following 400 mg ceftibuten administration (cross study comparison).
   c) The SAS output that was used to calculate the 90% confidence interval values.
   d) Only the Batch # was provided for the 100 mg capsule. The sponsor is requested to provide the formulation #, manufacturing site, Batch size ..etc.

11. Upon completion, the sponsor is requested to submit the results of study C89-267-02 in order to determine ceftibuten penetration into middle ear fluid.

12. The Cmax and AUC values obtained in study C90-876-01 were found to be relatively low when compared to other studies with similar design. The urinary excretion in this study was relatively low and did not exceed 10% of the administered dose in one

subject.

13. The sponsor recommended, in the labelling, the following dose adjustment is the renally impaired subjects:

(12)

Clcr	≥80	50-79	30-49	5-29	<5
$t_{1/2}$	2.70	3.85	7.07	13.39	22.28
Daily dose	400	400	200	100	100
Time interval for 400 mg	24 hr	24	48	96	120*

* In hemodialysis patients, a supplemental dose of ceftibuten (200 mg) should be administered at the end of each dialysis session in addition to the maintenance dosage regimen. An alternate dosing regimen would be a 400 mg dose at the end of each hemodialysis session, assuming that dialysis is performed two to three times a week.

Simulation of the plasma levels in each group using the two adjustment methods (dose and time intervals) clearly shows that the adjustment of the dose rather than adjustment in dosing time interval is more appropriate.

(14.) For study C87-099-01-05 the HPLC method used to evaluate the plasma levels of ceftibuten, at the was not adequately validated. The following is needed for prompt validation:

a. The sponsor indicated that modifying the assay methodology did not prevent the elution of interfering peaks. The sponsor added these interfering peaks was not always constant within a single kinetic analysis. The sponsor subtracted the interfering peak area from the peak of interest area or used the external standard method. The sponsor should give more explanation about the assay modification that was used, the interfering peaks size and eluting time, the solution for variable interfering peaks eluting at the same time with cetibuten and validation to the external standard method.

b. The inter- and intra-day variability were reported to be less than 6%, however no data was provided to support this conclusion.

c. The back calculated values for the QC samples should be provided rather than the area or high ratios of ceftibuten/IS.

d. The sponsor should compare the results from the two HPLC plasma method used in since the results from the two analyses were combined.

Emil Samara 9/10/92
Emil Samara, Ph.D.

RT BIOPHARM DAY Collins, Ludden, MALINOWSKI, LAM, HUNT, SAMARA
FT Initiated by Nicholas Fleischer, Ph.D. 12-11-92
CC: NDA 50-585 & 50-686 orig., HFD-520, HFD-426 (Fleischer, Samara), HFD-19 (FOI), Drug, Chron, Reviewer File. (Fod Fil)

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APPENDIX

I

Assay Validation for Ceftibuten and Trans-ceftibuten in Human Plasma and Urine for Clinical Studies (Vol. 1.44)

I. PLASMA PROCEDURES

1. Schering-Plough Procedure for ceftibuten

Sample Preparation: To a µl aliquot of plasma sample, µl of the internal standard solution µg/ml of acyclovir), and µl of M sodium phosphate buffer, pH 7, were added. A µl of the solution was injected onto the HPLC.

Chromatography: Detector at nm, Column with CN guard column. The mobile phase consisted of acetonitrile and M ammonium acetate delivered at a flow rate of ml/min.

Results:

Linearity: From µg/ml

Specificity: No interference from endogenous substances was found.

Sensitivity: µg/ml

Recovery: % with a CV of % (n=6)

Precision & Accuracy:

Accuracy within ± 5%. Intra-assay precision (%CV) was µg/ml and % (CV) at µg/ml. Inter-assay precision (%CV) was % at µg/ml and % at µg/ml.

2. Procedure

Sample Preparation: As described above except that µl instead of µl of the resulting solution was injected the HPLC system.

Chromatography: A C 8 Column with an SSI prefilter was used.

Results:

Linearity: From µg/ml

Specificity: There were no peak that interfered with either ceftibuten or trans-ceftibuten in plasma.

Sensitivity: µg/ml

Precision & Accuracy:

Accuracy within ± 6%. Intra-assay precision (%CV) was % at µg/ml and µg/ml. Inter-assay precision (%CV) was less than %.

3. Modified Procedure

Sample Preparation: To a µl aliquot of plasma sample, µl of the internal standard solution µg/ml of acyclovir), and µl of M sodium dodecyl sulfate were added. After vortixing, the samples were transferred to an Amicon (C 18) cartridge and centrifuged. µl was injected into the HPLC.

Chromatography: As before, except that a C 18 cclumn and RP-8 precolumn were used.

Results:
Linearity: µg/ml for ceftibuten and µg/ml for trans-ceftibuten
Specificity: There were no major peaks that interfered with quantitation of both compounds.
Sensitivity: µg/ml for ceftibuten and µg/ml for trans-ceftibuten with CV of % and % respectively.
Precision & Accuracy:
Accuracy within ± 6% for both compounds. Intra-assay precision (%CV) was % at µg/ml and % at µg/ml. Inter-assay precision was less than % for all concentration range.

II. URINE PROCEDURE

1. Schering-Plough Procedure (only cis-isomer)
Sample Preparation: A µl aliquot of urine sample was diluted to µl with M sodium phosphate buffer, pH 7. A µl volume of this solution was injected onto the column.

Chromatography: A technique was used. The sample was injected onto a cartridge and washed with M monobasic sodium phosphate at flow rate of ml/min. After column switching, the drug was eluted with acetonitrile and M sodium phosphate buffer, pH 7, onto column at a flow of ml/min.

Results:
Linearity: µg/ml
Specificity: No interference peaks in blank urine was found.
Sensitivity: µg/ml with a CV of %
Precision & Accuracy:
Accuracy within %. Intra-assay precision (%CV) was % at µg/ml and % at µg/nl. Inter-assay precision was % at µg/ml and % at µg/ml.

2. Procedure
Sample Preparation: A µl aliquot of urine was diluted to ml with M sodium phosphate buffer, pH 7. A µl aliquot of the diluted urine was further diluted with µl of M sodium phosphate buffer. µl was injected.

Chromatography: As above except that the first column was a column, and was washed with M ammonium phosphate buffer.

Results:
Linearity: µg/ml for both compounds.
Specificity: There were no peaks which interfered with the quantitation of both compounds.
Sensitivity: µg/ml for both compounds.

Precision & Accuracy:

Accuracy within 5%. Inter-assay precision (%CV) was less than 10% for ceftibuten and less than 6% for trans-ceftibuten.

III. Stability

Plasma pools were prepared for ceftibuten concentrations of and µg/ml and for trans-ceftibuten at concentrations of µg/ml, respectively. The samples were analyzed on three consecutive days. Both compounds were stable during the three freeze/thaw cycles.

COMMENTS

In general, the data presented for the assay validation show that the analytical methods are accurate and reproducible, however, the following information were not provided:

1. For the Schering Plough plasma method no calibration curves were presented and only the mean values were presented for the intra-assay variability.
2. For and modified plasma assay no chromatograms were presented and only the standard curve parameters were presented (slope, intercept and correlation coefficient).
3. For the Schering Plough urinary method only the mean values were presented for the inter- and intra-assay variability.
4. For the urinary method the intra-assay variability was not calculated and the two provided control urine chromatograms (Figures 6 and 7) were different, one showing no interference peaks the other showing large interfering peak.
5. The Schering Plough plasma method did not involve any extraction procedure the recovery as the sponsor stated was found to be 94%. The other methods involve column switching and solid phase clean up procedure, however, the sponsor did not provide any recovery data.
6. The stability of ceftibuten in plasma and urine during collection, storage and processing should be provided.

PHARMACOKINETICS

Absorption, Metabolism and Excretion of Orally Administered ^{14}C-ceftibuten In Male Volunteers (study C88-080-01, vol. 1.48).

OBJECTIVES: To evaluate the absorption, metabolism and excretion of a single oral dose of ^{14}C-ceftibuten in healthy volunteers.

INVESTIGATOR: Albert Cohen, Penninsular Testing Corporation, Opa-Locka, Florida 33054.

DOSAGE FORM: A suspension formulation was prepared by ml of water into the bottle containing mg of ^{14}C-ceftibuten (total radioactivity approximately µCi).

SUBJECTS: Six healthy male subjects. The subjects mean (range) age and weight were: 32 years and 164 lbs..

STUDY DESIGN: After an overnight fast, each volunteer received a 300 mg single oral dose of ceftibuten suspension with 90 ml water.

SAMPLING TIME: **Blood** (10 ml) samples were collected prior to and at 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 72 hours after dosing. **Urine** was collected before and at the following time intervals following drug administration: 0-6, 6-12, 12-24, 24-48, and 48-72 hr after dosing. **Feces** samples were collected up to 72 hours following drug administration.

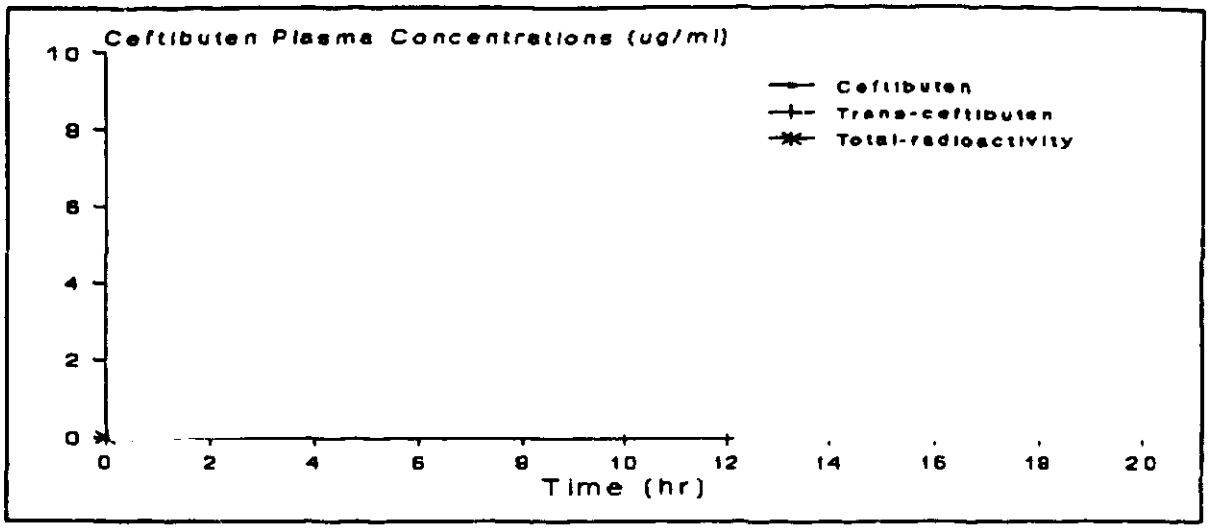
ANALYTICAL METHODOLOGY: Plasma and urinary concentrations of ceftibuten and trans-ceftibuten were determined by HPLC.
The radioactivity in the plasma, urine and feces were determined by liquid scintillation counting. The metabolite profiles were determined in selected plasma and urine samples using a semi-preparative HPLC procedure.

RESULTS:

1. **PLASMA**: The mean plasma levels and the mean (%CV) pharmacokinetic parameters of ceftibuten, trans-ceftibuten and total radioactivity are listed below.

Parameters	Ceftibuten	Trans-ceftibuten	Total-radioactivity
Cmax (µg/ml)	9.8(22)	0.76(15)	10.2(25)
Tmax (hr)	2:9(33)	4.2(36)	2.9(31)
$AUC_{0-\infty}$ (µg.h/ml)	46.3(18)	4.5(31)	52.2(20)
$t_{1/2}$ (hr)	2.2(10)	-------	2.7(9)

2. **EXCRETION**: 95% of the administered radioactivity was recovered in urine (56%) and feces (39%). Based on the HPLC assay, 48%



of the administered dose was recovered in urine as ceftibuten and 11% as trans-ceftibuten.

3. **METABOLISM**: The metabolite profiles in pooled plasma (taken from all six volunteers) are summarized below:

Time (hr)	Percent of Plasma Radioactivity: Ceftibuten	trans-Ceftibuten	B1	B2	total

The metabolite profiles in pooled urine are summarized below:

Time (hr)	Percent of Urinary Radioactivity: Ceftibuten	trans-Ceftibuten	B1	B2	total

CONCLUSIONS: Ceftibuten was the predominant component of both plasma and urine. Three minor metabolites or conversion products were detected in both plasma and urine.

COMMENTS: The analytical method was modified by to the plasma and urine samples and the use of technique for the plasma. However, only the Q.C. samples were reported.

Rising Single Dose Safety and Tolerance of Ceftibuten (7432-s) in Normal Volunteers (Study C86-063-01; Vol 1.54).

INVESTIGATOR: Michael Seiberling, Biodesign Gmbh Institute for Clinical Pharmacology, West Germany.

OBJECTIVES: 1) To evaluate the safety and tolerance of ceftibuten administered orally in doses of 200, 400, and 800 mg to normal volunteers, and 2) to evaluate the pertinent pharmacokinetic parameters.

SUBJECTS: Eighteen healthy male subjects were empaneled for this study. The volunteers mean (range) age and weight are: 26 years and 74.2 kg, respectively.

STUDY DESIGN: A randomized double-blind placebo-controlled study. Twelve volunteers received ceftibuten at doses of 200, 400 and 800 mg and six volunteers received placebo, as a control. Following a 10 hour fast, each volunteer received either ceftibuten or placebo with 120 ml of tab water.

FORMULATION: 200 mg capsules, batch # T6X01

SAMPLING: Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 hours after dosing. Urine samples were collected at the following time intervals: 0, 0-1, 1-2, 2-4, 4-8, 8-12, 12-16, 16-24, 24-36, 36-48, 48-60, and 60-72 hours after dosing.

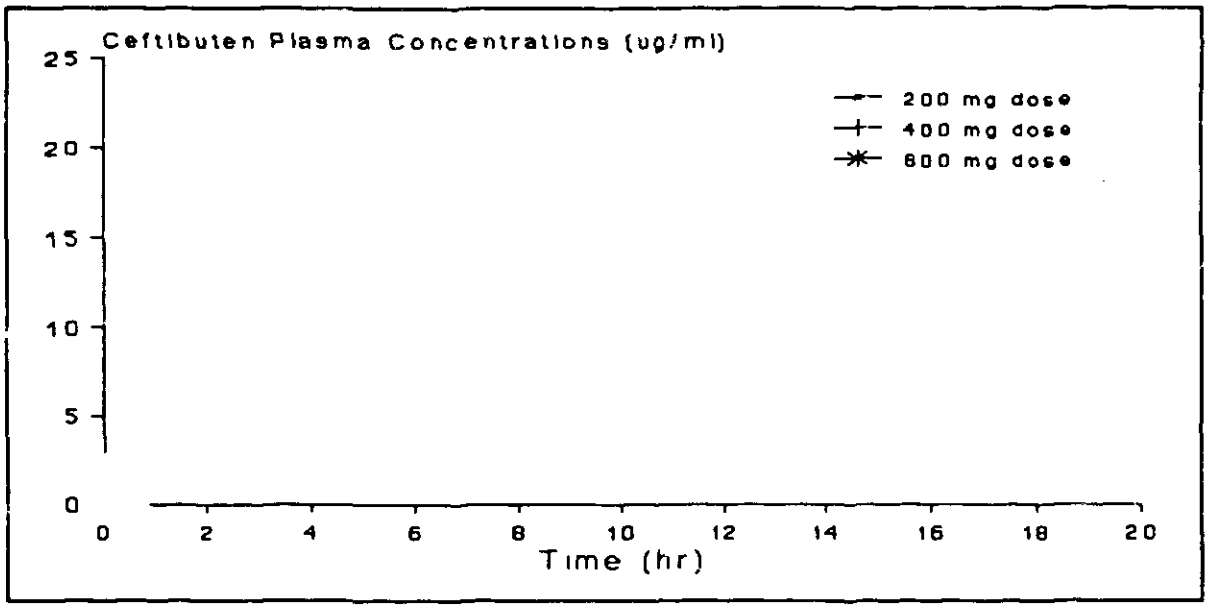
ANALYTICAL METHODOLOGY: Concentrations of ceftibuten in plasma and urine were determined by both HPLC and microbiological methods. In addition, the plasma and urinary concentrations of ceftibuten-trans, a metabolite of ceftibuten, were also determined by HPLC.

RESULTS: The mean pharmacokinetic parameters of ceftibuten, based on data obtained by HPLC are summarized below.

Parameter\Dose	200 mg	400 mg	800 mg
$AUC_{0-\infty}$ (μg.hr/ml)	42.1±5.1	79.2±16.4	118 ±29.8
Cmax (μg/ml)	9.85±1.6	17.0±3.6	23.3±4.2
Tmax (hr)	1.75±0.5	2.00±0.6	1.96±1.1
$t_{1/2}$ ka (hr)	0.47±0.2	0.50±0.3	0.53±0.4
$t_{1/2}$ ke (hr)	2.01±0.2	2.29±0.6	2.25±0.4
Ae (% of Dose)	67.9±7.3	62.4±17.6	52.7±26.4
Clr (ml/min)	54.6±8.2	53.3±8.3	60.5±9.4

AUC and C_{max} value from 400 and 800 mg doses were adjusted to the 200 mg dose. The results of ANOVA on the dose adjusted values are summarized below.

Comparison	parameter	p-value	RATIO (%) Point Estimate	C.I.
400 mg vs 200 mg	Cmax	0.03	86.2	76-96
	AUC	0.35	94.1	84-105
800 mg vs 200 mg	Cmax	<0.01	59.2	49-69
	AUC	<0.01	69.9	59-58



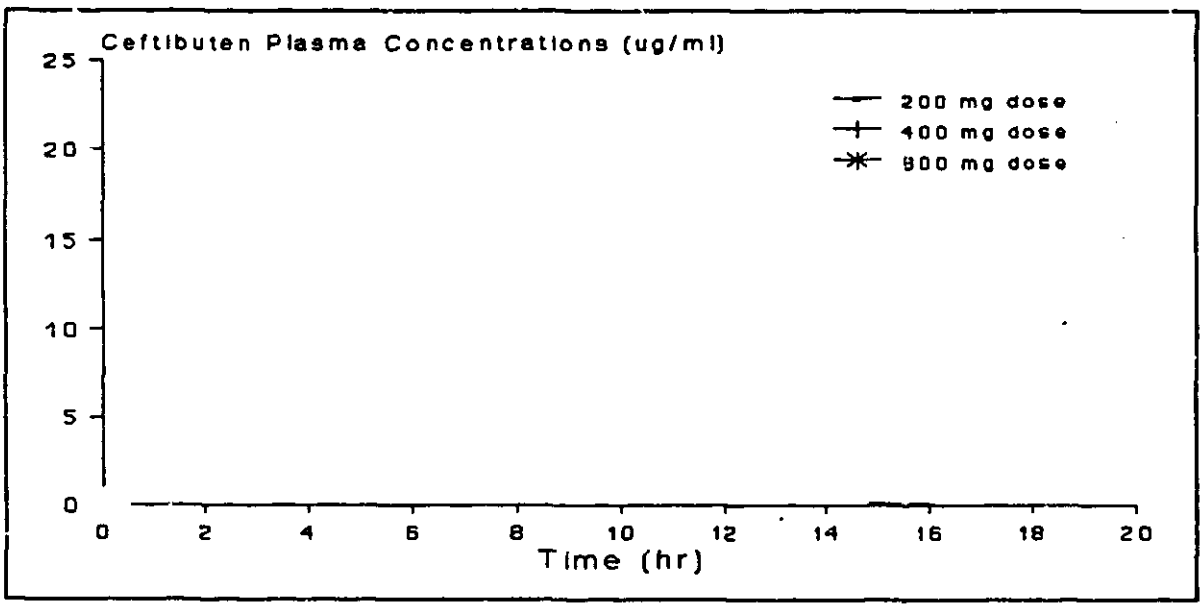
CONCLUSIONS:

1. There was dose proportionality in AUC and urinary excretion of ceftibuten at the 200 mg and 400 mg doses with deviation from dose proportionality at the 800 mg dose.
2. The t_{max}, $t_{1/2}$ Ka, and $t_{1/2}$ ke were dose independent.
3. Ceftibuten-trans was present in small amounts in plasma % of the AUC) and accounted for % of the dose in urine.

COMMENTS:

It was indicated that the study samples will be sent (in dry ice) both to Schering-Plough, USA and and that an HPLC and a microbiological assays will be used. Both the HPLC and the Microbiological methods were not described or validated. However, the submitted results showed good agreement between the HPLC method and the microbiological method.

Comparison	parameter	p-value	RATIO (%) Point Estimate	C.I.
400 mg vs 200 mg	Cmax	0.03	86.2	76-96
	AUC	0.35	94.1	84-105
800 mg vs 200 mg	Cmax	<0.01	59.2	49-69
	AUC	<0.01	69.9	59-58



CONCLUSIONS:

1. There was dose proportionality in AUC and urinary excretion of ceftibuten at the 200 mg and 400 mg doses with deviation from dose proportionality at the 800 mg dose.
2. The t_{max}, $t_{1/2}$ ka, and $t_{1/2}$ ke were dose independent.
3. Ceftibuten-trans was present in small amounts in plasma % of the AUC) and accounted for % of the dose in urine.

COMMENTS:

It was indicated that the study samples will be sent (in dry ice) both to Schering-Plough, USA and that an HPLC and a microbiological assays will be used. Both the HPLC and the Microbiological methods were not described or validated. However, the submitted results showed good agreement between the HPLC method and the microbiological method.

Multiple-Dose Pharmacokinetics of Ceftibuten in Normal Volunteers (Study C90-885-01, Vol 1.55).

INVESTIGATOR: Albert Cohen, Peninsular Testing Corporation, Opa-Locka, Florida 33054.

OBJECTIVES: To characterize the pharmacokinetics of ceftibuten and its conversion product, ceftibuten-trans, in normal male volunteers after multiple oral daily administration of 400 mg capsules.

SUBJECTS: Twelve healthy male subjects between the ages of 20 and 39 years with weights ranging from lbs. were impaneled for this study. However, the subjects individual age and body weight were not provided.

STUDY DESIGN: Each volunteer received a 400 mg capsule of ceftibuten once a day for seven days. Treatment was administered with 180 ml of tap water.

FORMULATION: 400 mg ceftibuten capsules, FRM No. 90870D02, Formula No. 2383, Batch No. 25529-133 and Batch size 233,333.

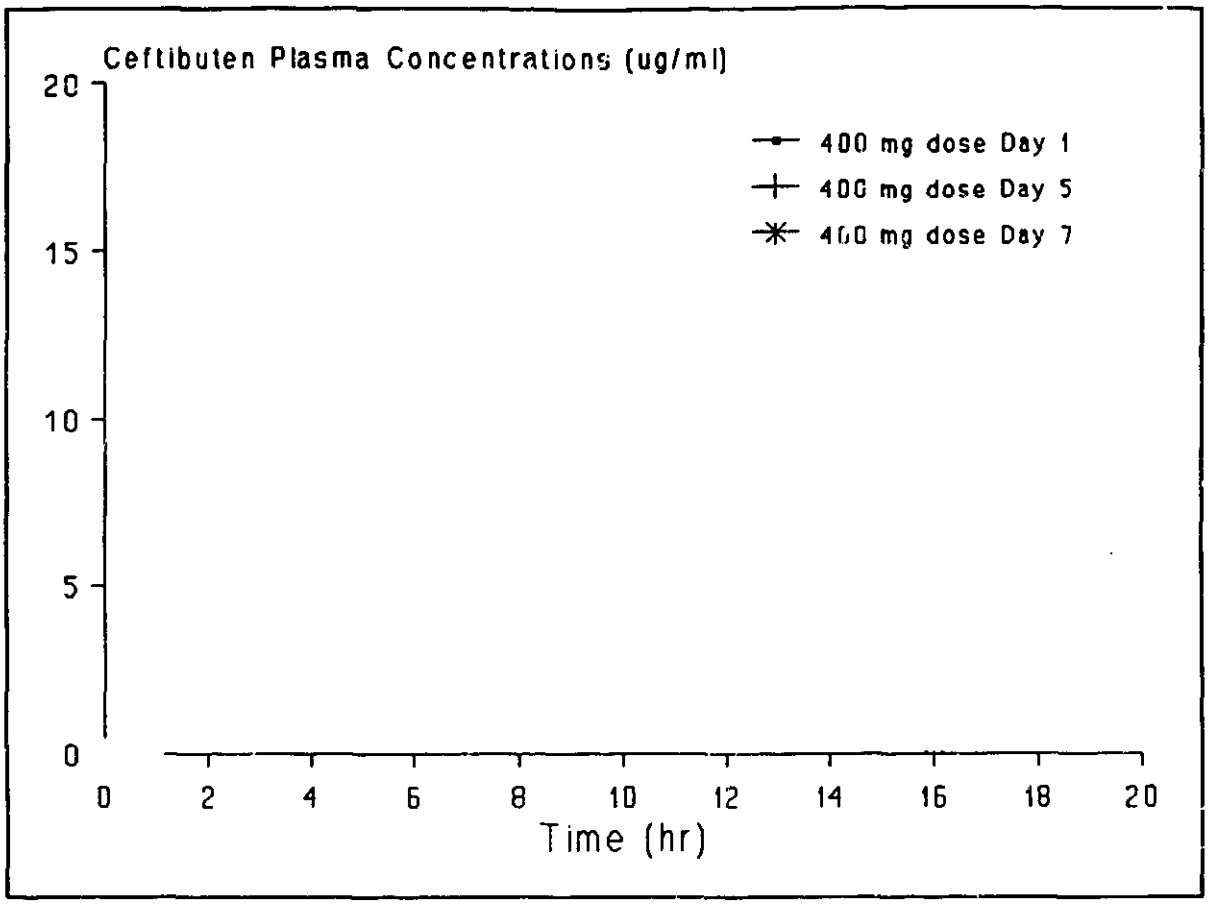
SAMPLING: On days 1, 5 and 7, blood samples (10 ml) were obtained at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours after dosing. Urine was collected at the following time intervals: 0, 0-4, 4-8, 8-12, 12-16, 16-20, and 20-24 hours after dosing.

ANALYTICAL METHODOLOGY: Plasma and urinary concentrations of ceftibuten and ceftibuten-trans were determined by HPLC at

RESULTS: The mean (n=12, ± SD) pharmacokinetic parameters for ceftibuten following multiple daily doses of 400 mg are summarized below.

Parameter (unit)	Day 1	Day 5	Day 7
AUC_{0-24} (μg.hr/ml)	73.7±16.0	82.5±14.9	80.2±9.9
Cmax (μg/ml)	15.0±3.3	18.7±3.2	17.9±1.8
Tmax (hr)	2.6±0.9	2.2±0.7	2.4±0.8
$t_{1/2}$ ke (hr)	2.5±0.2	2.4±0.2	2.4±0.3
Ae_{0-24} (mg)	229 ±44	229 ±52	237 ±35
Clr (ml/min)	50.2±8.8	46.7±10.9	50.0±10.7
R (Accumulation Factor)		1.14±0.18	1.13±0.25

Listed below are ceftibuten mean plasma levels.



CONCLUSIONS: No significant accumulation occurred, following multiple oral administration of 400 mg ceftibuten q24h for 7 days to adult volunteers.

COMMENTS: The analytical method used were not described.

Single Dose Pharmacokinetics, Safety and Tolerance of Ceftibuten in Pediatric Patients (Study C87-099-01, 02, 03, 04, and 05)

INVESTIGATORS: J. Blumer, Cleveland, OH; R.F. Jacobs, Little Rock, AR; M. Nahata, Columbus, OH; R. Yogev, Chicago, IL and W.M. Gooch, Salt Lake City, UT.

OBJECTIVES:
1. To evaluate, in four age groups, the safety and tolerance of ceftibuten at a dose of 9 mg/kg administered orally as either two 4.5 mg/kg doses 12 h apart or as one 9 mg/kg dose (maximum dose of 200 mg, 12 h apart or one 400 mg dose); and
2. To evaluate the pertinent pharmacokinetic parameters of ceftibuten in each group.

SUBJECTS: Sixty-three (63) pediatric patients between the ages of 6 months and 16 years participated in the study.

STUDY DESIGN: During this multicenter study, patients were enrolled into age-designated groups and randomized to receive ceftibuten either as a single dose (9 mg/kg) or two doses (4.5 mg/kg) given 12 hours apart. Age designations for each group were as follows:
Group I: 12 to 17 years **GROUP II: 6 to 11 years**
GROUP III: 3 to 5 years **GROUP IV: 6 mo to 2 yr**
All doses were given in suspension form and under overnight fasting conditions. All doses were administered with approximately 30-120 ml of tap water depending on the age of the patient.

DOSAGE FORM: Ceftibuten suspension (36 mg/ml) was used in this study. Just prior to dosing, ml of water were added to the bottle containing mg ceftibuten.

SAMPLING TIME: **Blood** samples (2 ml) were drawn prior to and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hrs after the initial dose. **Urine** was collected before and until 24 after dosing.

ANALYTICAL METHODOLOGY: Plasma and urine concentrations of ceftibuten were measured using an HPLC method. The plasma samples of 52 patients were assayed at The urine samples of these subjects were assayed at Schering-Plough Research. The plasma samples of the remaining 11 patients were assayed at

The analytical method used at was as:

Chromatography: Column: μBondpak C18, PreColumn: CN, Column temperature was maintained at 30°C, Mobile phase was % of M ammonium acetate and % acetonitrile on a flow rate of ml/min, detection at nm.

Sample Preparation: Serum ml) ml sodium phosphate buffer, pH 7, + acyclovir (IS) ml acetonitrile. Vortex, centrifuge, transfer the supernatant to ml methylene chloride, vortex and centrifuge. The organic layer was transferred to autosample vial for analysis.

RESULTS: Linearity from μg/ml; Recovery 87%; Accuracy within 10% of the nominal values (except the μg/ml concentration); Inter- and intra-day variability (%CV) was less than 6%.

RESULTS: The mean pharmacokinetic parameters for the four age groups following 4.5 and 9.0 mg/kg doses are shown below.

4.5 mg/kg dose

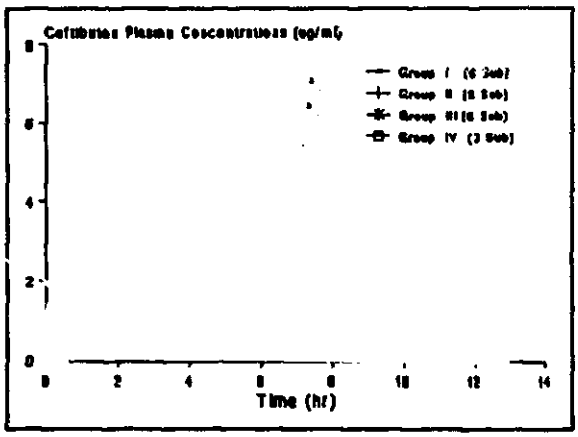
Parameter		Mean (%CV) Group I n=9	Group II n=6	Group III n=6	Group IV n=4
AUC0-oo	µg.hr/ml	37.2(20)	33.1(21)	28.1(26)	23.6(21)
Cmax	µg/ml	8.1(25)	9.1(29)	8.3(34)	6.8(21)
Tmax	hr	1.7(27)	2.2(54)	1.8(66)	1.7(35)
t1/2	hr	2.2(11)	2.1(24)	1.8(25)	1.5(18)
Cl/F	ml/min	97.2(18)	63.3(38)	48.2(22)	33.9(8)
	ml/min/kg	1.9(29)	2.4(19)	2.8(23)	3.3(21)
V/F	l	18.4(16)	11.4(39)	7.5(40)	4.3(26)
	l/kg	0.36(25)	0.43(36)	0.44(47)	0.43(39)
Ae	% of dose	50(29)	39(47)	51(38)	46(10)'
Clr	ml/min	51.6(41)	25.7(57)	23.7(34)	17.3()'

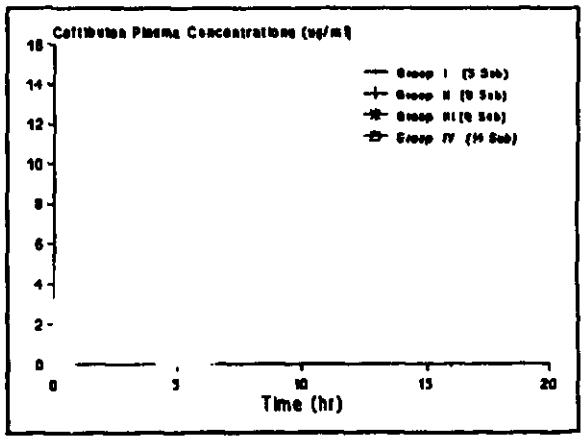
' mean of two subjects

9 mg/kg dose

Parameter	Unit	Mean (%CV) Group I n=5	Group II n=9	Group III n=8	Group IV n=15
AUC0-oo	µg.hr/ml	79.7(18)	67.2(37)	55.1(16)	49.8(21)
Cmax	µg/ml	16.3(10)	16.2(25)	12.9(43)	12.1(39)
Tmax	hr	1.4(39)	1.7(39)	1.8(37)	2.2(62)
t1/2	hr	2.5(11)	1.9(15)	2.1(36)	2.1(32)
Cl/F	ml/min	85.8(18)	61.0(38)	52.5(26)	34.7(28)
	ml/min/kg	1.6(32)	2.5(37)	2.8(17)	3.1(19)
V/F	l	18.1(17)	9.9(31)	10.0(53)	6.4(56)
	l/kg	0.33(31)	0.41(29)	0.52(41)	0.57(45)
Ae	% of dose	56(30)	54(43)•	56(29)	45(50)'
Clr	ml/min	46.3(25)	27.4(44)•	28.7(43)	20.8(51)'

' mean of 4 subjects; • mean of 6 subjects





CONCLUSION: The total body clearance, renal clearance and volume of distribution values increased with age. However, correction to body weight show that clearance values decreased as the age increase but the volume values were age independent.

COMMENTS:

1. The concern was raised if the pharmacokinetics in children is age dependent. specifically between children below the age of two years and older. Therefore, a population analysis of the data was performed, using The following results were obtained from this analysis:
   a. The Cl and V values are correlated to weight through A power model.
   b. No differences in the pharmacokinetics was observed in children above or below he age of 2 years.
   c. For subjects above the age of 12 years the Cl and V values were age independent and therefore could be dosed as adults.

2. The HPLC method used to evaluate the plasma levels of ceftibuten, at the was not adequately validated. The following is needed for prompt validation:
   a. The sponsor indicated that modifying the assay methodology did not prevent the elution of interfering peaks. The sponsor added these interfering peaks was not always constant within a single kinetic analysis. The sponsor subtracted the interfering peak area from the peak of interest area or used the external standard method. The sponsor should give more explanation about the assay modification that was used, the interfering peaks size and eluting time, the solution for variable interfering peaks eluting at the same time with cetibuten and validation to the external standard method.
   b. The inter- and intra-day variability were reported to be less than 6%, however no data was provided to support this conclusion.
   c. The back calculated values for the QC samples should be provided rather than the area or high ratios of ceftibuten/IS.
   d. The sponsor should compare the results from the two HPLC plasma method used in since the results from the two analyses were combined.

BIOAVAILABILITY STUDIES

Bioequivalence of Ceftibuten 400 mg Capsules and 400 mg Oral Suspension (Study C90-420-01; vol 1.49).

INVESTIGATOR: James Kisicki, Harris Laboratories, 624 Peach Street Lincoln, Nebraska 68501.

OBJECTIVES: To evaluate the bioequivalence of 400 mg capsule and a 400 mg oral suspension.

SUBJECTS: Eighteen healthy male subjects. The subjects mean (range) age, height and weight are 24.4 (19-35) yrs, 70.7 (66-75) inches and 166.6 (135-205) lb.

STUDY DESIGN: In a randomized two-way crossover design, volunteers, after an overnight fast, received a single oral dose of either 400 mg of ceftibuten oral suspension (treatment A) or one 400 mg ceftibuten capsule (treatment B). At least a one week washout period separated each phase. All doses were administered with 180 ml of tap water.

FORMULATION: 400 mg capsule, FMR No. 89682D09, Formula No. 2383, Batch No. 23235-50, and Batch size of 5000.

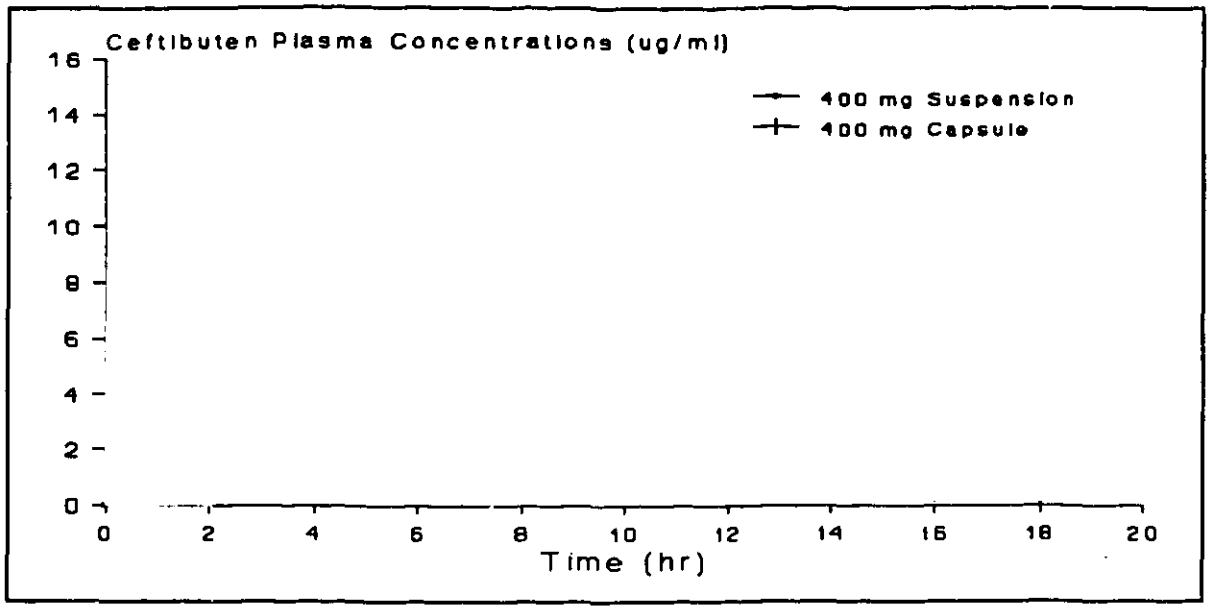
SAMPLING TIME: Plasma samples were collected before and then at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours after dosing.

ANALYTICAL METHODOLOGY: An HPLC method was used to determine ceftibuten plasma levels at

RESULTS: Mean plasma concentrations, mean (%CV) pharmacokinetic parameters and statistical analysis are summarized below.

Parameters	400 mg Suspension	400 mg Capsule	90% C.I.*
Cmax (μg/ml)	17.01 (19)	15.61 (20)	99 - 119
Tmax (hr)	2.06 (35)	2.19 (33)	
AUC $_{0t}$ (μg.hr/ml)	86.04 (14)	79.14 (18)	102 - 115
AUC $_{0\infty}$ (μg.hr/ml)	87.02 (14)	80.13 (18)	102 - 115
$t_{1/2}$ (hr)	2.52 (13)	2.45 (9)	

Based on non-transformed data.



CONCLUSION: The 400 mg suspension formulation of ceftibuten is bioequivalent to the 400 mg ceftibuten capsule formulation.

COMMENTS:

1. The sponsor indicated that "there was significant phase effect ($p<0.01$) for AUC with phase 2 means lower than phase 1." and "the treatment effect was significant ($p<0.04$) for AUC, with suspension higher than capsule."
2. The sponsor is requested to submit the SAS outputs used for the statistical analyses.
3. Subject 6 had an AUC and C_{max} values for the capsule treatment that were relatively much lower than the other subjects and much lower than the suspension AUC and C_{max}. Excluding this subject from data analysis did not change the study conclusion.
4. The analytical method used was not described.

Bioequivalency of Ceftibuten 400 mg capsules: Three-way Crossover Design (Study C90-875-01; Vol. 1.50)

INVESTIGATOR: Albert Cohen, Peninsular Testing Corporation, Opa-Locka, Florida.

OBJECTIVE: To compare the bioequivalency of one 400 mg capsule (a production batch) and two 200 mg capsules (a production batch) to two 200 mg capsules (a laboratory batch).

SUBJECTS: Eighteen healthy male subjects. The subjects mean (range) age and weight are: 27.9 (19 to 39) years and 168.3 (129-209) lbs.

STUDY DESIGN: Randomized three-way crossover design. Volunteers, after an overnight fast, received either one of the following treatments:

Treatment A: 400 mg production batch capsule (Formula # 2383, Batch # 25529-133, Batch Size 233,333)

Treatment B: 2*200 mg production batch capsule (Formula # 2136, Batch # 25529-117, Batch Size 466,666)

Treatment C: 2*200 mg laboratory batch capsule (Formula # 2136, Batch # 24764-014, Batch Size 116,000).

All doses were administered with 180 ml of tap water.

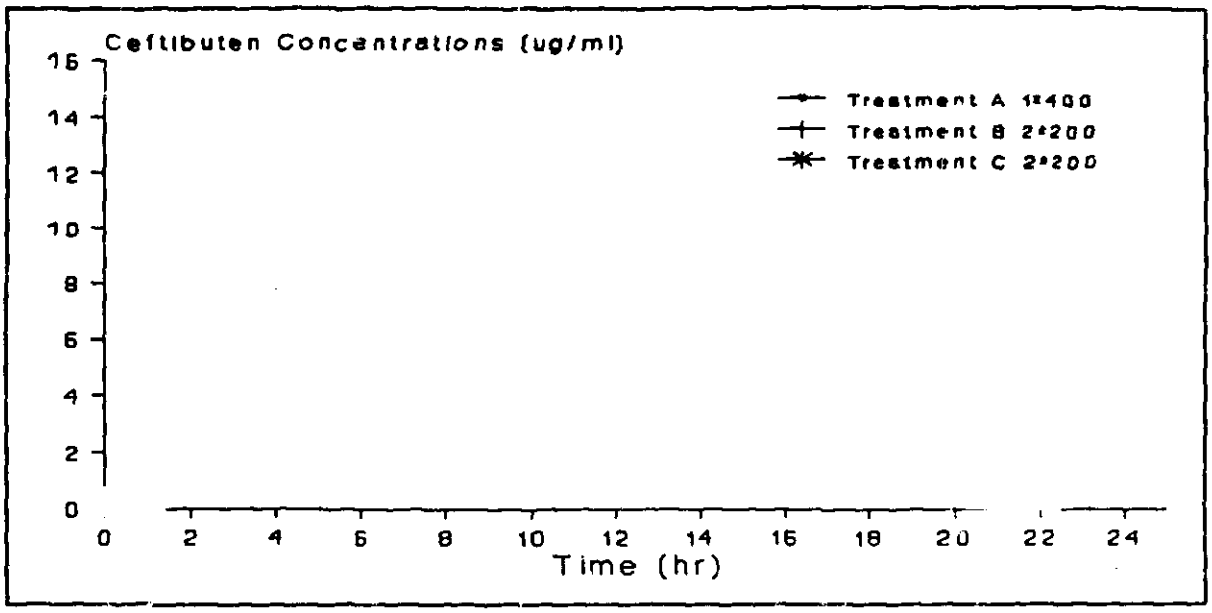
SAMPLING: Blood samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hours after dosing

ANALYTICAL METHODOLOGY: Plasma samples were analyzed by an HPLC method at

RESULTS: The mean plasma concentration and mean pharmacokinetic parameters (%CV) of ceftibuten are listed below.

Parameters	Treatment A	Treatment B	Treatment C
Cmax (μg/ml)	17.1 (21)	17.3 (17)	17.2 (21)
Tmax (hr)	2.8 (36)	2.5 (35)	2.4 (43)
$AUC_{0-\infty}$ (μg.hr/ml)	33.4 (20)	85.8 (20)	86.0 (13)
$t_{1/2}$ (hr)	2.4 (15)	2.4 (11)	2.4 (15)

The confidence intervals of the bioavailability parameters (C_{max} and AUC) among all three treatments were all between 89 to 109%.



CONCLUSIONS: The three capsule formulations used in this study are bioequivalent.

COMMENTS:

1. The sponsor is requested to provide the SAS output used for the statistical analyses.
2. The analytical method was not described.

Bioavailability of Ceftibuten 200 mg Capsules: Three-Way Cross-over Design. (Study C88-058-01, Vol. 1.52)

INVESTIGATOR: Albert Cohen, Peninsular Testing Corporation, Opa-Locka, Florida.

OBJECTIVE: To compare the bioavailability and bioequivalency of two 200 mg formulations of ceftibuten to a 100 mg capsule.

SUBJECTS: Fifteen healthy male volunteers participated in this study. The volunteers age and body weight ranged from 19 to 37 years and 132 to 188 lbs, respectively.

STUDY DESIGN: A randomized three-way crossover design. Each volunteer received (after overnight fast) the following treatment:
Treatment A: One 200 mg ceftibuten capsule; Formulation 2073, Batch # 19634-110 and batch size 3000 Manufactured at NJ.
Treatment B: One 200 mg ceftibuten capsule; Formulation 2077, Batch # 19634-129 and Batch size 3000 manufactured at NJ formulation).
Treatment C: Two 100 mg ceftibuten capsule; Batch # 21108-120 formulation).

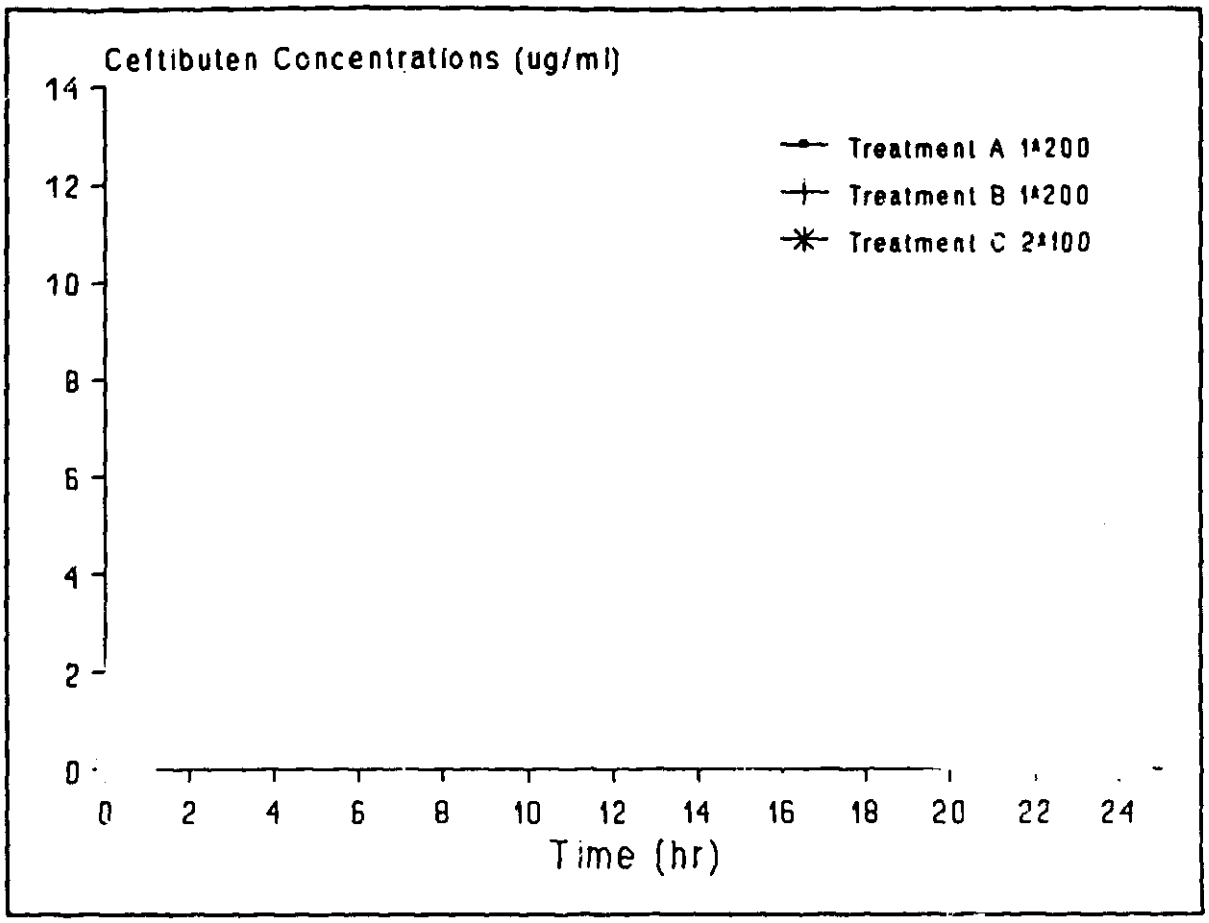
SAMPLING: Plasma samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 24 hrs after dosing.

ANALYTICAL METHODOLOGY: Plasma concentration of ceftibuten were determined by HPLC at The analytical method used was not described.

RESULTS: The mean (±SD) pharmacokinetic parameters for ceftibuten and the mean plasma levels are summarized below.

Treatment	$AUC_{0-\infty}$ (μg*hr/ml)	Cmax (μg/ml)	Tmax (hr)	t1/2 (hr)
A (1*200 mg)	64.5±13.8	13.8±3.3	2.1±0.54	4.42±4.11
B (1*200 mg)	69.6±9.3	15.7±1.7	1.9±0.67	3.03±1.32
C (2*100 mg)	64.6±11.2	14.3±2.5	2.0±0.69	3.62±2.83
90% C.I.*				
A vs C	92-109	87-105		
B vs C	99-116	101-118		
A vs B	86-101	80-96		

* Based on non-transformed data



CONCLUSION: Provided that the comments below are satisfactory resolved and based on the 90% confidence intervals results the three tested formulation are bioequivalent.

COMMENTS:

1. The variability in the half-life values (ranged from hrs) in this study were unreasonably high (%CV was as high as %). This variability was not observed in any of the other studies reviewed. This variability is of great importance since this is a bioequivalence study.
2. Compared to other studies, where a 200 mg dose of ceftibuten was administered, the individual and mean Cmax and AUC values were higher in this study. These values were comparable to values obtained following 400 mg ceftibuten administration (cross study comparison).
3. The sponsor is requested also to provide the SAS output that was used to calculate the 90% confidence interval values.
4. Only the Batch # was provided for the 100 mg capsule. The sponsor is requested to provide the formulation #, manufacturing site, Batch size ..etc.

Influence of Food on the Absorption of Ceftibuten 200 mg Capsules in Normal Male Volunteers: Two-Way Crossover Design (Study C89-134-01; Vol 1.57).

INVESTIGATOR: Albert Cohen, Peninsular Testing Corporation, Opa-Locka, Florida.

OBJECTIVE: To compare the bioavailability of a 200 mg ceftibuten capsule administered in the presence and absence of food.

SUBJECTS: Eighteen healthy male volunteers. Subjects mean (range) age and body weight were: 29 (19-36) years and 168 (128-194) Lbs.

STUDY DESIGN: A randomized two-way crossover design. Each volunteer received the following two treatments:

1. **Treatment A:** 200 mg capsule administered with standardized breakfast[1] following 10 hr fast.
2. **Treatment B:** 200 mg capsule given following a 10 hr fast.

All doses were administered with 120 ml of tab water, and subjects received a light lunch 4 hours after dosing.

FORMULATION: 200 mg capsule, Formula No. 2136, Batch No. 22023-083 and Batch Size 54,900.

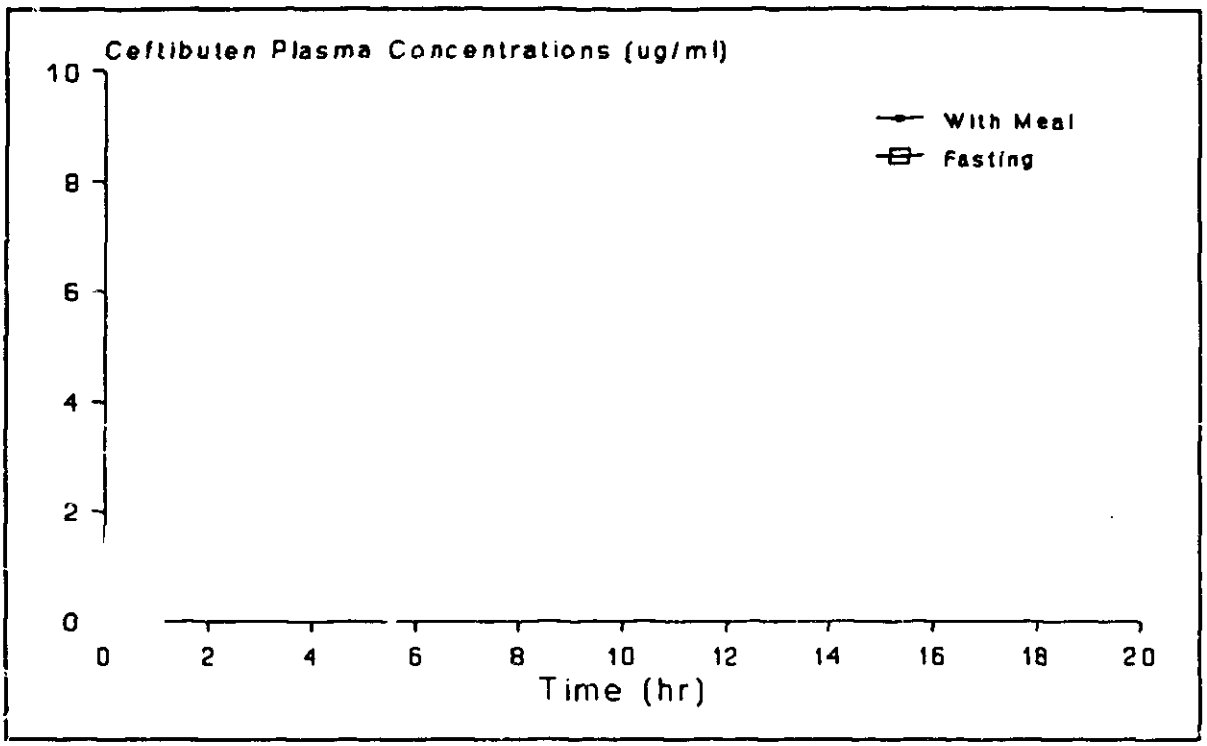
SAMPLING: Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hr after dosing.

ANALYTICAL METHODOLOGY: Plasma concentration of ceftibuten were determined by HPLC at The analytical method used was not described.

RESULTS: The mean (% CV, n=18) pharmacokinetic parameters for ceftibuten and the mean plasma levels are summarized below.

Treatment	$AUC_{0-\infty}$	Cmax	Tmax	$t_{1/2}$
A (fed)	42.4(20)	7.95(22)	3.39(31)	2.94(31)
B (fast)	51.94(14)	11.8(16)	2.04(44)	2.80(20)

[1]Two pieces of toast with butter, two eggs (any style), 8 oz whole milk, two strips of bacon and 2-4 oz hash brown potato patty.



Mean bioavailability of Treatment A relative to Treatment B is:

parameter	p-value	C.I.
Cmax	0.001	60-75
$AUC_{0-\infty}$	0.001	74-89

CONCLUSION: The ingestion of food reduced the rate (C_{max} and t_{max}) and extent (AUC) of absorption of ceftibuten when given as a 200 mg capsule. The C_{max} and AUC values were reduced by % and % respectively.

Influence of Food on the Absorption of Ceftibuten Capsules Administered to Normal Volunteers before a Meal: Four-Way Cross-Over Design (C90-228-01; Vol 1.58).

INVESTIGATOR: Albert Cohen, Peninsular Testing Corporation, Opa-Locka, Florida.

OBJECTIVE: To compare the bioavailability of a 400 mg ceftibuten capsule administered in the presence and absence of food and at various times before meal.

SUBJECTS: Twenty six of thirty healthy adult male volunteers completed the study. The subjects mean (range) age and weight are: 28.1 (18-40) years and 157 (129-183) Lbs.

STUDY DESIGN: A randomized, open label, four-way cross-over design. Each volunteer received one of the four treatments (A, B, C, D) during each dosing phase (I, II, III, IV) as follow:

Treatment A: One 400 mg ceftibuten capsule administered with a standardized breakfast[2] following a 10 hr fast.

Treatment B: 400 mg ceftibuten capsule taken 30 min before a standardized breakfast following a 10 hr fast.

Treatment C: 400 mg ceftibuten capsule taken 60 min before a standardized breakfast following a 10 hr fast.

Treatment D: One 400 mg ceftibuten capsule administered following a 10 hr fast.

All doses were administered with 120 ml of tab water, and subjects received a light lunch 4 hours after dosing.

FORMULATION: 400 mg capsule, Formula No. 2383, Batch No. 23235-101 and Batch Size 25,000.

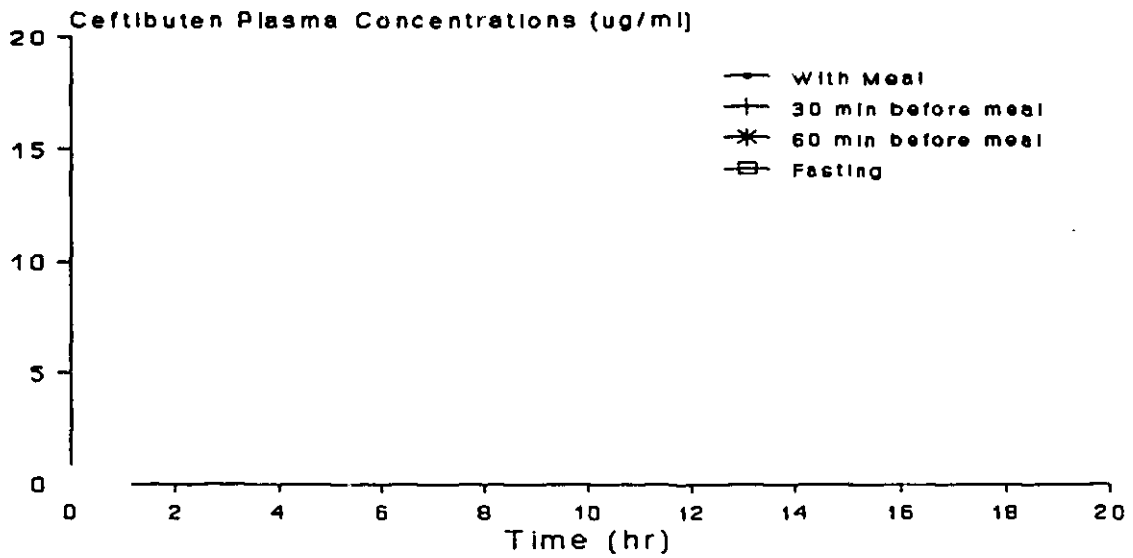
SAMPLING: Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hr after dosing.

ANALYTICAL METHODOLOGY: Plasma concentration of ceftibuten were determined by HPLC at The analytical method used was not described.

RESULTS: The mean (% CV, n=26) pharmacokinetic parameters for ceftibuten and the mean plasma levels are summarized below.

[2]Two pieces of toast with butter, two fried eggs, 8 oz whole milk, two strips of bacon and 2-4 oz hash brown potato patty.

Treatment	Cmax	Tmax	$AUC_{0-\infty}$	$t_{1/2}$
with meal	15.9(15)	4.0(24)	84.6(12)	2.38(17)
30 min before	17.8(20)	1.87(35)	82.4(18)	2.47(14)
60 min before	18.3(25)	1.87(34)	83.3(22)	2.41(14)
Fasting	19.5(24)	2.25(48)	91.6(23)	2.36(12)



The bioavailability, using the 90% confidence interval, of treatment D (fasted) relative to other treatments was as follows:

Parameter	90% Confidence Interval A/D	B/D	C/D
Cmax			
AUC			

CONCLUSIONS:

1. Coadministration of food with a 400 mg ceftibuten capsule decreased the rate of absorption (C_{max}, t_{max}), but not the extent of absorption (AUC).
2. A meal given either 30 min or 60 min after the administration of a 400 mg ceftibuten capsule did not affect the bioavailability of ceftibuten.

Influence of Food on the Absorption of ceftibuten Capsules Administered to Normal Male Volunteers After a Meal ; Four-Way Crossover Design (Study C90-229-02; Vol 1.59).

INVESTIGATOR: Jerry Herron, Arkansas Research Medical Testing Center, Little Rock, AR.

OBJECTIVES: To compare the bioavailability of a 400 mg ceftibuten capsule in the absence of food and at various times after a meal.

SUBJECTS: Twenty-four healthy male subjects. The subjects mean (range) age and weight are: 33 (26-38) years and 163 (140-200) Lbs.

STUDY DESIGN: A randomized, open label, four-way crossover design. Each volunteer received one of the four treatments (A, B, C, D) during each dosing phase (I, II, III, IV) as follow:

Treatment A: 400 mg ceftibuten capsule administered 60 min after standardized breakfast following a 10 hr fast.

Treatment B: 400 mg ceftibuten capsule taken 120 min after a standardized breakfast following a 10 hr fast.

Treatment C: 400 mg ceftibuten capsule taken 240 min after a standardized breakfast following a 10 hr fast.

Treatment D: One 400 mg ceftibuten capsule administered following a 10 hr fast.

All doses were administered with 120 ml of tab water, and subjects received a light lunch 4 hours after dosing.

FORMULATION: 400 mg capsule, Formula No. 2383, Batch No. 23235-101 and Batch Size 25,000.

SAMPLING: Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hr after dosing.

ANALYTICAL METHODOLOGY: Plasma concentration of ceftibuten were determined by HPLC at

The me od used was not described.

RESULTS: The mean (% CV, n=24) pharmacokinetic parameters for ceftibuten are summarized below.

Treatment	Cmax	Tmax	$AUC_{0-\infty}$	$t_{1/2}$
1 hr after	14.5(18)	2.85(30)	74.4(19)	2.83(19)
2 hr after	14.7(23)	2.73(43)	76.4(17)	2.85(18)
4 hr after	15.4(24)	2.13(33)	78.5(21)	2.80(16)
Fasting	14.0(31)	2.33(50)	70.0(23)	2.79(16)

CONCLUSIONS: A meal given 1, 2 or 4 hours before administration of a 400 mg ceftibuten capsule did not affect the bioavailability of ceftibuten when given under fasting conditions.

Influence of Food on the Absorption of a 400 mg Dose of Ceftibuten Oral Suspension in Normal Male Volunteers: Three-Way Crossover Design (Study C90-235-01; Vol 1.29)

INVESTIGATOR: Thomas L. Hunt, Pharmaco Dynamics Research Inc. Two Park Place, 4009 Banister Lane, Austin, Texas 78704.

OBJECTIVES: To compare the bioavailability of a 400 mg dose of ceftibuten suspension: a) in the presence and absence of food and b) in the presence of a high calorie, high-fat meal and a low calorie, non-fat meal.

SUBJECTS: Eighteen healthy adult male volunteers. The subjects mean (range) age and weight are: 24.6 (19 - 38) years and 163.6 (143 - 186) Lbs.

STUDY DESIGN: A randomized, open label, three way crossover study design. Following ten-hour fast, each volunteer received a 400 mg dose of ceftibuten suspension administered with:
Treatment A: a standardized (high-calorie, high-fat) breakfast.[3]
Treatment B: a standardized (low-calorie, non-fat) breakfast.[4]
Treatment C: fasting.
All doses were administered with 120 ml of tap water.

FORMULATION: 36 mg/ml suspension, FMR 90524-D02; Batch # 24764-087.

SAMPLING: **Plasma** samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 hr after dosing.

ANALYTICAL: Plasma concentrations of ceftibuten and trans-ceftibuten were determined by an HPLC at

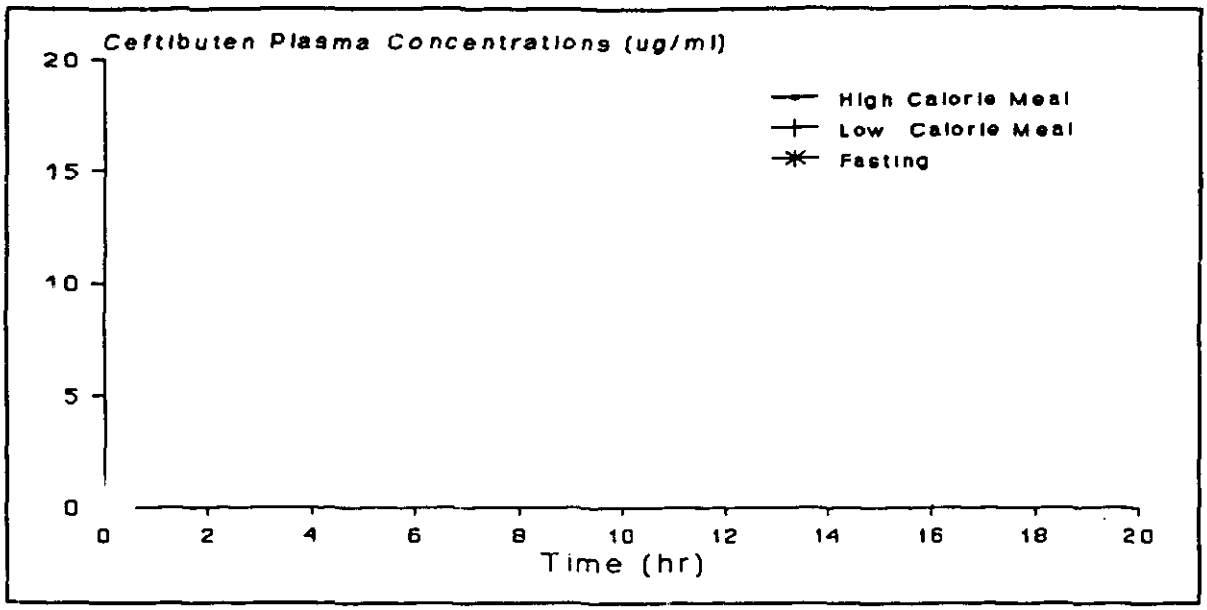
RESULTS: The mean (n=18; %CV) pharmacokinetic parameters and mean plasma levels of ceftibuten are as follows:

Parameters	High-Fat	Non-Fat	Fasting
Cmax (μg/ml)	14.0 (19)	15.4 (15)	19.0 (20)
Tmax (hr)	2.3 (31)	2.8 (37)	1.9 (37)
$AUC_{0-\infty}$ (μg.hr/ml)	76.7 (18)	81.2 (14)	92.3 (16)
t1/2 (hr)	2.6 (16)	2.6 (21)	2.7 (21)

CONCLUSION:

[3]Two pieces of toast with butter, two fried eggs, 8 oz whole milk, two strips of bacon and a 2-4 oz. hash brown potato patty (841 calories).

[4]Two pieces of dry toast, 8 oz skim milk, 2.5 oz raisin ran cereal and 1 piece of fresh fruit (416 calories).



1. Food decreased the rate and extent of absorption of ceftibuten from a suspension formulation, resulting in lower C_{max} and AUC.
2. The extent of the food effect appeared to depend on the type of meal, since the high-calorie, high-fat meal decreases C_{max} and AUC by 26% and 17%, respectively, whereas the low calorie, non-fat meal decreased C_{max} and AUC by 19% and 12%, respectively.

SPECIAL POPULATION

Multiple-Dose Pharmacokinetics of Ceftibuten in Geriatric Volunteers (Study C88-098-01; Vol. 1.60).

INVESTIGATOR: Albert Cohen, Peninsular Testing Corporation, Opa-Locka, Florida.

OBJECTIVE: To assess the pharmacokinetics of ceftibuten and its major metabolite, trans-ceftibuten, in geriatric volunteers.

SUBJECTS: Twelve volunteers (8 males and 4 females) between the ages of 65 and 76 years entered the study. The subjects mean age and body weight are 68.7 (65-76) years and 153 (120-221) Lbs.

STUDY DESIGN: Each Volunteer received a 200 mg capsule of ceftibuten twice a day for three days plus one dose on the morning of the fourth day. Treatment was administered with 120 ml of tab water and doses on days 1, 3 and 4 were taken following over night fast.

FORMULATION: 200 mg capsule, Formula No. 2136, Batch No. 22023-083 and Batch size 54,900.

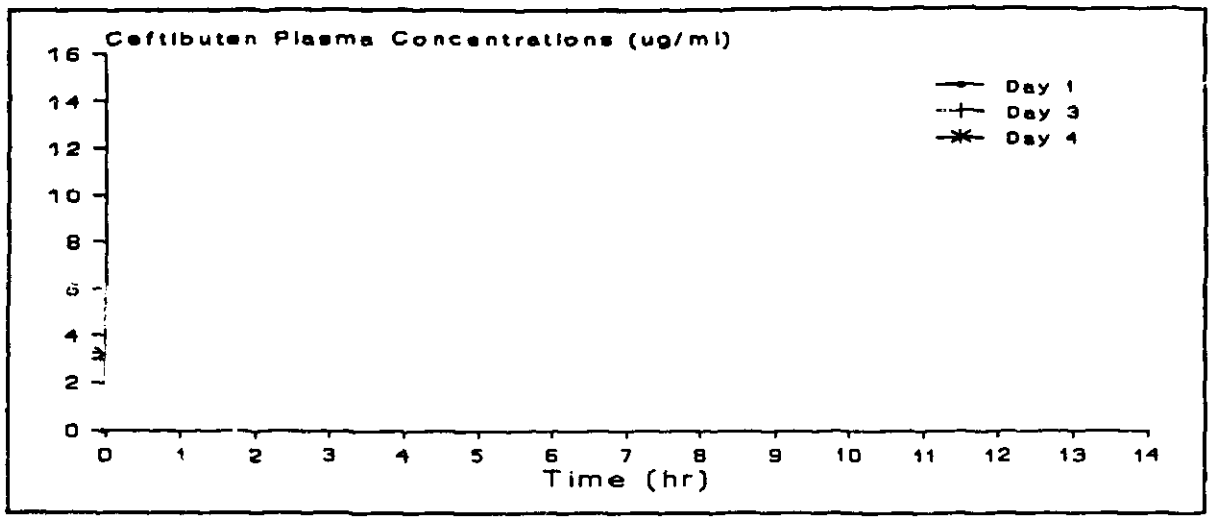
SAMPLING TIME: Blood (10 ml) samples were drawn at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the morning dose in days 1 and 3. On day 4 additional samples were obtained as follows: 14, 16, 18, 24, 30, and 36 hours. Urine was collected at the following time intervals 0, 0-4, 4-8, and 8-12 after dosing on day 1 and 3 and on day 4 additional samples were collected at 12-16, 16-24, 24-28, 28-32 and 32-36 hours.

ANALYTICAL METHODOLOGY: Plasma and urinary concentrations of ceftibuten and trans-ceftibuten were determined by HPLC at The analytical method used was not described.

RESULTS: The mean (n=12, %CV) pharmacokinetic parameters and plasma levels of ceftibuten are listed below.

Parameter	Day 1	Day 3	Day 4
Tmax (hr)	2.17(42)	2.00(50)	1.83(42)
Cmax (μg/ml)	12.9(16)	15.2(21)	17.5(21)
AUC_{0-12} (μg.hr/ml)	62.3(15)	79.4(21)	87.1(22)
$t_{1/2}$ (hr)	3.01(11)	3.18(9)	3.21(14)
Accumulation Factor	--	1.27[$]	1.40[$]
Ae_{0-12} (%)	59.3(21)	69.9(23)	69.3(18)
Clr (ml/min)	32.6(28)	30.2(26)	27.5(26)

[$] Higher than the projected accumulation of 1.1.



The mean pharmacokinetic parameters of trans-ceftibuten are:

Parameter	Day 1	Day 3	Day 4
Tmax (hr)	3.33(39)	3.54(46)	3.08(32)
Cmax (μg/ml)	1.05(40)	1.22(40)	1.36(28)
AUC_{0-12} (μg.hr/ml)	5.91(53)	8.57(64)	9.77(40)
Ae_{0-12} (%)	18.6(42)	22.2(45)	22.9(42)

CONCLUSION: The results of this study need to be reevaluated based on the individual creatine clearance values of the geriatric subjects.

COMMENTS:

1. The dosage regiment given in this study (200 mg bid) is not recommended in the labeling, a 400 mg once daily is the only recommended adult dosage regiment. Accordingly, the effect of age on ceftibuten pharmacokinetics given at a 400 mg dose once daily was not assessed. However, it is assumable that no accumulation is to be expected.

2. The sponsor indicated that, compared to healthy volunteers (receiving the same dosage regimen), the geriatric volunteers yielded higher C_{max} and higher AUC values and longer half-life. Age and/or renal function may be responsible for these changes in the pharmatokinetic parameters. In order to determine if these changes are age related the renal function of the geriatric patients need to be evaluated.

3. Based on the urinary excretion results obtained on day 3 and 4 the sponsor concluded that up to 95% of ceftibuten dose is absorbed. It is to be emphasized that this is the only

study where the amount excreted in urine was that high. Taking into consideration that this study was conducted in geriatric volunteers (age ≥65 years), and that these results were obtained under steady state conditions (with accumulation ratio higher than projected) using unrecommended dosage regiment make these results less reliable.

4. The amount of trans-ceftibuten excreted in urine was high and reached up to 51% of the administered dose on day 4.

Pharmacokinetics of Ceftibuten in Subjects with Chronic Liver Disease (Study C89-038-01; Vol. 1.60).

INVESTIGATOR: Philip Lesse, Quincy Research Center, Kansas City, Missouri.

OBJECTIVES: To determine and evaluate the pharmacokinetics of ceftibuten and trans-ceftibuten in subjects with chronic liver disease.

SUBJECTS: Twelve male subjects with chronic liver dysfunction participated in the study. The subjects mean (±SD) age and body weight are 60±9 years and 160±39 Lbs, respectively.

STUDY DESIGN: Each subject received an oral dose of 400 mg ceftibuten with 120 ml of tap water following 10 hr fast.

FORMULATION: 200 mg capsule, Formula No. 2136 Batch No. 22023-083 and Batch size 54,857.

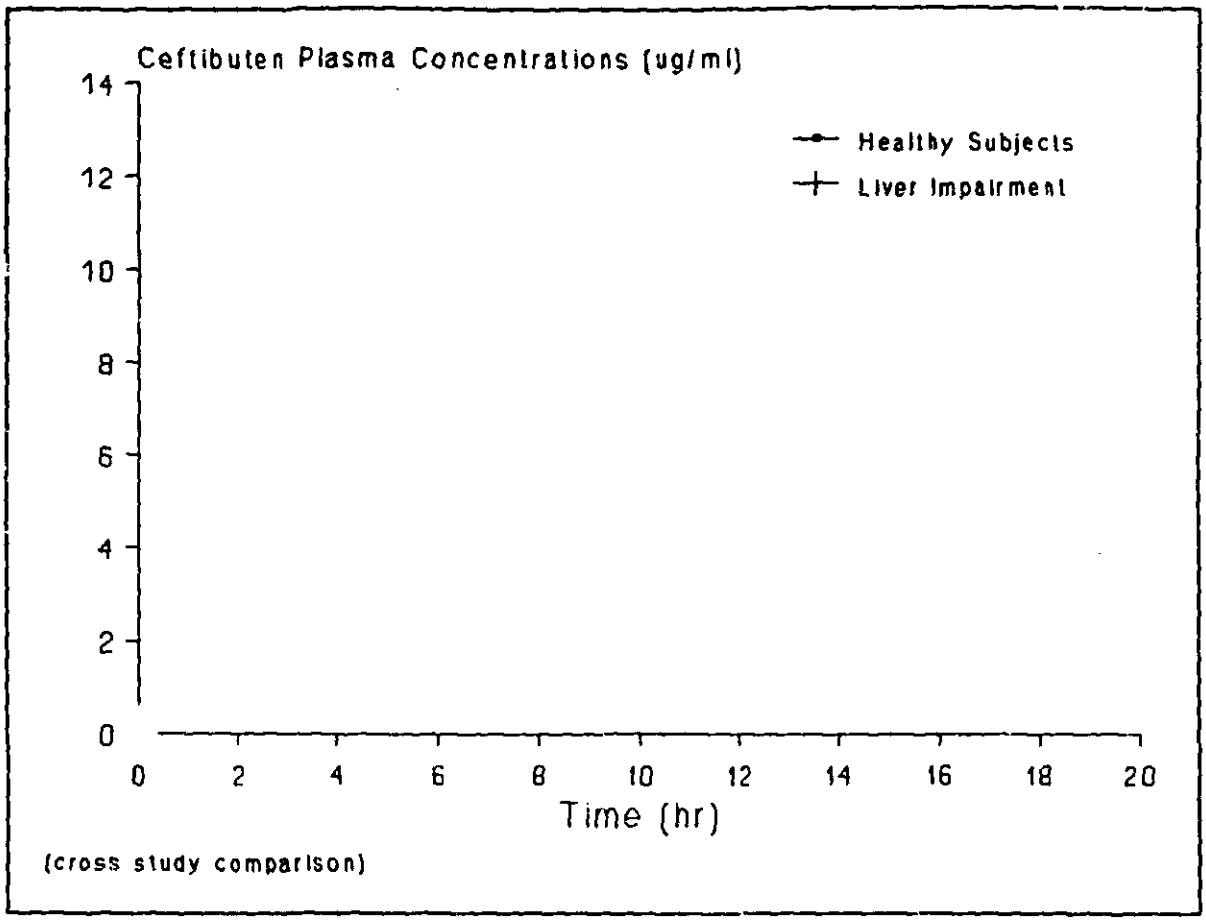
SAMPLING: Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hr after dosing. Urine was collected at 0, 0-6, 6-12, 12-24, 24-48, 48-72 hr after dosing.

ANALYTICAL METHODOLOGY: Ceftibuten plasma and urinary concentration were determined by HPLC at

The analytical method used was not described.

RESULTS: The mean plasma levels and mean (CV%) pharmacokinetic parameters obtained in subjects with chronic liver disease are summarized below. These results are compared to the results obtained from study C-90-885-01 (healthy volunteers receiving a 400 mg dose).

Parameter	Subjects with Liver Disease	Healthy Subjects (study C90-885-01)
AUC_{0-24} (μg.hr/ml)	103.4(35)	73.7(22)
C_{max} (μg/ml)	16.2 (25)	14.98(22)
T_{max} (hr)	3.1(40)	2.58(34)
$t_{1/2}$ ke (hr)	4.1(27)	2.45(9)
Ae (% dose)	54.8(20)	57.1(19)
Cl, (ml/min)	38.6(40)	50.2(18)



22% of the dose was recovered in urine as trans-ceftibuten.

CONCLUSION: The cross-study comparison shows that subjects with liver impairment appeared to have higher AUC, longer $t_{1/2}$, and lower Cl_r values than healthy volunteers. The sponsor indicated that its likely that these changes were related to renal function; most subject were more than 60 years old and all but three of the subjects had creatinine clearance less than 80).

Pharmacokinetics of Ceftibuten in Subjects with Chronic Renal Insufficiency (Study C87-091-01, Vol. 1.61).

INVESTIGATOR: Gary Matzke, Regional Kidney Disease Program, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, MN.

OBJECTIVES: To determine the pharmacokinetics of a single 300 mg oral dose of ceftibuten in subjects with impaired renal function.

SUBJECTS: Thirty of thirty-one volunteers, with normal and impaired renal function, completed the study.

STUDY DESIGN: Volunteers were divided into five different groups (6 each) based on their renal function as follow:

Group I: Creatinine Clearance >80 ml/min
Group II: Creatinine Clearance 50-80 ml/min
Group III: Creatinine Clearance 30-49 ml/min
Group IV: Creatinine Clearance 5-29 ml/min
Group V: Creatinine Clearance <5 ml/min

All subjects received a 300 mg dose (3*100 mg capsule) with 120 ml of tap water. In addition to the initial 300 mg dose (interdialysis day), subjects in group V received another 300 mg dose (dialysis day) two weeks later. Following the four-hr blood collection, two to four hr of hemodialysis was initiated.

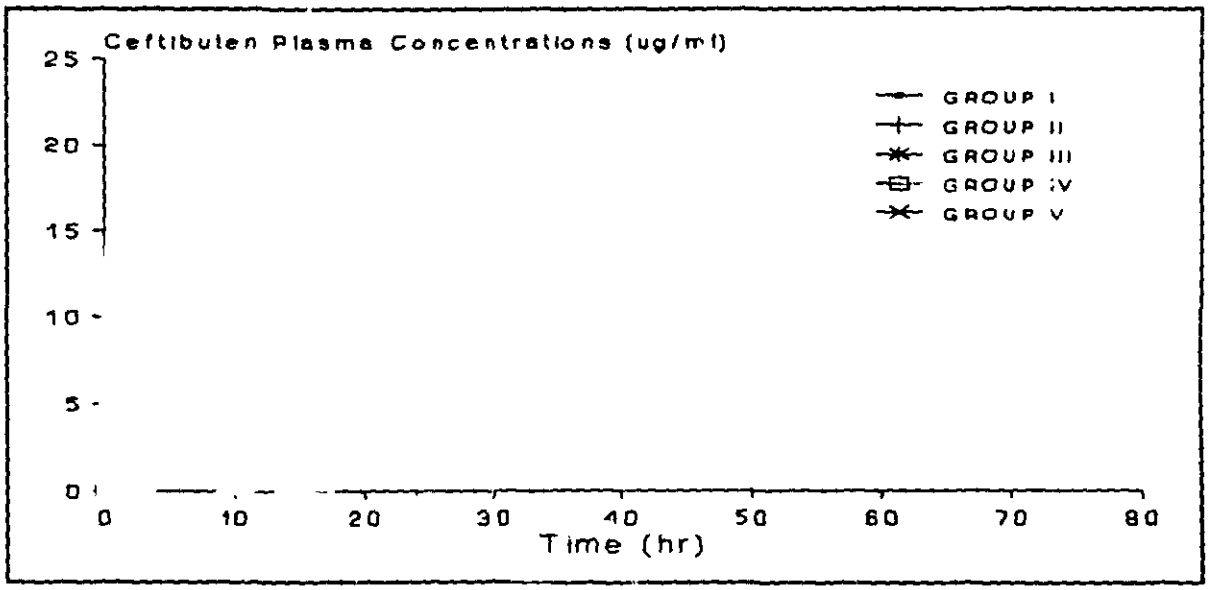
FORMULATION: 100 mg capsules, Formula No. 1845, Batch No. 20211-111

SAMPLING TIME: Blood samples (10 ml) were drawn at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 hr after dosing. Urine was collected at 0, 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-72, 72-96, and 96-120 hr after dosing. For Group V, following the second dose, additional venous blood samples were drawn at 4.5, 5, 7 and 9 hours after dosing. In addition, arterial blood was collected at 0.16, 0.33, 0.50, and 0.75 hr after the completion of hemodialysis. Dialysate samples were collected at the following time intervals 0, 0-0.5, 0.5-1, 1-2, 2-3, and 3-4 hrs after the start of dialysis.

ASSAY METHODOLOGY: Plasma and urinary concentrations of ceftibuten and trans-ceftibuten were determined by HPLC at schering-Plough Corporation. The sponsor indicated that the plasma samples were assayed by direct injections into a HPLC system. Some plasma samples, due to interfering peaks, were analyzed by HPLC column-switching method. The methods used for the quantitation of ceftibuten in plasma and urine were fully validated, however, only the mean values of the validation samples were reported.

RESULTS: Listed below are the mean plasma levels and mean (%CV) pharmacokinetic parameters of ceftibuten.

Mean (%CV) Parameter (unit)		Group I	Group II	Group III	Group IV	Group V
Cl_w	(ml/min)	117(23)	76(5)	36(7)	16(45)	2.9(141)
C_{max}	(μg/ml)	11.7(20)	13.9(14)	13.0(14)	20.7(36)	19.5(33)
T_{max}	(hr)	2.7(19)	2.8(26)	3.2(24)	4.3(32)	3.0(30)
$t_{1/2}$	(hr)	2.7(21)	3.9(33)	7.1(20)	13.4(35)	22.3(36)
$AUC_{0-\infty}$	(μghr/ml)	66(8)	94(20)	168(11)	360(40)	472(22)
CL/F	(ml/min)	77(9)	55(18)	30(11)	16(48)	11(24)
VB/F	(l/kg)	0.21(14)	0.22(23)	0.24(29)	0.22(23)	0.39(69)
Ae	(% of dose)	68(14)	53(18)	41(27)	31(47)	18(40)
Cl_r	(ml/min)	51.7(12)	28.6(23)	13.2(23)	5.6(95)	2.1(67)



The trans-ceftibuten pharmacokinetic parameters are listed below:

Mean (%CV) Parameter (unit)		Group I	Group II	Group III	Group IV
Cl_w	(ml/min)	117(23)	76(5)	36(7)	16(45)
C_{max}	(μg/ml)	2.12(65)	1.18(9)	1.71(22)	2.68(12)
T_{max}	(hr)	3.5(50)	4.3(32)	6.7(36)	11.3(41)
$AUC_{0-\infty}$	(μghr/ml)	10.3(48)	11.9(36)	31.6(33)	93.6(41)
Ae	(% of dose)	9.9(66)	15.3(95)	14.6(50)	5.82(94)

Subjects in group V, on average, excreted 38.6% of dose into dialysate during the 4 hr dialysis. There was a rise in the plasma concentrations of ceftibuten after the cessation of hemodialysis.

CONCLUSIONS: The total body clearance and the renal clearance values decreased while the terminal half-life and the AUC values

increased with decreasing renal function.

1. The sponsor recommended, in the labelling, the following dose adjustment is the renaly impaired subjects:

Cl cr	≥80	50-79	30-49	5-29	<5
t1/2	2.70	3.85	7.07	13.39	22.28
Daily dose	400	400	200	100	100
Time interval for 400 mg	24 hr	24	48	96	120*

* In hemodialysis patients, a supplemental dose of ceftibuten (200 mg) should be administered at the end of each dialysis session in addition to the maintenance dosage regimen. An alternate dosing regimen would be a 400 mg dose at the end of each hemodialysis session, assuming that dialysis is performed two to three times a week.

Simulation of the plasma levels in each group using the two adjustment methods (dose and time intervals) clearly shows that the adjustment of the dose rather than adjustment in dosing time interval is more appropriate.

2. The plasma levels of subject 25 (group V) were higher on the second dose (hemodialysis day) compared to the first dose (no hemodialysis).

DRUG-DRUG INTERACTION

Pharmacokinetic Drug Interaction Study: Ceftibuten Plus Theophylline (Study C88-119-01; Vol 1.66)

INVESTIGATOR: J. Schwartz, St. Vincent's Medical Center, Toledo, OH

OBJECTIVES: To determine the effect of ceftibuten on theophylline pharmacokinetics when given concomitantly.

SUBJECTS: Twelve healthy male subjects participated in the study. The subjects mean (range) of age and body weight are: 24 (21-37) kg and 164 (144-193) lbs, respectively.

STUDY DESIGN: A randomized cross-over study design. Each volunteer received the following two treatments:
Treatment A: a 15 minute IV infusion of theophylline (4 mg/kg).
Treatment B: a 200 mg ceftibuten every 12 hours on days 1 to 7 and a 15 minute intravenous infusion of theophylline (4 mg/kg) in conjunction with the morning dose of ceftibuten on day 6.

FORMULATION: Theophylline 4 mg/kg intravenous infusion, Travenol, lot number TF00944. Ceftibuten 200 mg capsule, Formula 2136, FMR # 88756-D02, Batch size 54,900.

SAMPLING: Blood samples (10 ml) were collected immediately prior to the theophylline infusion, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hours after the completion of the infusion period.

ASSAY METHODOLOGY: Theophylline plasma concentrations were determined by a HPLC at The method's recovery, sensitivity, and inter- and intra-variability was satisfactory reported, however the method was not described.

RESULTS: The mean (% CV) pharmacokinetic parameters of theophylline are summarized below:

Parameter	Treatment A (Theophylline only)	Treatment B
$AUC_{0-\infty}$ (µg.hr/ml)	66.99 (22)	66.74 (18)
$t_{1/2}$ (hr)	6.14 (19)	6.30 (18)
Cl (ml/min.kg)	1.04 (20)	1.03 (20)
Vd (ml/kg)	533.0 (11)	547.2 (10)

CONCLUSION: The pharmacokinetics of single intravenous dose of theophylline was not altered by multiple-dose ceftibuten administration. However, the effect of theophylline on ceftibuten pharmacokinetics was not assessed.

Pharmacokinetic Drug Interaction Study: Administration of ceftibuten Concurrently with Mylanta® II or with Ranitidine (Study C90-876-01)

INVESTIGATOR: Jerry Herron, Arkansas Research Medical Testing Center, 1207 Rebsamen Park Road, Little Rock, AR 72202.

OBJECTIVES: To evaluate the pharmacokinetics of ceftibuten when given concurrently with antacid Mylanta and ranitidine.

SUBJECTS: Eighteen healthy male volunteers. The volunteers mean (range) of age and body weight were 32.7 years (24-38) and 169.3 lbs (141-200), respectively.

STUDY DESIGN: Randomized three way cross over study design. Each volunteer received the following three treatments:
Treatment A: 400 mg ceftibuten alone,
Treatment B: 400 mg ceftibuten followed by 60 cc Mylanta II, and
Treatment C: Three days of dosing of ranitidine q12h followed by 400 mg ceftibuten followed by 150 mg ranitidine q12h.
All doses were given following overnight fast and with 180 ml of tap water. A one week washout period separated the study phases.

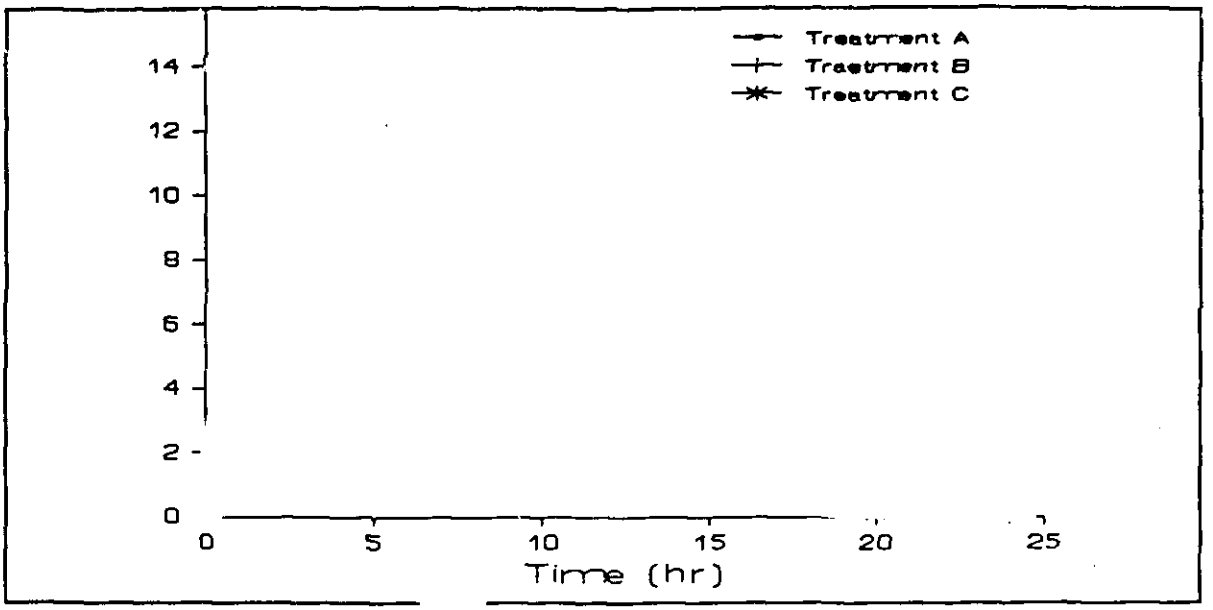
FORMULATION: 400 mg ceftibuten capsule (Formula 2383, batch #25529-133), Ranitidine (Zantac® lot # Z12150MP) and Mylanta® II (Lot # 5163K).

SAMPLING TIME: **Plasma** samples were collected at 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 hr after dosing. **Urine** samples were collected at 0, 0-4, 4-8, 8-12, 12-16, 16-20, and 20-24 hours after dosing.

ANALYTICAL METHODOLOGY: Ceftibuten and trans-ceftibuten levels were determined using an HPLC method at

RESULTS: Listed below are the mean plasma levels and the mean (n=17; %CV) pharmacokinetic parameters of ceftibuten in the three treatment groups. Plasma concentrations of ceftibuten for one subjects (# 10) were extremely low and therefore was excluded from the results.

Parameter	Treatment A (alone)	Treatment B (with Mylanta)	Treatment C (with ranitidine
C_{max} (μg/ml)	12.0 (31)	13.0 (25)	14.8 (22)
T_{max} (hr)	2.6 (43)	2.1 (55)	2.0 (31)
$AUC_{0-\infty}$ (μg.h/ml)	61.0 (27)	65.2 (18)	70.6 (26)
$t_{1/2}$ (hr)	2.63 (19)	2.63 (25)	2.44 (12)
Ae_{0-24} (% dose)	37.2 (39)	42.4 (30)	38.5 (41)
Cl, (ml/min)	43.6 (44)	44.1 (33)	38.6 (46)



13% of the administered dose was recovered in urine as trans-ceftibuten.

CONCLUSION:

1. Concurrent administration of ceftibuten with Mylanta did not affect ceftibuten bioavailability.
2. Multiple dose administration of Ranitidine did not affect the single dose administration of ceftibuten. The Cmax was not increased while the AUC increased by 15%.

COMMENT:

The individual and mean values of Cmax and AUC obtained in this study were low compared to other studies where ceftibuten was administered as a 400 mg capsule. The urinary excretion of ceftibuten was also low in this study and then not exceed 10% in one subject.

TISSUE DISTRIBUTION

Secretion of Ceftibuten in Breast Milk (Study C88-118-01; Vol 1.61)

INVESTIGATOR: Jerry Herron, Arkansas Research Medical Testing Center, 1207 Rebsamen Park Road, Little Rock, AR 72202.

OBJECTIVES: To measure the secretion of ceftibuten in the breast milk of nursing female volunteers.

SUBJECTS: Six nursing females volunteers participated in the study. The volunteers mean (range) age and body weight were 26.3 years (20 to 33) and 137.7 lbs (102 to 166), respectively.

STUDY DESIGN: Each subject received a 200 mg ceftibuten capsule (Formula 2136, Batch 22023-083) with 120 ml water.

SAMPLING TIME: **Blood** samples were collected at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose. **Breast milk** was collected at 0, 0-2, 2-4, 4-6, 6-8, 8-12 and 12-24 hours postdose.

ASSAY METHODOLOGY: Samples were analyzed for ceftibuten by HPLC.

RESULTS: The concentrations of ceftibuten in breast milk for all six volunteers were below the assay sensitivity limit of μg/ml. The pharmacokinetic parameters of ceftibuten obtained from plasma data are listed below.

	Cmax (μg/ml)	Tmax (hr)	AUC0-oo (μgh/ml)	t1/2 (hr)
Mean (%CV)	6.6 (11)	3.0 (37)	40.5 (19)	2.9 (11)

CONCLUSION:
The study results suggest that little or no drug is secreted into breast milk.

Penetration of Ceftibuten Into Inflammatory Fluid After Multiple Dosing (Study C88-070-01; Vol 1.62)

INVESTIGATOR: Richard Wise, Department of Medical Microbiology, Dudley Road Hospital, Dudley Road, Birmingham, England.

OBJECTIVES: To evaluate drug penetration into inflammatory fluid following oral administration of 400 mg ceftibuten for three days.

SUBJECTS: Eleven healthy male volunteers. The volunteers mean (range) age and weight are: 25 (20-31) years and 81 (68-97) kg.

STUDY DESIGN: Each subject received 400 mg capsule of ceftibuten at 8 AM for two days. On the evening of the second day, two 1cm * 1cm cantharides-impregnated plasters (0.2%) were placed on the anterior surface of the forearm. After overnight fasting, the subjects received the last dose on the morning of day three. All doses were administered with 120 ml of tap water.

FORMULATION: 200 mg ceftibuten capsules, Formula No. 2136, Batch No. 21959-111 and Batch size 116,666.

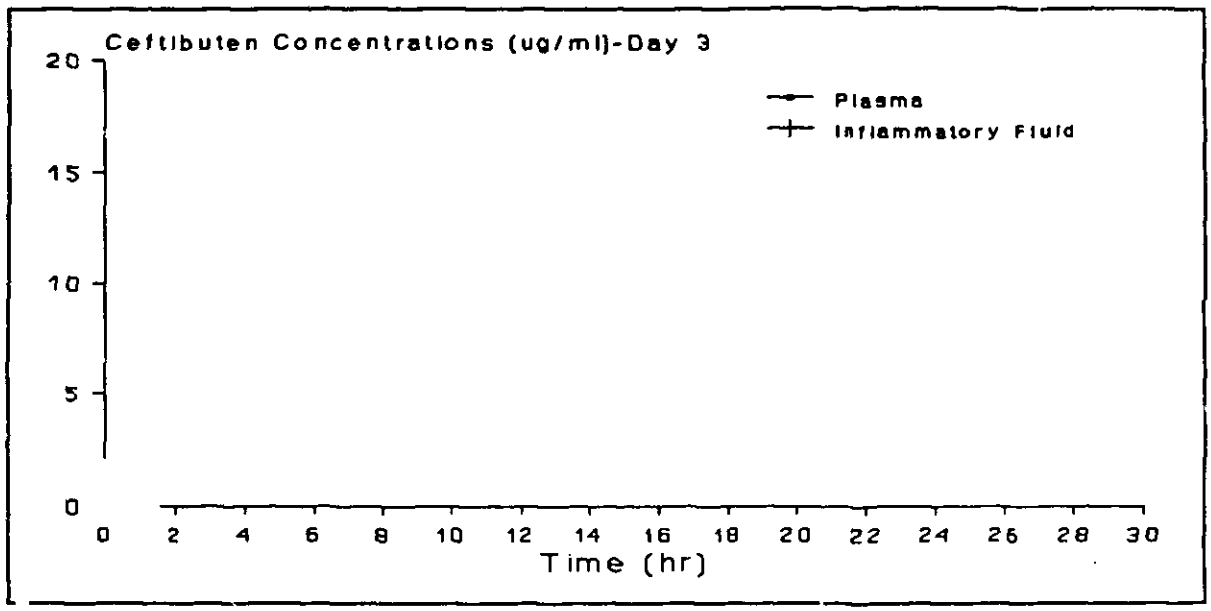
SAMPLING: **Blood** samples were drawn on day 1 and day 2 prior to and 2 hours after drug administration. On Day 3 blood samples were drawn at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 26, and 30 hrs. **Blister** fluid samples were obtained, on Day 3, at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 8, 12, and 26 hrs after dosing.

ANALYTICAL METHODOLOGY: Concentrations of Ceftibuten in plasma and inflammatory fluid were determined by a microbiological assay using a plate diffusion method at

RESULTS: The mean (%CV) plasma levels and mean pharmacokinetic parameters of ceftibuten in plasma and inflammatory fluid, obtained on day 3, are summarized below.

Parameter	Plasma	Inflammatory Fluid
C_{max} (μg/ml)	18.7 (21)	12.0 (26)
t_{max} (hr)	2.8 (33)	3.6 (23)
$t_{1/2}$ (hr)	2.5 (22)	3.0 (16)
$AUC_{0-\infty}$ (μghr/ml)	89.5 (15)	86.2 (25)

CONCLUSIONS: Ceftibuten concentration in the Blister fluid were



similar to those in plasma, indicating good penetration of ceftibuten into the inflammatory fluid.

Single-Dose Pharmacokinetics of Ceftibuten in Pulmonary Patients (Extension of C87-100-01, Vol. 1.63).

INVESTIGATOR: Peter Krumpe, V.A. Medical Center, 150 Muir Road, Martinez, CA 94553.

OBJECTIVES: To evaluate the penetration of ceftibuten into biological fluid and tissues in 12 pulmonary patients.

SUBJECTS: Twelve patients with lung disease scheduled for diagnostic bronchoscopy between the ages of 34 and 75 years participated in the study.

STUDY DESIGN: Following an overnight fast, each of twelve patients received a 200 mg ceftibuten capsule with 120 ml of tap water.

SAMPLING: Blood samples were collected at 0, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hr after dosing. Nasal secretion (NS), tracheal secretion (TS), bronchial secretions (BS), bronchial alveolar lavage fluid (BALF) and its button (CB) and lung (LT) biopsy tissue were also collected.

ANALYTICAL: The concentrations of ceftibuten in plasma and all other biological materials were determined by a HPLC method at Schering-Plough, Bloomfield, NJ.

RESULTS:

1. Six subjects were evaluated for nasal secretion (NS); the ratio of NS concentration/ plasma concentration averaged 0.39 and ranged from
2. Four subjects were evaluated for the average concentration ratio was 0.27 and ranged from
3. Four subjects were evaluated for the average concentration ratio was 0.37 and ranged from
4. Seven subjects were evaluated for the average concentration ratio was 0.097 and ranged from
5. Four subjects were evaluated for the average concentration ratio was 0.62 and ranged from
6. Five subjects were evaluated for the average concentration ratio was 0.47 and ranged from
7. No trend for the time effect on the concentration ratio was observed except for were the ratio increased as the time increased.

CONCLUSION: The high variability in the biological fluid and tissue levels and the small number of valuable patients make the study results inconclusive.

Penetration of Ceftibuten Into the Bronchial Secretion and Lung Tissue of Pulmonary Patients Following Single-Dose Oral Administration (Study C89-151-01, Vol. 1.64).

INVESTIGATOR: D. Honeybourne, Department of Thoracic Medicine, Dudley Road Hospital, Dudley Road, Birmingham, England.

OBJECTIVE: To evaluate the penetration of ceftibuten into the bronchial secretions and mucosa of patients undergoing bronchoscopy. In addition, the ceftibuten concentrations in macrophage and epithelial cells collected from the bronchial aspirate was determined.

SUBJECTS: Fifteen patients between the ages of 43 to 76 years scheduled to undergo bronchoscopy enrolled in the study.

STUDY DESIGN: Open label, single 400 mg dose.

SAMPLING: Sputum, bronchoalveolar lavage, macrophage and bronchial mucosal tissue were collected at times from 30 minutes to 24 hours after dosing. Blood samples were drawn at the same time that bronchoscopy specimens were obtained.
A microbiological assay was used.

RESULTS: The average (%CV)penetration of ceftibuten, expressed as ratios of epithelial lining fluid and tissue concentrations relative to plasma concentrations, were 15.0% (48) and 36.9% (36), respectively. Very low concentration of ceftibuten in alveolar macrophage were recorded in 3 subjects.

Three different studies were submitted to assess the penetration of ceftibuten into middle ear fluid in children. The following is synopsis of each study:

I. Study I88-115-11; Vol 1.30
Comparison of the Efficacy and Safety of Ceftibuten with that of Cefaclor in the Treatment of Acute Otitis Media in Children.

OBJECTIVE & STUDY DESIGN:
This study was part of multicentric, randomized, single blind comparison of the efficacy and safety of pediatric oral suspensions of ceftibuten and cefaclor. Through an amendment to the protocol, Dr. Kafetzis (Athens, Greece) also collected serum and middle ear fluid samples for subsequent drug assay and determination of penetration into middle ear fluid.
Thirty children (age 50±34 months and weigh 40.3±18.3 lbs) received ceftibuten 9 mg/kg/day (up to 400 mg) in a single oral dose for 10 days. And ten subjects (age 16±13 months and weight 26.3±15.6 lbs) received cefaclor 40 mg/kg/day (up to 1 g) in three divided doses. The investigator collected one serum and one middle ear fluid sample from each subject. These samples were collected on day-2 at 2, 4, 6, 8, and 12 hours. All samples were evaluated within 48 hours of collection using a bioassay method.

RESULTS: The mean (±SD) plasma levels and mean ear fluid levels of ceftibuten and cefaclor are listed below.

	Ceftibuten		Cefaclor	
Time	Plasma	Ear Fluid	Plasma	Ear fluid
2	6.73±1.92	0.85±0.45	3.63±1.49	0.96±0.19
4	5.93±1.48	1.03±2.95	0.69±0.09	0.49±0.15
6	3.15±1.26	1.28±1.14	--	--
8	1.56±0.54	0.62±0.14	--	--

II. Study C88-082-16; Vol 1.30
Comparison of the Efficacy and Safety of Ceftibuten with that of Cefaclor in the Treatment of Acute Otitis Media in Children.

OBJECTIVE & STUDY DESIGN:
Similar to the design of the above study, thirteen children were enrolled. The children's mean age was 17.3±12.9 and ranged from months.

RESULTS: The mean ear fluid and plasma levels and their ratios are listed below:

Time	Ear Fluid	Plasma	Ratio
2	4.41	14.48	0.38
4	14.27	10.02	1.40
6	0.81	2.72	0.49
12	1.29	0.23	6.33

III. Study C89-267-02; Vol 1.30
Penetration of Ceftibuten into Middle Ear Fluid Following Multiple-Dose Administration to Pediatric Patients (C89-267-02; Vol 1.30)

OBJECTIVE & STUDY DESIGN:
This multiple-dose middle ear fluid penetration study of ceftibuten suspension is on going. The study will enroll and treat twenty pediatric patients between 6 months and 8 years of age with chronic otitis media with effusion. To date, nine of twenty pediatric patients completed the study. Ceftibuten was given as an oral solution, at a dose of 9 mg/kg daily for three days. Blood and middle ear fluid samples were obtained on day 3. The partial study results are listed below:

Time (hr)	Subject	SCH 39720 Concentration (µg/ml) Middle Ear Fluid (A)	Plasma** (B)	Ratio(%) (A/B)
	Mean	3.30	18.33	
			Mean	15
AUC(0-4.75h)		6.38	64.08	10

CONCLUSION: The second study results where the concentration in the middle ear fluid exceed the plasma are skeptical. The results from the first and the third studies seems to be similar, however no conclusion could be made before receiving the final results of the third study.

PROTEIN BINDING

METHOD: The extent of binding of ceftibuten to plasma proteins was measured by ultrafiltration through a . Plasma samples (0.5 ml) were introduced into the reservoir and centrifuged a 1000 * g for 15 minutes. Ceftibuten concentration in the plasma prior to filtration and in the protein-free filtrate were determined by HPLC.

DESIGN:

1. Protein binding of ceftibuten *in vitro*: Plasma samples containing µg/ml were prepared.
2. Influence of other drugs on ceftibuten binding: Plasma samples containing µg/ml ceftibuten were spiked with µl of aspirin, acetaminophen, theophylline, tolbutamide or warfarin to give concentrations of and µg/ml.
3. Protein binding of ceftibuten *in vivo*: The protein binding was evaluated using plasma samples from a clinical study (C89-079-01). Plasma samples were selected from Day 1, Day 7 and Day 11 of the study.

RESULTS: The *in vitro* binding at different ceftibuten concentrations is shown below:

Concentration (µg/ml)	Protein Binding %
	62.44
	62.99
	62.46
	63.61
	61.47
	60.13
	56.07
	51.44
	50.17
	46.91

The influence of other drugs on ceftibuten protein binding expressed as % change in ceftibuten protein binding are listed

Competitor	Competitor concentration (μg/ml) 20	100
Aspirin	1	
Acetaminophen	3	
Theophylline	-3	
Tolbutamide	-7	
Warfarin	-3	

The *in vivo* binding results were similar to the *in vitro* results as shown below:

Treatment Day	Concentration (μg/ml)	Binding (%)
1		62.41
		61.67
		61.80
		60.25
7		63.82
		60.72
11		63.03
		63.35

CONCLUSIONS:
Changes in ceftibuten concentration from μg/ml did not influence the extent of binding (range %). However, further increase in drug concentrations reduced the percentage of binding.

COMMENTS:
1. It was not indicated how many replicates were used to evaluate the *in vitro* protein binding.
2. The influence of other drug on the protein binding of ceftibuten was provided, however the influence of ceftibuten on these other drugs binding was not provided.
3. The analytical method used to evaluate ceftibuten levels was not provided.

PROPOSED PRODUCT DISSOLUTION METHOD

Dosage Form: Ceftibuten Capsules
Strength: 200 mg and 400 mg
Apparatus Type: USP Apparatus 1, Basket Stirrer
Media: 0.05 M Phosphate Buffer, pH 7.0
Volume: 1000 ml
Speed Rotation: 100 rpm
Sampling Time: 15, 30, 45 and 60 minutes
Analytical Method: UV Spectrophotometric analysis at nm
Recommended Specification: Q % in minutes

RESULT:
Using this method more than 90% was dissolved within 15 minutes. This method was used in one batch only. Another method using a paddle with 50 rpm rotation speed was used for the rest of the batches. Using the paddle method, the dissolution rate is lower and therefore more discriminate.

Dosage Form: Ceftibuten Powder for Oral Suspension
Strength: 36 mg/ml
Apparatus Type: USP Apparatus 2, Paddle Stirrer
Media: 0.05 M Phosphate Buffer, pH 7.0
Volume: 1000 ml
Speed Rotation: 50 rpm
Sampling Time: 15 and 30 minutes
Analytical Method: UV Spectrophotometric analysis at 271 nm
Recommended Specification: Q % in minutes

RESULTS: Only one suspension batch was tested. More than 90% was dissolved within 15 minutes.

COMMENTS:
1. The analytical method used in the dissolution tests should be validated for specificity accuracy and linearity.
2. Since more than 90% of the capsule content was dissolved using the Basket method with a rotation speed of 100 rpm. The sponsor is recommended to consider using the paddle method with a rotation speed of 50 rpm. this rotation speed, as previously tested, is more sensitive to batch to batch differences.
3. The sponsor is recommended to test the dissolution of the suspension formulation using a 25 rpm as rotation speed rather the proposed 50 rpm.

MAY 3 1994

NDA 50-685 50-686
SUBMISSION DATES: 3/2/94 (50-685), 3/9/94 (50-686)
PRODUCT: Ceftibuten 200 mg & 400 mg Capsule(50-685)
Powder for Oral Suspension (50-686)
BRAND NAME: CEDAX
SPONSOR: Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033
REVIEWER: Dan Wang, Ph.D.
TYPE OF SUBMISSION: Amendment

BACKGROUND:

These are the sponsor's responses to the comments made by Dr. Emil Samara on the original NDA submission (NDA 50-685 & 50-686) and Dr. Dan Wang on the amendment NDA submission. The original recommendations and sponsor's responses are summarized as below.

COMMENTS:

3l?

1. The response to recommendations 1 and 2 in Dr. Wang's review dated January 1, 1994 is acceptable.

2. In response to recommendation #3 re: dissolution testing of suspension at 25 rpm, the sponsor indicated that suspension dissolution using USP apparatus 2 at 25 rpm was too slow. Due to the high viscosity and density of this suspension product, the sample aliquot rapidly sinks to the bottom of the dissolution vessel. After 60 minutes, only an average of 53% (n=6) dissolved. Dissolution performance was much better using apparatus 2 at 50 rp

3. The results of the middle ear penetration study are summarized in the table (next page).

   Additional data does not alter Dr. Samara's conclusion in his review of the NDA.

Time (hr)	Subject	SCH 39720 Concentration (µg/ml) Middle Ear Fluid(A)	Plasma** (B)	Ratio(%) (A/B)
	Mean	3.30	18.33	18
			Mean	15
AUC(0-4.75 hr)		6.38	64.08	10

* Contaminated with blood.
** For all subjects, concentrations of SCH 39720 in plasma samples obtained prior to initial administration of the drug were zero.

4. The sponsor provided a description of the assay and validation for study C87-099-01-05.

The sponsor indicated that modifying the assay methodology did not prevent the elution of interfering peaks. According to the sponsor, for samples from some subjects showing evidence of interfering peak eluting near the retention time of ceftibuten, the area of the interfering peak area was estimated for each sample and subtracted from the ceftibuten peak area of that particular sample. The sponsor should give more explanation about how this estimation was made.

The sponsor also indicated that for samples showing no distortion in ceftibuten peak shape but the 0 hour sample had shown the presence of a peak eluting at the retention time of ceftibuten, the area of this interference peak was subtracted from the ceftibuten peak areas of all samples for that subject. The sponsor did not show any evidence of that the size of interfering peaks for blood samples taken at different time points was constant or within certain range for the subject. Therefore, subtraction of the area of interference peak at time 0 from the ceftibuten peak areas of

all samples may not be proper. The assay results of this study are therefore questionable.

RECOMMENDATIONS:

1. The Human Pharmacokinetics and Bioavailability Section of NDA 50-685 (and 50-686) is acceptable.

2. The sponsor should include dissolution testing for CEDAX suspension, 90 mg/5 ml & 180 mg/5 ml, in their manufacturing and control procedures. The dissolution testing should be conducted using USP apparatus 2 at 50 rpm in 1000 ml 0.05 M phosphate buffer, pH 7.0. The Q value should be not less than % in minutes.

3. The sponsor should include dissolution testing for CEDAX capsule, 200 mg & 400 mg, in their manufacturing and control procedures. The dissolution testing should be conducted using USP apparatus 1 at 100 rpm in 1000 ml 0.05 M phosphate buffer, pH 7.0. The Q value should be not less than % in minutes.

4. The Division of Biopharmaceutics should be provided a copy of final product labeling for comment.

Dan Wang, Ph.D.
Pharmacokinetics Evaluation Branch

FT initialed by 6/2/94

cc: NDA 50-685 orig. NDA 50-686 orig, HFD-520(Clinical, ~~Fogarty~~ DEGELLAS), HFD-426(Fleischer), HFD-427(ML Chen, Pelsor), Chron, Drug, Reviewer, HFD-19(FOI), HFD-340(Viswanathan)

JAN - 1 1994

NDA 50-685	**SUBMISSION DATES:** 10/2/92
PRODUCT: Ceftibuten 200 mg & 400 mg Capsule.	6/4/93
BRAND NAME: CEDAX	
SPONSOR: Schering-Plough Corporation	
2000 Galloping Hill Road	
Kenilworth, NJ 07033	
REVIEWER: Dan Wang, Ph.D.	
TYPE OF SUBMISSION: Amendment	

BACKGROUND:

These are the sponsor's responses to the comments (4 to 14) made by Dr. Emil Samara on the original NDA submission (NDA 50-685 & 50-686). The sponsor responded to most of the comments but some of them were not responded. The original comments, sponsor's responses and recommendations are summarized as below.

COMMENT #4:

Please provide the analytical method used in each study and please submit validation data for the method in which the detergent and/or column switching were used.

RESPONSE:

The sponsor provided a listing of pharmacokinetic studies and analytical methods used. Validation for the methods was done for linearity, specificity, precision, accuracy and sensitivity.

COMMENTS:

1. **Column switching method:** The validation including linearity, specificity, precision, accuracy and recovery is acceptable. The sensitivity of the assay was established at μg/ml while the lowest concentration measured was μg/ml.

2. **The method in which the detergent was used:** The specificity, precision and accuracy are acceptable. In the linearity study, the variation of intercepts is considerably high (-0.85061 to 0.53509). The significant negative deviation of slope from unity (up to 27%) indicates the loss of ceftibuten during the assay procedure. However, no recovery data were provided for this analytical procedure.

COMMENT #5:

Please provide stability data for ceftibuten in plasma and urine during sample collection, storage and processing. Furthermore, please provide the individual recovery results from the Schering-Plough plasma method and recovery results from the other methods.

RESPONSE:

a. Stability data in both plasma and urine.
b. Procedure for sample collection, storage and processing.
c. Recovery results for the Schering-Plough and methods.

COMMENT:

Response is acceptable.

COMMENT #6:

Evaluate that the higher Cmax, higher AUC values and longer half-life of the geriatric volunteers compared to healthy volunteers are age related or renal function related.

RESPONSE:

It appears that the higher Cmax and AUC values and longer half-life in geriatric subjects compared with healthy volunteers may be due to the reduced renal function generally observed in the elderly.

COMMENT:

The sponsor's response is acceptable. The regression results of creatinine clearance versus ceftibuten renal clearance and total body clearance demonstrate the correlation between the changes of total body clearance and renal function very well.

COMMENT #7:

Please submit the following information on protein binding:
a. The effect of ceftibuten on the binding of the other tested drugs if available.
b. The number of replicates that were used to evaluate the in-vitro protein binding, and
c. A description and validation of the analytical method.

RESPONSE:

a. The effect of ceftibuten on the binding of the other tested drug was not studied.
b. Two replicates were used to evaluate the in-vitro protein binding.
c. The description and validation of the analytical method.

COMMENT:

Response is acceptable.

COMMENT #8:

a) Please provide the validation for the specificity, accuracy and linearity of the analytical method used in the dissolution test.

b) We recommend using the paddle method with a rotation speed of 50 instead of the basket method at 100 rpm.

c) The sponsor is recommended to test the dissolution of the suspension formulation with 25 rpm as rotation speed rather the proposed 50 rpm.

RESPONSE:

a) The sponsor provided validation reports for specificity, accuracy and linearity of the analytical methods used in the dissolution test for Ceftibuten Capsules.

b) The basket apparatus at 100 rpm was used because it had less influence on the ruggedness and reproducibility of dissolution study compared to the paddle apparatus for this product.

COMMENTS:

a) The validation reports for specificity, accuracy and linearity of the analytical methods are acceptable.

b) Since the basket apparatus at 100 rpm is generally recognized as equivalent to the paddle apparatus at 50 rpm, the basket method used in this dissolution test is acceptable.

COMMENT #9:

For studies C90-420-01, C90-875-01 and C88-058-01 the sponsor is requested to submit the SAS output used to analyze and

calculate the 90% confidence intervals.

RESPONSE:

On September 14, 1992, Mr. Dave Christopher, Assoc. Principal Systems Statistician and our Ms. A. Rubin called Dr. E. Samara about this comment. Dr. Samara was satisfied with the information provided by the firm and required no further input.

COMMENT:

Since Dr. Samara was satisfied and required no further information from the firm, no discussion about this comment is necessary.

COMMENT #10:

For study C88-058-01, please explain the following:

a) The variability in the half-life values.

b) Cross-comparison of study C88-058-01 results with other studies shows that the plasma levels in this study were higher compared to the plasma levels obtained after 200 mg administration in other studies and were comparable to the levels obtained following a 400 mg dose.

c) The SAS output that was used to calculate the 90% confidence interval values.

d) Only the batch # was provided for the 100 mg capsule used in clinical study C88-058-01. Please provide the formulation #, manufacturing site, batch size... etc.

RESPONSE:

a) The study results of C88-058-01 did establish bioequivalence between the formulations tested with adequate power, thus, indicating that the study was internally consistent and valid.

There were 5 subjects out of 15 who exhibited a biexponential decline in the disposition phase instead of the usual monoexponential decline. This caused the longer terminal phase half-life which contributes to the high variability in the data. In general, for these subjects, the terminal phase contributes only 10% to the total area under the curve.

b) We cannot provide any further information at this time to explain the higher ceftibuten plasma concentrations demonstrated by this subject population.

d)

Formula No.	1845
dosage Form	CAPSULE
Strength	100 MG
Batch No.	21108-120
Lot No.	CQL02
MFG Date	11/27/87
MFG Site	
Batch Size	Capsules

COMMENTS:

a) In study no. C88-058-01, the contribution of the terminal phase AUC to total area under the curve value for all of the subjects is less than 10% except subject 14 in phase 2 study (15.6%). The half-life of subject 14 (17.69 hr.) is very long comparing to that of the others. The mean β value of the rest subjects is 0.246/hr with standard deviation (SD) of 0.0908. Since the β value of subject 14 is less than the mean value -2xSD, it may be treated as an outlier. This eliminated the subject who caused the high variability. Therefore, bioequivalence between the formulations established by this study is acceptable.

b) Since the study C88-058-01 is internally consistent and three tested formulations are bioequivalent, this bioequivalency study is acceptable.

d) The information requested was provided by the sponsor. Therefore, the response is acceptable.

COMMENT #11:

Upon completion, the sponsor is requested to submit the results of study C89-267-02 in order to determine ceftibuten penetration into middle ear fluid.

RESPONSE:

The sponsor did not respond to this comment.

COMMENT #12:

The results obtained in study C90-876-01 were lower than

other studies where a 400 mg dose was administered. The urinary excretion in this study was relatively low and did not exceed 10% of the administered dose in one subject. Please explain?

RESPONSE:

A scattergram comparing Cmax after administration of 400 mg ceftibuten capsule from study no. C90-876-01 to the same 400mg capsule administered in other studies shows the plasma concentrations are within the range of values reported from other studies. In our opinion, the differences observed among these studies are within the range of normal variability.

COMMENT:

The scattergram shows no significant difference between the results obtained in study C90-876-01 and other 400 mg dose studies.

There is no explanation for the urinary excretion data.

COMMENT #13:

Based on simulation of plasma levels in each group by the two adjustment methods suggested in your draft labeling (dose and time interval), we recommend that dose adjustment, rather than adjustment in dosing interval, is more appropriate for renally-impaired patients.

RESPONSE:

The original draft package insert was designed to address information for both the capsule and suspension dosage forms. Since the original submission (December 1991), we have separated the inserts, so that each dosage form is addressed separately. Dose adjustment rather than adjustment in dosing interval is appropriate for suspension, however, it is inappropriate for the capsule form. Without the availability of the suspension dosage form, adjustment by dose is not possible. Therefore, we have provided a dosing regimen by time intervals for patients with renal dysfunction in the revised capsule package insert, submitted to the Division on September 24, 1992.

COMMENT:

Response is acceptable.

COMMENT #14:

Validation for study C87-099-01-05.

RESPONSE:

No response was provided on this comment.

RECOMMENDATION:

From a biopharmaceutics standpoint, the sponsor's response (to dated June 4, 1993) to our comments is unacceptable. The sponsor should be informed of the following:

1. Since the sensitivity of the assay was established at μg/ml for the column switching method, the confidence of the reported concentration value of μg/ml was questionable. The sponsor should provide the data to surport the reliability of the assay at μg/ml concentration level for column switching method of HPLC analysis.

2. The sponsor is requested to provide the recovery data for the method in which the detergent was used.

3. Comment 8(c) was not responded.

4. The sponsor is requested to submit the results of study C89-267-02 in order to determine ceftibuten penetration into middle ear fluid.

5. Validation for study C87-099-01-05 should be provided by the sponsor.

? Before or after approval

Dan Wang, Ph.D.
Pharmacokinetics Evaluation Branch

RD/FT initialed by Dr. F. Pelsor F. Pelsor 1/26/94

cc: NDA 19-537 orig. NDA 19-847, HFD-520(Clinical, Fogarty), HFD-426(Fleischer, Pelsor), Chron, Drug, Reviewer, HFD-19(FOI), HFD-340(Viswanathan)

OCT 5 1994

STATISTICAL REVIEW AND EVALUATION

ADDENDUM

NDA: 50-685
Applicant: Schering-Plough Corporation
Name of Drug: ceftibuten (CEDAX®) capsules

Indication: acute exacerbation of chronic bronchitis

Documents Reviewed:

- Draft Medical Officer's Review, dated 7/5/94
- Paradox Dbase file of applicant and medical officer assessments, received 9/21/94
- Volume 1 of the NDA amendment, stamp dated 11/8/93.
- Statistical review of the original NDA, stamp dated 2/19/93

Medical Officer: Janice Soreth, M.D., HFD-520

I. BACKGROUND 1

II. METHODS 2

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I. BACKGROUND

This NDA was originally submitted in December 1991 with a request for approval of the indication acute exacerbation of chronic bronchitis (AECB), acute bacterial bronchitis (AB),

A non-approvable letter for all three indications was issued in March, 1993, with the stipulation that one additional well controlled trial would be sufficient to garner the AECB indication.

In November, 1993, the applicant filed a clinical amendment, again requesting approval of the AECB indication. The amendment contains one study (C90045) which is to serve as pivotal evidence in support of the AECB claims. Study C90045 is the focus of this review amendment.

In the proposed draft labelling, the applicant requests the following indication:

Acute Bacterial Exacerbation of Chronic Bronchitis caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (beta-lactamase positive and negative strains), and *Streptococcus pneumoniae*. Culture and susceptibility testing of the causative pathogen to determine its susceptibility to ceftibuten is recommended.

The recommended dosage regimen is 400 mg in capsule form given as a single daily dose for 5-14 days.

Study C90045 was a randomized, multicenter, evaluator-blind, parallel group, active controlled trial to compare the efficacy and safety of ceftibuten capsules 400 mg q.d. to cefixime tablets 400 mg q.d. in the treatment of acute exacerbations of chronic bronchitis in adults.

This review is based upon analyses of the applicant's and medical officer's data. The medical officer's evaluability and efficacy assessments were performed blinded to treatment arm. The fundamental definitions and methods used by the applicant and medical officer are summarized in this review. Please refer to the Medical Officer's Review or the applicant's Clinical Study Report for the full details.

This reviewer conducted slightly different analyses than those presented by the applicant and the medical officer. All results presented in this review are from reviewer analyses of the applicant's and medical officer's data.

II. METHODS

***REVIEWER NOTES**: The applicant's methods outlined in the study report are different from the methods outlined in the study protocol. Unless otherwise specified, the methods described in this review are summarized from the applicant's study report.*

Unless otherwise specified, the applicant's and medical officer's study methods were similar.

Study C90045 was a randomized, multicenter, evaluator-blind, parallel group, active controlled trial to compare the efficacy and safety of ceftibuten capsules 400 mg q.d. to cefixime tablets 400 mg q.d. in the treatment of acute exacerbations of chronic bronchitis in adults. The trial was conducted only at US centers. Patients were randomized to treatment in a 1:1 ceftibuten:cefixime ratio.

The baseline screening visit (VISIT 1) was to occur within 48 hours of treatment initiation. Patients who met the selection criteria were enrolled and randomized to treatment. Although a baseline Gram's stain was required, a baseline sputum culture and susceptibility test was optional.

By protocol, patients were to be treated for 5-14 days. Treatment was to continue for at least 48 to 72 hours after the patient became asymptomatic, or until a confirmed clinical cure or improvement was demonstrated, or until there was no source to culture. In the applicant's study report, treatment duration was expanded to 5-15 days.

Post baseline follow up evaluations were to occur at 3-5 days during therapy (VISIT 2), at 0-6 days post therapy (VISIT 3, end of treatment visit) and at 7-21 days post therapy (VISIT 4, extended follow up visit). Clinical evaluations and, optionally, bacteriological evaluations were performed at each visit.

The applicant performed efficacy analyses on three patient populations: intent-to-treat, clinical efficacy, and microbiologic efficacy. The medical officer performed analyses in two patient populations: clinical efficacy and microbiologic efficacy. The results for the clinical efficacy and microbiologic efficacy populations are presented in this review. The microbiologic efficacy population is a subset of the clinical efficacy population. Please refer to the Medical Officer's Review for the definition of these patient populations.

At VISIT 3, the clinical and bacteriologic responses assigned by the applicant and medical officer were the same. Clinical response was assigned as cure, improvement, failure, or unassessable. Bacteriologic response was assigned as eradication (documented or presumed), persistence (documented or presumed), eradication with colonization, or superinfection.

At VISIT 4, the clinical and bacteriologic responses assigned by the applicant differed from those assigned by the medical officer. The applicant assigned clinical responses of sustained cure, sustained

improvement, relapse, or unassessable, while the medical officer assigned clinical responses of cure, improvement, or relapse. The applicant assigned bacteriologic responses of eradication (documented or presumed), persistence (documented or presumed), relapse (documented or presumed), reinfection, eradication with colonization, or unassessable, while the medical officer assigned bacteriologic responses of eradication (documented or presumed) or persistence (documented or presumed).

REVIEWER NOTES: *In the applicant's analyses presented in the study report, clinical failures and bacteriologic persistence at VISIT 3 were not carried forward to VISIT 4. Instead, these patients were classified as "unassessable" at VISIT 4. In this reviewer's analysis of the applicant's data, all clinical failures and bacteriologic persistences at VISIT 3 were carried forward to VISIT 4. However, if in the applicant's data a patient had a clinical response of "cure" or "improvement" or a bacteriologic response of "eradication" at VISIT 3 and a clinical response of "unassessable" or a bacteriologic response of "unassessable" at VISIT 4, the patient remained clinically or bacteriologically "unassessable" at VISIT 4. Unassessable patients were excluded from the analysis.*

Although the applicant did not carry clinical failures from VISIT 3 to VISIT 4, the applicant did perform an analysis of the "overall clinical assessment", which was the applicant's primary efficacy parameter. This parameter incorporated clinical responses from VISIT 3 and VISIT 4, where an overall clinical success was defined as a patient who had a clinical cure or clinical improvement at both VISIT 3 and VISIT 4. This method of analysis is the same as an analysis where VISIT 3 clinical failures are carried forward to VISIT 4.

This reviewer performed two types of bacteriologic analyses: on the patient level (for both the applicant and medical officer data), and on the pathogen level (at VISIT 4 for the medical officer data only). If a patient had more than one baseline pathogen and had a mixed bacteriologic response, this reviewer assigned a patient level bacteriologic response of persistence. In the pathogen level analysis, responses for individual pathogens from the same patient were counted separately.

In the analyses of the applicant and medical officer data, this reviewer collapsed some clinical response categories and some bacteriologic response categories. Clinical cure/improvement includes cure, improvement, sustained cure, or sustained improvement. Clinical failure includes failure or relapse. Bacteriologic eradication includes eradication (documented or presumed) and eradication with colonization. Bacteriologic persistence includes persistence (documented or presumed) and relapse (documented or presumed).

The clinical efficacy population was the primary efficacy population for both the applicant and the medical officer. The rate of clinical cure or improvement at VISIT 4 (with VISIT 3 failures carried through) was the primary efficacy parameter for the applicant and medical officer.

The rates of clinical cure/improvement at VISIT 3, bacteriologic eradication by patient at VISIT 3 and VISIT 4, bacteriologic eradication by pathogen at VISIT 4, and "complete success" at VISIT 3 and VISIT 4 (defined by this reviewer as a bacteriologic eradication and clinical cure or improvement) were considered to be secondary parameters. The applicant and medical officer only considered *H. influenzae, M. catarrhalis* and *S. pneumoniae* as evaluable pathogens.

The safety population included those patients who had documented receipt of at least one dose of study medication treatment.

This reviewer considers the primary safety parameter to be the overall rate of drug related (possibly, probably, or definitely) adverse events. The rate of discontinuation due to adverse events, and the rate of specific clinical and laboratory adverse events were considered as secondary safety parameters.

With respect to the proportion of patients evaluable for each efficacy population, this reviewer compared treatments, centers, and treatments within each center using a chi-square test or Fisher's exact test where appropriate.

Within each efficacy population, treatments were compared with respect to demographic and baseline disease characteristics using a chi-square test, Fisher's exact test, or Wilcoxon rank sum test where appropriate. Treatments were compared with respect to clinical cure or improvement rate and bacteriological eradication rate using 95% confidence intervals of the ceftibuten minus cefixime difference in outcome rate. These intervals were calculated by the reviewer using the normal approximation method an included a continuity correction. The confidence intervals were interpreted using the approach outlined on page 20 of the DAIDP draft *Points to Consider* document.

Subset efficacy analyses in the medical officer clinical efficacy population at VISIT 4 were performed by investigator, age (<45, 45-65, >65), sex, and race (white, black, other). Tests of treatment by subset interaction were performed using the Breslow-Day test. Strata which did not have at least 10 evaluable patients per treatment arm were pooled in tests of the treatment by subset interaction.

All confidence interval results are presented in the following format:

NT NC (LCL, UCL) PT PC

where NT = number evaluable test (ceftibuten) patients
NC = number of evaluable control (cefixime) patients
LCL = lower 95% confidence limit
UCL = upper 95% confidence limit
PT = proportion of test (ceftibuten) patients with outcome
PC = proportion of control (cefixime) patients with outcome

LCL, UCL, PT and PC are expressed as percentages, and are rounded to the nearest whole percentage point. Confidence interval results are presented only for those strata with at least 10 evaluable patients per treatment arm.

With respect to the overall rate of drug related (possibly, probably, or definitely) adverse events, the treatment groups were compared using Fisher's exact test.

All tests were two-sided. Tests of treatment by subset interaction were deemed significant at the 0.15 level. All other tests were considered significant at the 0.05 level.

III. RESULTS

REVIEWER NOTES: *Studies C90045 and C88044 (the US LRTI study in the original NDA submission) have common investigators; therefore, these studies are not independent. Six investigators (McLean, McCarty, McCabe, DeAbate, Jacobson, and Nolen) participated in both trials, and enrolled approximately 54% (201/373) and 42% (79/190) of the AECB patients in studies C90045 and C88044, respectively.*

Since AECB is a chronic disease, it is possible that the same patients were enrolled in both studies. This issue has not been discussed by the applicant or medical officer.

A total of 373 patients were enrolled across 23 centers in the US. Of these, 188 were randomized to ceftibuten and 185 were randomized to cefixime. Enrollment by center ranged from 1 to 81. Only 6 centers enrolled at least 10 patients per treatment arm.

Table 1 displays the number and percentage of evaluable patients by treatment in the applicant and medical officer clinical and microbiologic efficacy populations. There were no statistically significant treatment differences in the percentage of patients evaluable for each population. Only 3 centers had at least 10 clinically evaluable patients per treatment arm. Only 1 center had at least 10 microbiologically evaluable patients per treatment arm. Within each center, there was not a significant treatment imbalance with respect to the percentage of patients evaluable for each population. Due to the large number of small centers, the variation in the percentage of evaluable patients among centers could not be meaningfully assessed.

Table 1: Study C90045
Number and Percentage of Evaluable Patients By Treatment
For the Applicant and Medical Officer Clinical and Microbiologic Efficacy Populations

population	applicant		medical officer	
	ceftibuten (N = 188)	cefixime (N = 185)	ceftibuten (N = 188)	cefixime (N = 185)
clinical	150 (80%)	155 (84%)	161 (86%)	162 (88%)
microbiologic	52 (28%)	41 (22%)	58 (31%)	44 (24%)

With the exception of race, the treatment groups within the applicant and medical officer clinical efficacy population were not significantly different with respect to demographic or baseline disease characteristics. In both clinical efficacy populations, when race was analyzed as three categories (white, black, other) the distribution of race differed between treatments, where ceftibuten had a higher proportion of blacks than cefixime. When race was analyzed as two categories (white, black/other), the treatment groups were not significantly different with respect to race.

The treatment groups within the applicant and medical officer microbiologic efficacy population were not significantly different with respect to demographic or baseline disease characteristics.

Table 2 presents confidence interval results by visit for the treatment difference in clinical cure or improvement rate in the applicant and medical officer clinical efficacy population. The results in both populations are similar, and demonstrate that ceftibuten is therapeutically equivalent to cefixime with respect to the rate of clinical cure or improvement at VISIT 3 and VISIT 4.

Table 3 presents confidence interval results on the patient level by visit for the treatment difference in bacteriologic eradication rate, clinical cure or improvement rate, and complete success rate in the applicant and medical officer microbiologic efficacy population. The results in both populations are similar, and fail to demonstrate that ceftibuten is therapeutically equivalent to cefixime with respect to the rates of bacteriologic eradication, clinical cure or improvement, or complete success at VISIT 3 or VISIT 4. With respect to clinical cure or improvement rate at VISIT 3 in the set of microbiologically evaluable patients, ceftibuten is significantly inferior to cefixime.

Table 2: Study C90045
95% Confidence Intervals of the Ceftibuten Minus Cefixime Differences in Clinical Cure or Improvement Rate In the Applicant (APP) and Medical Officer (MO) Clinical Efficacy Populations

VISIT	POP	NT	NC	(LCL,	UCL)	PT	PC
VISIT_3	APP	150	155	(-13,	4)	83	88
	MO	161	162	(-14,	4)	81	86
VISIT_4	APP	150	155	(-14,	5)	78	83
	MO	161	162	(-13,	6)	77	81

Table 3: Study C90045
95% Confidence Intervals of the Ceftibuten Minus Cefixime Differences in Bacteriological Eradication Rate, Clinical Cure or Improvement Rate, and Complete Success Rate In the Applicant (APP) and Medical Officer (MO) Microbiological Efficacy Populations

OUTCOME	VISIT	POP	NT	NC	(LCL,	UCL)	PT	PC
BACTERIOLOGICAL ERAD	VISIT_3	APP	52	41	(-24,	11)	79	85
		MO	58	44	(-28,	9)	72	82
	VISIT_4	APP*	47	40	(-26,	16)	70	75
		MO	58	44	(-29,	8)	69	80
CLINICAL CURE/IMP	VISIT_3	APP	52	41	(-36,	-3)	73	93
		MO	58	44	(-33,	-1)	74	91
	VISIT_4	APP	52	41	(-35,	6)	63	78
		MO	58	44	(-29,	9)	67	77
COMPLETE SUCCESS**	VISIT_3	APP	52	41	(-33,	6)	69	83
		MO	58	44	(-28,	10)	71	80
	VISIT_4	APP*	47	40	(-26,	18)	66	70
		MO	58	44	(-27,	12)	67	75

* Six patients(5 ceftibuten, 1 cefixime) were unassessable at VISIT 4.
** Complete success = bacteriologic eradication and clinical cure or improvement.

Table 4 presents confidence interval results by pathogen for the treatment difference in bacteriologic eradication rate at VISIT 4 in the medical officer microbiologic efficacy population. The results fail to demonstrate that ceftibuten is therapeutically equivalent to cefixime with respect to the rate of bacteriologic eradication of *H. influenzae, M. catarrhalis*, or *S. pneumoniae*. The results demonstrate that ceftibuten is significantly inferior to cefixime with respect to the rate of bacteriologic eradication of *M. catarrhalis*. The lack of therapeutic equivalence in the eradication of *H. influenzae*, and *S. pneumoniae* may be due to inadequate power resulting from the small number of isolates per pathogen.

Table 5 displays confidence interval results by investigator, gender, age, and race subsets for the treatment difference in clinical cure or improvement rate at VISIT 4 in the medical officer clinical efficacy population. This table also presents p-values from the Breslow-Day test of homogeneity of treatment effect across the strata of each subset.

Table 4: Study C90045
95% Confidence Intervals of the Ceftibuten Minus Cefixime
Differences in Bacteriological Eradication Rate at Visit 4 by Pathogen
In the Medical Officer Microbiological Efficacy Population

PATHOGEN	NT	NC	(LCL,	UCL)	PT	PC
H. INFLUENZAE	31	20	(-29,	28)	74	75
M. CATARRHALIS	18	15	(-68,	-10)	61	100
S. PNEUMONIAE	16	11	(-32,	55)	75	64

Table 5: Study C90045
95% Confidence Intervals of the Ceftibuten Minus Cefixime
Differences in Clinical Cure or Improvement Rate at Visit 4 by Subset
In the Medical Officer Clinical Efficacy Population

SUBSET	NT	NC	(LCL,	UCL)	PT	PC	B-D+
NON-COMMON INV	74	73	(-25,	7)	66	75	0.366
COMMON INV*	87	[illegible]	(-11,	12)	86	85	
INV 01	16	19	(-33,	36)	75	74	0.230
INV 07	16	19	(-18,	45)	88	74	
INV 11	39	37	(-19,	3)	92	100	
SMALL INV**	90	87	(-21,	7)	69	76	
MALES	100	102	(-17,	8)	76	80	0.902
FEMALES	61	60	(-19,	13)	79	82	
AGE <45	50	55	(-16,	16)	84	84	0.733
AGE 45-65	56	50	(-26,	9)	73	82	
AGE >65	55	57	(-20,	15)	75	77	
RACE WHITE	130	139	(-19,	2)	74	82	0.035
RACE BLACK/OTHER	31	23	(-8,	41)	90	74	

+B-D = p-value from the Breslow-Day test for homogeneity of treatment effect across strata within a subset.
*Common inv = those investigators who also participated in study C88044.
**Small inv = those investigators with less than 10 evaluable patients per treatment

The treatment effect from those investigators common to study C88044 was not significantly different from those investigators who were not common to study C88044. However, it should be noted that the clinical cure or improvement rate in both treatment groups was much lower in the non-common investigators than in the common investigators. In this study, the results of the subset analysis in the non-common investigators cannot stand alone, since the results fail to demonstrate that ceftibuten is therapeutically equivalent to cefixime with respect to the rate of clinical cure or improvement at VISIT 4.

The variation in treatment effect across the investigator, gender, and age strata was not statistically significant. However, a significant variation in treatment effect across the race strata was observed, where the treatment effect favored cefixime in white patients and favored ceftibuten in black/other patients.

One hundred eighty five patients from each treatment group were included in the safety analysis. Twenty-six (14%) ceftibuten patients and 36 (19%) cefixime patients experienced at least one treatment

related adverse event. The treatment difference in the overall drug related adverse event rate was not statistically significant.

The treatment groups did not differ significantly with respect to the rate of discontinuation due to adverse events, or the rate of any specific clinical adverse event or laboratory adverse event.

IV. SUMMARY AND CONCLUSIONS

(Which May be Conveyed to the Sponsor)

Statistical evaluation of efficacy is based upon the 95% confidence interval of the ceftibuten minus cefixime difference in clinical cure or improvement rate at 7-21 days post treatment (VISIT 4) in the medical officer's clinical efficacy population.

Statistical evaluation of safety is based upon the Fisher's exact test treatment comparison of the drug related (possibly, probably or definitely) adverse event rate in the safety population.

1. With all investigators combined, the 95% confidence interval was $_{161,162}$(-13%, 6%) $_{77\%,81\%}$, which demonstrates that 5-15 days of ceftibuten 400 mg q.d. is equivalent in efficacy to 5-15 days of cefixime 400 mg q.d. in the treatment of acute exacerbation of chronic bronchitis.

2. In the subset of investigators who were not common to study C88044, the 95% confidence interval was $_{74,73}$(-25%, 7%) $_{66\%,75\%}$, which fails to demonstrate that 5-15 days of ceftibuten 400 mg q.d. is equivalent in efficacy to 5-15 days of cefixime 400 mg q.d. in the treatment of acute exacerbation of chronic bronchitis.

3. In the subset of patients who were also microbiologically evaluable, the 95% confidence interval of the difference in clinical cure or improvement rate was $_{58,44}$(-29%, 9%) $_{67\%,77\%}$, and the 95% confidence interval of the difference in bacteriological eradication rate was $_{58,44}$(-29%, 8%) $_{69\%,80\%}$. These intervals fail to demonstrate that 5-15 days of ceftibuten 400 mg q.d. is equivalent in efficacy to 5-15 days of cefixime 400 mg q.d. in the treatment of acute exacerbation of chronic bronchitis.

4. For individual pathogens, the 95% confidence interval of the difference in bacteriological eradication rate was $_{31,20}$(-29%, 28%) $_{74\%,75\%}$ for *H. influenzae*, $_{18,15}$(-68%, -10%) $_{61\%,100\%}$ for *M. catarrhalis*, and $_{16,11}$(-32%, 55%) $_{75\%,64\%}$ for *S. pneumoniae*. These intervals fail to demonstrate that 5-15 days of ceftibuten 400 mg q.d. is equivalent in efficacy to 5-15 days of cefixime 400 mg q.d. in the treatment of acute exacerbation of chronic bronchitis due to *H. influenzae, M. catarrhalis* or *S. pneumoniae*. Furthermore, the interval for *M. catarrhalis* demonstrates that ceftibuten is significantly inferior to cefixime with respect to the eradication of this pathogen.

5. A significant interaction of treatment by race was observed, where the treatment difference in clinical cure or improvement rate favored ceftibuten in black/other patients, but favored cefixime in white patients. The medical officer will have to determine whether this interaction is clinically meaningful. Significant interactions of treatment by sex, treatment by age, and treatment by investigator were not observed.

6. The safety analysis results show that 5-15 days of ceftibuten 400 mg q.d. is not significantly different in safety from 5-15 days of cefixime 400 mg q.d. in the treatment of acute exacerbation of chronic bronchitis.

RECOMMENDED REGULATORY ACTION: *For the approval of an acute exacerbation of chronic bronchitis indication, the Points to Consider guidance document suggests two statistically adequate and well controlled trials: one with clinically evaluable patients, and one with clinically and microbiologically evaluable patients. The results of study C90045 clearly meet the clinical only study guidelines; however a study with results which meet the clinical and microbiologic study guidelines has not been submitted by the applicant.*

If approval were to be based solely upon the clinical results from two adequate and well-controlled trials, studies C90045 and C88044 et. al. (C88044, I88111, I88217, and I88327 combined) fail to meet this criterion due to a lack of independence from the use of common investigators.

From a statistical standpoint, this reviewer cannot recommend approval of 5-14 days of ceftibuten capsules 400 mg q.d. for the treatment of acute exacerbation of chronic bronchitis.

Elizabeth A. Turney 9/28/94

Elizabeth A. Turney, M.S.
Mathematical Statistician, Group 7

Ralph Harkins, Ph D 10/4/94

Concur: Ralph Harkins, Ph.D.
Supervisory Statistician, group 7

Satya D. Dubey, Ph. D. 10-5-94
Branch Chief, SERB

cc:
Orig. NDA 50-685
HFD-520
HFD-520/DeBellas
HFD-520/Gavrilovich
HFD-520/Albrecht
HFD-520/Soreth
HFD-713/Dubey [File: DRU 1.3.2]
HFD-713/Harkins
HFE-713/Turney
HFD-344/Lisook
Chron.
This review contains 9 pages.

STATISTICAL REVIEW AND EVALUATION

FLO . 9

NDA#: 50-685
Drug Class: 1-S
Applicant: Schering Corporation
Name of Drug: Ceftibuten (CEDAX®) capsules

Documents Reviewed: Volumes 1.1, 1.2, 1.176-1.179, 1.181,1.182. 1.186-1.190, 1.192, 1.194, 1.203, 1.204, 1.224, 1.228, 1.234-1.237 1.248-1.253, stamp dated December 23, 1991, and data on diskettes provided by the applicant.

Indications:

B. Acute Exacerbations of Chronic Bronchitis

Medical Officer: Dr. Brad Leissa, DAIDP, HFD-520

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I. INTRODUCTION

B. ACUTE EXACERBATION OF CHRONIC BRONCHITIS (AECB)

In the draft labelling submitted by the applicant, ceftibuten 400 mg QD in capsule form is proposed for the treatment of **Acute Bronchitis** and **Acute Exacerbation of Chronic Bronchitis** caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Haemophilus parainflunzae, Moraxella (Branhamella) catarrhalis* (beta-lactamase positive and negative strains), *Streptococcus pneumoniae*, and *Klebsiella pneumoniae*.

The applicant has submitted data from two domestic controlled trials and ten foreign controlled trials comparing the efficacy and safety of various dosing regimens of ceftibuten and cefaclor in the treatment of These trials were designed when the DAIDP approved antibiotics for the general indication of however, the indication is no longer accepted by the division. However, since the DAIDP changed its review policies during the development of this product, the new policies could not be applied retroactively; therefore, the data were reviewed using AECB subset analyses. **Keep in mind that the use of post-hoc subset analyses severely limits the power of the trial to establish efficacy equivalence within in the subsets. The results of the subset analyses must be interpreted with caution.**

Unless otherwise noted, the efficacy results presented in the AECB review are from analyses of the medical officer's database as of October 21, 1992. The medical officer has made minor changes in the database since that time; however, these changes do not affect study conclusions.

Ceftibuten 400 mg QD in capsule form is also proposed for the treatment of

Although a general indication had been requested, the applicant has submitted data from one domestic controlled trial and six foreign controlled trials comparing the efficacy and safety of ceftibuten 400 mg QD and either trimethoprim-sulfamethoxazole 160/800 mg BID (TMP-SMX), norfloxacin 400 mg BID, or ofloxacin 200 mg BID in the treatment of It should be noted that the DAIDP does not approve antibiotics for the general indication of rather, and are labelled as separate indications. The submitted studies were reviewed in support of an indication for

Unless otherwise noted, the efficacy results presented in the review are from analyses of the medical officer's database as of November 24, 1992. The medical officer has made

minor changes in the database since that time; however, these changes do not affect study conclusions.

II. METHODS

B. ACUTE EXACERBATION OF CHRONIC BRONCHITIS (AECB)

The twelve trials had one of three basic study designs briefly described as follows:

a. Studies C88-044 (domestic), I88-111, I88-217, and I88-327 (foreign) were multi-center, single (investigator) blinded, active controlled, parallel group, randomized trials comparing the efficacy and safety of ceftibuten 400 mg QD or 200 mg BID and cefaclor 250 mg TID or 500 mg TID in the treatment of acute lower respiratory tract infections. Two randomization schedules were used at each center. Patients with bronchitis (including AB or AECB) or tracheitis were randomized to receive either ceftibuten 400 mg QD or cefaclor 250 mg TID. Patients with pneumonia or bronchiectasis were randomized to receive either ceftibuten 200 mg BID or cefaclor 500 mg TID. In each randomization schedule, patients were randomized in a 2:1 ceftibuten:cefaclor ratio. Study drugs were administered orally for 5-14 days.

b. Studies C87-001 (domestic), I87-107, I87-223, I87-233, I87-234, I87-236, and I87-325 (foreign) were multi-center, single (investigator) blinded, active controlled, parallel group, randomized trials comparing the efficacy and safety of ceftibuten 200 mg BID, ceftibuten 300 mg BID, and cefaclor 500 mg TID in the treatment of acute lower respiratory tract infections. One randomization schedule was used at each center. Patients were randomized in a 1:1:1 ceftibuten 200 mg BID:ceftibuten 300 mg BID: cefaclor 500 mg TID ratio. Study drugs were administered orally for 5-14 days.

c. Study I88-230 (foreign) was a multi-center, single (investigator) blinded, active controlled, parallel group, randomized trial comparing the efficacy and safety of ceftibuten 200 mg BID and cefaclor 250 mg TID or 500 mg TID in the treatment of acute lower respiratory tract infections. Two randomization schedules were used at each center. Patients with bronchitis (including AB or AECB) or tracheitis were randomized to receive either ceftibuten 200 mg BID or cefaclor 250 mg TID. Patients with pneumonia or bronchiectasis were randomized to receive either ceftibuten 200 mg BID or cefaclor 500 mg TID. In each randomization schedule, patients were randomized in a 2:1 ceftibuten:cefaclor ratio. Study drugs were administered orally for 5-14 days.

The classification and analysis of patient response was similar for all trials as follows:

The applicant considered end of treatment or 1-3 days post treatment (EOT) as the primary efficacy endpoint. The applicant did not specify a primary efficacy parameter.

According to the applicant, a clinical success was defined as cure or improvement at EOT, and a bacteriological success was defined as elimination, elimination with superinfection or elimination with colonization at EOT.

In contrast to the applicant, the medical officer considered an evaluation at 4 days post treatment or later (EXT) as the primary efficacy endpoint. The medical officer considered clinical efficacy as the primary efficacy parameter.

The medical officer assessed clinical response at EOT and EXT, and assessed bacteriological response at EXT only. According to the medical officer, a clinical success was defined as cure or improvement at EOT, and sustained cure, cure, or sustained improvement at EXT. A bacteriological success was defined as elimination, elimination with colonization or elimination with superinfection at EXT.

By request of the medical officer, results for clinical efficacy and bacteriological efficacy at EOT and EXT are reported. The medical officer's "clinical test-of-cure" and "valid" populations were used to assess clinical efficacy and bacteriological efficacy, respectively. For completeness, the applicant's results at EOT are summarized from the study reports. The applicants's "clinical efficacy" and "valid" populations were used to assess clinical efficacy and bacteriological efficacy, respectively.

The applicant has proposed the **ceftibuten 400 mg QD** dosing regimen for the label; therefore, only the "bronchitis" patients from studies C88-044, I88-111, I88-217, and I88-327 were reviewed as primary evidence for the applicant's claims. By request of the medical officer, the 200 mg BID AECB patients from studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, I87-325, and I88-230, and the pneumonia patients from all studies were reviewed as supportive evidence for the applicant's AECB claims.

With respect to demographic variables, baseline variables, evaluable patients rate, clinical success rate, and bacteriological success rate, the treatment groups were compared using Chi square tests, Fisher's exact tests, Wilcoxon rank sum tests, and Kruskall-Wallis tests where appropriate. For all tests, among group and between group differences were considered to be statistically significant at the 0.05 level.

The clinical and bacteriological success rates of the treatment groups were also compared using 95% confidence intervals of the ceftibuten minus cefaclor difference in clinical success rate and bacteriological success rate. The confidence intervals were based on a normal approximation and incorporated a continuity correction. Throughout this review, the confidence intervals are presented as n_t,n_c (LCL, UCL) p_t,p_c, where n_t = number of ceftibuten patients, n_c = number of comparator patients, p_t = cure rate of ceftibuten and p_c = cure rate of comparator. Evaluation of efficacy equivalence is based on the "two tailed 95% confidence interval around the difference in outcomes" approach outlined on page 20 of the draft DAIDP "Points to Consider" document.

Where appropriate, interactions of treatment effect with center, study, and geographic location were assessed via logistic regression models of clinical success at EOT and EXT, and bacteriological success at EXT. The homogeneity of treatment effect across studies

and geographic locations was also evaluated using the "meta-analysis" approach outlined by DerSimonian and Laird (Controlled Clinical Trials (1986) 7:177-188). Treatment interactions were considered significant at the 0.20 level.

If sample size warranted statistical evaluation, Chi-square tests and 95% confidence intervals (as described previously) were used to compare treatment groups with respect to bacteriological success rates against individual pathogens.

The applicant has acknowledged that studies C88-044, I88-111, I88-217, and I88-327 lack sufficient efficacy evaluable patients when analyzed individually. In volume 1.2, pages 37-38 of the submission, the applicant reports:

> "The Sponsor originally designed the program with adequate numbers of patients to provide two adequate and well controlled trials for bronchitis and pneumonia with one trial coming from the multi-center U.S. experience and the second trial coming from the multi-center international experience. On completion of the studies, the evaluability rate was lower than anticipated and as a consequence, neither the U.S. nor the international centers could stand alone and achieve the Sponsor's original study analysis expectations.
>
> At pre-NDA meetings, the Sponsor proposed pooling the U.S. and international experience for ceftibuten 400 mg once daily in the treatment of bronchitis to create one adequate and well controlled trial in support of the bronchitis claim. The Agency agreed with this proposal."

It is the opinion of this reviewer that the U.S. and international centers should be pooled only if the populations are reasonably similar with respect to baseline characteristics, and if there is not a significant treatment by location interaction ($p > 0.20$). It should also be noted that if the combined US and international studies are considered one "trial", there would not be two trials in support of the applicant's AECB claims for the ceftibuten 400 mg QD regimen.

All safety analyses were performed using the applicant's safety population and study report tables. According to the applicant, all patients randomized and treated were evaluable for safety. With respect to proportions of patients with clinical adverse events and abnormal laboratory parameters, the treatment groups were compared using 95% confidence intervals (as described previously), chi square tests and Fisher's exact tests where appropriate.

The study designs of the trials are summarized as follows:

Studies C87-069 (domestic), I87-247, and I87-326 (foreign) were multi-center, single (investigator) blinded, active controlled, parallel group, randomized trials comparing the efficacy and safety of ceftibuten 400 mg QD and trimethoprim-sulfamethoxazole 160/800 mg BID (TMP-SMX) in the treatment of culture confirmed, symptomatic complicated urinary tract infections, such as pyelonephritis, medically treatable lower UTI with

urological complications, or recurrent cystitis. Patients were randomized in a 2:1 ceftibuten:TMP-SMX ratio. Study drugs were administered orally for 10-14 days.

Studies I87-128 and I89-054 were foreign, multi-center, parallel group, active controlled, randomized trials comparing the efficacy and safety of ceftibuten 400 mg QD and norfloxacin 400 mg BID in the treatment of culture confirmed, symptomatic complicated urinary tract infections, such as pyelonephritis, medically treatable lower UTI with urological complications, or recurrent cystitis. Patients were randomized in a 2:1 ceftibuten:norfloxacin ratio. I87-128 was single (investigator) blinded, while I89-054 was double blinded. Study drugs were administered orally for 10-14 days.

Study I87-232 was a foreign, multi-center, single (investigator) blinded, active controlled, parallel group, randomized trial comparing the efficacy and safety of ceftibuten 400 mg QD and ofloxacin 200 mg BID in the treatment of culture confirmed, symptomatic complicated urinary tract infections, such as pyelonephritis, medically treatable lower UTI with urological complications, or recurrent cystitis. Patients were randomized in a 2:1 ceftibuten:ofloxacin ratio. Study drugs were administered orally for 10-14 days.

A cross reference was made to the ceftibuten suspension NDA (50-696) for the clinical study I88-116, which compared the efficacy and safety of ceftibuten 9 mg/kg QD to trimethoprim-sulfamethoxazole 4/20 mg/kg BID in the treatment of complicated urinary tract infections in children. This study was conducted internationally, and was similar in design to studies C87-069, I87-247 and I87-326. However, due to the large number of adult patients studied, the medical officer did not see the need to review the pediatric study at this time.

The classification and analysis of patient response was similar for all trials as follows:

Both the applicant and the medical officer considered 5-9 days post treatment as the primary efficacy endpoint. The medical officer considered bacteriological efficacy as the primary efficacy parameter. The applicant did not specify a primary efficacy parameter.

According to the applicant, a bacteriological response of elimination, elimination with superinfection or elimination with reinfection was considered a bacteriological success at DAY 5-9. A bacteriological response of elimination or elimination with reinfection was considered a bacteriological success at WEEK 4-6.

According to the medical officer, a bacteriological response of elimination was considered a bacteriological success at DAY 5-9 and at WEEK 4-6. The medical officer reviewed patients with superinfection or reinfection separately.

According to the medical officer and the applicant, a clinical response of cure or improvement was considered a clinical success at DAY 5-9. A clinical response of sustained cure or sustained improvement was considered a clinical success at WEEK 4-6.

The medical officer considered pyelonephritis (both complicated and uncomplicated) as a complicated UTI; however, he did not consider recurrent cystitis as a complicated UTI. The

medical officer considered the subset of evaluable patients with complicated UTI as the primary analysis subset. Patients without MO diagnosed complicated UTI were excluded from the primary efficacy analyses.

If patients numbers were adequate, the subset of pyelonephritis patients was examined in support of the applicant's pyelonephritis claim. According to the draft DAIDP "Points to Consider" document (page 31), a minimum of 30 pyelonephritis patients/arm/study must be successfully treated with the investigative agent in order to garner the pyelonephritis claim.

By request of the medical officer, results for bacteriological efficacy and clinical efficacy at DAY 5-9 and WEEK 4-6 are reported. The medical officer's "valid" population was used to assess bacteriological and clinical efficacy. For completeness, the applicant's results are summarized from the study reports. The applicant's "efficacy" population was used to assess bacteriological and clinical efficacy. Note that the applicant's "efficacy" population included patients with recurrent cystitis and other non-complicated UTI.

The statistical methods employed were similar to those described in section IIA/B. When calculating the applicant's success rates at WEEK 4-6, this reviewer carried through the bacteriological and clinical failures at DAY 5-9. The applicant failed to do this.

The applicant acknowledges that the three studies which used the comparator TMP-SMX (I87-069, I87-247 and I87-326) lack sufficient efficacy evaluable patients when analyzed individually. In NDA volume 1.2, page 41, the applicant reports:

> "The plan was to analyze the U.S. centers separately to provide one adequate and well controlled trial, and similarly to analyze the international centers as a second adequate and well controlled trial. On completion of the studies, the evaluability rate for the program did not meet expectations, and as a consequence neither the U.S. nor the international experience alone could provide adequate numbers of evaluable patients to support two independent analyses.
>
> At pre-NDA meetings the Sponsor proposed to the Agency pooling the U.S. and international experience into one single adequate and well controlled trial in support of the urinary tract infection indication. The Agency agreed with this proposal."

It is the opinion of this reviewer that the U.S. and international centers should be pooled only if the populations are not substantially different with respect to demographic and baseline parameters, and if there is not a significant treatment by location interaction.

The applicant pooled the three studies which used quinolone comparators (I87-128, I87-232 and I89-054) and presented these results as a second "trial". In NDA volume 1.2, page 42, the applicant provides the rationale for this pooled analysis:

> "At pre-NDA meetings the Sponsor proposed pooling the results of three international studies conducted with quinolones as comparators and presenting that experience as a second adequate and well controlled trial to support the urinary tract infection indication for adults. This proposal was acceptable to the Agency based on assumptions derived from the

Sponsor's presentation at the pre-NDA meetings in the comparability of the protocols and on the adequacy of evaluable patients for analysis."

It is the opinion of this reviewer that if the populations are not substantially different with respect to demographic and baseline parameters, and if there is not a significant treatment by study interaction, it may be reasonable to combine the two studies which used norfloxacin as the comparator (I87-128 and I89-054). However, the study with the ofloxacin comparator (I87-232) should be analyzed separately. **By request of the medical officer, a combined analysis of the three quinolone studies was performed.**

The methods of safety evaluation were similar to those described in the section IIA/B.

III. EFFICACY RESULTS

Note: Tracheitis patients were included with the acute bronchitis patients.

1. Study C88-044 (US Population)

A total of 157 AB patients were enrolled across 26 US centers. Of these, 102 received ceftibuten 400 mg QD, 48 received cefaclor 250 mg TID, and 7 received non-protocol specified regimens. Patients who received the non-protocol regimens were excluded from the analysis. Total center enrollment ranged from 1 to 19.

Clinical Efficacy: A total of 55 (54%) ceftibuten patients and 19 (40%) cefaclor patients were evaluable for clinical efficacy. Although small sample sizes precluded formal statistical testing, there were large differences among the centers in the percentage of evaluable patients, which ranged from 0% to 100%. The total number of clinically evaluable patients among the centers ranged from 0 to 14. Within center sample sizes were inadequate to formally assess the treatment by center interaction; therefore all centers were pooled for analysis.

At EOT the ceftibuten minus cefaclor difference in clinical success rate was -17%, with the 95% confidence interval at $_{55,19}$ (-43%, 9%) $_{62\%,79\%}$ (p=0.174). At EXT, the ceftibuten minus cefaclor difference in clinical success rate was -19%, with the 95% confidence interval at $_{55,19}$ (-45%, 7%) $_{60\%,79\%}$ (p=0.136).

According to the applicant, the ceftibuten minus cefaclor difference in clinical success rate at EOT was 0%, with the 95% confidence interval at $_{88,38}$ (-16%, 16%) $_{84\%,84\%}$ (p=0.987).

Bacteriological Efficacy: A total of 14 (14%) ceftibuten patients and 4 (8%) cefaclor patients were evaluable for bacteriological efficacy. Although small sample sizes precluded formal statistical testing, there were large differences in the percentage of evaluable patients among the centers, which ranged from 0% to 67%. The total number of bacteriologically evaluable patients among the centers ranged from 0 to 6. The number of

bacteriologically evaluable patients was inadequate to make a meaningful statistical comparison of bacteriological success rate.

According to the applicant, the ceftibuten minus cefaclor difference in bacteriological success rate at EOT was -1%, with the 95% confidence interval at $_{19,10}$ (-31%, 30%) $_{89\%,90\%}$ ($p>0.999$).

Reviewer Conclusions: **Since the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at EXT exceeds -20%, study C88-044 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute bronchitis. Results from the secondary analysis of clinical success rate at EOT support this conclusion. Furthermore, the results from the analysis of the applicant's data fail to support the efficacy claims.**

2. Studies I88-217, I88-111, and I88-327

Study I88-217 enrolled 90 AB patients across 15 centers located in either the United Kingdom, Belgium, Germany, Sweden, Greece, or Italy. Of these, 66 received ceftibuten 400 mg QD and 24 received cefaclor 250 mg TID. Total center enrollment ranged from 1 to 17. A total of 29 ceftibuten patients and 5 cefaclor patients were clinically evaluable. Sixteen ceftibuten patients and 2 cefaclor patients were bacteriologically evaluable.

Study I88-111 enrolled 22 AB patients across 5 centers located in either Mexico, Chile, or Argentina. Of these, 13 received ceftibuten 400 mg QD and 9 received cefaclor 250 mg TID. Total center enrollment ranged from 1 to 8. A total of 5 ceftibuten patients and 4 cefaclor patients were clinically evaluable. Four ceftibuten patients and 4 cefaclor patients were bacteriologically evaluable.

Study I88-327 enrolled 8 AB patients across 2 centers located in Canada. Of these, 6 received ceftibuten 400 mg QD and 2 received cefaclor 250 mg TID. One center enrolled 5 patients and one center enrolled 3 patients. A total of 3 ceftibuten patients and 1 cefaclor patient were clinically evaluable. One ceftibuten patient and 1 cefaclor patient were bacteriologically evaluable.

Individually, these studies lacked sufficient numbers of clinically and bacteriologically evaluable patients to make meaningful statistical comparisons of clinical and bacteriological success rate at EOT and EXT.

The applicant did not present results by individual study.

Reviewer Conclusion: **Studies I88-217, I88-111 and I88-327 lack sufficient numbers of clinically evaluable patients to make meaningful statistical comparisons of clinical efficacy. Therefore, these studies fail to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute bronchitis.**

3. Combined Analysis: Studies I88-217, I88-111, and I88-327 (International Population)

Since individually the three international trials lacked sufficient sample size to provide adequate estimates of the treatment effect, a combined analysis was performed in order to obtain more conclusive results.

Across the three studies, 85 ceftibuten patients and 35 cefaclor patients were enrolled. The study groups were significantly different with respect to age ($p<0.001$), where study I88-111 had a lower mean age than studies I88-217 and I88-327.

Clinical Efficacy: A total of 37 (44%) ceftibuten patients and 10 (29%) cefaclor patients were evaluable for clinical efficacy. Sample sizes were inadequate to make among study comparisons of demographic and baseline variables. The sample sizes within the studies were inadequate to formally assess the treatment by study interaction; therefore all studies were pooled for analysis.

At EOT the ceftibuten minus cefaclor difference in clinical success rate was -9%, with the 95% confidence interval at $_{37,10}$ (-38%, 20%) $_{81\%,90\%}$ ($p=0.667$). At EXT the ceftibuten minus cefaclor difference in clinical success rate was -2%, with the 95% confidence interval at 37,10 (-36%, 33%) 78%,80% ($p>0.999$).

According to the applicant, the ceftibuten minus cefaclor difference in clinical success rate at EOT was -7%, with the 95% confidence interval at $_{96,38}$ (-14%, -0.3%) $_{93\%,100\%}$, which demonstrates that ceftibuten is significantly inferior to cefaclor. However, the result of Fisher's exact test demonstrated the ceftibuten is only marginally inferior to cefaclor ($p=0.191$).

Bacteriological Efficacy: A total of 21 (25%) ceftibuten patients and 7 (20%) cefaclor patients were evaluable for bacteriological efficacy. The number of bacteriologically evaluable patients was insufficient to make a meaningful statistical comparison of bacteriological success rate.

According to the applicant, the ceftibuten minus cefaclor difference in bacteriologic success rate at EOT was -1%, with the 95% confidence interval at $_{40,17}$ (-23%, 2%) $_{87\%,88\%}$ ($p>0.999$).

Reviewer Conclusion: **Since the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at EXT exceeds -15%, the combined analysis of international studies I88-111, I88-217, and I88-327 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute bronchitis. Results from the secondary analysis of clinical success rate at EOT support this conclusion.**

Furthermore, the results from the analysis of the applicant's data fail to support the efficacy claims. The 95% confidence interval of the ceftibuten minus cefaclor difference in

clinical success rate at EOT demonstrates that ceftibuten 400 mg QD is significantly inferior to cefaclor 250 mg TID in the treatment of acute bronchitis.

4. Combined Analysis: US and International Populations

By request of the applicant and the medical officer (see section IIA/B), a combined analysis of the US and international studies was performed.

Across the US and international studies, 187 ceftibuten patients and 83 cefaclor patients were enrolled.

A total of 150 patients were enrolled in the US trial, and 120 patients were enrolled in the international trials. The location groups were significantly different with respect to race, gender, inpatient/outpatient status, age, and distribution of baseline pathogens ($p \leq 0.028$ for all tests). Compared to the US group, the international group had a higher mean age, and a higher percentage of whites, males, inpatients, and patients infected with *S. pneumoniae*.

Clinical Efficacy: A total of 92 (49%) ceftibuten patients and 29 (35%) cefaclor patients were evaluable for clinical efficacy. The treatment difference in patient evaluability rate was statistically significant ($p = 0.030$).

A total of 74 (49%) US patients and 47 (39%) international patients were evaluable for clinical efficacy. The clinically evaluable location groups were significantly different with respect to age and gender ($p \leq 0.027$ for both tests). Compared to the US group, the international group had a higher mean age, and a higher percentage of males.

The results of DerSimonian and Laird's "meta-analysis" and the logistic regression models of clinical response did not demonstrate a significant treatment by location interaction at EOT or EXT. Therefore, the location groups were combined for analysis.

At EOT the ceftibuten minus cefaclor difference in clinical success rate was -13%, with the 95% confidence interval at $_{92,29}$ (-32%, 6%) $_{70\%,93\%}$ ($p = 0.164$). At EXT the ceftibuten minus cefaclor difference in clinical success rate was -12%, with the 95% confidence interval at $_{92,29}$ (-32%, 8%) $_{67\%,79\%}$ ($p = 0.221$). The location weighted estimates of treatment effect at EOT and EXT were similar to the unweighted estimates.

According to the applicant, the ceftibuten minus cefaclor difference in clinical success rate at EOT was -4%, with the 95% confidence interval at $_{184,76}$ (-12%, 5%) $_{89\%,92\%}$ ($p = 0.398$).

Bacteriological Efficacy: A total of 35 (19%) ceftibuten patients and 11 (13%) cefaclor patients were evaluable for bacteriological efficacy.

A total of 18 (12%) US patients and 28 (23%) international patients were evaluable for bacteriological efficacy. The location difference in patient evaluability rate was statistically significant ($p = 0.014$). The bacteriologically evaluable location groups were significantly different with respect to distribution of baseline pathogens ($p = 0.043$), where the

international group had a higher percentage of patients with *S. pneumoniae* than the US group.

The results of DerSimonian and Laird's "meta-analysis" and the logistic regression model of bacteriological response did not demonstrate a significant treatment by location interaction at EXT. Therefore, the location groups were combined for analysis.

At EXT the ceftibuten minus cefaclor difference in bacteriological success rate was 1%, with the 95% confidence interval at $_{35,11}$ (-31%, 33%) $_{83\%,82\%}$ ($p>0.999$). The location weighted estimate of treatment effect at EXT was -8%, with standard error of 10% and 95% confidence interval of (-29%, 12%).

According to the applicant, the ceftibuten minus cefaclor difference in bacteriological success rate at EOT was -1%, with the 95% confidence interval at $_{59,27}$ (-18%, 16%) $_{88\%,89\%}$ ($p>0.999$).

Reviewer Conclusion: **Since the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at EXT exceeds -20%, the combined analysis of US study C88-044 and international studies I88-111, I88-217, and I88-327 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute bronchitis. Results from the secondary analyses of clinical success rate at EOT and bacteriological success rate at EXT support this conclusion. Furthermore, the results from the analysis of the applicant's data fail to support the efficacy claims.**

B. ACUTE EXACERBATION OF CHRONIC BRONCHITIS (AECB)

1. Study C88-044 (US Population)

A total of 19[illegible]ients with AECB were enrolled across 26 US centers. Of these, 127 received ceftibuten 400 mg QD, 61 received cefaclor 250 mg TID, and 3 received non-protocol specified regimens. Patients who received the non-protocol regimens were excluded from the analysis. Total center enrollment ranged from 1 to 50.

Clinical Efficacy: A total of 58 (46%) ceftibuten patients and 26 (43%) cefaclor patients were evaluable for clinical efficacy. Although small sample sizes precluded formal statistical testing, there were large differences in the percentage of evaluable patients among the centers, which ranged from 0 to 100%. The total number of clinically evaluable patients among the centers ranged from 0 to 30. Within center sample sizes were inadequate to formally assess the treatment by center interaction; therefore all centers were pooled for analysis.

The ceftibuten group had a significantly lower percentage of inpatients, and a significantly lower mean treatment duration ($p\leq 0.045$ for both tests).

At EOT the ceftibuten minus cefaclor difference in clinical success rate was -7%, with the 95% confidence interval at $_{58,26}$ (-32%, 17%) $_{62\%,69\%}$ ($p=0.527$). At EXT the ceftibuten minus cefaclor difference in clinical success rate was -6%, with the 95% confidence interval at $_{58,26}$ (-32%, 18%) $_{59\%,65\%}$ ($p=0.557$).

According to the applicant, the ceftibuten minus cefaclor difference in clinical success rate at EOT was 1%, with the 95% confidence interval at $_{102,40}$ (-12%, 15%) $_{89\%,88\%}$ ($p=0.773$).

Bacteriological Efficacy: A total of 25 (20%) ceftibuten patients and 13 (21%) cefaclor patients were evaluable for bacteriological efficacy. Although small sample sizes precluded formal statistical testing, there were large differences among the centers in the percentage of evaluable patients, which ranged from 0% to 100%. The total number of bacteriologically evaluable patients among the centers ranged from 0 to 20. Within center sample sizes were inadequate to formally assess the treatment by center interaction; therefore all centers were pooled for analysis.

The ceftibuten group had a significantly lower mean height and mean weight than the cefaclor group ($p \leq 0.038$ for both tests).

At EXT the ceftibuten minus cefaclor difference in clinical success rate was -1%, with the 95% confidence interval at $_{25,13}$ (-35%, 33%) $_{76\%,77\%}$ ($p>0.999$).

According to the applicant, the ceftibuten minus cefaclor difference in bacteriological success rate at EOT was 15%, with the 95% confidence interval at $_{21,11}$ (-15%, 45%) $_{97\%,82\%}$ ($p=0.163$).

Reviewer Conclusions: **Since the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at EXT exceeds -20%, study C88-044 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis. Results from the secondary analyses of clinical success rate at EOT and bacteriological success rate at EXT support this conclusion.**

Results from the analysis of the applicant's data demonstrate that at EOT, the treatments are comparable with respect to clinical efficacy, but not bacteriological efficacy.

2. Study I88-217

A total of 215 patients with AECB were enrolled across 17 centers located in either the United Kingoom, Belgium, Germany, Sweden, Switzerland, Greece, or Italy. Of these, 72 received ceftibuten 400 mg QD and 43 received cefaclor 250 mg TID. Total center enrollment ranged from 1 to 28.

Clinical Efficacy: A total of 39 (54%) ceftibuten patients and 24 (56%) cefaclor patients were evaluable for clinical efficacy. Although small sample sizes precluded formal

statistical testing, there were large differences in the percentage of evaluable patients among the centers, which ranged from 0 to 100%. The total number of clinically evaluable patients among centers ranged from 0 to 23. Within center sample sizes were inadequate to formally assess the treatment by center interaction; therefore all centers were pooled for analysis.

At EOT the ceftibuten minus cefaclor difference in clinical success rate was 9%, with the 95% confidence interval at $_{39,24}$ (-18%, 37%) $_{72\%,63\%}$ ($p=0.441$). At EXT the ceftibuten minus cefaclor difference in clinical success rate was 1%, with the 95% confidence interval at $_{39,24}$ (-28%, 30%) $_{51\%,50\%}$ ($p=0.921$).

The applicant did not present clinical results by individual international study.

Bacteriological Efficacy: A total of 29 (40%) ceftibuten patients and 15 (35%) cefaclor patients were evaluable for bacteriological efficacy. Although small sample sizes precluded formal statistical testing, there were large differences among centers in the percentage of evaluable patients, which ranged from 0% to 100%. The total number of bacteriologically evaluable patients among the centers ranged from 0 to 22. Within center sample sizes were inadequate to formally assess the treatment by center interaction; therefore all centers were pooled for analysis.

The ceftibuten group had a significantly higher percentage of inpatients than the cefaclor group ($p=0.036$).

At EXT the ceftibuten minus cefaclor difference in clinical success rate was 19%, with the 95% confidence interval at $_{29,15}$ (-17%, 55%) $_{66\%,47\%}$ ($p=0.228$).

The applicant did not present bacteriological results by individual international study.

Reviewer Conclusion: **Since the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at EXT exceeds -20%, study I88-217 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis. However, results from the secondary analyses of clinical success at EOT and bacteriological success at EXT demonstrate that ceftibuten and cefaclor are comparable in efficacy.**

3. Studies I88-111 and I88-327

Study I88-111 enrolled 23 AECB patients across 5 centers located in either Mexico, Chile, or Argentina. Of these, 16 received ceftibuten 400 mg QD and 7 received cefaclor 250 mg TID. Total center enrollment ranged from 2 to 9. A total of 10 ceftibuten patients and 4 cefaclor patients were clinically evaluable. Nine ceftibuten patients and 3 cefaclor patients were bacteriologically evaluable.

Study I88-327 enrolled 3 AECB patients across 3 centers located in Canada. Of these, 1 received ceftibuten 400 mg QD, 1 received cefaclor 250 mg TID, and 1 received a non-protocol specified regimen. One ceftibuten patient was clinically and bacteriologically evaluable.

Individually, these studies lacked sufficient numbers of clinically or bacteriologically evaluable patients to make meaningful statistical comparisons of clinical or bacteriological success rates at EOT or EXT.

The applicant did not present results by individual international study.

Reviewer Conclusion: **Studies I88-111 and I88-327 lack sufficient numbers of clinically evaluable patients to make meaningful statistical comparisons of clinical efficacy. Therefore, the studies fail to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis.**

4. Combined Analysis: Studies I88-217, I88-111, and I88-327 (International Population)

Since study I88-217 is underpowered to establish equivalence, and studies I88-111 and I88-327 lack sufficient sample size to provide adequate estimates of the treatment effect, a combined analysis was performed in order to obtain more conclusive results.

Across the three studies, 89 ceftibuten patients and 51 cefaclor patients were enrolled.

A total of 115, 23, and 3 patients were enrolled in studies I88-217, I88-111, and I88-327 respectively. One patient in study I88-327 received a non-protocol specified regimen and was excluded from the analyses.

Studies I88-217 and I88-111 were significantly different with respect to race, inpatient/outpatient status, age and treatment duration ($p \leq 0.043$ for all tests). Study I88-111 had a higher percentage of patients of "other" race, a higher percentage of outpatients, and a lower mean age, and shorter mean treatment duration. Due to its small number of patients, study I88-327 was excluded from the by study comparisons.

Clinical Efficacy: A total of 50 (56%) ceftibuten patients and 28 (55%) cefaclor patients were evaluable for clinical efficacy. Sample sizes within the studies were inadequate to formally assess the treatment by study interaction; therefore all studies were pooled for analysis.

A total of 14 (61%), 63 (55%), and 1 (50%) patients were clinically evaluable from studies I88-217, I88-111, and I88-327 respectively. Studies I88-217 and I88-111 were significantly different with respect to race, inpatient/outpatient status and age ($p \leq 0.031$ for all tests). Study I88-111 had a higher percentage of patients of "other" race and outpatients, and a lower mean age. Due to its small number of patients, study I88-327 was excluded from the by study comparisons.

At EOT the ceftibuten minus cefaclor difference in clinical success rate was 0%, with the 95% confidence interval at $_{50,28}$ (-24%, 25%) $_{68\%,68\%}$ ($p=0.990$). At EXT the ceftibuten minus cefaclor difference in clinical success rate was -2%, with the 95% confidence interval at $_{50,29}$ (-27%, 24%) $_{52\%,54\%}$ ($p=0.894$).

According to the applicant, the ceftibuten minus cefaclor difference in clinical success rate at EOT was -9%, with the 95% confidence interval at $_{73,41}$ (-23%, 4%) $_{84\%,93\%}$ ($p=0.167$).

Bacteriological Efficacy: A total of 39 (44%) ceftibuten patients and 18 (35%) cefaclor patients were evaluable for bacteriological efficacy. Sample sizes within the studies were inadequate to formally assess the treatment by study interaction; therefore all studies were pooled for analysis.

A total of 12 (52%), 44 (38%), and 1 (50%) patients were bacteriologically evaluable from studies I88-217, I88-111, and I88-327 respectively. The study groups were significantly different with respect to race, inpatient/outpatient status and age ($p \leq 0.043$ for all tests). Study I88-111 had a higher percentage of patients of "other" race and outpatients, and a lower mean age. Due to its small number of patients, study I88-327 was excluded from the by study comparisons.

At EXT the ceftibuten minus cefaclor difference in bacteriological success rate was 8%, with the 95% confidence interval at $_{39,18}$ (-23%, 40%) $_{64\%,56\%}$ ($p=0.538$).

According to the applicant, the ceftibuten minus cefaclor difference in bacteriologic success rate at EOT was 1%, with the 95% confidence interval at $_{42,22}$ (-24%, 23%) $_{81\%,82\%}$ ($p>0.999$).

Reviewer Conclusion: **Since the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at EXT exceeds -20%, the combined analysis of international studies I88-111, I88-217, and I88-327 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis. Results from the secondary analyses of clinical success rate at EOT and bacteriological success rate at EXT support this conclusion. Furthermore, the results from the analysis of the applicant's data fail to support the efficacy claims.**

5. Combined Analysis: US and International Populations

By request of the applicant and the medical officer (see section IIA/B), a combined analysis of the US and international studies was performed.

Across the US and international studies, 216 ceftibuten patients and 112 cefaclor patients with AECB were enrolled.

A total of 188 patients were enrolled in the US trial, and 140 patients were enrolled in the international trials. The location groups were significantly different with respect to race, inpatient/outpatient status, age, treatment duration, height, and weight ($p \leq 0.004$ for all tests). Compared to the US group, the international group had a higher mean age, longer mean treatment duration, lower mean height, lower mean weight and a higher percentages of whites and inpatients.

Clinical Efficacy: A total of 108 (50%) ceftibuten patients and 54 (48%) cefaclor patients were evaluable for clinical efficacy. The treatment groups were significantly different with respect to treatment duration ($p=0.029$), where the cefaclor group had a longer mean treatment duration then the ceftibuten group.

A total of 84 (45%) US patients and 78 (56%) international patients were evaluable for clinical efficacy. The international group had significantly more clinically evaluable patients than the US group ($p=0.048$).

The clinically evaluable location groups were significantly different with respect to race, inpatient/outpatient status, age, height and weight. However, since the international group was older and probably had greater disease severity (due to the higher percentage of inpatients), the medical officer felt it was reasonable to combine the US and international populations.

The results of DerSimonian and Laird's "meta-analysis" and the logistic regression models of clinical response did not demonstrate a significant treatment by location interaction at EOT or EXT. Therefore, the location groups were combined for analysis.

At EOT the ceftibuten minus cefaclor difference in clinical success rate was -4%, with the 95% confidence interval at $_{108,54}$ (-20%, 13%) $_{65\%,69\%}$ ($p=0.639$). At EXT the ceftibuten minus cefaclor difference in clinical success rate was -3%, with the 95% confidence interval at $_{108,54}$ (-21%, 14%) $_{56\%,59\%}$ ($p=0.654$). The location weighted estimates of treatment effect at EOT and EXT were similar to the unweighted estimates.

According to the applicant, the ceftibuten minus cefaclor difference in clinical success rate at EOT was -3%, with the 95% confidence interval at $_{175,81}$ (-12%, 6%) $_{97\%,90\%}$ ($p=0.456$).

Bacteriological Efficacy: A total of 64 (30%) ceftibuten patients and 31 (28%) cefaclor patients were evaluable for bacteriological efficacy.

A total of 38 (20%) US patients and 57 (41%) international patients were evaluable for bacteriological efficacy. The international group had significantly more bacteriologically evaluable patients than the US group ($p<0.001$).

The bacteriologically evaluable location groups were significantly different with respect to race, inpatient/outpatient status, height and weight. However, since the international group was older and probably had greater disease severity (due to the higher percentage of inpatients), the medical officer felt it was reasonable to combine the US and international populations.

The results of DerSimonian and Laird's "meta-analysis" and the logistic regression model of bacteriological response did not demonstrate a significant treatment by location interaction at EXT. Therefore, the location groups were combined for analysis.

At EXT the ceftibuten minus cefaclor difference in bacteriological success rates was 4%, with the 95% confidence interval at $_{64,31}$ (-18%, 27%) $_{69\%,85\%}$ (p=0.680). The location weighted estimate of treatment effect at EXT was similar to the unweighted estimate.

Only *H. influenzae* had an adequate number of isolates to make a statistical comparison of bacteriological success rate. At EXT the ceftibuten minus cefaclor difference in bacteriological success rate against *H. influenzae* was 8%, with the 95% confidence interval at $_{31,16}$ (-25%, 42%) $_{71\%,63\%}$ (p=0.555).

According to the applicant, the ceftibuten minus cefaclor difference in bacteriological success rate at EOT was 6%, with the 95% confidence interval at $_{73,33}$ (-12%, 23%) $_{88\%,82\%}$ (p=0.548).

Reviewer Conclusion: **Since the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at EXT exceeds -20%, the combined analysis of US study C88-044 and international studies I88-111, I88-217, and I88-327 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis. However, results from the secondary analyses of clinical success at EOT and bacteriological success at EXT demonstrate that ceftibuten and cefaclor are comparable in efficacy.**

The results from the analysis of the applicant's data demonstrates that at EOT, the treatments are comparable with respect to bacteriological efficacy, but not clinical efficacy.

6. Analysis of ceftibuten 200 mg BID AECB patients from studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, and I87-325

By request of the medical officer, the AECB patients from studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, and I87-325 who received ceftibuten 200 mg BID were reviewed as supportive evidence for the 400 mg QD regimen. The comparative agent in these studies was cefaclor 500 mg TID. Although some patients in these trials were randomized to receive ceftibuten 300 mg BID, these patients were excluded from this efficacy analysis.

Study C87-001 enrolled 31 AECB patients across 8 centers located in the US. Of these, 14 received ceftibuten 200 mg BID and 17 received cefaclor 500 mg TID. Total center enrollment ranged from 1 to 13. A total of 9 ceftibuten patients and 11 cefaclor patients were clinically evaluable. Three ceftibuten patients and 8 cefaclor patients were bacteriologically evaluable.

Study I87-107 enrolled 7 AECB patients across 3 centers located in either Guatemala or Chile. Of these, 3 received ceftibuten 200 mg BID and 4 received cefaclor 500 mg TID. Total center enrollment ranged from 1 to 5. A total of 2 ceftibuten patients and 4 cefaclor patients were clinically evaluable. One ceftibuten patient and 3 cefaclor patients were bacteriologically evaluable.

Study I87-223 enrolled 5 AECB patients across 2 centers located in South Africa. Of these, 2 received ceftibuten 200 mg BID and 3 received cefaclor 500 mg TID. One center each enrolled 1 and 4 patients. One cefaclor patient was clinically and bacteriologically evaluable.

Study I87-233 enrolled 9 AECB patients across 2 centers located in Germany. Of these, 5 received ceftibuten 200 mg BID and 4 received cefaclor 500 mg TID. One center enrolled 1 patient and the other enrolled 8 patients. Three cefaclor patients were clinically evaluable. No patients were bacteriologically evaluable.

Study I87-234 enrolled 10 AECB patients across 3 centers located in France. Of these, 8 received ceftibuten 200 mg BID and 2 received cefaclor 500 mg TID. Total center enrollment ranged from 2 to 5. A total of 4 ceftibuten patients and 2 cefaclor patients were clinically evaluable. Three ceftibuten patients and 2 cefaclor patients were bacteriologically evaluable.

Study I87-236 enrolled 1 AECB patient in Sweden. This patient received ceftibuten 500 mg TID. Study I87-236 did not have any clinically or bacteriologically evaluable patients.

Study I87-325 enrolled 53 AECB patients across 6 centers located in either England, Australia, or Canada. Of these, 27 received ceftibuten 200 mg BID and 26 received cefaclor 500 mg TID. Total center enrollment ranged from 1 to 16. A total of 12 ceftibuten patients and 15 cefaclor patients were clinically evaluable. Five ceftibuten patients and 8 cefaclor patients were bacteriologically evaluable.

Individually, these studies lacked sufficient numbers of clinically and bacteriologically evaluable patients to make meaningful statistical comparisons of clinical and bacteriological success rate at EOT or EXT.

Reviewer Conclusion: **Studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236 and I87-325 lack sufficient numbers of clinically evaluable patients to make meaningful statistical comparisons of clinical efficacy. These studies do not demonstrate that ceftibuten 200 mg BID is comparable in efficacy to cefaclor 500 mg TID for the treatment of acute exacerbation of chronic bronchitis. Therefore, the studies do not provide supportive evidence for the applicant's claim that ceftibuten 400 mg QD comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis.**

7. Combined Analysis of ceftibuten 200 mg BID AECB patients from studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, and I87-325

Since studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, and I87-325 lack sufficient sample size to provide adequate estimates of the treatment effect, a combined analysis was performed in order to obtain more conclusive results.

Across the seven studies, 59 ceftibuten 200 mg BID patients and 57 cefaclor 500 mg TID patients were enrolled.

Clinical Efficacy: A total of 27 (46%) ceftibuten patients and 36 (63%) cefaclor patients were evaluable for clinical efficacy. Compared to the cefaclor group, the ceftibuten group had a significantly higher mean weight ($p=0.039$). Within study sample sizes were inadequate to formally assess the treatment by study interaction; therefore all studies were pooled for analysis.

At EOT the ceftibuten minus cefaclor difference in clinical success rate was 7%, with the 95% confidence interval at $_{27,36}$ (-18%, 33%) $_{74\%,67\%}$ ($p=0.526$). At EXT the ceftibuten minus cefaclor difference in clinical success rate was -5%, with the 95% confidence interval at $_{27,36}$ (-32%, 23%) $_{59\%,64\%}$ ($p=0.708$).

The applicant did not present separate results for the AB and AECB patients.

Bacteriological Efficacy: A total of 12 (20%) ceftibuten patients and 22 (39%) cefaclor patients were evaluable for bacteriological efficacy. The treatment difference in percentage of evaluable patients was statistically significant ($p=0.031$). Within study sample sizes were inadequate to formally assess the treatment by study interaction; therefore all studies were pooled for analysis.

At EXT the ceftibuten minus cefaclor difference in bacteriological success rate was 3%, with the 95% confidence interval at $_{12,22}$ (-37%, 43%) $_{67\%,64\%}$ ($p>0.999$).

The applicant did not present separate results for the AB and AECB patients.

Reviewer Conclusion: **Since the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at EXT exceeds -20%, the combined analysis of studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, and I87-325 does not demonstrate that ceftibuten 200 mg BID is comparable in efficacy to cefaclor 500 mg TID for the treatment of acute exacerbation of chronic bronchitis. Therefore, the analysis does not provide supportive evidence for the applicant's claim that ceftibuten 400 mg QD comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis. The secondary analysis of bacteriological success at EXT supports this conclusion; however, the secondary analysis of clinical success at EOT demonstrates that ceftibuten 200 mg BID and cefaclor 500 mg TID are comparable in efficacy.**

8. Analysis of Ceftibuten 200 mg BID Patients from study I88-230

Study I88-230 enrolled 44 AECB patients across 4 centers located in either Canada or the Netherlands. Of these, 27 received ceftibuten 200 mg BID and 17 received cefaclor 250 mg TID. Total center enrollment ranged from 3 to 21. A total of 12 ceftibuten patients and 4 cefaclor patients were evaluable for clinical efficacy. Twelve ceftibuten patients and 3 cefaclor patients were evaluable for bacteriological efficacy.

The numbers of clinically or bacteriologically evaluable patients were inadequate to make meaningful statistical comparisons of clinical and bacteriological success rates.

Reviewer Conclusion: **Study I88-230 lacks sufficient numbers of clinically evaluable patients to make a meaningful statistical comparison of clinical efficacy. Therefore, this study does not demonstrate that ceftibuten 200 mg BID is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis, and thus does not provide supportive evidence for the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis.**

9. Combined Analysis of Ceftibuten 200 mg BID AECB Patients From Studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, I87-325, and I88-230

By request of the medical officer, a combined analysis of the ceftibuten 200 mg BID AECB patients from studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, and I87-325 (C87-001 *et al*) and I88-230 was performed. Note the comparator in C87-001 *et al* was 500 mg TID, while the comparator in I88-230 was cefaclor 250 mg TID. All cefaclor patients were combined as the comparator group for this efficacy analysis.

Across the eight studies, 86 ceftibuten 200 mg BID patients and 74 cefaclor 500 or 250 mg TID patients were enrolled.

A total of 116 patients were enrolled in the C87-001 *et al* studies, while 44 patients were enrolled in study I88-230. The patients in C87-001 *et al* and I88-230 were significantly different with respect to weight and treatment duration ($p \leq 0.006$ for both tests). Study I88-230 had heavier patients and a longer mean treatment duration.

Clinical Efficacy: A total of 39 (45%) ceftibuten patients and 40 (54%) cefaclor patients were evaluable for clinical efficacy. Compared to the cefaclor group, the ceftibuten group had a significantly higher mean weight ($p = 0.016$). Sample sizes within the study groups were inadequate to formally assess the treatment by study interaction; therefore all studies were pooled for analysis.

A total of 63 (54%) C87-001 *et al* patients and 16 (36%) I88-230 patients were clinically evaluable. C87-001 *et al* had a significantly higher percentage of clinically evaluable patients ($p = 0.043$). Compared to the patients in I88-230, the patients in C87-001 *et al*

had a significantly longer mean treatment duration (p=0.036). However, the medical officer felt it was reasonable to combine the studies.

At EOT the ceftibuten minus cefaclor difference in clinical success rate was -6%, with the 95% confidence interval at $_{39,40}$ (-30%, 18%) $_{59\%,65\%}$ (p=0.581). At EXT the ceftibuten minus cefaclor difference in clinical success rate was -16%, with the 95% confidence interval at $_{39,40}$ (-41%, 8%) $_{44\%,60\%}$ (p=0.144).

Bacteriological Efficacy: A total of 24 (28%) ceftibuten patients and 25 (34%) cefaclor patients were evaluable for bacteriological efficacy. Sample sizes within the study groups were inadequate to formally assess the treatment by study interaction; therefore all studies were pooled for analysis.

A total of 34 (29%) C87-001 *et al* patients and 15 (34%) I88-230 patients were bacteriologically evaluable.

At EXT the ceftibuten minus cefaclor difference in bacteriological success rate was 3%, with the 95% confidence interval at $_{24,25}$ (-29%, 34%) $_{63\%,60\%}$ (p=0.858).

Reviewer Conclusion: **Since the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at EXT exceeds -20%, the combined analysis of studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, I87-325, and I88-230 does not demonstrate that ceftibuten 200 mg BID is comparable in efficacy to cefaclor 500 mg TID or 250 mg TID for the treatment of acute exacerbation of chronic bronchitis. Therefore, this analysis does not provide supportive evidence for the applicant's claim that ceftibuten 400 mg QD comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis. Results from the secondary analyses of clinical success rate at EOT and bacteriological success rate at EXT support this conclusion.**

10. Combined Analysis of Applicant's Pneumonia Patients From Studies C88-044, I88-111, I88-217, I88-327, C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, I87-325 and I88-230.

By request of the medical officer, the applicant's pneumonia patients from studies C88-044, I88-111, I88-217, I88-327, C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, I87-325 and I88-230 who received either ceftibuten 200 mg BID or cefaclor 500 mg TiD were reviewed as supportive evidence for the AECB indication.

The applicant's "valid" patient population was used in the analysis. The patients from studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236 and I87-325 who received ceftibuten 300 mg BID were excluded from the analysis. Although all the pneumonia patients could receive ceftibuten 200 mg bid or cefaclor 500 mg tid, the randomization plan of studies C87-001, I87-107, I87-223, I87-233, I87-234, I87-236 and I87-325 differed from randomization plan of studies C88-044, I88-111, I88-217, I88-327 and I88-230. Results are summarized from the sponsor's "meta-analysis" presented in NDA volume 1.228.

The applicant's primary efficacy time point was EOT; however, the medical officer requested that analyses also be performed at the applicant's extended follow up visit (A_EXT), which was defined by the applicant as **7-14 days post treatment**. The medical officer considered A_EXT as the primary efficacy time point in this analysis.

When calculating clinical and bacteriological success rates at A_EXT, this reviewer carried through responses of "failure" or "persistence" at EOT. The applicant failed to do this.

Clinical Efficacy: According to the applicant, at EOT the ceftibuten minus cefaclor difference in clinical success rate was -3%, with the 95% confidence interval at $_{95,64}$ (-13%, 8%) $_{89\%,92\%}$ (p=0.566). At A_EXT the ceftibuten minus cefaclor difference in clinical success rate was -11%, with the 95% confidence interval at $_{56,43}$ (-29%, 8%) $_{73\%,84\%}$ (p=0.213).

Bacteriological Efficacy: According to the applicant, at EOT the ceftibuten minus cefaclor difference in bacteriological success rate was 8%, with the 95% confidence interval at $_{93,64}$ (-4%, 20%) $_{92\%,84\%}$ (p=0.109). At A_EXT the ceftibuten minus cefaclor difference in bacteriological success rate was 19%, with the 95% confidence interval at $_{23,16}$ (-17%, 56%) $_{57\%,38\%}$ (p=0.242).

Reviewer Conclusion: In the combined analysis of the applicant's pneumonia patients from studies C88-044, I88-111, I88-217, I88-327, C87-001, I87-107, I87-223, I87-233, I87-234, I87-236, I87-325 and I88-230, the lower 95% confidence bound of the ceftibuten minus cefaclor difference in clinical success rate at A_EXT exceeds -15%, and therefore does not demonstrate that ceftibuten 200 mg BID is comparable in efficacy to cefaclor 500 mg TID for the treatment of pneumonia. This combined analysis does not provide supportive evidence for the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute exacerbation of chronic bronchitis. Results from the secondary analysis of clinical success at EOT support this conclusion; however, results from the secondary analyses of bacteriological success at EOT and A_EXT demonstrate that the treatments are comparable in efficacy.

Notes: The medical officer included . In the applicant's clinical efficacy analyses, patients with neurogenic complications were excluded.

1. Study C87-069 (US population)

A total of 186 patients were enrolled across 8 US centers. Of these, 124 received ceftibuten and 62 received TMP-SMX. Total center enrollment ranged from 2 to 50. The MO classified 108 patients as complicated UTI (CUTI), 72 patients as uncomplicated UTI (UUTI) and 6 patients as "other" UTI. Five additional centers originally recruited for the study did not enroll patients.

Of the **CUTI patients**, 70 received ceftibuten and 38 received TMP-SMX. The treatment groups were significantly different with respect to distribution of gender ($p=0.001$), where TMP-SMX had a higher proportion of males. Total CUTI enrollment by center ranged from 2 to 34.

A total of 47 (67%) ceftibuten patients and 25 (66%) TMP-SMX patients were evaluable for efficacy. Total evaluable patients by center ranged from 1 to 18. Within center sample sizes were inadequate to formally assess the treatment by center interaction; therefore all centers were pooled for analysis.

The evaluable patient treatment groups were significantly different with respect to distribution of gender ($p=0.004$), where TMP-SMX had a higher proportion of males. Due to the gender imbalance among the treatment groups, the medical officer requested efficacy analyses by gender.

Bacteriological Efficacy: At DAY 5-9 the ceftibuten minus TMP-SMX difference in bacteriological success rate was -1%, with the 95% confidence interval at $_{47,25}$ (-20%, 18%) $_{87\%,88\%}$ ($p>0.999$). At WEEK 4-6 the ceftibuten minus cefaclor difference in bacteriological success rate was -22%, with the 95% confidence interval at $_{30,16}$ (-56%, 12%) $_{47\%,69\%}$ ($p=0.152$).

In **male** patients, the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -8%, with the 95% confidence interval at $_{23,21}$ (-35%, 20%) $_{78\%,86\%}$ ($p=0.701$). The ceftibuten minus cefaclor difference in bacteriological success rate at WEEK 4-6 was -20%, with the 95% confidence interval at $_{16,12}$ (-65%, 23%) $_{38\%,58\%}$ ($p=0.445$).

In **female** patients, the bacteriological success rate at DAY 5-9 was 96% (23/24) for ceftibuten and 100% (4/4) for TMP-SMX ($p>0.999$). The bacteriological success rate at WEEK 4-6 was 57% (8/14) for ceftibuten and 100% (4/4) for TMP-SMX ($p=0.245$). Sample sizes were inadequate to make a meaningful statistical comparisons of success rates via the confidence interval approach.

Among *E. coli* isolates, the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -9%, with the 95% confidence interval at $_{32,15}$ (-32%, 14%) $_{84\%,93\%}$ ($P=0.648$). At WEEK 4-6 the bacteriological success rate was 43% (10/23) for ceftibuten and 78% (7/9) for cefaclor ($P=0.122$). Sample sizes were inadequate to make a meaningful statistical comparison of success rate at WEEK 4-6 via the confidence interval approach.

According to the applicant, at DAY 5-9 the ceftibuten minus TMP-SMX difference in bacteriological success rate was -3%, with the 95% confidence interval at $_{69,31}$ (-15%, 11%) $_{91\%,94\%}$ ($p>0.999$). At WEEK 4-6 the ceftibuten minus cefaclor difference in bacteriological success rate was -14%, with the 95% confidence interval at $_{47,19}$ (-39%, 11%) $_{70\%,84\%}$ ($p=0.354$).

For *E. coli* isolates, the applicant's ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -1%, with the 95% confidence interval at $_{60,22}$ (-19%, 17%) $_{90\%,91\%}$ ($p>0.999$). The ceftibuten minus cefaclor difference in bacteriological success rate at WEEK 4-6 was -19%, with the 95% confidence interval at $_{35,13}$ (-39%, 12%) $_{66\%,85\%}$ ($p=0.292$).

Clinical Efficacy: At DAY 5-9 the ceftibuten minus TMP-SMX difference in clinical success rate was 0%, with the 95% confidence interval at $_{47,24}$ (-22%, 21%) $_{83\%,83\%}$ ($p>0.999$). At WEEK 4-6 the ceftibuten minus cefaclor difference in clinical success rate was -25%, with the 95% confidence interval at $_{32,16}$ (-57%, 7%) $_{50\%,75\%}$ ($p=0.098$)

In **male** patients, the ceftibuten minus TMP-SMX difference in clinical success rate at DAY 5-9 was -7%, with the 95% confidence interval at $_{23,20}$ (-34%, 21%) $_{78\%,86\%}$ ($p=0.704$). The ceftibuten minus cefaclor difference in clinical success rate at WEEK 4-6 was -27%, with the 95% confidence interval at $_{16,13}$ (-67%, 14%) $_{50\%,77\%}$ ($p=0.249$).

In **female** patients, the clinical success rate at DAY 5-9 was 88% (21/24) for ceftibuten and 75% (3/4) for TMP-SMX ($p=0.481$). The clinical success rate at WEEK 4-6 was 50% (8/16) for ceftibuten and 67% (2/3) for TMP-SMX ($p>0.999$). Sample sizes were inadequate to make meaningful statistical comparisons of success rates via the confidence interval approach.

According to the applicant, at DAY 5-9 the ceftibuten minus TMP-SMX difference in clinical success rate was -5%, with the 95% confidence interval at $_{63,28}$ (-13%, 3%) $_{95\%,100\%}$ ($p=0.550$). At WEEK 4-6 the ceftibuten minus cefaclor difference in clinical success rate was -26%, with the 95% confidence interval at $_{37,16}$ (-50%, -3%) $_{88\%,94\%}$, which demonstrates that ceftibuten is significantly inferior to TMP-SMX. However, the result of Fisher's exact test demonstrates that ceftibuten is only borderline inferior to TMP-SMX ($p=0.079$).

Reviewer Conclusions: **The lower 95% confidence bound of the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 exceeds -15%. Therefore, study C87-069 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to TMP-SMX 160/800 mg BID for the treatment of complicated urinary tract infections. Results from the secondary analyses of bacteriological efficacy at WEEK 4-6, clinical efficacy at DAY 5-9 and WEEK 4-6, the subset of *E. coli* isolates, and the subset of male patients support this conclusion. Furthermore, the results from the analysis of the applicant's data fail to support the efficacy claims.**

2. Study I87-326

A total of 210 patients were enrolled across 14 international centers located in either the United Kingdom, Canada, Australia, South Africa, Belgium, or the Netherlands. Of these, 141 received ceftibuten and 69 received TMP-SMX. Total center enrollment ranged from 1

to 37. The MO classified 170 patients as CUTI and 69 patients as UUTI. Ten additional centers originally recruited for the study did not enroll patients.

Of the **CUTI patients**, 110 received ceftibuten and 60 received TMP-SMX. Twelve centers enrolled CUTI patients. Total CUTI enrollment by center ranged from 1 to 34.

A total of 60 (55%) ceftibuten patients and 39 (65%) TMP-SMX patients were evaluable for efficacy. Although small sample sizes precluded formal statistical testing, there were large differences among the centers in the percentage of evaluable patients, which ranged from 0% to 100%. Eleven centers had evaluable patients, with the total evaluable patients by center ranging from 1 to 32. In center I87-326-19, the proportion of evaluable patients between treatments was significantly different ($p=0.015$), where ceftibuten had a higher proportion of evaluable patients than TMP-SMX. Within center sample sizes were inadequate to formally assess the treatment by center interaction; therefore all centers were pooled for analysis.

Bacteriological Efficacy: At DAY 5-9 the ceftibuten minus TMP-SMX difference in bacteriological success rate was -6%, with the 95% confidence interval at $_{60,39}$ (-25%, 13%) $_{73\%,79\%}$ ($p=0.485$). At WEEK 4-6 the ceftibuten minus cefaclor difference in bacteriological success rate was 7%, with the 95% confidence interval at $_{55,30}$ (-18%, 31%) $_{80\%,53\%}$ ($p=0.552$).

Among *E. coli* isolates, the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -10%, with the 95% confidence interval at $_{45,28}$ (-31%, 11%) $_{76\%,86\%}$ ($p=0.296$). At WEEK 4-6, the ceftibuten minus TMP-SMX difference in bacteriological success rate was 0%, with the 95% confidence interval at $_{44,22}$ (-28%, 28%) $_{64\%,64\%}$ ($p>0.999$).

Among pyelonephritis patients, the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -4%, with the 95% confidence interval at $_{21,10}$ (-36%, 27%) $_{86\%,90\%}$ ($p>0.999$). At WEEK 4-6, the bacteriological success rate was 75% (15/20) for ceftibuten, and 89% (8/9) for TMP-SMX ($p=0.633$). Sample sizes were inadequate to make a meaningful statistical comparison of success rate at WEEK 4-6 via the confidence interval approach.

The applicant did not present bacteriological results by individual international study.

Clinical Efficacy: At DAY 5-9 the ceftibuten minus TMP-SMX difference in clinical success rate was -4%, with the 95% confidence interval at $_{57,39}$ (-23%, 15%) $_{75\%,79\%}$ ($p=0.643$). At WEEK 4-6 the ceftibuten minus TMP-SMX difference in clinical success rate was -1%, with the 95% confidence interval at $_{47,26}$ (-27%, 26%) $_{57\%,58\%}$ ($p>0.999$).

Among pyelonephritis patients, the ceftibuten minus TMP-SMX difference in clinical success rate at DAY 5-9 was -24%, with the 95% confidence interval at $_{21,10}$ (-49%, 2%) $_{78\%,100\%}$ ($p=0.147$). At WEEK 4-6, the clinical success rate was 72% (13/18) for ceftibuten, and 86% (6/7) for TMP-SMX ($p=0.637$). Sample sizes were

inadequate to make a meaningful statistical comparison of success rate at WEEK 4-6 via the confidence interval approach.

The applicant did not present clinical results by individual international study.

Reviewer Conclusions: **The lower 95% confidence bound of the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 exceeds -20%; therefore, study I87-326 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to TMP-SMX 160/800 mg BID for the treatment of complicated urinary tract infections. Results from the secondary analyses of clinical efficacy at DAY 5-9 and WEEK 4-6, the subset of *E. coli* isolates and the subset of pyelonephritis patients support this conclusion. However, the secondary analysis of bacteriological efficacy at WEEK 4-6 demonstrated that the treatments are comparable in efficacy.**

3. Study I87-247

A total of 19 patients were enrolled in one center located in Finland. Of these, 13 received ceftibuten and 6 received TMP-SMX. The MO classified 1 patient as CUTI and 18 patients as UUTI. Three additional centers originally recruited for the study did not enroll patients.

The CUTI patient received TMP-SMX. This patient was not evaluable.

Reviewer Conclusions: **Study I87-247 did not have any evaluable CUTI patients; therefore it fails to provide statistical evidence in support of the applicant's complicated UTI claims.**

4. Combined Analysis of Studies I87-326 and I87-247 (International population)

Since I87-247 did not have any evaluable CUTI patients, the results from the combined analysis of studies I87-326 and I87-247 are equal to the results of study I87-326 alone.

However, the applicant presented results from the combined studies as follows:

Bacteriological Efficacy: At DAY 5-9 the ceftibuten minus TMP-SMX difference in bacteriological success rate was -6%, with the 95% confidence interval at $_{50,25}$ (-29%, 17%) $_{74\%,80\%}$ ($p=0.775$). At WEEK 4-6 the ceftibuten minus cefaclor difference in bacteriological success rate was 0%, with the 95% confidence interval at $_{45,20}$ (-29%, 29%) $_{60\%,60\%}$ ($p>0.999$).

Among *E. coli* isolates, the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -5%, with the 95% confidence interval at $_{36,19}$ (-33%, 24%) $_{69\%,74\%}$ ($p=0.742$). At WEEK 4-6, the ceftibuten minus cefaclor difference in bacteriological success rate was 2%, with the 95% confidence interval at $_{36,17}$ (-30%, 34%) $_{67\%,65\%}$ ($p=0.888$).

Among pyelonephritis patients, the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -33%, with the 95% confidence interval at $_{24,11}$ (-59%, -8%) $_{87\%,100\%}$ ($p=0.037$), which demonstrates that ceftibuten is inferior to TMP-SMX. At WEEK 4-6, the bacteriological success rate was 63% (15/24) for ceftibuten and 100% (9/9) for TMP-SMX ($p=0.039$). Sample sizes were inadequate to make a meaningful statistical comparison of success rate at WEEK 4-6 via the confidence interval approach.

Clinical Efficacy: At DAY 5-9 the ceftibuten minus TMP-SMX difference in clinical success rate was 0%, with the 95% confidence interval at $_{41,20}$ (-15%, 15%) $_{95\%,95\%}$ ($p>0.999$). At WEEK 4-6 the ceftibuten minus cefaclor difference in clinical success rate was -4%, with the 95% confidence interval at $_{31,16}$ (-29%, 22%) $_{84\%,88\%}$ ($p>0.999$).

Among pyelonephritis patients, the ceftibuten minus TMP-SMX difference in clinical success rate at DAY 5-9 was -8%, with the 95% confidence interval at $_{24,10}$ (-26%, 10%) $_{92\%,100\%}$ ($p>0.999$). At WEEK 4-6, the ceftibuten minus TMP-SMX difference in clinical success rate at DAY 5-9 was -2%, with the 95% confidence interval at $_{16,10}$ (-35%, 30%) $_{88\%,90\%}$ ($p>0.999$).

Reviewer Conclusion: **In the applicant's subset of evaluable patients, the lower 95% confidence bound of the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 exceeds -20%; therefore, the applicant's combined analysis of studies I87-326 and I87-247 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to TMP-SMX 160/800 mg BID for the treatment of complicated urinary tract infections. Results from the secondary analyses of bacteriological efficacy at WEEK 4-6, clinical efficacy at DAY 5-9 and WEEK 4-6, the subset of *E. coli* isolates, and the subset of pyelonephritis patients support this conclusion. Among pyelonephritis patients, ceftibuten was significantly inferior to TMP-SMX with respect to bacteriological efficacy at DAY 5-9 and WEEK 4-6.**

For results in the medical officer's evaluable patients, see study I87-326.

5. Combined Analysis of Studies C87-069, I87-326 and I87-247

By request of the applicant and the medical officer (see section IIC), a combined analysis of the US and international studies was performed.

Across the US and international studies, 278 ceftibuten patients and 137 cefaclor patients were enrolled. The MO classified 279 patients as CUTI, 130 patients as UUTI and 6 patients as "other" UTI.

Of all enrolled **CUTI patients**, 180 received ceftibuten and 99 received TMP-SMX. The treatment groups were significantly different with respect to distribution of gender ($p=0.002$), where TMP-SMX had a higher proportion of males.

A total of 108 patients were from the US study and 171 patients were from the international studies. The location groups were significantly different with respect to gender, inpatient/outpatient status, race, age, height, weight and treatment duration ($p \leq 0.001$ for all tests). Compared to the US patients, the international patients had a higher percentage of females, inpatients and caucasians, a lower mean age, height and weight, and a longer mean treatment duration.

A total of 107 (59%) ceftibuten patients and 64 (65%) TMP-SMX patients were evaluable for efficacy. The evaluable patient treatment groups were significantly different with respect to distribution of gender ($p = 0.004$), where TMP-SMX had a higher proportion of males. Due to the gender imbalance among the treatment groups, the medical officer requested efficacy analyses by gender.

A total of 72 (67%) US patients and 99 (58%) international patients were evaluable for efficacy. The location groups were significantly different with respect to gender, inpatient/outpatient status, race, age, height, weight and treatment duration ($p \leq 0.020$ for all tests). However, since the international group probably had greater disease severity (due to the higher percentage of inpatients), the medical officer felt it was reasonable to combine the US and international populations. The results of DerSimonian and Laird's "meta-analysis" and the logistic regression models of bacteriological and clinical response at DAY 5-9 did not demonstrate a significant treatment by location interaction; therefore, the location groups were combined for analysis.

Bacteriological Efficacy: At DAY 5-9 the ceftibuten minus TMP-SMX difference in bacteriological success rate was -4%, with the 95% confidence interval at $_{107,64}$ (-17%, 10%) $_{79\%,83\%}$ ($p = 0.589$). At WEEK 4-6 the ceftibuten minus cefaclor difference in bacteriological success rate was -4%, with the 95% confidence interval at $_{85,48}$ (-23%, 16%) $_{55\%,59\%}$ ($p = 0.708$). The location weighted estimates of treatment effect at were similar to the unweighted estimates.

In **male** patients, the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -12%, with the 95% confidence interval at $_{44,41}$ (-33%, 8%) $_{68\%,80\%}$ ($p = 0.196$). The ceftibuten minus cefaclor difference in bacteriological success rate at WEEK 4-6 was -4%, with the 95% confidence interval at $_{37,30}$ (-30%, 24%) $_{43\%,47\%}$ ($p = 0.779$).

In **female** patients, the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was 0%, with the 95% confidence interval at $_{63,23}$ (-19%, 19%) $_{87\%,87\%}$ ($p > 0.999$). The ceftibuten minus cefaclor difference in bacteriological success rate at WEEK 4-6 was -16%, with the 95% confidence interval at $_{48,16}$ (-44%, 11%) $_{65\%,81\%}$ ($p = 0.213$).

Among *E. coli* isolates the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -9%, with the 95% confidence interval at $_{77,43}$ (-24%, 6%) $_{79\%,88\%}$ ($p = 0.206$). At WEEK 4-6, the ceftibuten minus cefaclor difference in bacteriological success rate was -11%, with the 95% confidence interval at $_{67,31}$ (-34%, 12%) $_{57\%,68\%}$ ($p = 0.300$).

Among pyelonephritis patients the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -3%, with the 95% confidence interval at $_{24,11}$ (-32%, 25%) $_{88\%,81\%}$ ($p>0.999$). At WEEK 4-6, the ceftibuten minus TMP-SMX difference in bacteriological success rate was -17%, with the 95% confidence interval at $_{22,10}$ (-51%, 16%) $_{73\%,90\%}$ ($p=0.387$).

According to the applicant, the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -4%, with the 95% confidence interval at $_{119,56}$ (-16%, 9%) $_{84\%,88\%}$ ($p=0.548$). At WEEK 4-6 the ceftibuten minus cefaclor difference in bacteriological success rate was -7%, with the 95% confidence interval at $_{92,39}$ (-26%, 12%) $_{65\%,72\%}$ ($p=0.464$).

In *E. coli* isolates the applicant's ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -2%, with the 95% confidence interval at $_{86,41}$ (-17%, 14%) $_{81\%,83\%}$ ($p=0.834$). The ceftibuten minus cefaclor difference in bacteriological success rate at WEEK 4-6 was -7%, with the 95% confidence interval at $_{71,30}$ (-29%, 15%) $_{66\%,73\%}$ ($p=0.481$).

In pyelonephritis patients, the applicant's ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 was -33%, with the 95% confidence interval at $_{27,12}$ (-57%, -10%) $_{67\%,100\%}$ ($p=0.036$), which demonstrates that ceftibuten is inferior to TMP-SMX. The ceftibuten minus cefaclor difference in bacteriological success rate at WEEK 4-6 was -42%, with the 95% confidence interval at $_{26,10}$ (-68%, -16%) $_{58\%,100\%}$ ($p=0.016$), which also demonstrates that ceftibuten is inferior to TMP-SMX .

Clinical Efficacy: At DAY 5-9 the ceftibuten minus TMP-SMX difference in clinical success rate was -2%, with the 95% confidence interval at $_{104,63}$ (-16%, 12%) $_{79\%,81\%}$ ($p=0.743$). At WEEK 4-6 the ceftibuten minus cefaclor difference in clinical success rate was -10%, with the 95% confidence interval at $_{79,42}$ (-30%, 10%) $_{54\%,64\%}$ ($p=0.296$). The location weighted estimates of treatment effect at DAY 5-9 and WEEK 4-6 were similar to the unweighted estimates.

In **male** patients, the ceftibuten minus TMP-SMX difference in clinical success rate at DAY 5-9 was -3%, with the 95% confidence interval at $_{44,40}$ (-23%, 17%) $_{77\%,80\%}$ ($p=0.761$). The ceftibuten minus cefaclor difference in clinical success rate at WEEK 4-6 was -10%, with the 95% confidence interval at $_{34,29}$ (-37%, 18%) $_{56\%,66\%}$ ($p=0.454$).

In **female** patients, the ceftibuten minus TMP-SMX difference in clinical success rate at DAY 5-9 was -3%, with the 95% confidence interval at $_{60,23}$ (-24%, 19%) $_{80\%,83\%}$ ($p>0.999$). The ceftibuten minus cefaclor difference in clinical success rate at WEEK 4-6 was -9%, with the 95% confidence interval at $_{45,13}$ (-43%, 27%) $_{53\%,62\%}$ ($p=0.600$).

Among pyelonephritis patients, the ceftibuten minus TMP-SMX difference in clinical success rate at DAY 5-9 was -21%, with the 95% confidence interval at $_{24,11}$ (-44%, 2%) $_{79\%,100\%}$ ($p=0.157$). At WEEK 4-6, the clinical success rate was 74% (14/19) for ceftibuten and 88% (7/8) for cefaclor ($p=0.633$). Sample sizes were

inadequate to make a meaningful statistical comparison of clinical success rate at WEEK 4-6 via the confidence interval approach.

According to the applicant, the ceftibuten minus TMP-SMX difference in clinical success rate at DAY 5-9 was -3%, with the 95% confidence interval at $_{104,48}$ (-10%, 5%) $_{95\%,98\%}$ (p=0.665). At WEEK 4-6, the ceftibuten minus cefaclor difference in clinical success rate was -14%, with the 95% confidence interval at $_{66,32}$ (-30%, 3%) $_{77\%,91\%}$ (p=0.109).

In pyelonephritis patients, the applicant's ceftibuten minus TMP-SMX difference in clinical success rate at DAY 5-9 was -11%, with the 95% confidence interval at $_{27,11}$ (-29%, 7%) $_{89\%,100\%}$ (p=0.542). At WEEK 4-6, the ceftibuten minus cefaclor difference in clinical success rate was -11%, with the 95% confidence interval at $_{15,11}$ (-45%, 23%) $_{80\%,91\%}$ (p=0.614).

Reviewer Conclusions: **The lower 95% confidence bound of the ceftibuten minus TMP-SMX difference in bacteriological success rate at DAY 5-9 exceeds -15%. Therefore, the combined analysis of studies C87-069, I87-326, and I87-247 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to TMP-SMX 160/800 mg BID for the treatment of complicated urinary tract infections. Results from the secondary analyses of bacteriological efficacy at WEEK 4-6, clinical efficacy at DAY 5-9 and WEEK 4-6, the subset of *E. coli* isolates, the gender subsets and the subset of pyelonephritis patients support this conclusion. With the exception of clinical success at DAY 5-9, the results from the analyses of the applicant's data fails to provide statistical evidence in support of the efficacy claims.**

6. Study I87-128

A total of 113 patients were enrolled across 4 international centers located in either Mexico, Argentina, Venezuela, or Italy. Of these, 75 received ceftibuten and 38 received norfloxacin. Total center enrollment ranged from 17 to 42. The MO classified 85 patients as CUTI and 28 patients as UUTI.

Of the CUTI patients, 58 received ceftibuten and 27 received norfloxacin. Total enrollment by center ranged from 6 to 42. A total of 49 (84%) ceftibuten patients and 27 (100%) norfloxacin patients were evaluable for efficacy. The total number of evaluable patients by center ranged from 5 to 40. Within center sample sizes were inadequate to formally assess the treatment by center interaction; therefore, all centers were pooled for analysis.

Bacteriological Efficacy: At DAY 5-9 the ceftibuten minus norfloxacin difference in bacteriological success rate was -10, with the 95% confidence interval at $_{49,27}$ (-32%, 12%) $_{71\%,81\%}$ (p=0.333). At WEEK 4-6 the ceftibuten minus cefaclor difference in bacteriological success rate was -14%, with the 95% confidence interval at $_{46,26}$ (-38%, 11%) $_{63\%,77\%}$ (p=0.225).

Among *E. coli* isolates, the ceftibuten minus norfloxacin difference in bacteriological success rate at DAY 5-9 was -16%, with the 95% confidence interval at $_{27,14}$ (-46%, 15%) $_{70\%,86\%}$ (p=0.447). At WEEK 4-6, the ceftibuten minus norfloxacin difference in bacteriological success rate was -26%, with the 95% confidence interval at $_{25,14}$ (-58%, 6%) $_{60\%,86\%}$ (p=0.151).

Among pyelonephritis patients, the ceftibuten minus norfloxacin difference in bacteriological success rate at DAY 5-9 was -3%, with the 95% confidence interval at $_{15,10}$ (-49%, 42%) $_{67\%,70\%}$ (p>0.999). At WEEK 4-6, the bacteriological success rate was 62% (8/13) for ceftibuten, and 67% (6/9) for norfloxacin (p>0.999). Sample sizes were inadequate to make a meaningful statistical comparison of success rate at WEEK 4-6 via the confidence interval approach.

The applicant did not present efficacy results by individual norfloxacin study.

Clinical Efficacy: At DAY 5-9 the ceftibuten minus norfloxacin difference in clinical success rate was -11%, with the 95% confidence interval at $_{49,27}$ (-29, 7%) $_{82\%,93\%}$ (p=0.309). At WEEK 4-6 the ceftibuten minus norfloxacin difference in clinical success rate was -19%, with the 95% confidence interval at $_{41,21}$ (-42%, 3%) $_{71\%,90\%}$ (p=0.111).

Among pyelonephritis patients, the ceftibuten minus norfloxacin difference in clinical success rate at DAY 5-9 was -7%, with the 95% confidence interval at $_{15,10}$ (-28%, 14%) $_{93\%,100\%}$ (p>0.999). At WEEK 4-6, the clinical success rate was 92% (12/13) for ceftibuten, and 100% (9/9) for norfloxacin (p>0.999). Sample sizes were inadequate to make a meaningful statistical comparison of success rate at WEEK 4-6 via the confidence interval approach.

The applicant did not present efficacy results by individual norfloxacin study.

Reviewer Conclusions: The lower 95% confidence bound of the ceftibuten minus norfloxacin difference in bacteriological success rate at DAY 5-9 exceeds -15%; therefore, study I87-128 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to norfloxacin 400 mg BID for the treatment of complicated urinary tract infections. Results from the secondary analyses of bacteriological efficacy at WEEK 4-6, clinical efficacy at DAY 5-9 and WEEK 4-6, the subset of *E. coli* isolates and the subset of pyelonephritis patients support this conclusion.

7. Study I89-054

This study was ongoing at the time the NDA was submitted. The results presented below reflect data collected as of August 19, 1991. According to the medical officer, no additional data from this study will be submitted by the applicant.

A total of 37 patients were enrolled across 6 centers located in France. Of these, 25 received ceftibuten and 12 received norfloxacin. Total center enrollment ranged from 3 to

11. The MO classified 32 patients as CUTI, 4 patients as UUTI, and 1 patient as "other" UTI.

Of the **CUTI patients**, 20 received ceftibuten and 12 received norfloxacin. Total enrollment by center ranged from 3 to 10. The treatment groups were significantly different with respect to mean age and mean weight ($p \leq 0.018$ for both tests), where ceftibuten had older and heavier patients than norfloxacin.

A total of 16 (80%) ceftibuten patients and 8 (67%) norfloxacin patients were evaluable for efficacy. Five centers had evaluable patients, with the total number of evaluable patients by center ranging from 1 to 9. The treatment groups were significantly different with respect to mean age ($p = 0.035$), where ceftibuten had older patients than norfloxacin. The number of evaluable patients was inadequate to make statistical comparisons of bacteriological and clinical success rates.

The applicant did not present efficacy results by individual norfloxacin study.

Reviewer Conclusions: **The number of evaluable patients was inadequate to evaluate efficacy; therefore study I89-054 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to norfloxacin 400 mg BID for the treatment of complicated urinary tract infections.**

8. Study I87-232

This study was ongoing at the time the NDA was submitted. The results presented below reflect data collected as of August 19, 1991. According to the medical officer, no additional data from this study will be submitted by the applicant.

A total of 67 patients were enrolled across 4 centers located in either France or Germany. Of these, 47 received ceftibuten and 20 received ofloxacin. Total center enrollment ranged from 6 to 30. The MO classified 63 patients as CUTI and 4 patients as UUTI. One additional center originally recruited for the study had not enrolled patients at the time of the study report.

Of the **CUTI patients**, 44 received ceftibuten and 19 received ofloxacin. Total enrollment by center ranged from 6 to 29. A total of 11 (25%) ceftibuten patients and 9 (47%) ofloxacin patients were evaluable for efficacy. The total number of evaluable patients by center ranged from 2 to 8. The number of evaluable patients was inadequate to make statistical comparisons of bacteriological or clinical success rates.

According to the applicant, only 4 ceftibuten patients and 5 ofloxacin patients were evaluable for efficacy. This is an inadequate number of patients to make a statistical evaluation of efficacy.

Reviewer Conclusions: **The number of evaluable patients was inadequate to statistically evaluate efficacy; therefore study I87-232 fails to provide statistical evidence in support of**

the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to ofloxacin 200 mg BID for the treatment of complicated urinary tract infections.

9. Combined Analysis of Norfloxacin Comparator Studies: I87-128 and I89-054

Since study I87-128 is underpowered to establish efficacy equivalence, and study I89-054 lacks sufficient sample size to provide adequate estimates of the treatment effect, a combined analysis was performed in order to obtain more conclusive results. Across the two studies, 100 ceftibuten patients and 50 cefaclor patients were enrolled. The MO classified 117 patients as CUTI, 32 patients as UUTI and 1 patient as "other" UTI.

Of all enrolled **CUTI patients**, 78 received ceftibuten and 39 received norfloxacin. A total of 65 (83%) ceftibuten patients and 35 (90%) norfloxacin patients were evaluable for efficacy.

A total of 85 patients were from study I87-128 and 32 patients were from study I89-054. The study groups were significantly different with respect to age, weight and treatment duration ($p \leq 0.040$ for all tests), where study I87-128 had a higher mean age and weight, and a shorter mean treatment duration than study I89-054.

A total of 76 (89%) from study I87-128 and 24 (75%) patients from study I89-054 were evaluable for efficacy. The study groups were significantly different with respect to treatment duration ($p = 0.012$); however, the medical officer felt it was reasonable to combine across studies.

The results of DerSimonian and Laird's "meta-analysis" and the logistic regression models of bacteriological and clinical response at DAY 5-9 demonstrated a potential study by treatment interaction for bacteriological response. However, the interaction was due to a difference in magnitude, rather than direction of the treatment effect; therefore, the studies were combined for analysis.

Bacteriological Efficacy: At DAY 5-9 the ceftibuten minus norfloxacin difference in bacteriological success rate was -14%, with the 95% confidence interval at $_{85,34}$ (-33%, 4%) $_{71\%,95\%}$ ($p = 0.109$). At WEEK 4-6 the ceftibuten minus norfloxacin difference in bacteriological success rate was -16%, with the 95% confidence interval at $_{60,33}$ (-37%, 6%) $_{60\%,76\%}$ ($p = 0.126$). The study weighted estimates of treatment effect at DAY 5-9 and WEEK 4-6 were similar to the unweighted estimates.

Among *E. coli* isolates, the ceftibuten minus norfloxacin difference in bacteriological success rate at DAY 5-9 was -20%, with the 95% confidence interval at $_{43,21}$ (-43%, 1%) $_{70\%,90\%}$ ($p = 0.144$). At WEEK 4-6 the ceftibuten minus norfloxacin difference in bacteriological success rate was -25%, with the 95% confidence interval at $_{39,21}$ (-51%, 2%) $_{66\%,81\%}$ ($p = 0.057$).

Among pyelonephritis patients, the ceftibuten minus norfloxacin difference in bacteriological success rate at DAY 5-9 was -12%, with the 95% confidence interval at

$_{29,18}$ (-43%, 18%) $_{69\%,91\%}$ (p=0.491). At WEEK 4-6 the ceftibuten minus norfloxacin difference in bacteriological success rate was -11%, with the 95% confidence interval at $_{26,15}$ (-47%, 25%) $_{58\%,87\%}$ (p=0.505).

According to the applicant, the ceftibuten minus norfloxacin difference in bacteriological success rate at DAY 5-9 was -6%, with the 95% confidence interval at $_{56,33}$ (-21%, 8%) $_{88\%,94\%}$ (p=0.475). At WEEK 4-6 the ceftibuten minus norfloxacin difference in bacteriological success rate was -16%, with the 95% confidence interval at $_{53,31}$ (-35%, 2%) $_{74\%,90\%}$ (p=0.065).

In *E. coli* isolates, the applicant's ceftibuten minus norfloxacin difference in bacteriological success rate at DAY 5-9 was -9%, with the 95% confidence interval at $_{39,22}$ (-29%, 12%) $_{92\%,91\%}$ (p=0.467). *The ceftibuten minus norfloxacin difference* in bacteriological success rate at WEEK 4-6 was -26%, with the 95% confidence interval at $_{36,20}$ (-50%, -2%) $_{64\%,90\%}$ (p=0.034), which demonstrates that ceftibuten is inferior to norfloxacin.

In pyelonephritis patients, the applicant's ceftibuten minus norfloxacin difference in bacteriological success rate at DAY 5-9 was 3%, with the 95% confidence interval at $_{29,13}$ (-16%, 9%) $_{97\%,100\%}$ (p>0.999). The ceftibuten minus norfloxacin difference in bacteriological success rate at WEEK 4-6 was -11%, with the 95% confidence interval at $_{27,11}$ (-29%, 7%) $_{89\%,100\%}$ (p=0.542).

Clinical Efficacy: At DAY 5-9 the ceftibuten minus norfloxacin difference in clinical success rate was -11%, with the 95% confidence interval at $_{65,34}$ (-25%, 3%) $_{83\%,94\%}$ (p=0.209). At WEEK 4-6 the ceftibuten minus norfloxacin difference in clinical success rate was -19%, with the 95% confidence interval at $_{54,28}$ (-38%, 1%) $_{70\%,89\%}$ (p=0.054). The study weighted estimates of treatment effect at DAY 5-9 and WEEK 4-6 were similar to the unweighted estimates.

Among pyelonephritis patients, the ceftibuten minus norfloxacin difference in clinical success rate at DAY 5-9 was -10%, with the 95% confidence interval at $_{29,18}$ (-26%, 6%) $_{90\%,100\%}$ (p=0.542). At WEEK 4-6, the ceftibuten minus norfloxacin difference in clinical success rate was -14%, with the 95% confidence interval at $_{24,15}$ (-40%, 12%) $_{79\%,93\%}$ (p=0.376).

According to the applicant, the clinical success rate at DAY 5-9 was 100% (49/49) for ceftibuten and 100% (29/29) for norfloxacin. At WEEK 4-6, the ceftibuten minus norfloxacin difference in clinical success rate was -20%, with the 95% confidence interval at $_{44,25}$ (-36%, -5%) $_{80\%,100\%}$ (p=0.021), which demonstrates that ceftibuten is inferior to norfloxacin.

In pyelonephritis patients, the applicant's clinical success rate at DAY 5-9 was 100% (26/26) for ceftibuten and 100% (12/12) for norfloxacin. At WEEK 4-6, the ceftibuten minus norfloxacin difference in clinical success rate was -4%, with the 95% confidence interval at $_{24,12}$ (-18%, 10%) $_{96\%,100\%}$ (p>0.999).

Reviewer Conclusions: The lower 95% confidence bound of the ceftibuten minus norfloxacin difference in bacteriological success rate at DAY 5-9 exceeds -15%; therefore, the combined analysis of studies I87-128 and I89-054 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to norfloxacin 400 mg BID for the treatment of complicated urinary tract infections. Results from the secondary analyses of bacteriological efficacy at WEEK 4-6, clinical efficacy at DAY 5-9 and WEEK 4-6, the subset of *E. coli* isolates and the subset of pyelonephritis patients support this conclusion. With the exception of clinical success at DAY 5-9, the results from the analyses of the applicant's data fail to provide statistical evidence in support of the efficacy claims.

10. Combined Analysis of Quinolone Comparator Studies: I87-128, I89-054, and I87-232

By request of the applicant and medical officer (see section IIC), a combined analysis of the studies I87-128, I89-054, and I87-232 was performed. In this analysis, patients who received norfloxacin or ofloxacin were considered as a single quinolone treatment group.

Across the three studies, 147 ceftibuten patients and 70 quinolone patients were enrolled. The MO classified 180 patients as CUTI, 36 patients as UUTI and 1 patient as "other" UTI.

Of all enrolled CUTI patients, 122 received ceftibuten and 58 received quinolone. A total of 76 (62%) ceftibuten and 44 (76%) quinolone patients were evaluable for efficacy.

A total of 117 patients were from the norfloxacin comparator studies and 63 patients were from the ofloxacin comparator study. The study groups were significantly different with respect to gender, age, weight and treatment duration ($p \leq 0.001$ for all tests), where the norfloxacin studies had a lower percentage of males, a lower mean age and weight, and a longer mean treatment duration than the ofloxacin study.

A total of 100 (85%) patients from the norfloxacin studies and 20 (32%) patients were from the ofloxacin study were evaluable for efficacy. The evaluable study groups were significantly different with respect to age, weight and treatment duration ($p \leq 0.033$ for all tests); however, the medical officer felt it was reasonable to combine across studies.

The results of DerSimonian and Laird's "meta-analysis" and the logistic regression models of bacteriological and clinical response at DAY 5-9 did not demonstrate a potential treatment by study interaction; therefore, the studies were combined for analysis.

Bacteriological Efficacy: At DAY 5-9 the ceftibuten minus quinolone difference in bacteriological success rate was -17%, with the 95% confidence interval at $_{76,43}$ (-34%, 0.5%) $_{87\%,84\%}$ ($p = 0.050$), which demonstrates that ceftibuten is borderline significantly inferior to quinolone. At WEEK 4-6 the ceftibuten minus quinolone difference in bacteriological success rate was -14%, with the 95% confidence interval at $_{70,38}$ (-34%, 7%) $_{87\%,71\%}$ ($p = 0.155$). The study weighted estimates of treatment effect at DAY 5-9 and WEEK 4-6 were equal to the unweighted estimates.

Among *E. coli* isolates, the ceftibuten minus quinolone difference in bacteriological success rate at DAY 5-9 was -24%, with the 95% confidence interval at $_{62,27}$ (-44%, -3%) $_{85\%,89\%}$ (p=0.025), which demonstrates that ceftibuten is significantly inferior to quinolone. At WEEK 4-6, the ceftibuten minus quinolone difference in bacteriological success rate was -26%, with the 95% confidence interval at $_{47,24}$ (-51%, -1%) $_{53\%,78\%}$ (p=0.033), which demonstrates that ceftibuten is significantly inferior to quinolone.

Among pyelonephritis patients, the ceftibuten minus quinolone difference in bacteriological success rate at DAY 5-9 was -15%, with the 95% confidence interval at $_{32,16}$ (-46%, 14%) $_{66\%,81\%}$ (p=0.328). At WEEK 4-6, the ceftibuten minus quinolone difference in bacteriological success rate was -13%, with the 95% confidence interval at $_{28,15}$ (-48%, 22%) $_{54\%,87\%}$ (p=0.407).

According to the applicant, the ceftibuten minus quinolone difference in bacteriological success rate at DAY 5-9 was -5%, with the 95% confidence interval at $_{60,38}$ (-20%, 9%) $_{87\%,92\%}$ (p=0.521). At WEEK 4-6, the ceftibuten minus quinolone difference in bacteriological success rate was -13%, with the 95% confidence interval at $_{54,33}$ (-32%, 7%) $_{72\%,85\%}$ (p=0.174).

For *E. coli* isolates, the applicant's ceftibuten minus quinolone difference in bacteriological success rate at DAY 5-9 was -12%, with the 95% confidence interval at $_{41,24}$ (-31%, 9%) $_{80\%,92\%}$ (p=0.301). The ceftibuten minus quinolone difference in bacteriological success rate at WEEK 4-6 was -28%, with the 95% confidence interval at $_{37,20}$ (-52%, -4%) $_{62\%,90\%}$ (p=0.026), which demonstrates that ceftibuten is significantly inferior to quinolone.

For pyelonephritis patients, the applicant's ceftibuten minus quinolone difference in bacteriological success rate at DAY 5-9 was -6%, with the 95% confidence interval at $_{31,13}$ (-21%, 8%) $_{94\%,100\%}$ (p>0.999). The ceftibuten minus quinolone difference in bacteriological success rate at WEEK 4-6 was -14%, with the 95% confidence interval at $_{28,11}$ (-34%, 5%) $_{86\%,100\%}$ (p=0.309).

<u>Clinical Efficacy</u>: At DAY 5-9 the ceftibuten minus quinolone difference in clinical success rate was -7%, with the 95% confidence interval at $_{78,43}$ (-23%, 9%) $_{79\%,86\%}$ (p=0.338). At WEEK 4-6 the ceftibuten minus quinolone difference in clinical success rate was -14%, with the 95% confidence interval at $_{60,35}$ (-35%, 7%) $_{63\%,77\%}$ (p=0.162).

The study weighted estimate of treatment effect at DAY 5-9 was -10%, with standard error of 6%, and 95% confidence interval of (-22%, 1%). At WEEK 4-6, the study weighted estimate of treatment effect was -21%, with standard error of 8%, and 95% confidence interval of (-36%, -6%). Note that these intervals do not incorporate a continuity correction.

Among pyelonephritis patients, the ceftibuten minus quinolone difference in clinical success rate at DAY 5-9 was -16%, with the 95% confidence interval at $_{32,16}$ (-33%, 2%) $_{84\%,100\%}$ (p=0.154). At WEEK 4-6, the ceftibuten minus quinolone difference in clinical success rate was -20%, with the 95% confidence interval at

$_{26,15}$ (-47%, 6%) $_{73\%,93\%}$ (p=0.220).

According to the applicant, the ceftibuten minus quinolone difference in clinical success rate at DAY 5-9 was 3%, with the 95% confidence interval at $_{63,34}$ (-5%, 11%) $_{100\%,97\%}$ (p=0.391). At WEEK 4-6, the ceftibuten minus quinolone difference in clinical success rate was -13%, with the 95% confidence interval at $_{45,27}$ (-31%, 6%) $_{80\%,93\%}$ (p=0.191).

In pyelonephritis patients, the applicant's clinical success rate at DAY 5-9 was 100% (28/28) for ceftibuten and 100% (12/12) for quinolones. At WEEK 4-6, the ceftibuten minus quinolone difference in clinical success rate was -4%, with the 95% confidence interval at $_{24,12}$ (-18%, 10%) $_{96\%,100\%}$ (p>0.999).

Reviewer Conclusions: **The lower 95% confidence bound of the ceftibuten minus quinolone difference in bacteriological success rate at DAY 5-9 exceeds -15%; therefore, the combined analysis of studies I87-128, I89-054, and I87-232 fails to provide statistical evidence in support of the applicant's claim that ceftibuten 400 mg QD is comparable in efficacy to norfloxacin 400 mg BID and ofloxacin 200 mg BID for the treatment of complicated urinary tract infections. Moreover, ceftibuten was borderline inferior to quinolone with respect to bacteriological efficacy at DAY 5-9. Results from the secondary analyses of bacteriological efficacy at WEEK 4-6, clinical efficacy at DAY 5-9 and WEEK 4-6, the subset of *E. coli* isolates and the subset of pyelonephritis patients support this conclusion. The analysis of *E. coli* isolates demonstrated that ceftibuten is significantly inferior to quinolone with respect to bacteriological efficacy at DAY 5-9 and WEEK 4-6. With the exception of clinical success at DAY 5-9, the results from the analyses of the applicant's data fail to provide statistical evidence in support of the efficacy claims.**

11. Ceftibuten Patients From Studies C87-069, I87-326, I87-247, I87-128, I89-054, and I87-232: Complicated UTI Versus Recurrent Cystitis

By request of the medical officer, ceftibuten patients with medical officer diagnosed recurrent cystitis were compared to ceftibuten patients with medical officer diagnosed CUTI. These groups were compared with respect to bacteriological and clinical success rates. For this analysis, the medical officer's primary efficacy parameter was bacteriological efficacy at DAY 5-9.

Across all studies, 302 patients were diagnosed with CUTI, and 91 patients were diagnosed with recurrent cystitis. Compared to the recurrent cystitis patients, the CUTI patients had a significantly lower mean age, and a significantly higher mean weight and mean height ($p \leq 0.019$ for all tests). All the recurrent cystitis patients were females.

According to the medical officer, 183 (61%) CUTI patients and 57 (63%) recurrent cystitis patients were evaluable for this analysis. Compared to the recurrent cystitis patients, the CUTI patients had a significantly lower mean age, and a significantly higher mean weight and mean height ($p \leq 0.006$ for all tests).

Bacteriological Efficacy: At DAY 5-9, the recurrent cystitis patients had a significantly higher bacteriologic success rate than the CUTI patients, where the success rate was 88% (50/57) for the recurrent cystitis patients and 74% (136/183) for the CUTI patients ($p=0.034$). At WEEK 4-6, the recurrent cystitis patients had numerically lower bacteriologic success rate than the CUTI patients [49% (19/39) vs. 56% (87/155)]; however, the difference was not statistically significant ($p=0.406$).

Clinical Efficacy: At DAY 5-9, the recurrent cystitis patients had numerically lower clinical success rate than the CUTI patients [69% (38/55) vs. 79% (142/180)]; however, the difference was not statistically significant ($p=0.133$). At WEEK 4-6 the recurrent cystitis patients had a significantly lower clinical success rate than the CUTI patients, where the success rate was 38% (14/37) for the recurrent cystitis patients and 58% (81/139) for the CUTI patients ($p=0.027$).

Reviewer Conclusions: **The combined analysis of patients from studies C87-069, I87-326, I87-247, I87-128, I89-054, and I87-232 shows that at DAY 5-9, recurrent cystitis patients on ceftibuten 400 mg QD have a significantly higher bacteriological success rate than CUTI patients on ceftibuten 400 mg QD; therefore indicating that recurrent cystitis may not be supportive of CUTI. However, results from the secondary analyses of bacteriological efficacy at WEEK 4-6 and clinical efficacy at DAY 5-9 and WEEK 4-6 do not support this conclusion.**

IV. SAFETY RESULTS

Note: All safety results are based on the applicant's study report tables.

B. ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Note: All acute bronchitis, tracheitis, and acute exacerbation of chronic bronchitis patients who received either ceftibuten 400 mg QD or cefaclor 250 mg TID were combined for the safety analysis.

1. Studies C88-044, I88-111, I88-217 and I88-327 Combined

A total of 603 patients from studies C88-044, I88-111, I88-217 and I88-327 were evaluable for safety. Of these patients, 411 received ceftibuten 400 mg QD and 192 received cefaclor 250 mg TID.

The ceftibuten minus cefaclor difference in the adverse event rate was 2%, with the 95% confidence interval at $_{411,192}$ (-5%, 9%) $_{19\%,17\%}$ ($p=0.539$). The ceftibuten minus cefaclor difference in the treatment related adverse event rate was 1%, with the 95% confidence interval at $_{411,192}$ (-5%, 6%) $_{11\%,10\%}$ ($p=0.776$).

Adverse events in the gastrointestinal system were the most common. The ceftibuten minus cefaclor difference in the gastrointestinal adverse event rate was 2%, with the 95% confidence interval at $_{411,192}$ (-3%, 7%) $_{8\%,7\%}$ (p=0.405). The ceftibuten minus cefaclor difference in the **treatment related** gastrointestinal adverse event rate was 1%, with the 95% confidence interval at $_{411,192}$ (-3%, 5%) $_{6\%,5\%}$ (p=0.562). There were no statistically significant differences between treatment groups with respect to the rate of adverse events in the other body systems.

The ceftibuten minus cefaclor difference in the rate of withdrawals due to adverse events was -1%, with the 95% confidence interval at $_{411,192}$ (-5%, 2%) $_{3\%,4\%}$ (p=0.426). The ceftibuten minus cefaclor difference in the death rate was 1%, with the 95% confidence interval at $_{411,192}$ (-1%, 4%) $_{2\%,1\%}$ (p=0.335).

There were no statistically significant differences between treatment groups with respect to proportions of patients with abnormal hematology, blood chemistry or urinalysis parameters. Among ceftibuten patients, the most frequently abnormal hematology parameter was hemoglobin, where the ceftibuten minus cefaclor difference in the percentage of patients with abnormal hemoglobin was 1%, with the 95% confidence interval at $_{365,163}$ (-3%, 6%) $_{5\%,4\%}$ (p=0.446). The most frequently abnormal blood chemistry parameter was BUN, where the ceftibuten minus cefaclor difference in the percentage of patients with abnormal BUN was -1%, with the 95% confidence interval at $_{321,149}$ (-7%, 4%) $_{7\%,8\%}$ (p=0.551). The most frequently abnormal urinalysis parameter was epithelium, where the ceftibuten minus cefaclor difference in the percentage of patients with abnormal epithelium was 0%, with the 95% confidence interval at $_{262,120}$ (-9%, 9%) $_{19\%,19\%}$ (p=0.945). Patients who had a baseline laboratory assessment with subsequent assessment during treatment were included in this analysis.

Reviewer Conclusions: **Ceftibuten was not significantly worse than cefaclor with respect to the rate of adverse events, treatment related adverse events or percentage of patients with abnormal laboratory parameters. Therefore, the combined safety analysis of studies C88-044, I88-111, I88-217 and I88-327 supports the applicant's claim that ceftibuten 400 mg QD is comparable in safety to cefaclor 250 mg TID in the treatment of acute bronchitis, tracheitis, and acute exacerbation of chronic bronchitis.**

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1. Studies C87-069, I87-326, and I87-247 Combined (TMP-SMX Comparator Studies)

A total of 409 patients from studies C87-069, I87-326 and I87-247 were evaluable for safety. Of these patients, 273 received ceftibuten 400 mg QD and 136 received TMP-SMX 160/800 mg BID.

The ceftibuten minus TMP-SMX difference in the adverse event rate was 5%, with the 95% confidence interval at $_{273,136}$ (-4%, 13%) $_{20\%,15\%}$ (p=0.249). The ceftibuten minus TMP-SMX difference in the **treatment related** adverse event rate was 1%, with the 95% confidence interval at $_{273,136}$ (-7%, 9%) $_{16\%,15\%}$ (p=0.860).

Adverse events in the gastrointestinal system were the most common. The ceftibuten minus TMP-SMX difference in the gastrointestinal adverse event rate was 4%, with the 95% confidence interval at $_{273,136}$ (-2%, 11%) $_{13\%,9\%}$ (p=0.196). The ceftibuten minus TMP-SMX difference in the **treatment related** gastrointestinal adverse event rate was 3%, with the 95% confidence interval at $_{273,136}$ (-3%, 10%) $_{11\%,8\%}$ (p=0.305). There were no statistically significant differences between treatment groups with respect to the rate of adverse events in the other body systems.

The ceftibuten minus cefaclor difference in the rate of withdrawals due to adverse events was -1%, with the 95% confidence interval at $_{273,136}$ (-6%, 3%) $_{4\%,5\%}$ (p=0.479). The ceftibuten minus cefaclor difference in the death rate was -0.3%, with the 95% confidence interval at $_{273,136}$ (-2.5%, 1.8%) $_{0.4\%,0.7\%}$ (p>0.999).

With respect laboratory parameters, ceftibuten had significantly fewer patients with abnormal BUN, creatinine, hemoglobin, and total bilirubin than TMP-SMX. The ceftibuten minus TMP-SMX difference in the percentage of patients with abnormal BUN was -9%, with the 95% confidence interval at $_{170,84}$ (-19%, -0.2%) $_{6\%,15\%}$ (p=0.012). The ceftibuten minus TMP-SMX difference in the percentage of patients with abnormal creatinine was -10%, with the 95% confidence interval at $_{172,86}$ (-18%, -1%) $_{3\%,13\%}$ (p=0.005). The ceftibuten minus TMP-SMX difference in the percentage of patients with abnormal hemoglobin was -7%, with the 95% confidence interval at $_{242,122}$ (-13%, -1%) $_{3\%,10\%}$ (p=0.005). The ceftibuten minus cefaclor difference in the percentage of patients with abnormal total bilirubin was -4%, with the 95% confidence interval at $_{162,83}$ (-9%, 1%) $_{0\%,4\%}$ (p=0.038). Patients who had a baseline laboratory assessment with subsequent assessment during treatment were included in this analysis.

Reviewer Conclusions: **Ceftibuten was not significantly worse than TMP-SMX with respect to the rate of adverse events, treatment related adverse events, or percentage of patients with abnormal laboratory parameters. Therefore, the combined safety analysis of studies C87-069, I87-326, and I87-247 supports the applicant's claim that ceftibuten 400 mg QD is comparable in safety to TMP-SMX 160/800 mg BID in the treatment of urinary tract infections.**

2. Studies I87-128 and I89-054 Combined (Norfloxacin Comparator Studies)

A total of 149 patients from studies I87-128 and I89-054 were evaluable for safety. Of these patients, 99 received ceftibuten 400 mg QD and 50 received norfloxacin 400 mg BID.

The ceftibuten minus norfloxacin difference in the adverse event rate was 11%, with the 95% confidence interval at $_{99,50}$ (-0.2%, 23%) $_{17\%,6\%}$ (p=0.059). The ceftibuten minus norfloxacin difference in the **treatment related** adverse event rate was 10% with the 95% confidence interval at $_{99,50}$ (-1%, 21%) $_{16\%,6\%}$ (p=0.079).

Adverse events in the gastrointestinal system were the most common. The ceftibuten minus norfloxacin difference in the gastrointestinal adverse event rate was 9%, with the

95% confidence interval at $_{99,50}$ (-1%, 19%) $_{13\%,4\%}$ (p=0.080). The ceftibuten minus norfloxacin difference in the **treatment related** gastrointestinal adverse event rate was 8%, with the 95% confidence interval at $_{99,50}$ (-2%, 18%) $_{12\%,4\%}$ (p=0.142). There were no statistically significant differences between treatment groups with respect to the rate of adverse events in the other body systems.

The ceftibuten minus norfloxacin difference in the rate of withdrawals due to adverse events was 0%, with the 95% confidence interval at $_{99,50}$ (-6%, 6%) $_{2\%,2\%}$ (p>0.999). The ceftibuten minus norfloxacin difference in the death rate was -1%, with the 95% confidence interval at $_{99,50}$ (-7%, 5%) $_{1\%,2\%}$ (p>0.999).

There were no statistically significant differences between treatment groups with respect to proportions of patients with abnormal hematology, blood chemistry or urinalysis parameters. Among ceftibuten patients, the most frequently abnormal hematology parameter was hemoglobin, where the ceftibuten minus norfloxacin difference in the percentage of patients with abnormal hemoglobin was -4%, with the 95% confidence interval at $_{94,49}$ (-15%, 10%) $_{6\%,10\%}$ (p=0.511). The most frequently abnormal blood chemistry parameter was creatinine, where the ceftibuten minus norfloxacin difference in the percentage of patients with abnormal creatinine was 6%, with the 95% confidence interval at $_{92,49}$ (-3%, 14%) $_{8\%,2\%}$ (p=0.262). The most frequently abnormal urinalysis parameter was pH, where the ceftibuten minus norfloxacin difference in the percentage of patients with abnormal pH was -2%, with the 95% confidence interval at $_{94,48}$ (-18%, 15%) $_{23\%,25\%}$ (p=0.833). Patients who had a baseline laboratory assessment with subsequent assessment during treatment were included in this analysis.

<u>Reviewer Conclusions:</u> **Compared to norfloxacin, ceftibuten had a borderline significantly higher rate of adverse events and treatment related adverse events. Therefore, the combined safety analysis of studies I87-128 and I89-054 does not clearly support the applicant's claim that ceftibuten 400 mg QD is comparable in safety to norfloxacin 400 mg BID in the treatment of urinary tract infections.**

<u>3. Study I87-232 (Ofloxacin Comparator Study)</u>

A total of 67 patients from study I87-232 were evaluable for safety. Of these patients, 47 received ceftibuten 400 mg QD and 20 received ofloxacin 200 mg BID.

The ceftibuten minus ofloxacin difference in the adverse event rate was 12%, with the 95% confidence interval at $_{47,20}$ (-6%, 30%) $_{17\%,5\%}$ (p=0.260). The applicant considered all events to be treatment related.

Adverse events in the gastrointestinal system were the most common. The ceftibuten minus ofloxacin difference in the gastrointestinal adverse event rate was 6%, with the 95% confidence interval at $_{47,20}$ (-11%, 22%) $_{11\%,5\%}$ (p=0.660). There were no statistically significant differences between treatment groups with respect to the rate of adverse events in the other body systems.

The ceftibuten minus ofloxacin difference in the rate of withdrawals due to adverse events was 2%, with the 95% confidence interval at $_{47,20}$ (-6%, 10%) $_{2\%,0\%}$ ($p>0.999$). The ceftibuten minus ofloxacin difference in the death rate was 2%, with the 95% confidence interval at $_{47,20}$ (-6%, 10%) $_{2\%,0\%}$ ($p>0.999$).

There were no statistically significant differences between treatment groups with respect to proportions of patients with abnormal hematology, blood chemistry or urinalysis parameters. Among ceftibuten patients, the most frequently abnormal hematology parameter was hemoglobin, where the ceftibuten minus ofloxacin difference in the percentage of patients with abnormal hemoglobin was 8%, with the 95% confidence interval at $_{45,20}$ (-13%, 29%) $_{18\%,10\%}$ ($p=0.711$). The most frequently abnormal blood chemistry parameter was creatinine, where the ceftibuten minus ofloxacin difference in the percentage of patients with abnormal creatinine was 11%, with the 95% confidence interval at $_{45,20}$ (-7%, 28%) $_{16\%,5\%}$ ($p=0.417$). The most frequently abnormal urinalysis parameter was protein, where the ceftibuten minus ofloxacin difference in the percentage of patients with abnormal protein was -13%, with the 95% confidence interval at $_{44,20}$ (-43%, 16%) $_{32\%,45\%}$ ($p=0.308$). Patients who had a baseline laboratory assessment with subsequent assessment during treatment were included in this analysis.

Reviewer Conclusions: **Ceftibuten was not significantly worse than ofloxacin with respect to the rate of adverse events, treatment related adverse events, or percentage of patients with abnormal laboratory parameters. Therefore, the safety analysis of study I87-232 supports the applicant's claim that ceftibuten 400 mg QD is comparable in safety to ofloxacin 200 mg BID in the treatment of urinary tract infections. However, due to the small number of ofloxacin patients, these results must be interpreted with caution.**

D. INTEGRATED SAFETY ANALYSIS ACROSS ALL INDICATIONS

Across all studies of AB, AECB, and UTI, a total of 1228 patients were evaluable for safety. Of these patients, 830 received ceftibuten 400 mg QD, 192 received cefaclor 250 mg TID, 136 received TMP-SMX 160/800 mg BID, 50 received norfloxacin 400 mg BID, and 20 received ofloxacin 200 mg BID.

At least one adverse event was reported in 157 (19%) ceftibuten patients, 32 (17%) cefaclor patients, 21 (15%) TMP-SMX patients, 3 (6%) norfloxacin patients and 1 (5%) ofloxacin patient. The variation in adverse event rate among the treatment groups was borderline statistically significant ($p=0.078$). With respect to pairwise treatment comparisons versus ceftibuten, the 95% confidence interval of the ceftibuten minus norfloxacin difference in the adverse event rate was $_{830,50}$ (5%, 21%) $_{19\%,6\%}$ ($p=0.021$); the 95% confidence interval of the ceftibuten minus ofloxacin difference in the adverse event rate was $_{830,20}$ (1%, 26%) $_{19\%,5\%}$ ($p=0.149$); the 95% confidence interval of the ceftibuten minus cefaclor difference in the adverse event rate was $_{830,192}$ (-4%, 8%) $_{19\%,17\%}$ ($p=0.469$); and the 95% confidence interval of the ceftibuten minus TMP-SMX difference in the adverse event rate was $_{830,136}$ (-4%, 11%) $_{19\%,15\%}$ ($p=0.333$).

At least one **treatment related** adverse event was reported in 114 (14%) ceftibuten patients, 20 (10%) cefaclor patients, 21 (15%) TMP-SMX patients, 3 (6%) norfloxacin patients and 1 (5%) ofloxacin patient. The variation in treatment related adverse event rate among the treatment groups was not statistically significant ($p=0.235$). With respect to pairwise treatment comparisons versus ceftibuten, the 95% confidence interval of the ceftibuten minus norfloxacin difference in the treatment related adverse event rate was $_{830,50}$ (-0.3%, 16%) $_{14\%,6\%}$ ($p=0.118$); the 95% confidence interval of the ceftibuten minus ofloxacin difference in the treatment related adverse event rate was $_{830,20}$ (-4%, 21%) $_{14\%,5\%}$ ($p=0.503$); the 95% confidence interval of the ceftibuten minus cefaclor difference in the treatment related adverse event rate was $_{830,192}$ (-2%, 9%) $_{14\%,10\%}$ ($p=0.220$); and the 95% confidence interval of the ceftibuten minus TMP-SMX difference in the treatment related adverse event rate was $_{830,136}$ (-9%, 5%) $_{14\%,15\%}$ ($p=0.595$).

Adverse events in the gastrointestinal system were the most common, occurring in 90 (11%) ceftibuten patients, 13 (7%) cefaclor patients, 12 (9%) TMP-SMX patients, 2 (4%) norfloxacin patients and 1 (5%) ofloxacin patient. The variation in gastrointestinal adverse event rate among the treatment groups was not statistically significant ($p=0.228$). There were no statistically significant differences among treatment groups with respect to the rate of adverse events in the other body systems.

Withdrawals due to adverse events occurred in 25 (3%) ceftibuten patients, 8 (4%) cefaclor patients, 7 (5%) TMP-SMX patients, 1 (2%) norfloxacin patient and 0 (0%) ofloxacin patients. The treatment variation in the percentage of withdrawals due to adverse events was not statistically significant ($p=0.553$).

Deaths occurred in 13 (2%) ceftibuten patients, 2 (1%) cefaclor patients, 1 (1%) TMP-SMX patients, 1 (2%) norfloxacin patient and 0 (0%) ofloxacin patients. The treatment variation in death rate was not statistically significant ($p=0.859$).

Among the laboratory parameters, the treatment groups differed significantly only with respect to the proportion of patients with abnormally high BUN ($p=0.030$). An abnormally high BUN occurred in 41/620 (7%) ceftibuten patients, 12/149 (8%) cefaclor patients, 13/84 (15%) TMP-SMX patients, 1/48 (2%) norfloxacin patients and 2/20 (10%) ofloxacin patients. With respect to pairwise treatment comparisons versus ceftibuten, the 95% confidence interval of the ceftibuten minus norfloxacin difference in the percentage of patients with abnormally high BUN was $_{830,50}$ (-1%, 10%) $_{7\%,2\%}$ ($p=0.352$); the 95% confidence interval of the ceftibuten minus ofloxacin difference in the percentage of patients with abnormally high BUN was $_{830,20}$ (-19%, 12%) $_{7\%,10\%}$ ($p=0.638$); the 95% confidence interval of the ceftibuten minus cefaclor difference in the percentage of patients with abnormally high BUN was $_{830,192}$ (-7%, 4%) $_{7\%,8\%}$ ($p=0.533$); and the 95% confidence interval of the ceftibuten minus TMP-SMX difference in the percentage of patients with abnormally high BUN was $_{830,136}$ (-18%, -0.2%) $_{7\%,15\%}$ ($p=0.004$). Patients who had a baseline laboratory assessment with subsequent assessment during treatment were included in this analysis.

Reviewer Conclusions: **Although ceftibuten had a significantly higher rate of adverse events than norfloxacin, the rate of drug related adverse events among the treatment**

groups was not statistically significant. Therefore, the integrated safety analysis supports the applicant's claim that ceftibuten 400 mg QD is comparable in safety to cefaclor 250 mg TID, TMP-SMX 160/800 mg BID, norfloxacin 400 mg BID, and ofloxacin 200 mg BID.

V. SUMMARY AND CONCLUSIONS
(which may be conveyed to the applicant)

Statistical evaluation of the comparative efficacy of ceftibuten 400 mg QD and cefaclor 250 mg TID in the treatment of acute bronchitis (secondary bacterial infection) and acute bacterial exacerbation of chronic bronchitis is limited to the medical officer's clinically evaluable "test of cure" population. The primary efficacy parameter is clinical response at 4-28 days post treatment for acute bronchitis and at 4-21 days post treatment for acute exacerbation of chronic bronchitis. Studies C88-044, I88-111, I88-217, and I88-327 were considered the pivotal trials.

Statistical evaluation of the comparative efficacy of ceftibuten 400 mg QD, trimethoprim-sulfamethoxazole 160/800 mg BID, norfloxacin 400 mg BID and ofloxacin 200 mg BID in the treatment of complicated urinary tract infections is limited to the medical officer's bacteriologically evaluable "valid" population with complicated urinary tract infections, including pyelonephritis. The primary efficacy parameter is bacteriological response at 5-9 days post treatment. Studies C87-069, I87-326 and I87-247 were considered pivotal trials, while studies I87-128, I89-054 and I87-232 were considered supportive trials.

Statistical evaluation of comparative safety of ceftibuten 400 mg QD and cefaclor 250 mg TID in the treatment of acute bronchitis and acute exacerbation of chronic bronchitis and ceftibuten 400 mg QD, trimethoprim-sulfamethoxazole 160/800 mg BID, norfloxacin 400 mg BID and ofloxacin 200 mg BID in the treatment of complicated urinary tract infections, is limited to the applicant's safety populations. The primary safety parameter was the rate of drug related adverse events. Safety analyses were performed by indication and integrated across indications. The acute bronchitis and acute exacerbation of chronic bronchitis patients were combined for the safety analysis; these results are summarized with the results for acute exacerbation of chronic bronchitis.

The study results must be interpreted with the following caveats:

1. The trials submitted in support of the bronchitis indications were designed to study the general indication of they were not designed to study and acute exacerbation of chronic bronchitis as a separate indications.

2. The trials submitted in support of the UTI indication were designed to study complicated UTI, pyelonephritis, and recurrent cystitis; however, the medical officer did not consider recurrent cystitis as a complicated UTI. These and all other patients not diagnosed with complicated UTI or pyelonephritis were excluded from the primary efficacy analyses.

3. The efficacy results presented are from post-hoc subset analyses.

4. The use of post-hoc subset analyses severely limits the power of the trials to establish efficacy equivalence within in the subsets.

5. All trials were multicenter; however, the within center sample sizes were inadequate to formally assess the treatment by center interaction.

6. The results are combined across centers, and in some cases, across multicenter trials. In these analyses, some centers only had efficacy evaluable patients in one of the treatment arms.

7. With respect to baseline characteristics, there is evidence of significant differences between studies and between geographic locations. It is not possible to determine the impact on conclusions from such imbalances.

The 95% confidence intervals for the ceftibuten 400 mg QD minus cefaclor 250 mg BID difference in clinical success rate between 4-28 days post treatment from the analysis of study C88-044 (US), the combined analysis of studies I88-111, I88-217, and I88-327 (INT), and the combined analysis of studies C88-044, I88-111, I88-217, and I88-327 (ALL) are presented in Table 1.

Table 1: Acute Bronchitis Patients
95% Confidence Intervals of the Ceftibuten Minus Cefaclor Difference in Clinical Success[1] rate at 4-28 Days Post Treatment

Study Population	n_t, n_c (LCL, UCL) p_t, p_c
C88-044 (US)	$_{55,19}$ (-45%, 7%) $_{80\%,79\%}$
I88-111, I88-217, I88-327 (INT)	$_{37,10}$ (-36%, 33%) $_{78\%,80\%}$
C88-044, I88-111, I88-217, I88-327 (ALL)	$_{92,29}$ (-32%, 8%) $_{87\%,79\%}$

[1]Clinical success is defined as a clinical response of cure or improvement.
[2]LCL = lower 95% confidence limit , UCL = upper 95% confidence limit , n_t = number of ceftibuten patients, n_c = number of cefaclor patients, p_t = cure rate of ceftibuten and p_c = cure rate of cefaclor. The confidence intervals were based on a normal approximation and incorporated a continuity correction.

The lower 95% confidence limits from the US, INT, and ALL analyses exceed -20%, -15%, and -20%, respectively, and therefore do not demonstrate that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 TID for the treatment of acute bronchitis. **The applicant's claim that ceftibuten 400 mg QD and cefaclor 250 TID are comparable in efficacy for the treatment of acute bronchitis is not supported.**

In the US, INT, and ALL populations, results from secondary analyses of clinical efficacy at end of treatment or 1-3 days post treatment and bacteriological efficacy at 4-28 days post-treatment support this conclusion.

B. ACUTE EXACERBATION OF CHRONIC BRONCHITIS

The 95% confidence intervals for the ceftibuten 400 mg QD minus cefaclor 250 mg BID difference in clinical success rate between 4-21 days post treatment from the analysis of study C88-044 (US), the combined analysis of studies I88-111, I88-217, and I88-327 (INT), and the combined analysis of studies C88-044, I88-111, I88-217, and I88-327 (ALL) are presented in Table 2.

Table 2: Acute Exacerbation of Chronic Bronchitis Patients
95% Confidence Intervals of the Ceftibuten Minus Cefaclor Difference in Clinical Success[1] rate Between 4-21 Days Post Treatment

Study Population	n_t, n_c (LCL, UCL) p_t, p_c[2]
C88-044 (US)	$_{58,26}$ (-32%, 18%) $_{69\%,65\%}$
I88-111, I88-217, I88-327 (INT)	$_{50,28}$ (-27%, 24%) $_{52\%,54\%}$
C88-044, I88-111, I88-217, I88-327 (ALL)	$_{108,54}$ (-21%, 14%) $_{56\%,59\%}$

[1]Clinical success is defined as a clinical response of cure or improvement.
[2]LCL = lower 95% confidence limit , UCL = upper 95% confidence limit , n_t = number of ceftibuten patients, n_c = number of cefaclor patients, p_t = cure rate of ceftibuten and p_c = cure rate of cefaclor. The confidence intervals were based on a normal approximation and incorporated a continuity correction.

The lower 95% confidence limits from the US, INT, and ALL analyses exceed -20%, and therefore do not demonstrate that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 TID for the treatment of acute exacerbation of chronic bronchitis. **The applicant's claim that ceftibuten 400 mg QD and cefaclor 250 TID are comparable in efficacy for the treatment of acute exacerbation of chronic bronchitis is not supported.**

In the US and INT populations, results from the secondary analyses of clinical efficacy at end of treatment or 1-3 days post treatment and bacteriological efficacy at 4-28 days post-treatment support this conclusion. However, in the ALL population, ceftibuten 400 mg QD and cefaclor 250 TID were comparable in efficacy with respect to these parameters.

Additional supportive analyses of the medical officer's ceftibuten 200 mg BID AECB patients and the applicant's 200 mg BID pneumonia patients were performed. The AECB analysis failed to demonstrate that ceftibuten 200 mg BID is comparable to cefaclor 500 mg TID or 250 mg TID with respect to clinical efficacy between 4-28 days post treatment. The pneumonia analysis failed to demonstrate that ceftibuten 200 mg BID is comparable to cefaclor 500 mg TID with respect to clinical efficacy between 7-14 days post treatment.

Therefore, these additional analysis do not provide supportive evidence for the applicant's claim that ceftibuten 400 mg QD and cefaclor 250 TID are comparable in efficacy for the treatment of acute exacerbation of chronic bronchitis.

In the combined AB/AECB safety analysis of studies C88-044, I88-111, I88-217 and I88-327, ceftibuten 400 mg QD and cefaclor 250 mg TID were not significantly different with respect to the rates of adverse events, drug related adverse events, adverse events by body system, patient withdrawals due to adverse events, or patient deaths. **The applicant's claim that ceftibuten 400 mg QD is comparable in safety to cefaclor 250 mg TID in the treatment of acute bronchitis, tracheitis or acute exacerbation of chronic bronchitis is supported.**

C. URINARY TRACT INFECTIONS

The 95% confidence intervals for the ceftibuten 400 mg QD minus trimethoprim-sulfamethoxazole 160/800 mg BID difference in bacteriological success rate at 5-9 days post treatment from the analysis of study C87-069 (US), study I87-326 (INT), and the combined analysis of studies C87-069 and I87-326 (ALL) are presented in Table 3. Study I87-247 did not have any evaluable complicated UTI patients and is therefore not represented in these analyses.

Table 3: 95% Confidence Intervals of the Ceftibuten Minus Trimethoprim-Sulfamethoxazole Difference in Bacteriological Success[1] rate at 5-9 Days Post Treatment
Patients

Study Population	n_t, n_c (LCL, UCL) p_t, p_c[2]
C87-069 (US)	$_{47,25}$ (-20%, 18%) $_{87\%,88\%}$
I87-326 (INT)	$_{60,39}$ (-25%, 13%) $_{73\%,79\%}$
C87-069, I87-326 (ALL)	$_{107,64}$ (-17%, 10%) $_{79\%,83\%}$

[1]Bacteriological success is defined as a bacteriological response of elimination.
[2]LCL = lower 95% confidence limit , UCL = upper 95% confidence limit , n_t = number of ceftibuten patients, n_c = number of trimethoprim-sulfamethoxazole patients, p_t = cure rate of ceftibuten and p_c = cure rate of trimethoprim-sulfamethoxazole. The confidence intervals were based on a normal approximation and incorporated a continuity correction.

The lower 95% confidence limits from the US, INT, and ALL analyses exceed -15%, -20%, and -15% respectively, and therefore do not demonstrate that ceftibuten 400 mg QD is comparable in efficacy to trimethoprim-sulfamethoxazole 160/800 mg BID for the treatment of complicated urinary tract infections. **The applicant's claim that ceftibuten 400 mg QD and trimethoprim-sulfamethoxazole 160/800 mg BID are comparable in efficacy for the treatment of complicated urinary tract infections is not supported.**

In the US and ALL populations, results from the secondary analyses of bacteriological efficacy at 4-6 weeks post treatment, clinical efficacy at 5-9 days post treatment and 4-6 weeks post treatment, the subset of E. coli isolates, the gender subsets, and the subset of pyelonephritis patients support this conclusion. With the exception of bacteriological efficacy at 4-6 weeks post treatment, all the aforementioned secondary analyses in the INT population also support this conclusion.

In the combined safety analysis of studies C87-069, I87-326, and I87-247, ceftibuten 400 mg QD and trimethoprim-sulfamethoxazole 160/800 mg BID were not significantly different with respect to the rates of adverse events, drug related adverse events, adverse events by body system, patient withdrawals due to adverse events, or patient deaths. **The applicant's claim that ceftibuten 400 mg QD and trimethoprim-sulfamethoxazole 160/800 mg BID are comparable in safety for the treatment of complicated urinary tract infections is supported.**

The 95% confidence intervals for the ceftibuten 400 mg QD minus norfloxacin 400 mg BID or ofloxacin 200 mg BID difference in bacteriological success rate at 5-9 days post treatment from the combined analysis of studies I87-128 and I89-054 (norfloxacin comparator) and the combined analysis of studies I87-128, I89-054 and I87-232 (quinolone comparator) are presented in Table 4. Study I87-232, the ofloxacin comparator study, did not have an adequate number of evaluable complicated UTI patients to make a meaningful statistical comparison of bacteriological success rate.

Table 4: 95% Confidence Intervals of the Ceftibuten Minus Quinolone Difference in Bacteriological Success[1] rate at 5-9 Days Post Treatment	Patients
Study Population	n_t, n_c (LCL, UCL) p_t, p_c[2]
I87-128 and I89-054 (norfloxacin)	$_{65,34}$ (-33%, 4%) $_{71\%,85\%}$
I87-128, I89-054 and I87-232 (quinolones)	$_{78,43}$ (-34%, 0.5%) $_{67\%,84\%}$

[1]Bacteriological success is defined as a bacteriological response elimination.
[2]LCL = lower 95% confidence limit , UCL = upper 95% confidence limit , n_t = number of ceftibuten patients, n_c = number of quinolone patients, p_t = cure rate of ceftibuten and p_c = cure rate of quinolone. The confidence intervals were based on a normal approximation and incorporated a continuity correction.

The lower 95% confidence limits from the combined norfloxacin comparator and combined quinolone comparator analyses exceed -15%, and therefore do not demonstrate that ceftibuten 400 mg QD is comparable in efficacy to norfloxacin 400 mg BID or ofloxacin 200 mg BID for the treatment of complicated urinary tract infections. **The applicant's claim that ceftibuten 400 mg QD, norfloxacin 400 mg BID, and ofloxacin 200 mg BID are comparable in efficacy for the treatment of complicated urinary tract infections is not supported.**

In the norfloxacin and quinolone populations, results from the secondary analyses of bacteriological efficacy at 4-6 weeks post treatment, clinical efficacy at 5-9 days post treatment and 4-6 weeks post treatment, the subset of E. coli isolates and the subset o. pyelonephritis patients support this conclusion.

In the combined safety analysis of studies I87-128 and I83-054, ceftibuten 400 mg QD and norfloxacin 400 mg BID were not significantly different with respect to the rates of patient withdrawals due to adverse events, or patient deaths. However, the rates of adverse events and drug related adverse events were borderline statistically significant ($p=0.059$ and 0.079, respectively). **The applicant's claim that ceftibuten 400 mg QD and norfloxacin 400 mg BID are comparable in safety for the treatment of complicated urinary tract infections is not clearly supported.**

In the safety analysis of study I87-232, ceftibuten 400 mg QD and ofloxacin 200 mg BID were not significantly different with respect to the rates of adverse events, drug related adverse events, adverse events by body system, patient withdrawals due to adverse events, or patient deaths. **The applicant's claim that ceftibuten 400 mg QD and ofloxacin 200 mg BID are comparable in safety for the treatment of complicated urinary tract infections is supported.** However, due to the small number of ofloxacin patients ($n=20$), these results must be interpreted with caution.

D. INTEGRATED SAFETY

In the integrated safety analysis across all indications, ceftibuten 400 mg QD had a significantly higher rate of adverse events than norfloxacin 400 mg BID ($p=0.021$). However, ceftibuten 400 mg QD, cefaclor 250 mg TID, trimethoprim-sulfamethoxazole 160/800 mg BID, norfloxacin 400 mg BID, and ofloxacin 200 mg BID were not significantly different with respect to the rates of drug related adverse events, patient withdrawals due to adverse events, or patient deaths. **The applicant's claim that ceftibuten 400 mg QD, cefaclor 250 mg TID, trimethoprim-sulfamethoxazole 160/800 mg BID, norfloxacin 400 mg BID, and ofloxacin 200 mg BID are comparable in safety is supported.**

REVIEWER COMMENTS: The results for the three indications must be interpreted in light of the caveats stated above. A critical flaw in many of the trials presented here is their failure to accrue the number of efficacy evaluable patients planned in the protocols. In this review, the trials were analyzed individually and in a variety of combinations, where the definition of a "trial" was expanded to include combinations of studies. It is the opinion of this reviewer that combining studies should not be considered a standard analytical practice, and that results from such analyses should not be used as primary evidence in support of applicant claims.

From a statistical standpoint, the applicant has not submitted two adequate and well controlled "trials" (individual or combined) which clearly demonstrate that ceftibuten 400 mg QD is comparable in efficacy to cefaclor 250 mg TID for the treatment of acute bronchitis and acute exacerbation of chronic bronchitis, or which clearly demonstrate that

ceftibuten 400 mg QD is comparable in efficacy to trimethoprim-sulfamethoxazole 160/800 mg BID, norfloxacin 400 mg BID or ofloxacin 200 mg BID for the treatment of complicated urinary tract infections.

Elizabeth A. Turney, M.S.
Biomedical Statistician, Group 7

Concur: Ralph Harkins, Ph.D. 2/18/93

Dr. Satya D. Dubey 2-19-93

cc:
Orig. NDA 50-685
HFD-520
HFD-520/DeBellas
HFD-520/Lumpkin
HFD-520/Albrecht
HFD-520/Leissa
HFD-713/Dubey [File: DRU 1.3.2]
HFD-713/Harkins
HFD-713/Turney
HFD-344/Lisook
Chron.
This review contains 51 pages.
WordPerfect 5.1/nda50685/February 5, 1993

micro

MAY 20 ..

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Microbiology and Drug Control Review Notes #1

NDA # 50-685 **Date Completed:** April 30, 1992

Sponsor: *Schering Corporation*
2000 Galloping Hill Road Division
Kenilworth, NJ 07033
Attn: Douglas B. Given, M.D., Ph.D.; V.P. U.S. Regulatory Affairs
(908) 298-2780

Submission Reviewed: Original NDA dated December 20, 1991
Amendment dated March 13, 1992

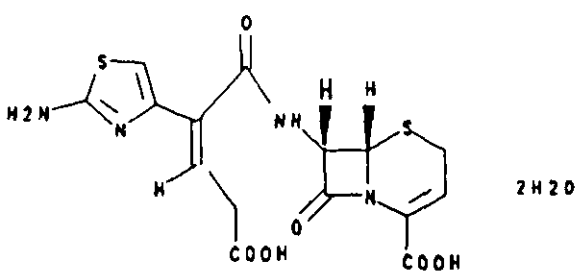
Providing For: Amendment provides information and confirmation that samples were sent to the FDA laboratory.

Names:
Trade: CEDAX™ capsules
Non-Proprietary: ceftibuten capsules
Chemical: (+)-(6R,7R)-7-[(Z)-2-(2-amino-4-thiazoly)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Dosage Form: 200 milligram and 400 milligram capsules

Pharmacological Category: semi-synthetic cephalosporin antibiotic

Structural Formula:



$C_{15}H_{14}N_4O_6S_2 \bullet 2H_2O$
M.W.= 446.43

Related NDA, IND, DMF, Form 5's:
IND ; IND
NDA 50-686 Ceftibuten for oral suspension;
DMF
DMF
DMF

Initial Submission: Received by CDR: 12/20/91; Received by reviewer: 3/16/92; Reviewed initiated: 4/1/92; Review completed: April 30, 1992

Remarks:

Ceftibuten is another third generation cephalosporin. It is systemically available after oral administration. It has a carboxyethylidene side chain, which makes it different from most orally absorbed cephems which have a phenylglycine side chain. It has the aminothiazolyl moiety that is found in several other broad spectrum cephems such as cefotaxime and ceftazidime. The drug has good activity against most gram-negative bacteria. In general it was highly active against *Escherichia coli, Klebsiella, Proteus, Providencia, Salmonella, Haemophilus influenzae,* and *Streptococcus pyogenes*. It has limited activity against *Citrobacter, Enterobacter, Serratia* and *Streptococcus pneumoniae*. It has no activity against staphylococci, enterococci, *Pseudomonas, Acinetobacter, Flavobacterium* and obligately anaerobic bacteria. Ceftibuten is stable to most plasmid mediated beta-lactamases (except SHV-4 and SHV-5). The drug is not stable to the chromosomal beta-lactamases found in *Citrobacter, Enterobacter,* and *Serratia*. Ceftibuten is a poor inhibitor of most of the plasmid-mediated beta-lactamases, except SHV-4 and SHV-5. Ceftibuten is a weak inducer of the Class I chromosomal beta-lactamases.

PART I--MANUFACTURING AND CONTROLS

1) Components and Composition — Satisfactory

Ceftibuten capsules will be marketed in 200mg and 400mg doses

A. **200 mg/capsule**

Ingredient	mg/capsule
Ceftibuten	200*
Microcrystalline Cellulose NF	
Sodium Starch Glycolate NF	
Magnesium Stearate NF	
Approximate Fill Weight	____ mg***

BAND SEAL SOLUTION****

Polysorbate 80 NF	
Gelatin NF	
Approximate Band Seal Weight	_____ mg

* The amount of ceftibuten varies according to the potency of the lot used. Up to a 5% excess may be added.

** The amount of sodium starch glycolate is adjusted, depending on the amount of ceftibuten used, to maintain the correct capsule fill weight.

*** Filled into No. 1 white opaque, branded, two-piece hard gelatin capsules.
DMF

**** DMF

B. **400 mg/capsule**

Ingredient	mg/capsule
Ceftibuten	400*
Microcrystalline Cellulose NF	
Sodium Starch Glycolate NF	
Magnesium Stearate NF	
Approximate Fill Weight	____ mg***

BAND SEAL SOLUTION****

Polysorbate 80 NF	
Gelatin NF	
Approximate Band Seal Weight	_____ mg

* The amount of ceftibuten varies according to the potency of the lot used. Up to a 5% excess may be added.

** The amount of sodium starch glycolate is adjusted, depending on the amount of ceftibuten used, to maintain the correct capsule fill weight.

*** Filled into No. 0 white opaque, branded, two-piece hard gelatin capsules.
DMF

**** DM

NDA 50-685 **CEFTIBUTEN CAPSULES**

BRANDING INK*

* OPACODE S-1-8100HV, BLACK or OPACODE S-1-8084-G, BLACK
Manufactured by
DMF

These two inks are the same except for the used. Opacode S-1-8100HV contains an that is CFR acceptable and Opacode S-1-8084-G contains an that is CFR and EEC acceptable.

A batch formula for of the 200 milligram capsules and for of the 400 milligram capsules is given on pages 03 0552 and 03 0553 of the NDA.
Letters of authorization are included for the capsules and banding solution, and for

NDA 50-685 **CEFTIBUTEN CAPSULES**

2) Source and Synthesis Satisfactory EER Needed

Manufacturing and control operations for the new drug substance, ceftibuten dihydrate, will be performed at:

DMF

Control operations for the drug substance will also be performed at:

Schering Corporation
13900 N. W. 57th Court
Miami Lakes, Florida 33014

The intermediate, benzyloxycarboxamide (prenyl half ester) may be manufactured and purchased from the following source:

DMF

A GMP Establishment Evaluation request for these three facilities was sent to the Division of Manufacturing & Product Quality (HFD-320) on February 3, 1992.
is acceptable. The other two facilities will be inspected.
will be ready for inspection at the end of September 1992 and the Schering facility in Miami Lakes will be ready in August 1992.

Chemical reactions with graphic formulas used to produce ceftibuten dihydrate including the names and amounts of all substances used in the process, are described in the NDA pages 03 0277 to 03 0308.

DEFICIENCY:

A satisfactory EER Evaluation is needed for the facilities that manufacture and test the new drug substance.

The manufacturing process for ceftibuten

Pages 8-11
deleted

Starting material specifications and tests are listed on pages 03 0310 to 03 0311. The benzylpenicillin sulfoxide benzhydryl ester is tested for description, identification, moisture, residual solvents and assay. Methyl 4-chloro-3-oxobutanoate is tested for description, identity, moisture and assay. Methyl 3-methoxyprop-2-enoate is tested for description, identity, moisture, and assay. Thiourea is tested for description, identity, loss on drying and assay. Typical suppliers are listed for each of these starting materials. The following tests and specifications are given for the starting materials:

Benzylpenicillin Sulfoxide Benzhydryl Ester (Sulfoxide Ester)

Description
Identification
Moisture
Assay (HPLC)
Residual Solvents

Methyl 4-chloro-3-oxobutanoate

Description
Identification
Moisture
Assay (GC)

Methyl 3-methoxyprop-2-enoate

Description
Identification
Moisture
Assay (GC)

Thiourea

Description
Identification
Loss on drying
Assay
(acid-base titration)

Reagents and solvent specifications and analytical methods are presented on pages 03 0315 to 03 0345 of the NDA.

Potential Impurities

Pages 14-21
deleted

3) Raw Materials Controls

Unsatisfactory
Method Validation Needed

A. Active Drug Substance

Specifications and methods used to test the active drug substance are given below:

Parameter	Specification	Method
Description		Visual
Identification		
HPLC		HPLC
IR		USP<851>
TLC		USP<201>
Water (K.F.)		USP<921>
Specific Rotation		USP<781>
Surface Area		
Assay		HPLC
Heavy Metals		USP<231>
Residual Solvent (acetonitrile)		GC
Residue on Ignition		USP<281>

Related Compounds	
Group X	HPLC Gel filtration
HPLC Related Compounds	HPLC
Total	
Any Individual Peak	
Unknowns and I1 (RRT 0.12 to 0.50)	
N1 (RRT 0.50 to 0.60)	
N2, L2, L3 (RRT 0.60 to 0.74)	
Trans (RRT 0.75 to 0.85)	
L4, L5 and Unknowns (RRT 0.86 to 1.5)	
Total Related Compound	

RRT = Relative Retention Time

DEFICIENCIES:

1) Samples were requested on February 3, 1992 for method validation. Samples were sent to the FDA laboratory on February 12, 1992. Method validation must still be completed .
2) The tests for heavy metals, residue on ignition, and surface area are not needed. They will not be included in the official monograph for this product. The sponsor may continue to perform these tests as "in house" specifications.
3) The test for the related substances I (HPLC) will not be included in the official monograph for this product. Unless present in high amounts or toxic, FDA has been controlling the amount of impurities by using the purity(assay) of the bulk material. The sponsor should continue to perform these tests, however. The structures of these compounds have been determined and they are present in only small amounts under normal storage conditions. The trans compound which is usually the most common one will be controlled by the specific rotation specification. Since the Group X compounds have not been fully characterized and this group is usually the most prominent degradation product they will be tested for in the official monograph.
4) The test for acetonitrile will not be included in the official monograph. This is a residual solvent and is present in only very small amounts. The sponsor should continue to perform this test, however.
5) The TLC identity test will be the identification method in the official monograph, since the use of the IR method would require that two different reference standards be established.
6) A crystallinity test should be performed on the new drug substance.

B. Excipients:

The tests specified for the excipients are carried out by the applicant. Alternatively, a vendor's certificate of analysis will be obtained and appropriate identification testing will be performed.

The following inactive components will meet the specifications described in the current edition of the NF or USP.

Microcrystalline Cellulose, NF
Sodium Starch Glycolate, NF
Magnesium Stearate, NF
Polysorbate 80, NF
Gelatin, NF

Specifications for the rest of the inactive ingredients are as follow:

Hard Gelatin Capsules No. 0–opaque white-ELC

Description	White, opaque hard gelatin capsule, Size No. 0, with the name "Cedax" spin printed with black ink on the caps and "400 mg" spin printed with black ink on the body, free from foreign matter
Identification	
A. Gelatin	
B. Titanium Dioxide	
C. Absence of Preservatives	
Loss on Drying	

Hard Gelatin Capsules No. 1–opaque white-ELC

Description	White, opaque hard gelatin capsule, Size No. 1, with the name "Cedax" spin printed with black ink on the caps and "200 mg" spin printed with black ink on the body, free from foreign matter
Identification	
A. Gelatin	
B. Titanium Dioxide	
C. Absence of Preservatives	
Loss on Drying	

Hard Gelatin Capsules No. 0--opaque white-QX

Description	White, opaque hard gelatin capsule, Size No. 0, with the name "Cedax" spin printed with black ink on the caps and "400 mg" spin printed with black ink on the body, free from foreign matter

Identification

A. Gelatin

B. Titanium Dioxide

C. Preservatives

Loss on Drying

Hard Gelatin Capsules No. 1--opaque white-QX

Description	White, opaque hard gelatin capsule, Size No. 1, with the name "Cedax" spin printed with black ink on the caps and "200 mg" spin printed with black ink on the body, free from foreign matter

Identification

A. Gelatin

B. Titanium Dioxide

C. Preservatives

Loss on Drying

4) Manufacturing and Processing — Acceptable Establishment Evaluation Needed

The capsules are manufactured, processed, packaged, and control tested at:

Schering Corporation
13900 N. W. 57th Court
Miami Lakes, Florida 33014

An Establishment Evaluation Request for this facility was sent to the Division of Manufacturing & Product Quality (HFD-320) on February 3, 1992. This facility will be ready for inspection in August, 1992, according to the applicant.

DEFICIENCY:

An acceptable EER is needed for the facility that manufactures, processes, packages, and tests the capsules.

MANUFACTURING PROCEDURE

200 mg/capsule dosage

400 mg/capsule dosage

Clear Banding Solution

In-Process Controls

200 mg/capsule

Capsules are sampled throughout the filling process and check weighed. Results are recorded. Capsule fill weight is 300 mg ± 5% for individual capsules and 300 mg ± 3% for the average of 10 capsules.

400 mg/capsule

Capsules are sampled throughout the filling process and check weighed. Results are recorded. Capsule fill weight is 600 mg ± 5% for individual capsules and 600 mg ± 3% for the average of 10 capsules. The tap density (compacted) is 0.55 to 0.75 g/mL.

5) Laboratory Controls Method Validation Pending

Specifications and methods used to test the finished capsules are given below:

Parameter	Specification	Test Method
Appearance	200 mg--No. 1 clear banded capsule with "Cedax" printed in black ink on the white opaque cap and "200 mg" printed with black ink on the white opaque body containing white to light yellowish tan powder; 400mg--same but a No. 0 capsule with "400 mg" printed on body.	Visual
Identification		TLC
		HPLC
Assay		HPLC
Uniformity of Dosage Units		USP<905>
Dissolution		USP<711>
Karl Fischer Moisture		USP<921>

NDA 50-685 **CEFTIBUTEN CAPSULES**

Related Compounds	Release	Shelf-life
Group X		
Related Substance I		
Individual		
UNK +I1		
N1		
N2,L2,L3		
Trans		
L4,L5,+UNKs		
Total Related Substances I		
Total		

NOTE:

The tests for related substances will not be part of the official monograph for this product. The applicant should continue to perform these tests.

6) Containers and Closures Satisfactory

NEW DRUG SUBSTANCE

CAPSULES

The capsules will be packaged in bottles of 20 and 100 capsules or unit dose strip packs. All surfaces in contact with the product are in conformance with applicable Food Additive Regulations. The bottles are white high density polyethylene molded from either
(used for stability study samples only)--DMF
-DMF DMF high density polyethylene resin and closed with a non-child resistant single shell screw cap closure or a child resistant two piece plastic screw cap closure both having a pulp/polyethylene liner with a glassine innerseal. The tamper evident innerseal is adhered to the lip of the bottle by the application of glue during the packaging operation. The supplies of these packaging components are listed below:

Plastic Bottles DMF
DMF
DMF
DMF

Screw-Cap Closure
(Non-Child Resistant) DMF

Screw-Cap Closure
(Child Resistant)
DMF

Liner DMF

DMF

Innerseal DMF

Glue-Linebacker DMF

Each container size conforms to requirements for tight containers under USP<671> Containers-Permeation. The bottles conform to USP <661> limits for light transmission and meet USP XXII criteria for interchangeability of containers for packaging dry oral dosage forms.

The strip package unit consists of a laminated structure composed of paper/polyethylene/aluminum foil/low density polyethylene (from outside to inside). One capsule is packaged in each pocket. Suppliers of the laminate are as follow:

DMF

DMF

Authorization letters from each vendor authorizing FDA to refer to their DMF are included in the NDA

A description of the packaging components is listed below:

200 mg and 400 mg
20 capsules

Plastic Bottle:	50 mL High Density Polyethylene, white opaque, 28mm-400 finish, flamed.
Closure	28mm-400 double shell, child resistant white plastic cap with pulp/polyethylene liner and glassine innerseal, printed.*

200 mg
100 capsules

Plastic Bottle	120 mL High Density Polyethylene, white opaque, 38mm-400 finish, flamed.
Closure	38mm-400 single shell metal, maroon with pulp/polyethylene liner (waxed) and glassine innerseal, printed.*

400 mg
100 capsules

Plastic Bottle	200 mL High Density Polyethylene, white opaque, 38-400 finish, flamed.
Closure	38mm-400 single shell metal, maroon with pulp/polyethylene liner (waxed) and glassine innerseal, printed.*

* Linerback glue is applied to lip of bottle prior to application of the closure to adhere the tamper evident innerseal to the bottle.

NDA 50-685 CEFTIBUTEN CAPSULES

Strip Package Unit

Laminate lbs. pouch paper polyethylene/. aluminum foil/ low density polyethylene

USP tests were conducted by Each size (50 mL, 120 mL, and 200 mL) was tested in all three resins. The following tests were performed.

USP TEST	USP LIMITS
Non Volatile Residue Extraction by	
A. Deionized water	< 12.0 mg
B. Alcohol	< 75.0 mg
C. Hexanes	< 100.0 mg
Heavy Metals Extraction by Deionized water	< 1 ppm
Light transmission	NMT 10% at any wavelength 290 to 450 nm
Container Permeation	< 100 mg/day/liter
Multiple internal reflectance	Same as HDPE reference
Thermal analysis	Exotherm does not differ from standard by more than 6.0°C

All containers and all resins met all the tests.
Diagrams of each bottle size and each closure with their dimensions are given in the NDA on pages 03 0846 to 03 0855. The bottles are tested for visual inspection, dimensional analysis, and certification of resin/colorant and infrared scan. The closures are tested for visual inspection, dimensional analysis, and infrared scan of liner and inner seal. Flexible packaging materials are tested for visual inspection, dimension analysis and infrared scan.

7) Stability

18 months @ -20°C for bulk
24 months for capsules

NEW DRUG SUBSTANCE (BULK)

Stability studies were performed at [redacted] Batches were made from 1984 to 1989.

Stability Conditions

Samples were stored under the following conditions:

-20°C
5°C
15°C
RT=room temperature
40°C
25°C/75% RH
25°C/90% RH
40°C/75% RH
LT= 10000-lux white light at 25°

Batch numbers tested

Batch #	MFG date	Packaging
4X803	10/84	These lots were stored in stoppered glass bottles for the 5°C to 40°C conditions. Samples were stored in open glass containers at RH or LT conditions.
4X804	11/84	
4Y805	11/84	
88ZC03	12/88	
88ZC04	12/88	
88ZC05	12/88	
88ZC06	12/88	
886006	6/88	Polyethylene Bag (720 ± 9 mm wide, 1510 ± 20 mm long, and 0.10 ± 0.02 mm thick) made of low-density polyethylene (LDPE) virgin sheets which are doubled and placed in fiber drums.
886007	6/88	
886010	6/88	
893004	5/89	
893005	5/89	
893006	5/89	

NOTE: THE SIZE OF THE LOTS SHOULD BE GIVEN FOR EACH LOT USED IN THE STABILITY STUDIES ON THE NEW DRUG SUBSTANCE. THE STABILITY REPORT SHOULD ALSO STATE WHETHER OR NOT PRODUCTION TYPE EQUIPMENT WAS USED TO PRODUCE EACH BATCH.

Test performed

Description (Physical Appearance)
Specific Rotation
Moisture
Assay (HPLC)
Related Substances I
Related Substances II (group X compounds)

Sampling Times and conditions

Lots 4X803, 4X804, 4Y405

5°C	(0, 3, 6, 9, 12, 18, 24, 27 months)
15°C	(0, 3, 6, 9, 12, 18, 24, 27 months)
RT	(0, 3, 6, 9, 12, 18, 24, 27 months)
40°C	(0, 2, 4, 6 months)
25°C/75% RH	(0, 2, 4, 6 months)
25°C/90% RH	(0, 2, 4, 6 months)
40°C/75% RH	(0, 2, 4, 6 months)
10000 lux	(0, 7, 14, 28 days)

Lots 88ZC03, 88ZC04, 88ZC05, 88ZC06

5°C	(0, 3, 6, 9, 12, 18 months)
RT	(0, 3, 6, 9, 12, 18 months)
40°C	(0, 1, 2, 3, 4, 6 months)
25°C/75% RH	(0, 1, 2, 3, 4, 6 months)
40°C/75% RH	(0, 1, 2, 3, 4, 6 months)
10000 lux	(0, 7, 14, 28 days)

Lots 886006, 886007, 886010

5°C	(0, 3, 6, 9, 12, 18 months)
15°C	(0, 3, 6, 9, 12, 18 months)
RT	(0, 3, 6, 9, 12, 18 months)

Lots 893004, 893005, 893006

-20°C	(0, 6, 12, 18 months)

RESULTS

Physical Appearance

Samples stored at 15°C or less for up to 27 months remain within specification (white to yellowish white). Discoloration to yellowish brown occurs after 12 months at RT and even sooner at elevated temperatures and/or humidity conditions.

Specific Rotation

Specific rotation values decrease upon further degradation of ceftibuten. The change in specific rotation is observed to parallel a decrease in drug substance potency and to provide a satisfactory control of optical purity.

Moisture

Samples stored at all conditions were observed to remain within the specification limits %) for up to 27 months. No increasing or decreasing trends could be seen. The moisture level seems to be sufficient to maintain the dihydrate form.

Assay (HPLC)

The potency of ceftibuten decreases appreciably with time when stored at 5°C or higher. At 5°C the rate of loss is about 2 to 3% per year. An increase in relative humidity is also observed to further enhance the degradation rate. Exposure to light produces about a 4 to 5% loss in potency in 4 weeks. Ceftibuten stored in polyethylene bags inside of fiber drums and stored at -20°C is still within specifications after 18 months. This storage condition is the one the applicant is going to use.

Related Substance-I and Related Substances -II

Both related substances increase with a decrease in ceftibuten potency. Related substances I remain within specifications (NMT %) when stored at 5°C or less for up to 24 months. Related substances II (group X compounds) and the total related substances remain with specifications (NMT % and NMT %, respectively) when stored at -20°C for up to 18 months.

A stability protocol is included in the NDA on pages 03 0188 and 03 0189. The first three production batches will be stored in one liter metal containers with a gasket and contain one 400 gram sample packaged in an inner liner of LDPE, flushed with nitrogen and sealed with a plastic tie. An outer liner composed of polyvinylidene chloride coated nylon/LDPE and sealed with a plastic tie will be used. An oxygen absorbent will be placed between the inner and outer liners. These samples will be tested for appearance, specific rotation, moisture, HPLC assay, and related substances. Samples will be stored at -20°C, 5°C, and 25°C and tested at 0, 3, 6, and 9 months. Samples stored at -20°C and 5°C will be tested at 12 months and samples stored at -20°C will be tested at 18 and 24 months. One batch per 50 production batches (at least one per year) will be stored at -20°C and tested at 0, 3, 6, 12, 18, and 24 months.

CONCLUSION FOR NEW DRUG SUBSTANCE STABILITY

Ceftibuten drug substance stored in low-density polyethylene double bags and placed in fiber or steel drums at -20°C is stable for 18 months.

CAPSULE STABILITY--200 mg

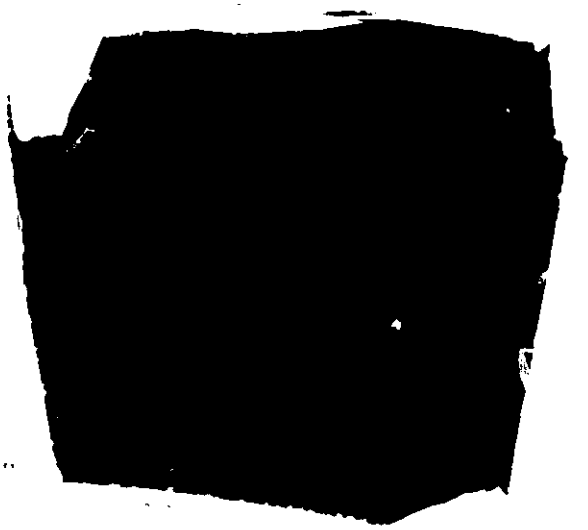
Batches Numbers

The following batches were tested: 22023-062, 22023-083, 22023-099, 21959-105, 21959-111 and 0-GEN-238.

Manufacturing Data

Batch No.	MFG. date	Stability date
22023-062	8/88	10/88
22023-083	10/88	12/88
22023-099	11/88	12/88
21959-105	2/89	3/89
21959-111	2/89	3/89
0-GEN-238	10/90	1/91*

* Laminate strip package placed on stability 3/91



Packaging Information

22023-062A	120 mL HDPE bottle, cotton coil, 28 mm-400 polypropylene child-resistant cap with pulp/polyethylene liner and [illegible]
21959-105C 21959-111C 0-GEN-238A	Same as above but no cotton coil
22023-062B	50 mL HDPE bottle, cotton coil, 28 mm-400 polypropylene child-resistant cap with pulp/polyethylene liner and glassine innerseal--20 capsules
21959-105D 21959-111D 0-GEN-238B	Same as above but no cotton coil
22023-083A 22023-099A 21959-105E 21959-111E 0-GEN-238C	Laminate composed of low density polyethylene/aluminum foil/low density polyethylene/paper--1 capsule per pouch

Stability Conditions

The following conditions were used during the stability testing of the 200 mg capsules:
Ref, 4°C ± 2°C
RT, 25°C ± 2°C
30°C ± 2°C
35°C ± 2°C
35°C at 75 % RH
Fluorescent light, 250 foot-candles--1 month is equivalent to about 33 months of home lighting at 18 hours/day

Test Performed

Description (Physical Appearance)
Moisture
Assay for Ceftibuten
Estimation of Related Compounds
Dissolution

Sampling Times and Conditions

Batches 22023-062A and 22023-062B (HDPE bottles of 20 and 100)

Initial	
4°C	(12, 24 months)
25°C	(6, 9, 12, 18, 24, 36 months)
30°C	(6, 12, 24 months)
35°C	(3, 6, 12 months)
35°C/75% RH	(3 months)

Related compounds were not tested at initial or 3 months.
Dissolution was not tested at 30°C at 6 months.
Moisture was only tested at 35°C/75% RH at 3 months and at the 24 and 36 month testing points.

Batches 22023-083A and 22023-099A (laminate strips)

Initial	
4°C	(6, 12, 24 months)
25°C	(3, 6, 9, 12, 18, 24, 36 months)
30°C	(6, 12, 24 months)
35°C	(3, 6, 12 months)

Related compounds were not tested at initial, 3, or 9 months. for either lot and at 6 months only for lot 22023-099A.
Dissolution was not tested at 4°C at 6 months.

Batches 21959-105C, D, E and 21959-111C, D, E
(HDPE bottles of 20 and 100 capsules and laminate strips)

Initial	
4°C	(6, 12, 24 months)
25°C	(3, 6, 9, 12, 18, 24 months)
30°C	(6, 9, 12, 18 months)
35°C	(3, 6 months)
35°C/75% RH	(3 months)
Light	(1 month)

Related compounds were not tested at initial or 6 months at 4°C, 25°C, or 30°C.
Dissolution was not tested under light conditions.
Moisture was not tested at light, 25°C at 3 months, or at 9 months.
Physical appearance was not tested at 3 months.
Only lots 21959-105C and 21959-105D were tested under light conditions.

Batch 0-GEN-238A, B, C
(HDPE bottles of 20 and 100 and Laminate strips)

Initial	
4°C	(6, 12, 24 months)
25°C	(3, 6, 9, 12, 18, 24, 36 months)
30°C	(3, 6, 12, 24 months)
35°C/75% RH	(3 months)

Dissolution is not tested at 3 months 35°C/75% RH
Future research lots will also follow this last testing protocol.

A stability protocol for production batches is given in the NDA on pages 03 1270. Representative samples of the first three batches in the marketed packages will be placed on stability at room temperature (23°C ± 2°C). Testing will be performed at 3, 6, 9, 12, 18, 24 months and as required. Samples will also be stored at 35°C and tested at three and six months. If the product is packaged in multiple package sizes and types, a total of three batches of each type will be added to the program, including the smallest and largest of each type of packaging. One batch for every 50 batches in a production year (at least one per year), will be placed on stability and stored at room temperature. Testing will be done every six months. Samples are tested for assay, related compounds, moisture, dissolution and appearance. Any batch that fails will be investigated and withdrawn form the market if warranted.

RESULTS

Description

Capsule powder from refrigerated samples for all batches and at all times points tested up to and including 24 months show no change in physical appearance. The powder contained in capsules stored at accelerated conditions of 30°C and 35°C for up to 12 months and 35°C/75% RH for three months appeared to be slightly to moderately discolored or darker. Room temperature samples stored for up to 24 months may be slightly discolored. The opaque capsule shell hides this discoloration and the product maintains its appearance during its shelf-life.

Capsule shells from some samples packaged in laminate strips show a tendency to soften when stored at 4°C for an extended period of time. The same capsules appear normal when in bottles. Only some and not all the capsules in laminates soften. Strips with soft capsules were observed to have defective seals. This defect has been corrected. The soft capsules are not sticky or tacky and are swallowable. They assume their normal hardness in a manner of minutes when exposed to ambient conditions.

Water Content

Initial values ranged from %. Capsules stored in HDPE bottles maintain a moisture level during 24 months at room temperature of 7.6 to 10.8% which is close to that of the initial samples. Refrigerated samples in HDPE bottles show a similar range after 24 months of 8.8 to 11.6%. Storage at 30 or 35°C produced moisture levels of 8.0 to 11.5%. There were not definite trends in the data with time for capsules stored in HDPE bottles.

Laminate strip storage at RT shows moisture levels of 5.4 to 10.9% with no apparent trend with time. There is, however, a definite trend in moisture levels with respect to temperature. Refrigerated samples show a moisture range of %, 30°C samples range from % and samples at 35°C range from %. Water content seems to decrease with an increase in temperature for some samples. Loss of moisture from the capsule is due to defective seals on the laminate strip. This defect is being corrected.

Assay for Ceftibuten

The assay value decreases with an increase of time and/or temperature. In general, the value does not change significantly after one year at refrigeration. Storage at 35°C shows a % decrease per year when packaged in HDPE bottles and up to 1% per year when stored in laminate strips. This greater assay loss is again due to a high moisture loss from the poor seal integrity of the laminate strip package. This loss in moisture lead to more extensive formation of N1, the decarboxylation product that predominates when dehydration of the molecule occurs. Capsules stored in HDPE bottles or laminate strips are observed to decrease in potency by % a year at room temperature. Capsules stored at 2 to 25°C appear to stay within assay specifications for at least two years.

Related Compounds

Total Related Compounds increase with time and temperature with the exception of I1 which is only an impurity. As a group, the related compounds increase about % per year for capsules at room temperature.

The maximum level of each individual or designated group of related substances observed at 24 months RT storage is given below:

Group X	%
Unknowns and I1	%
N1	%*
N2, L2, L3	%
Trans	%
L4, L5, and Unks	%
Total	%

* Laminate strip at 24 months, at 18 months maximum %. HDPE bottle maximum at 24 months is %.

Three batches packaged in the laminate strip remain with the N1 specification of NMT %. None of these batches was above % N1 after 24 months. Only lot 21959-105E had a value of % at 24 months which is above the specification limit. This lot had samples with defective seals.

D· ·n

Satisfactory dissolution of the capsules after minutes is observed for samples stored at refrigerated or RT conditions for 18 to 24 months. No trend in the data is observed.

CONCLUSION FOR THE 200 MG CAPSULE

Ceftibuten capsules, 200 mg are stable for 24 months when stored between 2°C and 25°C.

CAPSULE STABILITY--400 mg

Batch Numbers

The following batches were tested: 23235-099, 23235-101, 23235-103 and 0-GEN-239.

Manufacturing Data

Batch No.	MFG. date	Stability date
23235-099	4/90	5/90
23235-101	4/90	5/90
23235-103	4/90	5/90
0-GEN-239	10/90	1/91*

* Laminate strip package placed on stabil[illegible]



Packaging Information

23235-099A 23235-101A 23235-103A 0-GEN-239B	50 mL HDPE bottle, 2 mm-4 polypropylene child-resistant cap wit.. pulp/polyethylene liner and glassine innerseal--20 capsules
23235-099B 23235-101B 23235-103B 0-GEN-239A	200 mL HDPE bottle, 38 mm-400 metal cap with pulp/polyethylene liner and glassine innerseal--100 capsules
23235-099C 23235-101C 23235-103C 0-GEN-239C	Laminate composed of low density polyethylene/aluminum foil/low density polyethyle.e/paper--1 capsule per pouch

Stability Conditions

The following conditions were used during the stability testing of the 400 mg capsules:
Ref, 4°C ± 2°C
RT, 25°C ± 2°C
30°C ± 2°C
35°C at 75 % RH
Fluorescent light, 250 foot-candles--1 month is equivalent to about 33 months of home lighting at 18 hours/day

Test Performed

Description (Physical Appearance)
Moisture
Assay for Ceftibuten
Estimation of Related Compounds
Dissolution

Sampling Times and Conditions

Batches 23235-099A, B, C, 23235-101A, B, C, 23235-103A, B, C (HDPE bottles of 20 and 100 and laminate strips)

Initial	
4°C	(6, 12 months)
25°C	(3, 6, 9, 12 months)
30°C	(3, 6, 12 months)
35°C/75% RH	(3 months)
Light	(1 month)

Dissolution was not tested at 35°C/75% RH or under light conditions.
Moisture was not tested under light conditions.
Light condition testing was only done on batches 23235-099A, B, and C.

Batch 0-GEN-239A, B, C (HDPE bottles of 20 and 100 and laminate strips)

Initial	
4°C	(6 months)
25°C	(3, 6 months)
30°C	(3, 6 months)
35°C/75% RH	(3 months)

Dissolution was not tested at 35°C/75% RH.
Laminate strips were only tested through 3 months.

RESULTS

Description

Capsule powder from refrigerated samples at 12 months show no change in physical appearance. Powder from capsules stored at accelerated conditions of 30°C for up to 12 months and 35°C/75% RH for three months appeared to be slightly darker. Room temperature samples stored for up to 12 months are very slightly to slightly darker. The opaque capsule shell hides this discoloration and the product maintains its appearance during its shelf-life.

Capsule shells from some samples packaged in laminate strips show a tendency to soften when stored at 4°C for an extended period of time. The same capsules appear normal when in bottles. Only some and not all the capsules in laminates soften. Strips with soft capsules were observed to have defective seals. This defect has been corrected. The soft capsules are not sticky or tacky and are swallowable. They assume their normal hardness in a manner of minutes when exposed to ambient conditions.

Water Content

Initial values for the capsules on stability ranged from %. Capsules stored in bottles maintain a moisture level during twelve months of storage at 4°C or room temperature of %. The capsules in the laminated strips ranged from %. All moisture values are within specifications of NMT %.

Assay for Ceftibuten

The assay value decreases with an increase of time and/or temperature. The assay does not significantly change after refrigeration for six months, however, a slight decrease can be seen in some batches at the 12 month timepoint. Storage at 35°C/75% RH shows decreases of about % per year when packaged in HDPE bottle or laminate strips. Capsules stored in bottles or strips at room temperature decrease in potency by about 2 to 4% per year. This is about the decrease seen in the 200 mg capsules. Since the two formulations are identical with respect to identity and ratio of excipients to active ingredients this is not unexpected.

Related Compounds

Total related compounds increase with time and temperature with the exception of which is only an impurity. As a group, the related compounds increase about % in twelve months for capsules at room temperature.

The maximum level of each individual or designated group of related substances observed after 12 months RT storage is given below:

Group X	%
Unknowns and I1	%
N1	%
N2, L2, L3	%
Trans	%
L4, L5, and Unks	%
Total	%

Dissolution

Satisfactory dissolution of the capsules after minutes is observed for samples stored at refrigerated or RT conditions. No trend in the data is observed.

CONCLUSION FOR THE 400 MG CAPSULE

Ceftibuten capsules, 400 mg are stable for at least twelve months. Since this formulation is the same as that for the 200 mg capsule except that twice the fill weight is used and the 200 mg capsule is stable for 24 months this dosage may also use an expiry of 24 months. The loss in potency and the increase in related compounds through 12 months is almost identical for both dosages. This reviewer feels that the data from the 200 mg dosage can be used to support the same expiry for both dosages, even through the 400 mg dosage has data only through 12 months and this normally would allow only an 18 month expiry. This reviewer feels that two different expiry periods would be confusing and a 24 month expiry is justified for both dosages.

8) Environmental Impact Analysis Unsatisfactory

A copy of the environmental assessment report for this product was sent to Phillip G. Vincent, Environmental Assessment Officer (HFD-102) as requested of all new NDAs as of January 2, 1990. This copy was sent on January 17, 1992. A list of deficiencies was received on March 10, 1992. These deficiencies were sent to the sponsor. A separate environmental assessment is needed for each of the two NDAs. Appendix A has to be moved to the main body of the document. Actual test reports must be submitted for review. The appropriate environmental fate tests have not been submitted and the environmental assessment is not adequate. The appropriate environmental effects tests have not been submitted. In item 11 the applicant must include as an alternative to the proposed action the "no action" or not approvable alternative. Item 15 as defined in 21 CFR 25.31a(a) must be provided. Dr. Vincent suggested that this application not be filed as the environmental assessment is incomplete and inadequate and the required testing may exceed the 180 day review period.

DEFICIENCY:

A satisfactory environmental assessment is needed for this product. The submitted environmental assessment is incomplete and inadequate. The applicant must conduct tests and submit the information requested in the list of deficiencies dated March 10, 1992.

9) Labeling Needs minor revision
Microbiology section will be discussed in Part II

Draft copies of the label for a professional sample, a 20 capsule bottle, a 100 capsule bottle, and a 100 capsule unit dose package for both the 200 mg and 400 mg dosages are included in the NDA in volume 10 beginning on page 04 0529. These labels contain the NDC code, the number of capsules in the container, the product's trade and nonproprietary names, the capsule's strength, storage conditions, and the company's name and address. The statement "Caution: Federal law prohibits dispensing without prescription." is also included as is the statement "Usual Dose: See Product Information. Read Accompanying Directions Carefully.". A place for the Control number and expiration date is indicated.

DEFICIENCIES:

1) **The words "brand of" should be deleted from the labels.**

2) **The number of capsules in each container should be moved from the left margin of the label to the center of the label and it should read "Contains # capsules" or # capsules".**

3) **The statement "Each capsule contains 200 mg ceftibuten as the dihydrate" should be revised to read "Each capsule contains ceftibuten dihydrate equivalent to 200 mg of ceftibuten.**

A draft copy of the package insert is also included. The **Description Section** complies with 21 CFR 201.57. It contains the proprietary and established names of the drug product, the types of dosage forms, route of administration, ingredient information, the therapeutic class or the product, and the chemical name and structural formula of the drug. The **How Supplied Section** also complies with 21 CFR 201.57. It states the dosage forms and the number of units per package and the National Drug Code number for each dosage. Handling and storage conditions are given. The **Dosage and Administration Section** contains instructions on the preparation of the suspension. Both the **How Supplied Section** and the **Dosage and Administration Section** state that the unused portion of the oral suspension should be discarded 14 days after reconstitution.

DEFICIENCIES:

1) **The title of the product in the package insert heading should be listed as follows:**

CEDAX
Ceftibuten capsules and
Ceftibuten for oral suspension

2) **The inactive ingredients should be listed in alphabetical order.**

PART II--MICROBIOLOGY

The microbiology part of this review will be provided in a separate document.

CONCLUSIONS:

The sponsor should be notified of the following:

1) A satisfactory establishment evaluation is needed for the facilities that manufacture and test the new drug substance.

2) Samples were requested on February 3, 1992 for method validation. Samples were sent to the FDA laboratory on February 12, 1992. Method validation for the new drug substance must still be completed.

3) The tests for heavy metals, residue on ignition, and surface area performed on the new drug substance are not needed. They will not be included in the official monograph for this product. The sponsor may continue to perform these tests as "in house" specifications.

4) The test for the related substances 1 (HPLC) will not be included in the official monograph for the new drug substance. Unless present in high amounts or toxic, FDA has been controlling the amount of impurities by using the purity (assay) of the bulk material. The sponsor should continue to perform these tests, however. The structures of these compounds have been determined and they are present in only small amounts under normal storage conditions. The trans compound which is usually the most common one will be controlled by the specific rotation specification. Since the Group X compounds have not been fully characterized and this group is usually the most prominent degradation product they will be tested for in the official monograph.

5) The test for acetonitrile will not be included in the official monograph for the new drug substance. This is a residual solvent and is present in only very small amounts. The sponsor should continue to perform this test, however.

6) The TLC identity test will be the identification method in the official monograph of the new drug substance, since the use of the IR method would require that two different reference standards be established.

7) A crystallinity test should be performed on the new drug substance.

8) An acceptable EER is needed for the facility that manufacturers, processes, packages, and tests the capsules.

9) Method validation for the capsules must be completed by FDA laboratories. The tests for related substances will not be part of the official monograph for this product. The applicant should continue to perform these tests.

10) The possibility of the heat-sealed polyethylene-paper laminate sheets used to seal the iron oxide in the oxygen absorber used in the packaging of the new drug substance breaking should be addressed. What will the applicant do if this sheet breaks open and the iron oxide in the oxygen absorber gets into the new drug substance.

11) The size of the lots should be given for each lot used in the stability studies on the new drug substance. The stability report should also state whether or not production type equipment was used to produce each batch.

12) An expiry of 18 months at -20°C may be used for the new drug substance.

13) An expiry of 24 months at 2°C to 25°C may be used for the capsules.

14) A satisfactory environmental assessment is needed for this product. The submitted environmental assessment is incomplete and inadequate. The applicant must conduct tests and submit the information requested in the list of deficiencies sent to them.

15) The words "brand of" should be deleted from the labels.

16) The number of capsules in each container should be moved from the left margin of the label to the center of the label and it should read "Contains # capsules" or # capsules".

17) The statement "Each capsule contains 200 mg ceftibuten as the dihydrate" should be revised to read "Each capsule contains ceftibuten dihydrate equivalent to 200 mg of ceftibuten.

18) The title of the product in the package insert heading should be listed as follows:

CEDAX
Ceftibuten capsules and
Ceftibuten for oral suspension

19) The inactive ingredients should be listed in the package insert in alphabetical order

Peter A. Dionne

Peter A. Dionne
Microbiologist, HFD-520
April 30, 1992

This review contains 52 pages

Orig. NDA #50-685
cc: HFD-473
HFD-635
HFD-502/JWeissenger
HFD-520
HFD-520/Micro/Dionne
HFD-520/MO/Leissa
HFD-520/Pharm/Buko
HFD-520/CSO/Debellas

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/SMicro/ATSheldon
TS 5/19/92

6 /992

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Microbiology and Drug Control Review Notes #1

NDA # 50-685 **Date Completed:** June 29, 1992

Sponsor: Schering Corporation
2000 Galloping Hill Road Division
Kenilworth, NJ 07033
Attn: Douglas B. Given, M.D., Ph.D.; V.P. U.S. Regulatory Affairs
(908) 298-2780

Submission Reviewed: Original NDA dated December 20, 1991
Amendment dated March 13, 1992

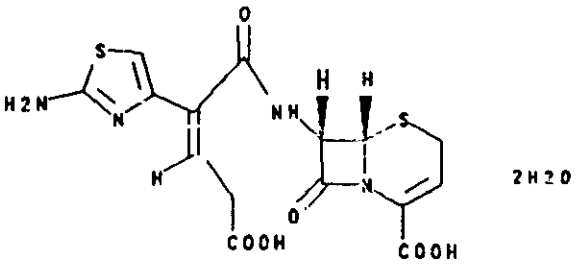
Providing For: Amendment provides information and confirmation that samples were sent to the FDA laboratory.

Names:
Trade: CEDAX™ capsules
Non-Proprietary: ceftibuten capsules
Chemical: (+)-{6R,7R)-7-[(Z)-2-(2-amino-4-thiazoly)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Dosage Form: 200 milligram and 400 milligram capsules

Pharmacological Category: semi-synthetic cephalosporin antibiotic

Structural Formula:



$C_{15}H_{14}N_4O_6S_2 \bullet 2H_2O$
M.W.= 446.43

Related NDA, IND, DMF, Form 5's:

IND IND NDA 50-686 Ceftibuten for oral suspension;
DMF

Initial Submission: Received by CDR: 12/20/91; Received by reviewer: 3/16/92; Reviewed initiated: 5/5/92; Review completed: June 29, 1992

Remarks:

Ceftibuten is another third generation cephalosporin. It is systemically available after oral administration. It has a carboxyethylidene side chain, which makes it different from most orally absorbed cephems which have a phenylglycine side chain. It has the aminothiazolyl moiety that is found in several other broad spectrum cephems such as cefotaxime and ceftazidime. The drug has good activity against most gram-negative bacteria. In general it was highly active against *Escherichia coli, Klebsiella, Proteus, Providencia, Salmonella, Haemophilus influenzae,* and *Streptococcus pyogenes*. It has limited activity against *Citrobacter, Enterobacter, Serratia* and *Streptococcus pneumoniae*. It has no activity against staphylococci, enterococci, *Pseudomonas, Acinetobacter, Flavobacterium* and obligately anaerobic bacteria. Ceftibuten is stable to most plasmid mediated beta-lactamases (except SHV-4 and SHV-5). The drug is not stable to the chromosomal beta-lactamases found in *Citrobacter, Enterobacter,* and *Serratia.* Ceftibuten is a poor inhibitor of most of the plasmid-mediated beta-lactamases, except SHV-4 and SHV-5. Ceftibuten is a weak inducer of the Class I chromosomal beta-lactamases.

PART I--MANUFACTURING AND CONTROLS

The manufacturing and controls for this NDA have been reviewed and submitted in a separate document labeled Review #1 and dated April 30, 1992.

PART II--MICROBIOLOGY

MECHANISM OF ACTION

The mechanism of action of ceftibuten, like that of all beta-lactams, depends on the binding to specific penicillin binding proteins (PBPs). These proteins are transpeptidases and are found in cytoplasmic membranes. They are responsible for crosslinking cell wall peptidoglycan chains. There are eight known PBPs in bacteria. Inhibition of PBPs 1 (1a and 1b), 2 and 3 result in interference with synthesis of rigid cell walls, leading to death of the organisms. PBPs 4, 5, 6, 7 and 8 are not lethal targets in bacteria. PBP-1a and 1b are transglycosylase transpeptidases involved in cell elongation. Binding of beta lactams to these PBPs results in cell lysis. PBP-2 is a transpeptidase responsible for maintenance of rod shape and septum formation. Binding to PBP-2 results in spheroplast formation. PBP-3 is a transglycosylase transpeptidase responsible for crosswall formation at cell division. Binding to PBP-3 results in filament formation.

While the aminothiazolyl moiety on ceftibuten is found in several other cephems such as cefotaxime and ceftazidime, the carboxyethylidene moiety has replaced the commonly found oximo ether moiety and is unique to ceftibuten. Apparently, this moiety is responsible for the oral absorption of the drug as well as its stability to broad-spectrum beta-lactamases.

Binding to PBPs is determined by competition experiments in which the test beta-lactam is allowed to compete for PBP binding with ^{14}C-penicillin G. Binding affinities (ID_{50}) obtained from these experiments are defined as the concentration of the beta-lactam in mcg/mL required for 50% inhibition of penicillin G binding. The affinities of ceftibuten for PBPs from *E. coli* K-12 were compared to those of other cephalosporins. Ceftibuten showed high affinity for PBP-3 with an ID_{50} of 0.025 μg/mL. Its ID_{50} for PBP-1a and 1b were 20 and 6 mcg/mL, respectively. Ceftibuten showed no affinity for PBP-2, -4, -5 and -6 at concentrations of 400 μg/mL [See TABLE 1]

TABLE 1
Competition of ceftibuten for PBPs of *E. coli* K-12

PBPs	ID_{50} (μg/mL)[a]		
	Ceftibuten	Cefaclor	cephalexin
1a	20	0.56	0.062
1bs	6	8.0	>12.5
2	>400	>12.5	6.3
3	0.025	1.8	1.0
4	400	1.3	2.3
5	>400	>12.5	>12.5
6	>400	>12.5	>12.5

a) Concentration required to reduce [^{14}C] penicillin G binding to PBPs by 50%.

Consistent with its high affinity for PBP-3 in *E. coli* ceftibuten caused the formation of filamentous cells at low concentrations against *E. coli* and *Klebsiella*.

Affinity of ceftibuten for the PBPs from *Proteus vulgaris* was shown to be high for PBP-3 and only slightly lower for PBP-1a and 1b. Like, cefotaxime, cefpodoxime and cefixime, ceftibuten had high affinities for PBP-2, -4, and -5 of *H. influenzae*. [See TABLE 2].

Table 2
Affinity of the PBPs of *H. influenzae* MAP for four cephalosporins

PBP	IC_{50} (μg/mL)			
	Cefotaxime	Ceftibuten	Cefpodoxime	Cefixime
1	0.2	2.37	0.3	0.4
2	0.037	0.016	0.013	0.0089
3	0.28	Not detected	0.2	0.48
4	0.00076	0.038	0.042	0.0093
5	0.002	0.023	0.12	0.017
6	Not detected	Not detected	Not detected	Not detected
7	>8.0	>4.0	>4.0	>4.0
8	0.02	0.47	0.18	Not detected

PBP-4 and -5 of *H. influenzae* are known to be involved in cell wall synthesis and appear to have transpeptidase activity which, together with the affinity data, suggest that these two proteins are important targets for the cephems.

Ceftibuten had low affinity for PBP-2 and -3 of *S. aureus*, which are thought to be the lethal targets in this organism and this fact may be the cause for the weak antibacterial activity of ceftibuten against this species.

PHARMACOKINETICS

Results of pharmacokinetics studies show that ceftibuten is well absorbed, and is rapidly eliminated primarily in the urine (about 57 to 70% of the dose in 24 hours). The drug is 75 to 90% absorbed when administered without food. A single 400 mg capsule of ceftibuten produces an average peak plasma concentration (C_{max}) of 15 μg/mL. Peak plasma concentrations occur between 2 to 3 hours after dosing.

Ceftibuten was not metabolized to any meaningful extent; 89% and 85% of the radioactivity in plasma and urine, respectively, after an orally administered ^{14}C-ceftibuten dose was observed to be ceftibuten. A larger percent of the radioactive dose was excreted into the urine (56%) than into the feces (39%). The plasma elimination half-life is 2 to 4 hours. The major drug-derived product, ceftibuten-trans, is present in plasma and urine in small amounts (about one-tenth the concentration of ceftibuten). Ceftibuten-trans has only one-eighth of the ceftibuten antibacterial activity. At plasma concentrations ranging between μg/mL, ceftibuten is % bound to plasma proteins.

The bioavailability of ceftibuten is dose proportional from 200 to 400 mg, but less than dose proportional at 800 mg. Plasma drug concentrations reach steady-state by the third day of a 200 mg twice a day dose regimen with little or no accumulation. The C_{max} at steady-state is about 19 mcg/mL after 400 mg twice a day dosing. Administration of a 400 mg capsule with food delays the time of C_{max} by about 1.75 hours, but does not affect the peak concentration and the extent of absorption. Administration of a 400 mg dose of suspension with food reduces peak plasma concentration by 26% and area under the plasma concentration-time curve (AUC) by 17%.

Average AUCs at steady-state in elderly subjects are about 58% higher than average AUCs in young adults. Steady-state in both populations is achieved by day three.

In subjects with hepatic dysfunction, the average AUC was higher and the plasma half-life longer than in healthy subjects. In subjects with renal impairment, both AUC and plasma half-life increase with increasing degree of renal impairment.

Ceftibuten penetrates into inflammatory fluid, middle ear fluid and tissues of the respiratory tract. Ceftibuten was not detected in the milk of nursing women.

ANTIMICROBIAL ACTIVITY

Numerous studies were performed to determine the *in vitro* spectrum of ceftibuten. Most studies tested between 20 and 50 strains of each species. One study looked at the activity of ceftibuten, cefixime, and cefuroxime against 4735 clinical isolates. In this study ceftibuten inhibited nearly 92% of the 3072 Enterobacteriaceae at ≤ 8 μg/mL, cefixime inhibited 78.7% at ≤1.0 μg/mL and cefuroxime inhibited 45.1% at ≤ 2.0 μg/mL. [See TABLE 3]

Table 3
The *in vitro* activity of ceftibuten against gram-negative organisms

Organism	Ceftibuten		Cefixime		Cefuroxime	
	MIC 50	MIC 90	MIC 50	MIC 90	MIC 50	MIC 90
Citrobacter						
amalonaticus (16)	0.06	1.0	≤0.12	2.0	16	>16
diversus (32)	0.06	0.25	≤0.12	0.5	8.0	>16
freundii (109)	2.0	>32	4.0	>4.0	8.0	>16
Enterobacter						
aerogenes (124)	0.5	>32	4.0	>4.0	4.0	>16
agglomerans (16)	0.12	>32	0.25	>4.0	4.0	>16
cloacae (223)	1.0	>32	2.0	>4.0	16	>16
Escherichia coli (965)	0.12	0.5	0.25	1.0	4.0	8.0
Hafnia alvei (11)	>32	>32	>4.0	>4.0	>16	>16
Klebsiella						
oxytoca (83)	≤0.015	0.06	≤0.12	0.5	2.0	4.0
pneumoniae (433)	0.03	0.12	≤0.12	0.25	2.0	8.0
Morganella morganii (71)	0.25	16	4.0	>4.0	>16	>16
Proteus						
mirabilis (224)	≤0.015	0.03	≤0.12	≤0.12	1.0	2.0
vulgaris (30)	0.03	0.03	≤0.12	0.25	>16	>16

Table 3 (cont)

Organism	Ceftibuten		Cefixime		Cefuroxime	
	MIC 50	MIC 90	MIC 50	MIC 90	MIC 50	MIC 90
Providencia						
rettgeri (10)	≤0.015	0.03	≤0.12	≤0.12	≤0.5	>16
stuartii (25)	≤0.015	1.0	≤0.12	>4.0	8.0	>16
Salmonella spp. (19)	0.06	0.5	≤0.12	1.0	4.0	8.0
Serratia liquefaciens (5)	0.06	–	0.5	–	>16	–
Serratia marcescens (92)	0.25	4.0	0.5	>4.0	>16	>16
Achromobacter xylosoxidans (5)	>32	–	>4.0	–	>16	–
Acinetobacter spp. (54)	16	>32	>4.0	>4.0	>16	>16
Aeromonas hydrophila (5)	0.25	–	0.25	–	≤0.5	–
Alcaligenes odorans (5)	16	–	4.0	–	>16	–
Pseudomonas aeruginosa (465)	>32	>32	>4.0	>4.0	>16	>16
Pseudomonas spp. (50)[a]	>32	>32	>4.0	>4.0	>16	>16

a) Includes *P. fluorescens-putida* (22 strains) and *P. maliophilia* (28 strains)

In a study in which a collection of 108 different strains, many with β-lactamases, were tested against the trans-isomer of ceftibuten, it was found that trans-ceftibuten was 4 to 8-fold less potent than ceftibuten.

Listed below in alphabetical order by organism are summaries of all of the *in vitro* studies presented in the NDA to determine the activity of ceftibuten.

The following abbreviations are used in the following charts to indicate the type of media used:

MHA	Mueller-Hinton Agar
MHB	Mueller-Hinton Broth
STA	Standard Test Agar
ISA	Iso-Sensitest Agar
ISB	Iso-Sensitest Broth
W-C	Wilkens-Chalgren
GAM	GAM (Nissui)
LHB	Laked Horse Blood
HS	Horse Serum
HTM	Haemophilus Test Medium
BF	Bacto-Fildes enrichment
SB	Sheep Blood
LSB	Laked Sheep Blood

Achromobacter xylososidans [Data not shown].

Only one study done with 5 strains using MHB media MIC_{50} >32 μg/mL.

Table 4
The *in vitro* activity of ceftibuten against *Acinetobacter* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
54	MHB	USA		16	>32
38	MHB	EUROPE		>16	>16
34	STA	JAPAN	*A. calcoaceticus*	12.5	100
20	MHA	GERMANY	*A. anitratus*	32	32
20	MHA	GERMANY	*A. lwoffi*	1	16
10	MHA	BELGIUM		32	32
9	ISA	UK	*A. anitratus*	>32	>32
9	ISA	UK	*A. lwoffi*	4	>32
20	ISA	UK		16	64

Aeromonas hydrophila [Data not shown].

Only one study with five strains using MHB done in USA with MIC_{50} = 0.25 μg/mL.

Alcaligenes odorans [Data not shown].

Only one study with five strains using MHB done in USA with MIC_{50} = 16 μg/mL.

Table 5
The *in vitro* activity of ceftibuten against anaerobic bacteria

# Strains	Media	Location	Comments	MIC 50	MIC 90
12	--	GERMANY	*C. difficile*	>64	>64
5	--	GERMANY	*Clostridium* spp.	4	>64
11	--	GERMANY	*Bacteroides* spp.	>64	>64
4	--	GERMANY	*Peptococcus magnus*	>64	>64
14	W-C	UK	*Bacteroides fragilis*	16	>128
9	W-C	UK	*Clostridium* spp. 0.12 (4), 4.0 (5)	--	--
3	W-C	UK	*C. difficile* >128 (3)	--	--
8	W-C	UK	*Peptostreptococcus* spp.	--	--
7	W-C	UK	*P. asacchrolyticus* 0.008 (2), 0.015, 1, 4	--	--
33	GAM	JAPAN	*B. fragilis*	12.5	>100

Table 6
The *in vitro* activity of ceftibuten against *Bordetella* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
33	IAS+LHB	GERMANY	*B. pertussis*	--	16
33	ISA+LHB	GERMANY	*B. parapertussis*	--	32

Brucella spp. [Data not shown].

Only one study with 5 strains done with MHA in Germany with MIC_{50} = 8.0 μg/mL and MIC_{90} = 8.0 μg/mL.

Table 7
The *in vitro* activity of ceftibuten against *Campylobacter jejuni*

# Strains	Media	Location	Comments	MIC 50	MIC 90
27	MHB	S.E. ASIA		2.0	16
16	MHA	GERMANY		8.0	8.0
16	MHA	GERMANY	*C. pylori*	4.0	8.0
100	MHB	BELGIUM		6.25	100
100	MHB	RWANDA		12.5	25

Acinetobacter species are not usually susceptible to ceftibuten. The MIC_{50} range for the *Acinetobacter* species tested was μg/mL and the MIC_{90} range was μg/mL. *A. lwoffi* appears to be the most sensitive species tested with MIC_{50}s of μg/mL, but the MIC_{90} were 16 and >32 μg/mL [Table 4].

There is insufficient data to evaluate the susceptibility of *Achromobacter xylososidans, Aeromonas hydrophila,* or *Alcaligenes odorans* to ceftibuten.

Anaerobic bacteria are not susceptible to ceftibuten. The *C. difficile* MIC_{50} was 64 μg/mL and other *Clostridium* species tested had MIC_{50}s of ≤4 μg/mL, but MIC_{90}s >64 μg/mL. *B. fragilis* MICs ranged from μg/mL and appeared to be media independent [Table 5].

Bordetella species are not very susceptible to ceftibuten, the two species tested had MIC_{90} values ≥ 16 μg/mL. There is not enough studies to evaluated the susceptibility of *Brucella* species, but they appear to be resistant to ceftibuten [Table 6].

Campylobacter jejuni is not susceptible to ceftibuten, all MIC_{90} values were ≥8 μg/mL and many studies had MIC_{50} values above 8 μg/mL [Table 7].

Table 8
The *in vitro* activity of ceftibuten against *Citrobacter diversus*

# Strains	Media	Location	Comments	MIC 50	MIC 90
10	MHB	USA		<0.25	--
10	MHB	USA		<0.06	<0.06
32	MHB	USA		0.06	0.25
3	MHA	GERMANY		0.13	0.13
6	ISA	UK		0.03	0.06

Table 9
The *in vitro* activity of ceftibuten against *Citrobacter freundii*

# Strains	Media	Location	Comments	MIC 50	MIC 90
10	MHB	USA		2.0	--
10	MHB	USA		>32	>32
109	MHB	USA		2.0	>32
48	STA	JAPAN		0.39	50
20	MHA	GERMANY		0.5	4
17	ISA	UK		0.03	2.0
5	ISA	UK	0.015, 0.5, 1, 2, 32	--	--

Table 10
The *in vitro* activity of ceftibuten against other *Citrobacter* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
16	MHB	USA	*C. amalonaticus*	0.06	1.0
10	MHB	EUROPE	Cefazolin-resistant	2.0	>16
23	MHA	BELGIUM		32	>32

Citrobacter diversus appears to be susceptible to ceftibuten. The sixty-one strains of *C. diversus* tested for susceptibility to ceftibuten resulted in MIC_{90}s of ≤ 0.25 µg/mL [Table 8]. Studies with *C. freundii*, however, resulted in low MIC_{50} values but high MIC_{90} values suggesting that this organism may produce a type I chromosomally mediated cephalosporinase which can hydrolyze ceftibuten [Table 9]. If strains with these enzymes are present, they will give high MICs and make the MIC_{90} for the study high. Other *Citrobacter* species gave MIC values similar to those in the *C. freundii* studies [Table 10]. In order to be included in the package insert the MIC_{90} value in most studies must be below the susceptibility cut-off, *Citrobacter* species will not be included.

Table 11
The *in vitro* activity of ceftibuten against *Enterobacter aerogenes*

# Strains	Media	Location	Comments	MIC 50	MIC 90
19	MHB	USA		<0.25	--
20	MHB	USA		0.5	>32
124	MHB	USA		0.5	>32
37	STA	JAPAN		0.2	100
10	MHA	GERMANY		0.5	64
7	ISA	UK		0.125	>32

Table 12
The *in vitro* activity of ceftibuten against *Enterobacter agglomerans*

# Strains	Media	Location	Comments	MIC 50	MIC 90
10	MHB	USA		<0.25	--
10	MHB	USA		0.12	8.0
16	MHB	USA		0.12	>32
4	MHA	GERMANY		0.03	0.03

Table 13
The *in vitro* activity of ceftibuten against *Enterobacter cloacae*

# Strains	Media	Location	Comments	MIC 50	MIC 90
20	MHB	USA		<0.25	--
22	MHB	USA		>32	>32
223	MHB	USA		1.0	>32
33	STA	JAPAN		0.38	>100
20	MHA	GERMANY		1.0	>64
42	ISA	UK		0.5	>32
5	ISA	UK	0.015 (2), 0.5, 2, 32	--	--

Table 14
The *in vitro* activity of ceftibuten against other *Enterobacter* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
89	MHB	EUROPE	Cefazolin-resistant	2.0	>16
11	MHA	GERMANY	*E. sakazakii*	0.03	0.06
61	MHA	BELGIUM		>32	>32
2	ISA	UK	*E. intermedius*	>32	>32
1	ISA	UK	*E. amigenus*	0.25	--

Enterobacter species including *E. aerogenes*, *E. agglomerans* and *E. cloacae* produced susceptible MIC_{50}s ($\leq$ 8 μg/mL) in most studies but the MIC_{90}s in these studies were usually above 32 μg/mL [Tables 11-14]. This is due to the fact that *Enterobacter* species often produce a type I chromosomally mediated cephalosporinase that will hydrolyze ceftibuten and if these strains are included in the study the MIC_{90} value will be high. Since inclusion of a species into the microbiology section of the package insert requires that the species have an MIC_{90} value less than or equal to the susceptible cut-off, *Enterobacter* species will be excluded since the MIC_{90}s were greater than the susceptible cut-off of μg/mL.

Table 15
The *in vitro* activity of ceftibuten against *Enterococcus faecalis*

# Strains	Media	Location	Comments	MIC 50	MIC 90
423	MHB	USA		>32	>32
20	MHA	GERMANY		>64	>64
10	MHA+LHB	BELGIUM		>32	>32
20	ISA	UK		128	>128
30	STA+HS	JAPAN		>100	>100

Table 16
The *in vitro* activity of ceftibuten against *Enterococcus faecium*

# Strains	Media	Location	Comments	MIC 50	MIC 90
14	MHB	USA		>32	>32
17	MHA	GERMANY		>64	>64
5	ISA	UK	>128 (5)	--	--

Table 17
The *in vitro* activity of ceftibuten against other *Enterococcus* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
15	MHB	USA	*E. avium*	>32	>32
13	MHA	GERMANY	*E. liquefaciens*	>64	>64

Enterococcus species are resistant to ceftibuten, both the MIC_{50} and MIC_{90} value in most studies were greater than 32 μg/mL [Tables 16-17]. *Enterococcus* species will not be included in the package insert.

NDA 50685

II. This submission also provides labeling for draft pouches for the hospital unit dose package. The hospital unit dose package will contain 40 capsules. Box labels for capsules of both strengths are also provided. Four pouches (1 capsules per pouch) will be contained in each carton for the 200 mg capsule and two pouches (1 capsule per pouch) for the 400 mg capsule. These will only be used at launch to stock pharmacies.

The draft pouch and box labels are satisfactory.

III. Most of the changes made are small changes in the quantities of materials used in the synthesis of the drug product and to provide more details in the methods used.

Minor changes in the synthesis are satisfactory.

CONCLUSIONS:

1) The facility that produces the new drug substance must still be inspected and found satisfactory.

2) Method validation is still being done on the new drug substance.

3) Test for heavy metals, residue on ignition, and surface area will be performed as "in-house" tests on the new drug substance.

4) The test for related substances I will be an "in-house" test, the test for Group X compounds will be in the official monograph for the new drug substance.

5) T... or acetonitrile will be done "in-house."

6) The TLC identity test will be the official monograph method for the new drug substance.

7) The USP <695> crystallinity test has been added to the specifications for the new drug substance. The revised specifications for the new drug substance are satisfactory.

8) Schering's Miami Lakes facility must still be inspected and found satisfactory to produce the drug product.

9) Method validation for the capsules is still being done.

10) The explanation of how the oxygen absorber is packaged to prevent leakage into the new drug substance is satisfactory.

11) The revised stability report for the new drug substance stating the size of each lot is satisfactory.

12) An expiry of 18 months at -20°C will be used for the new drug substance.

13) An expiry of 24 months at 2°C to 25°C will be used for the capsules.

14) The Environmental Assessment report submitted on August 14, 1992, must still be reviewed and found satisfactory.

15) The deletion of the words "brand of" from the labels is satisfactory.

16) The listing of the number of capsules per container is now satisfactory.

17) The wording of the potency in the product is now satisfactory.

18) The revised package insert must be submitted and reviewed to see if the title of the product in the package insert is satisfactory.

19) The revised package insert must be submitted and reviewed to see if the inactive ingredients are properly listed.

20) The draft container labels for the pouches and box labels are satisfactory.

21) The minor corrections and revisions made in the method of manufacture and specifications for the new drug product are satisfactory.

The applicant should be notified that the following items are still outstanding on this application and are needed for approval.

1) **Method validation still must be completed on the new drug and its dosage forms.**

2) **A monograph must still be written and published for the new drug substance and its dosage forms. This will be done after method validation is complete and the drug approved.**

3) **A satisfactory establishment evaluation is needed for the sites that are involved in the production and testing of the new drug substance and its dosage forms.**

4) **A satisfactory environmental assessment report is still needed. This must be reviewed and approved by our environmental assessment officer.**

5) **A revised package insert must still be submitted and reviewed.**

Peter A. Dionne
Peter A. Dionne
Microbiologist HFD-520
September 1, 1992

This review contains 12 pages

cc: Orig. NDA # 50-685
HFD-473
HFD-635
HFD-502
HFD-520
HFD-520/Micro/Dionne
HFD-520/MO/Leissa
HFD-520/Pharm/Buko
HFD-520/CSO/Debellas 9/4/92

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/Smicro/ATSheldon 9/3/92

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS OCT 9 1992
Microbiology and Drug Control Review Notes #3

NDA # 50-685 **Date Completed:** October 6, 1992

Sponsor: Schering Corporation
2000 Galloping Hill Road Division
Kenilworth, NJ 07033
Attn: Alexander R. Giaquinto, Ph.D.; V.P. Worldwide Regulatory Affairs
(908) 298-2780

Submission Reviewed: Amendment dated September 24, 1992

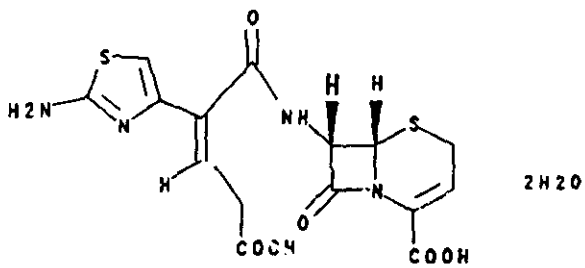
Providing For: Revised package insert

Names:
Trade: CEDAX™ capsules
Non-Proprietary: ceftibuten capsules
Chemical: (+)-(6R,7R)-7-[(Z)-2-(2-amino-4-thiazoly)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Dosage Form: 400 milligram capsules (200 milligram capsule deleted)

Pharmacological Category: semi-synthetic cephalosporin antibiotic

Structural Formula:



$C_{15}H_{14}N_4O_6S_2 \bullet 2H_2O$
M.W. = 446.43

Related NDA, IND, DMF, Form 5's:
IND IND
NDA 50-686 Ceftibuten for oral suspension;
Initial Submission: Received by CDR: 12/20/91; Received by reviewer: 3/16/92; Reviewed initiated: 4/1/92; Review completed: April 30, 1992

Remarks:

DESCRIPTION--This section is now satisfactory. The heading has been revised and is now satisfactory and the inactive ingredients are now given and are in alphabetical order.

HOW SUPPLIED--This section is satisfactory. The 200 milligram capsules are been deleted.

MICROBIOLOGY--This section has been revised and is now written almost exactly as requested in my microbiology review #1. The applicant has, however, added some organisms, especially in the *in vitro* listing. The applicant has also added *Enterobacter aerogenes* and *Enterobacter cloacae* to the *in vivo* list, but has added the qualifying statement "excluding strains hyper-producing chromosomal cephalosporinases." Also since the first review, NCCLS has eliminated the moderately susceptible category and now both this and the intermediate category are called intermediate and the definitions have been combined into one definition.

The opening paragraph for this section is satisfactory. The applicant has added the statement "Like other beta-lactam agents, ceftibuten should not be used against strains resistant to beta-lactams due to general mechanisms such as permeability or penicillin-binding protein changes like penicillin-resistant *S. pneumoniae*." They have excluded the statement "(excluding penicillin-resistant strains)" after *Streptococcus pneumoniae* in the listing of organisms.

REVIEWER COMMENT: I believe that since the list of organisms stands out from the rest of the information in the MICROBIOLOGY section that the statement "(excluding penicillin-resistant strains)" should not be deleted. The statement added to the end of the first paragraph in the MICROBIOLOGY section is good and should be retained, but somebody that does not read the whole package insert may miss this statement and think that all *S. pneumoniae* strains are susceptible.

The MEDICAL OFFICER will have to decide if *Enterobacter aerogenes* and *Enterobacter cloacae* should be included in the *in vivo* section. If these organisms are not included in this section then the Division will have to decide exactly what should be done for organisms such as these that technically should not be included using our current standard of MIC_{90} being below the susceptibility cutoff (8 mcg/mL for this drug). These organisms and the others qualified with an * in the package insert have some strains that produce a beta-lactamase and if these strains are included in the study a high MIC_{90} results, but most of the strains do not produce these beta-lactamases and have low MICs. **THIS REVIEWER FEELS THAT THESE ORGANISMS SHOULD PROBABLY BE ALLOWED AS LONG AS A QUALIFYING STATEMENT IS GIVEN.**

REVIEWER COMMENT: The following organisms should be deleted since only one or two studies were reported and usually only ten or fewer strains were included in each study:

Streptococcus C
Streptococcus G
Brucella

Haemophilus parainfluenzae should be deleted due to no *in vitro* studies being performed unless the MEDICAL OFFICER allows it in the *in vivo* section.

Neisseria should be deleted since this drug does not have an indication for sexually transmitted diseases.

Morganella should be listed as *Morganella morganii* since most studies were performed on this species and we now list only species in the package insert.

CONCLUSIONS:

From the CMC and Microbiology viewpoint the DESCRIPTION and HOW SUPPLIED sections of the package insert are now satisfactory.

The MICROBIOLOGY section should be written as follows:

> As with other beta-lactam agents, ceftibuten exerts its bactericidal action by binding to essential target proteins of the bacterial cell wall, leading to inhibition of cell-wall synthesis. Ceftibuten is stable in the presence of most plasmid-mediated beta-lactamases, but it is not stable in the presence of chromosomally-mediated cephalosporinases produced in organisms such as *Bacteroides, Citrobacter, Enterobacter, Morganella,* and *Serratia.* Like other beta-lactam agents, ceftibuten should not be used against strains resistant to beta-lactams due to general mechanisms such as permeability or penicillin-binding protein changes like penicillin-resistant *S. pneumoniae.*
>
> Ceftibuten has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections at the indicated body sites: (See **INDICATIONS AND USAGE** section.):
>
> <u>Gram-positive aerobes:</u>
>
> *Streptococcus pyogenes*
> *Streptococcus pneumoniae* (excluding penicillin-resistant strains)
>
> <u>Gram-negative aerobes:</u>
>
> *Enterobacter aerogenes**
> *Enterobacter cloacae**
> *Escherichia coli*
> *Haemophilus influenzae* (including beta-lactamase-producing strains)
> *Haemophilus parainfluenzae*
> *Klebsiella pneumoniae*
> *Moraxella (Branhamella) catarrhalis* (including beta-lactamase-producing strains)
> *Proteus mirabilis*
> *Proteus vulgaris*

The following *in vitro* data are available; however, their clinical significance is unknown. Ceftibuten exhibits *in vitro* MICs of 8 μg/mL or less against most strains of the following organisms; however, the safety and efficacy of ceftibuten in treating clinical infections due to these organisms have not been established in adequate and well-controlled trials.

Gram-negative aerobes

Citrobacter diversus
*Citrobacter freundii**
Enterobacter agglomerans
Klebsiella oxytoca
Morganella morganii
Providencia rettgeri
Providencia stuartii
Serratia marcescens
Serratia liquefaciens

* (excluding strains hyper-producing chromosomal cephalosporinases)

NOTE: Ceftibuten is inactive *in vitro* against Enterococci, Staphylococci, or *Acinetobacter, Enterobacter, Flavobacterium, Listeria,* and *Pseudomonas* species. In addition, it shows little *in vitro* activity against most anaerobes, including most species of *Bacteroides*. Ceftibuten transformed by isomerization to the trans-form has one-fourth to one-eighth the activity of ceftibuten.

SUSCEPTIBILITY TESTING

Susceptibility Tests: *Diffusion Techniques:* Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standardized procedure[1] that has been recommended for use with disks to test the susceptibility of organisms to ceftibuten uses the 30-μg ceftibuten disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ceftibuten.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-μg ceftibuten disk should be interpreted according to the following criteria:

Zone diameter	Interpretation
≥ 21	Susceptible (S)
18-20	Intermediate (I)
≤ 17	Resistant (R)

A report of "susceptible" implies that an infection due to the strain may be appropriately treated with the dosage of antimicrobial agent recommended for that type of infection and infecting species, unless otherwise contraindicated. A report of "intermediate" indicates that the result should be considered equivocal, and, if the organism is not fully susceptible to alternative, clinically feasible drug, the test should be repeated. This category implies 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 that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that these strains are not inhibited by the usually achievable systemic concentrations of the tested agent with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms (β-lactamases) are likely and clinical efficacy has not been reliable in treatment studies.

Standardized susceptibility procedures require the use of laboratory control organisms. The 30-μg ceftibuten disk should give the following zone diameters in these laboratory test quality control strains:

Organism	Zone diameter (mm)
Escherichia coli ATCC 25922	29-35

Cephalosporin class disks should not be used to test for susceptibility to ceftibuten.

Dilution Techniques: Use a standardized dilution method[2,3] (broth, agar, or microdilution) or equivalent with ceftibuten powder. The MIC values obtained should be interpreted according to the following criteria:

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

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard ceftibuten powder should provide the following MIC values:

Organism	MIC range (mcg/mL)
Escherichia coli ATCC 25922	
Pseudomonas aeruginosa ATCC 27853	
Staphylococcus aureus ATCC 29213	

The following references should be added in the REFERENCES section of the labeling:

1. National Committee for Clinical Laboratory Standards, Performance Standard for Antimicrobial Disk Susceptibility Tests - Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS, Villanova, PA, April, 1990.

2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Second Edition. Approved Standard NCCLs Document M7-A2 , Vol. 10, No. 8 NCCLS, Villanova, PA, April 1990.

3. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Susceptibility Testing; Third Information Supplement, NCCLS Document M100-S3, Vol. 11, No. 17 NCCLS, Villanova, PA, December 1991.

The remainder of the package insert is satisfactory from the microbiology viewpoint and CMC viewpoint.

NDA 50-685 CEFTIBUTEN CAPSULES

The following items are still outstanding on this application and are needed before approval unless otherwise stated:

1) Method validation still must be completed on the new drug and its dosage form. This may be completed after approval.

2) A monograph must still be written and published for the new drug substance and its dosage form. This will be done after method validation is complete and the drug approved.

3) A satisfactory establishment evaluation is needed for the sites that are involved in the production and testing of the new drug substance and its dosage forms. A trip to Japan is planned for the end of October and will include which produces the new drug substance. Mike Chappel of the Orlando District Office states that an inspection will be scheduled soon for Schering Laboratories in Miami Lakes, Florida, which manufactures the capsules.

4) The environmental assessment report for this product is still being reviewed. It must be found satisfactory and a FONSI written before approval.

Peter A. Dionne
Microbiologist, HFD-520
October 6, 1992

This review contains 9 pages

Orig. NDA #50-685
cc: HFD-473
HFD-635
HFD-502
HFD-520
HFD-520/Micro/Dionne
HFD-520/MO/Leissa
HFD-520/Pharm/Buko
HFD-520/CSO/Debellas

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/SMicro/ATSheldon
10/9/92
10/9/92

Table 18
The *in vitro* activity of ceftibuten against *Escherichia coli*

# Strains	Media	Location	Comments	MIC 50	MIC 90
24	MHB	USA		<0.25	–
35	MHB	USA		0.12	0.25
965	MHB	USA		0.12	0.5
20	MHB	EUROPE	Cefazolin-susceptible	<0.125	0.25
44	MHB	EUROPE	Cefazolin-resistant	0.125	16
10	MHB	S.E. ASIA	Enterotoxigenic strains	0.03	0.03
45	MHB	S.E. ASIA	Enteropathogenic strains	0.12	0.5
23	MHB	S.E. ASIA	Enterohemorrhagic strains	0.12	0.25
40	MHB	S.E. ASIA	Enteroinvasive strains	0.12	0.25
20	MHB	S.E. ASIA	Enteroadherent strains	0.06	0.25
103	STA	JAPAN		0.1	0.2
17	MHA	GERMANY	Ampicillin-susceptible	0.13	0.25
8	MHA	GERMANY	Ceftazidime-susceptible	0.13	0.25
116	MHA	BELGIUM		0.25	16
124	ISA	UK		0.25	0.5
3	MHA	GERMANY	Ceftazidime-resistant	1.0	1.0
50	ISA	UK		0.06	0.25

Escherichia coli appear to be susceptible to ceftibuten. Two studies had MIC_{90}s of μg/mL, but all other studies had MIC_{90}s below μg/mL [Table 18]. These results were independent of media used and location of the performance of the study, suggesting a rather homogeneous response of this microorganism to ceftibuten. *Escherichia coli* will be in the package insert.

Flavobacterium spp. [Data not shown].

Only one study was reported with 29 strains done in Japan with STA media. The MIC_{50} value was μg/mL and MIC_{90} value was mcg/mL. *Flavobacterium* species appear to be resistant to ceftibuten, but only one study was included and only a limited about of data are available. *Flavobacterium* species will not be included in the package insert.

Table 19
The *in vitro* activity of ceftibuten against *Haemophilus influenzae*

# Strains	Media	Location	Comments	MIC 50	MIC 90
18	HTM	USA	Ampicillin-sensitive beta-lactamase -	0.04	0.08
13	HTM	USA	Ampicillin-resistant beta-lactamase +	0.08	0.08
7	HTM	USA	Ampicillin-resistant beta-lactamase -	3.84	7.68
24	HTM	USA	Beta-lactamase -	--	<0.25
24	HTM	USA	Beta-lactamase +	--	<0.25
24	HTM	USA	Chloramphicol-Res	--	<0.25
22	HTM	USA	Beta-lactamase -	<0.06	<0.06
20	HTM	USA	Beta-lactamase +	<0.06	<0.06
20	MHA+LHB	USA	Beta-lactamase -	0.06	0.06
20	MHA+LHB	USA		0.06	0.06
42	STA+BF	JAPAN		0.1	0.2
24	MHA+LHB	GERMANY	Beta-lactamase -	0.06	0.13
16	MHA+LHB	GERMANY	Beta-lactamase +	0.06	0.13
6	MHA+LHB	GERMANY	*H. parainfluenzae*	0.06	0.06
35	MHA+LHB	BELGIUM		0.03	0.03
56	HTM	USA	Beta-lactamase +	<0.06	<0.06
94	HTM	USA	Beta-lactamase -	<0.06	0.25
50	ISB	SPAIN	Beta-lactamase +	--	0.03
75	ISB	SPAIN	Beta-lactamase -	--	0.03
33	ISA+LHB	UK	11 stains β-lactamase +	0.06	0.5
42	STA+BF	JAPAN		0.1	0.2

Haemophilus influenzae isolates are usually susceptible to ceftibuten. Beta-lactamase production does not effect susceptibility. Ampicillin-resistant, beta-lactamase negative strains have a higher MIC than other strains, but the MIC_{90} may still be below the μg/mL susceptibility cut-off [Table 19]. Results were independent of media used for testing. These data suggest the *H. influenzae* should be in the microbiology section of the package insert.

Table 20
The *in vitro* activity of ceftibuten against *Hafnia alvei*

# Strains	Media	Location	Comments	MIC 50	MIC 90
11	MHB	USA		>32	>32
5	MHA	GERMANY		0.5	1.0

Only two studies were performed using *Hafnia alvei* and they produced conflicting evidence on the susceptibility of this organism to ceftibuten [Table 20]. Only a total of 16 strains were tested. There is not enough data to determine whether this species is susceptible. *H. alvei* will not be included in the package insert.

Table 21
The *in vitro* activity of ceftibuten against *Klebsiella pneumoniae*

# Strains	Media	Location	Comments	MIC 50	MIC 90
21	MHB	USA		<0.25	--
23	MHB	USA		<0.06	0.25
433	MHB	USA		0.03	0.12
50	STA	JAPAN		0.025	0.050
16	MHA	GERMANY	Ceftazidime-susceptible	0.06	0.13
122	ISA	UK		0.01	0.03
4	MHA	GERMANY	Ceftazidime-resistant	0.25	0.5

Table 22
The *in vitro* activity of ceftibuten against other *Klebsiella* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
83	MHB	USA	*K. oxytoca*	<0.015	0.06
40	MHB	EUROPE	Cefazolin-resistant	<0.125	0.125
33	STA	JAPAN		<0.01	0.025
19	MHA	GERMANY	*K. oxytoca* Ceftazidime-susceptible	0.06	0.13
65	MHA	BELGIUM		0.06	1.0
16	ISA	UK	*K. oxytoca*	0.01	0.03
2	MHA	GERMANY	*K. oxytoca* Ceftazidime-resistant	0.13	0.13
50	ISA	UK		0.015	0.06

Klebsiella species including *K. pneumoniae* appear to be susceptible to ceftibuten. In most of the studies in which *K. pneumoniae* was not tested *K. oxytoca* was the tested species [Tables 21 and 22]. Comparisons of *K. pneumoniae* and *K. oxytoca* MIC results by media and location suggest that *K. oxytoca* may be slightly more susceptible to ceftibuten than *K. pneumoniae* but both strains have MICs below the proposed susceptible cut-off of μg/mL. Ceftazidime and cefazolin resistant strains appear to be susceptible to ceftibuten. Sufficient numbers of isolates were provided to justify inclusion of both organisms in the package insert.

Listeria spp. [Data not shown].

Only one study was done using MHA in Germany the MIC_{50} μg/mL and the MIC_{90} μg/mL.

Listeria species appear to be resistant to ceftibuten but there is very limited data available. They will not be included in the package insert.

Table 23
The *in vitro* activity of ceftibuten against *Moraxella catarrhalis*

# Strains	Media	Location	Comments	MIC 50	MIC 90
20	MHA+SB	USA		<0.25	4.0
20	MHA+SB	USA	17 strains resistant to penicillin	0.25	4.0
20	MHA+SB	USA	85% beta-lactamase +	<0.25	2.0
31	STA+HS	JAPAN		1.56	3.13
13	MHA	GERMANY		1.0	4.0
81	MHB	USA	Beta-lactamase +	2.0	4.0
19	MHB	USA	Beta-lactamase -	0.12	2.0
29	ISA	UK		0.05	4.0

Moraxella catarrhalis studies had MIC_{90} values of about μg/mL [Table 23]. This species is susceptible to ceftibuten, irrespective of the country of origin or the media used for testing. Beta-lactamase production did not effect the MIC values in these studies. *M. catarrhalis* will be included in the package insert.

Table 24
The *in vitro* activity of ceftibuten against other *Morganella* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
10	MHB	USA		<0.25	--
10	MHB	USA		0.12	8.0
71	MHB	USA		0.25	16
13	MHB	EUROPE	Cefazolin-resistant	<0.125	>16
33	STA	EUROPE		0.05	100
20	MHA	GERMANY	*M. morganii*	0.25	32
40	MHA	BELGIUM	*M. morganii*	8.0	>32
6	ISA	UK	*M. morganii*	0.03	1.0
25	ISA	UK	*M. morganii*	0.03	1.0

Morganella species including *M. morganii* studies produced MIC_{50}s that were low (except for one μg/mL value), but the MIC_{90} values were usually above μg/mL and most studies had a MIC_{90} value of μg/mL or higher [Table 24]. This is again due to the presence of chromosomal mediated cephalosporinases in this genus. *M. morganii* will not be included in the package insert.

Table 25
The *in vitro* activity of ceftibuten against *Neisseria* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
20	MHA+LHB	USA	*N. meningitidis*	<0.25	<0.25
19	MHA+LHB	USA	*N. meningitidis*	<0.06	<0.06
5	MHA+LHB	GERMANY	*N. gonorrhoeae* Pen-S	0.06	0.25
29	MHA+LHB	BELGIUM	*N. gonorrhoeae*	0.015	0.015
9	MHA+LHB	GERMANY	*N. gonorrhoeae* Pen-R	0.13	0.5
19	ISA+LHB	UK	*N. gonorrhoeae* 3 stains Pen-R	0.008	0.06
9	MHA+LHB	JAPAN		0.025	0.025

Neisseria species (*N. gonorrhoeae* and *N. meningitidis*) are susceptible to ceftibuten [Table 25]. Penicillin resistant (beta-lactamase positive) strains were as susceptible as penicillin sensitive (beta-lactamase negative) strains. *N. gonorrhoeae* has not been included in the package insert, may be added to the *in vitro* activity section if the sponsor desires.

Table 26
The *in vitro* activity of ceftibuten against *Proteus mirabilis*

# Strains	Media	Location	Comments	MIC 50	MIC 90
25	MHB	USA		<0.25	--
20	MHB	USA		<0.06	<0.06
224	MHB	USA		<0.015	0.03
6	MHB	EUROPE	Cefazolin-resistant	<0.125	--
34	STA	JAPAN		<0.01	0.025
20	MHA	GERMANY		0.03	0.03
94	MHA	BELGIUM		0.015	0.06
65	ISA	UK		0.01	0.03
50	ISA	UK		0.008	0.015

Table 27
The *in vitro* activity of ceftibuten against *Proteus vulgaris*

# Strains	Media	Location	Comments	MIC 50	MIC 90
10	MHB	USA		<0.25	--
10	MHB	USA		<0.06	<0.06
30	MHB	USA		0.03	0.03
15	MHB	EUROPE	*Proteus* spp. Cefazolin-resistant	<0.125	<0.125
38	STA	JAPAN		0.025	0.05
15	MHA	GERMANY		0.03	0.13
39	MHA	BELGIUM		0.015	0.03
5	ISA	UK		0.01	0.06
20	ISA	UK		0.015	0.03

Table 28
The *in vitro* activity of ceftibuten against *Providencic* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
30	MHB	USA		<0.25	--
10	MHB	USA	*P. rettgeri*	<0.06	<0.06
19	MHB	USA	*P. stuartii*	<0.06	<0.06
10	MHB	USA	*P. rettgeri*	<0.015	0.03
25	MHB	USA	*P. stuartii*	<0.015	1.0
26	STA	JAPAN	*P. rettgeri*	<0.01	0.025
38	STA	JAPAN	*P. stuartii*	<0.01	<0.01
20	MHA	GERMANY	*P. rettgeri*	0.03	0.13
16	MHA	GERMANY	*P. stuartii*	0.13	0.25
44	MHA	BELGIUM		0.015	0.06
8	ISA	UK	*P. stuartii*	0.01	0.01
3	ISA	UK	*P. rettgeri*	0.003	0.006
19	ISA	UK		0.008	0.015
5	ISA	UK	*P. rettgeri* 0.004, 0.008 (4)	--	--

Proteus mirabilis [Table 26], *Proteus vulgaris* [Table 27] and *Providencia* species (*Providencia rettgeri* and *Providencia stuartii*) [Table 28] are all susceptible to ceftibuten. The MIC_{50} and MIC_{90} values for all studies were below μg/mL. The type of media used or the location of the study did not alter the MIC values, suggesting a rather homogenous response of these genera to ceftibuten. *P. mirabilis*, *P. vulgaris*, *P. rettgeri*, and *P. stuartii* will be in the package insert.

Table 29
The *in vitro* activity of ceftibuten against *Pseudomonas aeruginosa*

# Strains	Media	Location	Comments	MIC 50	MIC 90
49	MHB	USA		>32	--
465	MHB	USA		>32	>32
17	MHA	GERMANY	Carbenicillin-susceptible	64	>64
13	MHA	GERMANY	Carbenicillin-resistant	>64	>64
10	MHA	BELGIUM		>32	>32
43	STA	JAPAN		50	>100

Table 30
The *in vitro* activity of ceftibuten against other *Pseudomonas* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
50	MHB	USA		>32	>32
155	MHB	EUROPE		>16	>16
8	MHA	GERMANY	*P. fluorescens*	>64	>64
9	MHA	GERMANY	*P. putida*	>64	>64
5	MHA	GERMANY	*P. stutzeri*	32	32
14	MHA	GERMANY	*P. cepacia*	2	64
20	MHA	GERMANY	*X. maltophilia*	>64	>64
10	MHA	BELGIUM	*X. maltophilia*	32	>32
10	MHA	BELGIUM		>32	>32
27	STA	JAPAN	*P. cepacia*	1.56	6.25

Pseudomonas species including *P. aeruginosa* are resistant to ceftibuten. In almost all studies both the MIC_{50} and the MIC_{90} value was μg/mL or higher [Tables 29 and 30]. *Pseudomonas* species including *P. aeruginosa* will not be in the package insert.

Table 31
The *in vitro* activity of ceftibuten against *Salmonella* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
19	MHB	USA		0.06	0.5
23	MHB	S.E. ASIA	*S. choleraesuis*	0.015	0.03
45	MHB	S.E. ASIA	*S. enteriditis*	0.03	0.06
13	MHB	S.E. ASIA	*S. typhi*	0.03	0.06
5	MHA	GERMANY		0.03	0.03
30	MHA	BELGIUM		0.06	0.12
5	ISA	UK	0.03 (5)	--	--

Salmonella species including *S. enteriditis* and *S. typhi* are susceptible to ceftibuten [Table 31]. This genus will not be included in the package insert because the drug does not have an indication for gastroenteritis and these organisms are not usually found in the body sites for which clinical efficacy for other pathogens has been established.

Table 32
The *in vitro* activity of ceftibuten against *Serratia* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
25	MHB	USA		<0.25	--
29	MHB	USA	*S. marcescens*	0.5	32
5	MHB	USA	*S. liquefaciens*	0.5	--
92	MHB	USA	*S. marcescens*	0.25	4.0
32	MHB	EUROPE	Cefazolin-resistant	<0.125	2.0
64	STA	JAPAN		3.13	50
20	MHA	GERMANY	*S. marcescens*	0.25	4.0
9	MHA	GERMANY	*S. liquefaciens*	0.25	0.5
70	MHA	BELGIUM	*S. marcescens*	1.0	8.0
25	ISA	UK	*S. marcescens*	0.125	4.0
7	ISA	UK	*S. liquefaciens*	0.125	1.0
1	ISA	UK	*S. rubidea*	0.25	0.25
10	ISA	UK		0.25	8.0

In most studies testing *Serratia* species the MIC_{50} value is very low, but the MIC_{90} value in many cases are somewhat higher. In one study the MIC_{90} is μg/mL and in one other study it is μg/mL, but in all other studies the MIC_{90} value is below or equal to mcg/mL which is the susceptibility cut-off [Table 32]. The somewhat higher MIC_{90} values are due to the fact that this genus often produces chromosomally mediated beta-lactamases which hydrolyze ceftibuten. *S. marcescens* may be placed in the package insert if the sponsor desires, but a statement excluding strains containing chromosomally mediated beta-lactamases should be included.

Table 33
The *in vitro* activity of ceftibuten against *Shigella* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
22	MHB	S.E. ASIA	*S. dysenteriae*	0.06	0.25
40	MHB	S.E. ASIA	*S. flexneri*	0.06	0.25
14	MHB	S.E. ASIA	*S. boydii*	0.06	0.5
61	MHB	S.E. ASIA	*S. sonnei*	0.12	0.25
22	MHA	GERMANY		0.13	0.25
5	ISA	UK	*S. sonnei* 0.06 (2), 4 (2), 8	--	--

Shigella species including *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei* are susceptible to ceftibuten [Table 33]. This genus will not be included in the package insert, however, because the drug does not have an indication for gastroenteritis and these organisms are not usually found in the body sites for which clinical efficacy for other pathogens has been established.

Table 34
The *in vitro* activity of ceftibuten against *Staphylococcus aureus*

# Strains	Media	Location	Comments	MIC 50	MIC 90
581	MHB	USA		>32	>32
30	MHB	EUROPE	Cefazolin-susceptible	>16	>16
46	MHB	EUROPE	Cefazolin-resistant	>16	>16
51	MHA	GERMANY		>64	>64
12	MHA	BELGIUM		>32	>32
31	ISA	UK		32	128
41	ISA	JAPAN		>100	>100

Table 35
The *in vitro* activity of ceftibuten against other *Staphylococcus* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
622	MHB	USA	Coagulase-negative	>32	>32
90	MHB	EUROPE	Cefazolin-susceptible *S. epidermidis*	>16	>16
122	MHB	EUROPE	Cefazolin-resistant *S. epidermidis*	>16	>16
16	MHA	GERMANY	MRSE	>64	>64
8	MHA	GERMANY	Penicillin-resistant *S. epidermidis*	16	>64
16	MHA	GERMANY	Penicillin-susceptible *S. epidermidis*	16	16
6	MHA	GERMANY	*S. saprophyticus*	>64	>64
4	MHA	GERMANY	*S. warneri*	16	32
13	MHA	BELGIUM	*S. epidermidis*	32	>32
5	MHA	GERMANY	*S. haemolyticus* Met-R	>64	>64
13	MHA	GERMANY	*S.haemolyticus* Met-S	64	>64
10	MHA	GERMANY	*S. simulans*	64	>64
9	MHA	GERMANY	*S. hominis*	8	>64
5	MHA	GERMANY	*S. cohnii*	>64	>64
30	ISA	UK	*S. saprophyticus*	>128	>128
29	ISA	UK	*S. epidermidis*	16	64
36	STA	JAPAN	*S. epidermidis*	>100	>100

Staphylococcus species including *S. aureus* are all resistant to ceftibuten [Tables 34 and 35]. In almost all studies the MIC_{50} and the MIC_{90} value was μg/mL and μg/mL, respectively. *Staphylococcus* species will not be included in the package insert.

Table 36
The *in vitro* activity of ceftibuten against *Streptococcus agalactiae* Group B

# Strains	Media	Location	Comments	MIC 50	MIC 90
20	MHA+SB	USA		>8.0	--
15	MHB	USA		16	>32
11	MHA+LSB	BELGIUM		16	32
16	MHA+LHB	GERMANY		16	16
5	ISA+LSB	UK	8 (2), 16 (3)	--	--
26	STA+HS	JAPAN		12.5	25

Table 37
The *in vitro* activity of ceftibuten against *Streptococcus* Group C

# Strains	Media	Location	Comments	MIC 50	MIC 90
10	MHA+SB	USA		0.5	1.0
5	MHA+LHB	GERMANY		1.0	1.0

Table 38
The *in vitro* activity of ceftibuten against *Streptococcus* Group G

# Strains	Media	Location	Comments	MIC 50	MIC 90
10	MHA+SB	USA		1.0	1.0
8	MHA+LHB	GERMANY		0.5	1.0

Streptococcus agalactiae is resistant to ceftibuten. All studies had high MIC_{50} and MIC_{90} values [Table 36]. *S. agalactiae* will not be included in the package insert.

Streptococcus Group C and *Streptococcus* Group G studies gave susceptible MIC_{90} values, but there were a limited amount of data [Tables 37 and 38]. Due to the lack of data *Streptococcus* Group C and Group G will not be included in the package insert.

Table 39
The *in vitro* activity of ceftibuten against *Streptococcus pneumonia*

# Strains	Media	Location	Comments	MIC 50	MIC 90
10	MHA+SB	USA	Penicillin-susceptible	--	4.0
10	MHA+SB	USA	Penicillin-resistant	--	>8.0
19	MHA+SB	USA	Penicillin-susceptible	4.0	8.0
11	MHA+SB	USA	Penicillin-resistant	>32	>32
6	MHA+SB	USA	Penicillin-susceptible	2.0	4.0
9	MHA+SB	USA	Penicillin-resistant	>16	>16
27	STA+HS	JAPAN		3.13	3.13
6	MHA+LHB	GERMANY	Penicillin-resistant	32	64
12	MHA+LHB	BELGIUM		2.0	2.0
20	MHA+LHB	GERMANY	Penicillin-susceptible	4.0	4.0
48	MHA+LHB	USA		3.0	3.0
38	MHA+LHB	USA		3.0	4.0
64	MHA+LHB	USA		4.0	>16
64	MHB+LHB	USA		6.0	>16
28	ISA+LHB	UK		4.0	16
543	MHA+SB	CANADA	Penicillin-susceptible	1.0	2.0

It can be seen that several investigators have looked at the level of activity of ceftibuten against *S. pneumoniae*. Most found that penicillin-susceptible strains had a narrow MIC range with MIC_{50} and MIC_{90} values in the range between μg/mL. Penicillin-resistant strains were resistant to ceftibuten with MICs μg/mL [Table 39].

The study done in Canada with five hundred forty-three penicillin-susceptible strains had MICs which ranged from μg/mL, with an MIC_{50} of μg/mL and an MIC_{90} of μg/mL. Eleven addition strains, 2% of the total strains tested, had reduced susceptibility to penicillin and were resistant to ceftibuten (MIC_{50} μg/mL). *S. pneumoniae* will be included in the package insert but the statement "excluding penicillin-resistant strains" will be added.

Table 40
The *in vitro* activity of ceftibuten against *Streptococcus pyogenes* Group A

# Strains	Media	Location	Comments	MIC 50	MIC 90
21	MHA+SB	USA		<0.25	0.5
20	MHA+SB	USA		0.5	0.5
32	STA+HS	JAPAN		0.39	0.78
10	MHA+LHB	BELGIUM		0.5	0.5
9	MHA+LHB	GERMANY		1.0	1.0
5	ISA+LSB	UK	0.5 (4)	--	--

Table 41
The *in vitro* activity of ceftibuten against other *Streptococcus* species

# Strains	Media	Location	Comments	MIC 50	MIC 90
7	MHA+LHB	GERMANY	*S. mitior*	32	64
11	MHA+LHB	GERMANY	*S. milleri*	16	64
3	ISA+SB	UK	*S. viridans* 16 (2), 32	--	--
5	ISA+SB	UK	*S. mitis* 1, 2, 8, 32, >128	--	--
5	ISA+SB	UK	*S. sanguis* 1, 8, 16 (2), 32	--	--
5	ISA+SB	UK	*S. milleri* 32 (2), 64 (2), >128	--	--

Streptococcus pyogenes studies show that this organism is susceptible to ceftibuten. Unlike most other *Streptococcus* species it had very low MIC_{90} values in all studies [Table 40]. *S. pyogenes* will be included in the package insert.

All other streptococci, except for *Streptococcus pneumonia* in which penicillin susceptible strains are susceptible to ceftibuten, are resistant to ceftibuten and will not be included in the package insert.

Table 42
The *in vitro* activity of ceftibuten against *Yersinia enterocolitica*

# Strains	Media	Location	Comments	MIC 50	MIC 90
15	MHA	GERMANY		0.13	0.25
30	MHA	BELGIUM		0.12	4.0

It appears from the limited data available that *Yersinia enterocolitica* is susceptible to ceftibuten [Table 42]. *Y. enterocolitica* will not be included in the package insert, however, because the drug does not have an indication for gastroenteritis and these organisms are not usually found in the body sites for which clinical efficacy for other pathogens has been established.

Conclusions about *in vitro* activity of ceftibuten:

The following two tables [Table 43 and 44] give a weighted MIC_{50} and MIC_{90} (MIC_{50} or MIC_{90} x # of isolates in each study/total # of isolates in all studies) for each genera studied. If different species gave widely different values, individual data is given. These two tables allow us to quickly get some idea what the susceptibility of most genera is to ceftibuten without referring to a number of tables. These tables provide a quick overview of the genera/species that have a least 100 strains tested and MIC_{90} values μg/mL, which qualifies them for inclusion in the microbiology section of the package insert.

When these weighted values are compared to the MIC_{50} and MIC_{90} values for the studies performed in the United States the values are similar in both cases. This suggests that data derived from many geographic areas and tested with different methods produce similar results.

Table 43
Weighted MIC_{50} and MIC_{90} values for ceftibuten against gram-negative aerobes

GENERA OR SPECIES (NO. STUDIES)	NUMBER OF ISOLATES	MIC_{50}	MIC_{90}
Achromobacter (1)	5	>32	--
Acinetobacter (9)	214	16	>32
Aeromonas (1)	5	0.25	--
Alcaligenes (1)	5	16	--
Bordetella (2)	66	--	32
Brucella (1)	5	8	8
Campylobacter (5)	259	8	16
Citrobacter diversus (5)	61	0.06	0.13
Citrobacter freundii (7)	219	1.0	>32
Citrobacter species (3)	49	2.0	>16
Enterobacter (22)	782	1.0	>32
Escherichia coli (17)	1647	0.12	0.25
Flavobacterium (1)	29	100	>100
Haemophilus influenzae (21)	665	<0.06	0.06
Hafnia alvei (2)	16	>32	>32
Klebsiella (15)	977	0.03	0.12
Moraxella catarrhalis (8)	233	1.0	4.0
Morganella (9)	228	0.12	16
Neisseria (7)	110	<0.06	0.06
Proteus (18)	720	<0.03	0.03
Providencia (14)	233	<0.03	0.03
Pseudomonas (16)	905	>32	>32
Salmonella (7)	140	0.03	0.06
Serratia (13)	389	0.5	8
Shigella (6)	144	0.06	0.25
Yersinia enterocolitica (2)	45	0.12	4.0

Table 44
Weighted MIC_{50} and MIC_{90} values for ceftibuten against gram-positive aerobes

GENERA OR SPECIES (NO. STUDIES)	NUMBER OF ISOLATES	MIC_{50}	MIC_{90}
Enterococcus (10)	567	>32	>32
Listeria (1)	13	>64	>64
Staphylococcus (24)	1826	>32	>32
Streptococcus agalactiae (6)	93	16	>32
Streptococcus Group C + G (4)	33	1.0	1.0
Streptococcus pneumonia (16)	915	4.0	8.0
Streptococcus pyogenes (6)	97	0.5	1.0

Anaerobic bacteria

Ceftibuten has very little activity against anaerobic bacteria. There were ten studies with a total of 106 strains tested. The weighted average MIC_{50} was μg/mL as was the weighted average MIC_{90}.

The above organisms can be broken into three groups: those that ceftibuten has good activity against; those which ceftibuten has some activity against, but which contain beta-lactamases that hydrolyze ceftibuten; and organisms which ceftibuten has no useful activity against. Some of the genera and species are included in this list even though there is not enough evidence to place them in the package insert. Only specific species and not genera are allowed to be listed in the package insert in both cases. In most cases the organisms in the "some activity" lists will not be allowed in the package insert because the MIC_{90} values were μg/mL. *Salmonella* species, *Shigella* species, and *Yersinia enterocolitica* will not be allowed in the package insert because they are usually not found in infections for which ceftibuten will be approved.

Gram-Negative Aerobes

Good Activity	Some Activity	No Activity
Citrobacter diversus	*Citrobacter freundii*	*Acinetobacter* species
Escherichia coli	*Citrobacter* species	*Bordetella* species
Haemophilus influenzae	*Enterobacter* species	*Campylobacter* species
Klebsiella species	*Morganella* species	Hafnia alvei
Moraxella catarrhalis	*Serratia* species	*Pseudomonas* species
Neisseria species		
Proteus species		
Providencia species		
Salmonella species		
Shigella species		
Yersinia enterocolitica		

Gram-Positive Aerobes

Good Activity	Some Activity	No Activity
Streptococcus Group C,G	*Streptococcus pneumoniae*	*Enterococcus* species
Streptococcus pyogenes		*Staphylococcus* species
		Streptococcus agalactiae

The following organisms will be allowed in the package insert:

Citrobacter diversus	*Neisseria gonorrhoeae*
Escherichia coli	*Proteus mirabilis*
Haemophilus influenzae	*Proteus vulgaris*
Klebsiella pneumoniae	*Providencia rettgeri*
Klebsiella oxytoca	*Providencia stuartii*
Moraxella catarrhalis	*Serratia marcescens* (excluding beta-lactamase positive strains)
Streptococcus pyogenes	*Streptococcus pneumoniae* (excluding penicillin-resistant strains)

ACTIVITY AGAINST β-LACTAMASE CONTAINING STRAINS

Activity Against Strains with Plasmid-Mediated Penicillinases

Ceftibuten has good activity against strains containing the classical plasmid-mediated penicillinases: TEM-1, TEM-2, SHV-1, HMS-1, OXA-1, OXA-2, OXA-3, OXA-4, OXA-5, OXA-6, OXA-7, PSE-1, PSE-2, PSE-3 and PSE-4. These enzymes confer resistance to penicillins like ampicillin and piperacillin but not most cephalosporins. Since *Pseudomonas aeruginosa* is resistant to ceftibuten the effect of the enzymes from this organism could not be determined; as can be seen from the table below the MIC values were all greater than 128 μg/mL. [See TABLE 45].

Table 45
MICs of Ceftibuten Against β-Lactamase Reference Strains

Enzyme	Pathogen	MIC (μg/mL)	
		Ceftibuten	Cefaclor
OXA-1	E. COLI	0.13	1
OXA-2	E. COLI	0.13	1
OXA-3	E. COLI	0.13	1
OXA-4	E. COLI	0.13	2
OXA-5	E. COLI	0.25	8
OXA-6	P. AERUG	>128	>128
OXA-7	E. COLI	0.25	32
TEM-1	E. COLI	0.13	1
TEM-2	E. COLI	0.25	4
TLE-1	E. COLI	0.13	2
SHV-1	E. COLI	0.25	2
HMS-1	E. COLI	0.25	16
LCR-1	P. AERUG	>128	>128
PSE-1	P. AERUG	ALL >128	ALL >128
PSE-2	P. AERUG		
PSE-3	P. AERUG		
PSE-4	P. AERUG		
AER-1	A. HYRDO	0.5	>128
OTX-1	K. PNEUM	0.25	16

Activity Against Strains Containing Plasmid-Mediated Cephalosporinases

Ceftibuten had good activity against the characterized plasmid-mediated cephalosporinases. A large number of strains of *E. coli* and *K. pneumoniae* that were resistant to cefotaxime, ceftazidime and aztreonam were susceptible to ceftibuten. TABLE 46 is a summary of the activity of ceftibuten against this type of strain. In this table, if different studies had a different MIC value, each MIC value is given. It appears that ceftibuten is not affected by most of these enzymes, except for CMY-1 and MIR-1. There does appear to be decrease activity with SHV-4 and SHV-5.

Table 46
Activity of Ceftibuten Against Plasmid-Mediated Cephalosporinases

ORGANISM	MIC (μg/mL)
E. coli TEM-3 (CTX-1)	0.12, 0.25, 0.5
E. coli TEM-4	0.25
E. coli TEM-5 (CAZ-1)	0.03, 1
E. coli TEM-6	1,2
E. coli TEM-7	0.12
E. coli TEM-8	0.5
K. pneumoniae SHV-2	0.25
K. pneumoniae SHV-3	0.25, 1
K. pneumoniae SHV-4	8, 2, 1
K. pneumoniae SHV-5	8,1,4
K. pneumoniae CMY-1	>64
E. coli CTX-M	1
E. coli MIR-1	>256

One study looked at the activity of ceftibuten against a collection of 150 *Klebsiella* strains, 120 of which contained broad-spectrum plasmid-mediated cephalosporinases. Against those strains having the classical β-lactamases, SHV-1 and TEM-1, ceftibuten had activity close to that of cefotaxime, ceftazidime, and aztreonam. This level of activity was maintained by ceftibuten but not cefotaxime and ceftazidime against strains producing TEM-3 (CTX-1), SHV-2, and SHV-3 β-lactamases. The MICs of ceftibuten against the strains producing SHV-4 and SHV-5 were higher μg/mL). [See TABLE 47]

Table 47
Comparative Activity of Ceftibuten and Other Antibiotics against 150 *K. pneumoniae* Strains Producing Different Types of Beta-Lactamases

TYPE OF BETA-LACTAMASE	ANTIBIOTIC	MIC 50 (μg/mL)	MIC 90 (μg/mL)	EXTREME VALUES
SHV-1 (15 strains)	Ceftibuten	0.03	0.06	0.03 - 0.125
	Cefotaxime	0.03	0.06	0.03 - 0.125
	Cefotaxime-clavulanic acid	0.03	0.06	0.03 - 0.125
	Ceftazidime	0.25	0.5	0.125 - 1
	Aztreonam	0.125	0.25	0.125 - 0.5
TEM-1 (15 strains)	Ceftibuten	0.03	0.06	0.03 - 0.125
	Cefotaxime	0.06	0.125	0.03 - 0.25
	Cefotaxime-clavulanic acid	0.03	0.125	0.03 - 0.25
	Ceftazidime	0.25	0.5	0.125 - 1
	Aztreonam	0.125	0.25	0.125 - 0.5
CTX-1/TEM-3 (48 strains)	Ceftibuten	0.125	0.25	0.03 - 0.5
	Cefotaxime	16	32	4 - 64
	Cefotaxime-clavulanic acid	0.03	0.125	0.03 - 1
	Ceftazidime	32	64	4 - 64
	Aztreonam	8	16	4 - >128
SHV-2 (9 strains)	Ceftibuten	0.25	1	0.06 - 1
	Cefotaxime	8	32	2 - 32
	Cefotaxime-clavulanic acid	0.12	0.25	0.06 - 0.25
	Ceftazidime	16	32	2 - 32
	Aztreonam	4	64	2 - 64
SHV-3 (4 strains)	Ceftibuten	0.25	0.25	0.125 - 0.25
	Cefotaxime	4	16	4 - 16
	Cefotaxime-clavulanic acid	0.125	0.25	0.125 - 0.25
	Ceftazidime	4	4	0.25 - 4
	Aztreonam	1	2	1 - 2
SHV-4/CAZ-5 (35 strains)	Ceftibuten	2	16	0.125- 16
	Cefotaxime	8	64	2 - 64
	Cefotaxime-clavulanic acid	0.125	0.25	0.125 - 0.25
	Ceftazidime	64	>128	32 - >128
	Aztreonam	>128	>128	32 - >128
SHV-5/CAZ-4 (24 strains)	Ceftibuten	1	8	0.06 - 8
	Cefotaxime	8	32	0.25 - 64
	Cefotaxime-clavulanic acid	0.06	0.25	0.03 - 64
	Ceftazidime	>128	>128	4 - >128
	Aztreonam	64	>128	8 - >128

Activity Against Strains Containing Chromosomal Cephalosporinases

The studies included in the NDA show that ceftibuten has poor activity against strains of Enterobacteriaceae that produce chromosomal cephalosporinases. These enzymes are usually classified as Class I beta-lactamases and are produced by *Citrobacter*, *Enterobacter*, and *Serratia*. Table 48 shows that ceftibuten has poor activity against the beta-lactamases produced by these species.

Table 48
Activity* of Ceftibuten Against Gram-Negative Organisms

Organism	No. Tested	Beta-lactamase present**	Geometric mean MIC	MIC 90[a]/100[b]
Acinetobacter	6 1	+ +++	9.0 64	32[b] --
Citrobacter	14 19	+ +++	0.82 13	4[a] --
E. coli	13 27	- ++	0.24 1.1	1[a] --
Enterobacter	14 29	+ +++	2.1 33	8[a] --
Klebsiella	7 9	+ ++	0.084 0.16	0.5[a] --
P. mirabilis	9 3	- +	0.073 0.050	0.5[a] --
P. vulgaris	1 3	+ ++	0.031 0.039	- --
Providencia	8 4	+ ++	0.016 0.026	0.016[b] --
Salmonella	5 9	- +	0.063 0.099	0.125b[b] --
Serratia	11 3	+ ++	0.39 1.6	0.5[a] --

* Geometric mean MICs (mcg/mL)

** Presence and level of beta-lactamase [+ means a low level of beta-lactamase is present, +++ means a high level of beta-lactamase is present]

[a] MIC_{90} [b] MIC_{100}

CONCLUSION --ACTIVITY AGAINST β-LACTAMASE CONTAINING STRAINS

Ceftibuten has good activity against strains containing the classical plasmid-mediated penicillinases. The drug also has good activity against strains producing plasmid-mediated cephalosporinases, except strains which produce SHV-4 or SHV-5 which have higher MICs than against wild-type strains.

INTERACTIONS WITH BETA-LACTAMASES

Stability to Plasmid-Mediated Beta-Lactamases

Studies were conducted that determined the stability of ceftibuten to a variety of plasmid-mediated β-lactamases (PSEs, OXAs, SHV-1, HMS, LCR, TEM-1 and TEM-2). Table 49 shows that there was essentially no hydrolysis of ceftibuten by any of the common plasmid-mediated enzymes.

Table 49
Stability of Ceftibuten to Plasmid-Mediated β-Lactamases

TYPE	PLASMID	RELATIVE RATE OF HYDROLYSIS[a]					
		Ceftibuten	CZX	CEX	CER	CBPC	MCIPC[b]
PSE-1	RPL11	<0.02	<0.02	0.1	22	100	7
PSE-2	R151	<0.05	4	0.2	8	35	57
PSE-3	Rms149	<0.5	<0.5	2	12	160	5
PSE-4	PMG19	<0.02	<0.02	0.1	22	87	6
OXA-1	RGN238	0.2	41	1	10	31	53
OXA-2	R46	<0.2	0.3	2	27	18	29
OXA-3	RIP64	<0.2	<0.2	3	31	20	6
OXA-5	PMG54	0.1	10	1	20	44	140
OXA-6	PMG39	0.05	8	1	13	53	93
OXA-7	PMG202	0.02	3	0.5	9	10	47
SHV-1	R1010	<0.05	0.05	1	47	35	4
LCR-1	PMG76	0.4	0.5	1	8	8	13
HMS-1	R997	<0.1	<0.1	1	31	50	2
TEM-1	RTEM	<0.02	0.1	1	29	23	6
TEM-1	RGN14	<0.03	0.05	0.5	25	22	3
TEM-2	RGN823	<0.01	0.05	0.6	21	10	4
TEM-2	RPI	<0.03	0.05	0.7	41	23	6

[a] Hydrolysis rates are based on an arbitrary value of 100 for ampicillin
[b] CZX= ceftizoxime, CEX= cephalexin, CER= cephaloridine, CBPC= carbenicillin, MCIPC = cloxacillin

Another factor that affects the stability of antibiotic against beta-lactamases is the affinity of the antibiotic for the enzyme. The affinity of antibiotics was determined and presented as K_m or K_i. K_m represents the amount of the beta-lactam required to bind with one-half of the total amount of enzyme present in solution. The higher the K_m value the poorer the beta-lactam is as a substrate for the enzyme (the lower the affinity for the beta-lactam). The K_i value is a measure of the affinity of the beta-lactamase for the beta-lactam acting as an inhibitor in the reaction in which nitrocefin is acting as the substrate. The K_i value is used when no detectable hydrolysis of the beta-lactam could be seen. Table 50 below shows that ceftibuten is a poor substrate for many of the plasmid-mediated β-lactamases (high K_m) and when bound by these enzymes it is only very slowly hydrolyzed (low V_{max}). One study showed that only when the amino acid at position 240 in the enzyme is changed to lysine (a positive change that can attract the carboxyl of the side chain) as in SHV-4 and SHV-5 is there significant binding and/or hydrolysis. SHV-4 is derived from SHV-3 by altering the glutamic acid in position 240 to lysine and SHV-5 is derived from SHV-2 in the same manner.

Table 50
Stability and Affinity of Ceftibuten for Plasmid-Mediated β-Lactamases

DRUG	CTX-1/TEM-3		SHV-2		SHV-3		SHV-4		SHV-5	
	Vm[a]	Km[b]	Vm	Km	Vm	Km	Vm	Km	Vm	Km
Ceftibuten	ND[c]	33	ND	100	ND	90	110	350	80	300
Cefotaxime	450	100	78	40	70	40	115	25	134	30
Ceftazidime	40	100	4	100	5	90	52	60	50	50
Aztreonam	8	20	ND	25	ND	20	2	1.1	1	1.1
Penicillin G	100	4	100	3.5	100	4	100	4.0	100	5.0

All beta-lactamases were produced by *K. pneumoniae* strains (not further identified)

[a] The rates of hydrolysis are given in relation to penicillin G (Vm=100).

[b] Km is in μM.

[c] When the hydrolysis was not detectable (ND), the Km value was replaced by a Ki value.

Stability to Chromosomal Beta-Lactamases

Several studies were done to determine the stability of ceftibuten to the chromosomal β-lactamases found in *Citrobacter, Enterobacter, Klebsiella, Morganella, Providencia, Proteus*, and *Serratia*. In one study the crude enzymes were added to an antibiotic solution containing 50 milligrams per liter of ceftibuten and incubated at 37°C. As a control phosphate buffered saline was added instead of the enzyme. At time intervals of 0, 1, 2, 4, 6 and 24 hours samples were assayed for antibiotic activity. The table 51 below gives the results of this study.

Table 51
Hydrolytic activity of β-lactamases against ceftibuten

SOURCE OF β-LACTAMASE	CONCENTRATION OF CEFTIBUTEN AT (HRS) (mg/L)					
	0	1	2	4	6	24
M. catarrhalis	55	7	5	0	0	0
H. influenzae	55	46	56	50	52	46
E. coli B3	55	56	54	54	54	41
Ent. cloacae B53	55	45	46	37	36	11
K. pneumoniae 2919	55	52	54	53	50	47

From the above table it can be seen that ceftibuten is hydrolyzed by the enzyme from *M. catarrhalis* and from the enzyme from *E. cloacae*. These two enzymes are chromosomal.

Table 52 shows that ceftibuten has very high affinity for most cephalosporinases except *P. vulgaris* enzyme, but its affinity for penicillinases and *P. vulgaris* enzyme was very low. Affinity for ceftizoxime and ceftibuten were similar.

Table 52
Affinity of Ceftibuten to β-Lactamases

SOURCE OF β-LACTAMASE	SUBSTRATE SPECIFICITY[a]	Ki(μM)/Km(μM)			
		Ceftibuten	CER	CEX	CZX
E. coli SR6	C	0.040/	/750	/20	/0.90
E. cloacae 214	C	0.32/	/670	/170	/1.6
C. freundii SR19	C	0.20/	/1200	/250	/2.2
P. aeruginosa SR24-12	C	3.5/4.9	/690	/170	/18
P. vulgaris SR31	C	(3000)/	/170	/2100	1100/
K. pneumoniae GN69	P	(2800)/1	/190	/1000	(3400)/
K. oxytoca SR753	P	(4800)/	/190	/140	(3800)/
E. coli W3110 (TEM-1)	P	(2400)/	/790	/1000	(7000)/
E. coli ML 1410 (OXA-1)	P	(4300)/	/270	/490	/170

[a] C and P indicate cephalosporinase and penicillinase, respectively.
[b] Hydrolysis rates are determined by UV assay at 30°C
V_{max} is relative to an arbitrary value of 100 for cephaloridine.
CZX= ceftizoxime, CEX= cephalexin, CER= cephaloridine

It appears from these studies that ceftibuten has high affinity for most of the chromosomally-mediated cephalosporinases, except that from *Proteus vulgaris* and is hydrolyzed by them but not plasmid-mediated penicillinases.

Stability to Beta-lactamase from Bacteroides

One study was performed using β-lactamase from *Bacteroides fraglis*. This study showed that ceftibuten is rapidly broken down by this enzyme. The V_{max} for ceftibuten was 30-fold higher than ceftizoxime and 10-fold higher than cephalexin. Beta-lactamases of *Bacteroides* are mostly chromosomal and constitutive. About 90% of *Bacteroides* strains causing infections in the human intestine produce beta-lactamase. Table 53 shows the stability and affinity of ceftibuten to beta-lactamases of *B. fragilis*.

Table 53
Stability and affinity to β-lactamase of *B. fragilis* V-283

β-LACTAMS	RELATIVE V_{max}	Ki (μM)/Km (μM)
Cephaloridine	100	/420
Ceftibuten	41	/560
Cephalexin	3.9	/89
Ceftizoxime	1.4	/9.0
Latamoxef	<0.05	0.12/
Flomoxef	<0.05	0.035/
Ampicillin	1.0	/7.0

Inhibition of Beta-Lactamases by Ceftibuten

The NDA contained three studies on this subject. They showed that ceftibuten was a poor inhibitor of most of the plasmid-mediated beta-lactamases with the exception of SHV-4 [See TABLE 54]. Since ceftibuten shows only moderate activity against strains containing this enzyme (SHV-4), the data suggest that not only is ceftibuten binding to these enzymes, but it is also being hydrolyzed by them. In contrast, ceftibuten did inhibit the hydrolysis of nitrocefin by the chromosomal beta-lactamases tested. [See TABLE 55]. These data indicate that ceftibuten is a substrate for the chromosomal beta-lactamases and can compete for binding sites with nitrocefin, but is not a good substrate for the plasmid-mediated beta-lactamases except SHV-4. This data helps explain the fact that ceftibuten is active against plasmid-mediated beta-lactamases, but is inhibited by chromosomally-mediated beta-lactamases.

Table 54
Inhibition Profile of Plasmid-Mediated β-Lactamases

BETA-LACTAMASE	CLAVULANATE[1]	SULBACTAM	CEFOXITIN	CEFTAZIDIME	CEFTIBUTEN	CLOXACILLIN
TEM-1	60	86	21	3	7	84
TEM-2	57	85	25	10	0	82
TEM-3	60	79	57	1	8	87
TEM-5	33	39	87	6	14	92
TEM-6	81	93	83	49	29	96
CAZ-1	64	83	78	38	22	89
TEM-7	81	97	83	7	10	96
TEM-101	82	93	86	4	12	94
TEM-9	54	76	53	11	2	88
TEM-10	73	77	81	38	24	84
SHV-1	51	44	4	6	10	46
OHIO-1	50	54	10	14	10	56
SHV-2	69	86	78	13	19	91
SHV-4	71	88	76	63	56	87

1) AVERAGE OF MAXIMUM PERCENT INHIBITION

Table 55
Inhibition Profiles of Chromosomal Beta-Lactamases

HOST SPECIES	NO.	CLAVULANATE[1]	SULBACTAM	CEFOXITIN	CEFTAZIDIME	CEFTIBUTEN	CEFOTAXIME
E. cloacae	81010504	5	2	94	96	88	91
E. cloacae	55M	14	0	92	90	88	93
E. cloacae	83120215	4	5	98	94	94	94
E. aerogenes	83101021	13	5	98	92	94	95
S. marcescens	83120234	6	2	90	83	84	90
S. marcescens	83110701	1	10	80	72	76	80
E. coli	87120702	1	1	95	84	88	95
A. calcoaceticus	83111835	6	9	87	88	78	85

1) AVERAGE OF MAXIMUM PERCENT INHIBITION

Induction of Beta-Lactamases by Ceftibuten

Two studies looked at the ability of ceftibuten to induce the Class I chromosomal beta-lactamases of *Enterobacter aerogenes* and *Serratia marcescens*. The results from the study in which both organisms were studied can be seen in the table 56 below.

Table 56
Induction of β-lactamase by antibiotics

DRUG	ORGANISM	DRUG CONCENTRATION	INDUCTION RATIO
CEFTIBUTEN	*S. marcescens* 75-299 MIC = 1 µg/mL	1/32 MIC	1
		1/16 MIC	2
		1/8 MIC	1
		1/4 MIC	1
		1/2 MIC	1
	E. aerogenes 78080457 MIC = 2 µg/mL	1/32 MIC	1
		1/16 MIC	1
		1/8 MIC	1
		1/4 MIC	1
		1/2 MIC	1
CEFOTAXIME	*S. marcescens* 75-299 MIC = 1 µg/mL	1/32 MIC	1
		1/16 MIC	1
		1/8 MIC	1
		1/4 MIC	1
		1/2 MIC	1
	E. aerogenes 78080457 MIC = 0.25 µg/mL	1/32 MIC	1
		1/16 MIC	1
		1/8 MIC	1
		1/4 MIC	1
		1/2 MIC	1

Table 56 (Cont.)
Induction of β-lactamase by antibiotics

DRUG	ORGANISM	DRUG CONCENTRATION	INDUCTION RATIO
CEFOXITIN	*S. marcescens* 75-299 MIC = 16 μg/mL	1/32 MIC	2
		1/16 MIC	2
		1/8 MIC	4
		1/4 MIC	8
		1/2 MIC	8
	E. aerogenes 78080457 MIC = >64 μg/mL	1/32 MIC	1
		1/16 MIC	1
		1/8 MIC	2
		1/4 MIC	3
		1/2 MIC	7
IMIPENEM	*S. marcescens* 75-299 MIC = 0.25 μg/mL	1/32 MIC	1
		1/16 MIC	1
		1/8 MIC	2
		1/4 MIC	1
		1/2 MIC	4
	E. aerogenes 78080457 MIC = 0.12 μg/mL	1/32 MIC	1
		1/16 MIC	1
		1/8 MIC	1
		1/4 MIC	1
		1/2 MIC	2

The data in the table show that ceftibuten, like cefotaxime is a weak inducer of these enzymes increasing β-lactamase production less than two-fold in most cases. Cefoxitin was a good inducer of these enzymes.

Table 57 shows the beta-lactamase activity determined as the nanomoles of nitrocefin degraded per minute per milligram of enzyme. These data demonstrate that resistance of clinical isolates to ceftibuten is most likely to arise from the selection of stably-derepressed mutant strains that hyperproduce the Class I beta-lactamases rather than by inducing the strain to produce more β-lactamase as is the case with cefoxitin.

Table 57
Induction of β-lactamase of *E. cloacae* 75043003
by subinhibitory concentrations of antibiotic

INDUCER CONCENTRATION	BETA-LACTAMASE ACTIVITY[a]			
	CEFOXITIN MIC= >64 μg/mL	CEFOTAXIME MIC= 0.25 μg/mL	CEFTIBUTEN MIC= 2 μg/mL	IMIPENEM MIC= 0.12 μg/mL
1/2 MIC	50.35	3.61	3.45	12.69
1/4 MIC	14.97	3.36	2.66	4.73
1/8 MIC	25.29	3.16	2.99	2.47
1/16 MIC	9.79	2.42	2.52	2.54
1/32 MIC	12.61	2.42	2.80	3.06
GROWTH CONTROL	2.5	3.08	2.52	2.18

a) nmol of nitrocefin/min/μg of protein

CONCLUSIONS ON CEFTIBUTEN'S INTERACTIONS WITH β-LACTAMASES

Ceftibuten is stable to the common plasmid-mediated β-lactamases. It is a poor substrate (high K_m value) for most plasmid-mediated β-lactamases, and when bound is only very slowly hydrolyzed (low V_{max} value). Ceftibuten is hydrolyzed by the SHV-4 and SHV-5 enzymes and is a slightly better substrate for these two enzymes than for the other plasmid-mediated β-lactamases.

Ceftibuten has high affinity (low K_m values) for most of the chromosomally-mediated cephalosporinases and is hydrolyzed by them. The drug is also hydrolyzed by β-lactamases from *Bacteroides fragilis*.

Ceftibuten is a poor inhibitor of most plasmid-mediated β-lactamases with the exception of SHV-4 (data on SHV-5 not given). In contrast, ceftibuten did inhibit the hydrolysis of nitrocefin by the chromosomally-mediated β-lactamases. This indicates that ceftibuten is a substrate for the chromosomally-mediated β-lactamases and can compete for binding sites with nitrocefin, but is not a substrate for the plasmid-mediated β-lactamases, except for SHV-4 and possibly SHV-5.

Ceftibuten is only a weak inducer of Class I chromosomal β-lactamases. This indicates that resistance to ceftibuten is most likely to arise from the selection of stably-derepressed mutant strains that hyperproduce Class I β-lactamases, rather than by inducing the strain to produce more β-lactamase.

ANTIMICROBIAL ACTIVITY--MISCELLANEOUS STUDIES

Effect of Inoculum Size on Antibacterial Activity

The NDA included several studies in which the influence of inoculum on the antibacterial activity of ceftibuten was determined. In one of the typical studies the investigator used three different inocula between 10^4 and 10^7 CFU/mL in broth microdilution. MICs at the lowest inoculum were equal to or 2-fold lower than those at the standard inoculum of 5×10^5 CFU/mL. At the high inoculum of 10^7 CFU/mL, several β-lactamase containing strains had MICs which were increased 4-fold or greater. [See TABLE 58]. This study indicates that as long as a huge inoculum (10^7 CFU/mL) is not used, a slight error in the standard inoculum of 5×10^5 CFU/mL will not cause an error.

Table 58
MBCs and Inoculum Effects on Ceftibuten

ORGANISM	MIC(μg/mL) 10^4 CFU/mL	5 x 10^5 CFU/ML		MIC (μg/mL) 10^7 CFU/mL
		MIC (μg/mL)	MBC (μg/mL)	
E. coli				
ATCC 25922*	0.25	0.25	0.5	0.25
OXA-2	0.25	0.5	0.5	1.0
TEM-1	0.25	0.25	0.25	>32
E. cloacae				
P99	>32	>32	>32	>32
63*	0.5	1.0	2.0	1.0
76*	0.25	0.5	1.0	1.0
341-82*	0.25	0.5	1.0	1.0
K. oxytoca				
35*	≤0.06	≤0.06	≤0.06	8.0
K1	≤0.06	≤0.06	0.12	0.25
K14	≤0.06	≤0.06	0.5	0.25
M. catarrhalis				
β-lact +	4.0	4.0	4.0	16
β-lact -	0.12	0.12	0.25	0.25
H. influenzae				
β-lact +	≤0.06	≤0.06	0.25	0.12
β-lact -	≤0.06	≤0.06	0.12	≤0.06
S. pneumoniae Pen-S	4.0	4.0	4.0	8.0

* Wild-type clinical or quality control isolates without unusual resistance

Agar dilution MICs from inocula of 10^8, 10^7, 10^6, or 10^5 CFU/mL were used by investigators in one paper to study inoculum effects. No effects were seen at the three lowest inocula and only two strains (an *Enterobacter* and a *P. vulgaris*) had 4-fold higher MICs at inocula of 10^8 CFU/mL. [See TABLE 59]. Since the standard inoculum is about 10^4 CFU/spot on the plate, small errors in the amount of inoculum used will not cause errors.

Table 59
Effect of Inoculum Size on Ceftibuten Activity by Agar Dilution Method

ORGANISM	MIC (μg/mL) of Ceftibuten			
	10^8	10^7	10^6	10^5
E. coli ATCC 25922	0.2	0.2	0.2	0.2
E. coli W3110 RTEM	0.2	0.1	0.1	0.1
E. coli ML1410 RGN238	0.39	0.2	0.2	0.2
E. coli SR 73	0.39	0.39	0.39	0.39
K. pneumoniae SR 1	0.025	0.0125	0.0125	0.0125
E. cloacae SR 233	1.56	0.39	0.2	0.2
S. marcescens ATCC 13880	0.1	0.1	0.1	0.05
P. vulgaris CN 329	0.025	0.025	0.0125	0.0125
P. vulgaris SR 31	0.02	0.05	0.05	0.025

Medium was sensitivity test agar (STA)

Effect of Media, and Serum Proteins

The MICs of ceftibuten against 11 strains were determined on four different agar media. No consistent differences were seen between the media studied. The MICs in each media were within 4-fold of each other. [See TABLE 60]. The data in this table confirm that seen in the *in vitro* testing studies in which many different kinds of media were used for testing with very little change in the MIC results.

Table 60
Effect of Agar Medium on Activity of Ceftibuten

ORGANISM	MIC (μg/mL) of Ceftibuten			
	STA	MHA	HIA	TSA
E. coli ATCC 25922	0.2	0.2	0.2	0.39
E. coli W3110 RTEM	0.1	0.1	0.1	0.1
E. coli ML1410 RGN238	0.1	0.2	0.2	0.2
E. coli SR 73	0.39	0.39	0.39	0.39
K. pneumoniae SR 1	0.0125	0.0125	0.0125	0.0125
K. pneumoniae GN69	0.05	0.05	0.05	0.05
K. oxytoca 53	0.05	0.025	0.05	0.05
E. cloacae SR 233	0.2	0.2	0.39	0.78
S. marcescens ATCC 13880	0.1	0.1	0.1	0.1
P. vulgaris CN 329	0.025	0.025	0.0125	0.0125
P. vulgaris SR 31	0.05	0.05	0.025	0.025

Medium STA: Sensitivity Test Agar (Nissui)
MHA: Mueller Hinton Agar (Eiken)
HIA: Heart Infusion Agar (Eiken)
TSA: Trypto soy Agar (Eiken)

MICs were also determined on Sensitivity Test Agar at three different pHs. MICs determined at pH 7 and 8.5 were very similar while those at pH 5.5 were often 2 to 8-fold higher except *Enterobacter cloacae* SR 233 which had a markedly higher MIC at pH 5.5. [See TABLE 61]

Table 61
Effect of Medium pH on the Activity of Ceftibuten

ORGANISM	MIC (μg/mL) of Ceftibuten		
	pH 5.5	pH 7.0	pH 8.5
E. coli ATCC 25922	0.39	0.2	0.2
E. coli W3110 RTEM	0.39	0.1	0.1
E. coli ML1410 RGN238	0.78	0.1	0.39
E. coli SR 73	0.39	0.39	0.39
K. pneumoniae SR 1	0.2	0.0125	0.025
E. cloacae SR 233	25	0.2	0.2
S. marcescens ATCC 13880	0.78	0.1	0.1
P. vulgaris CN 329	0.05	0.0125	0.025
P. vulgaris SR 31	0.2	0.05	0.05

Medium: STA
Inoculum size: 10^6 CFU/mL

No consistent increase in MICs or MBCs were observed when horse serum was added to different media in order to achieve concentrations between 20 and 70%. This is consistent with the moderate serum protein binding of 60 to 65%. [See TABLE 62].

Table 62
Effect of Horse Serum on the Activity of Ceftibuten

ORGANISM	MIC (μg/mL) of Ceftibuten	
	0%	50%
E. coli ATCC 25922	0.2	0.2
E. coli W3110 RTEM	0.1	0.1
E. coli ML1410 RGN238	0.1	0.39
E. coli SR 73	0.2	0.39
K. pneumoniae SR 1	0.0125	0.025
E. cloacae SR 233	0.2	0.2
S. marcescens ATCC 13880	0.1	0.1
P. vulgaris CN 329	0.0125	0.05
P. vulgaris SR 31	0.05	0.1

* Supplement of horse serum (v/v) %
Medium: STA
Inoculum size: 10^6 CFU/mL

THE BACTERICIDAL ACTIVITY OF CEFTIBUTEN

Several investigators compared the rate of killing of a variety of different organisms by ceftibuten to that of other beta-lactams. One of these studies looked at *E. coli* NIHJ JC-2 at concentrations up to 8 x MIC (See FIGURE 1). From this figure it can be seen that the number of viable cells decreased at ceftibuten concentrations of 1/2 MIC and greater. At concentrations greater than or equal to 2 x MIC, killing was 99.9% (reduction usually used to determine bactericidal activity) and regrowth was not seen in 24 hours.

These same investigators also compared the MICs of ceftibuten to its MBCs (6 and 24 hour) against 17 ampicillin-sensitive and 13 ampicillin-resistant *E. coli* (See FIGURE 2). MICs and 24 hour MBCs were very similar, while 6 hour MBCs were on the average of 4-fold higher. The cidal activity of ceftibuten against both groups of *E. coli* was almost identical (average 24 hour MBC of 0.22 and 0.32, respectively).

As can be seen in table 58 above, one investigator compared the MICs of ceftibuten to its MBCs, against several strains of *E. coli, E. cloacae, K. oxytoca, M. catarrhalis, H. influenzae* and penicillin-susceptible *S. pneumoniae*. The observed MBCs were within 2-fold of the MICs except for one *K. oxytoca* (8-fold) and an *H. influenzae* (4-fold).

In another paper the bactericidal activity of ceftibuten was determined against two ampicillin-resistant strains of *H. influenzae*. Both strains showed similar CFU/mL reductions under conditions simulating ceftibuten serum levels following an oral dose of 200 mg. [See FIGURE 3]. The organisms were reduced to 10^5 CFU/mL, 10^4 CFU/mL, 10^3 CFU/mL, 10^2 CFU/mL and 10 CFU/mL from an initial 10^6 CFU/mL in approximately 7, 9, 12, 15, and 25 hours, respectively.

Another paper looked at the bactericidal activity of ceftibuten at 4 mcg/mL against strains containing the plasmid-mediated cephalosporinases. Good killing was seen with ceftibuten against all four strains. Cefotaxime only killed strains with the SHV-1 and TEM-1 beta-lactamases. The strains with the SHV-2 and CTX-1 were not killed by cefotaxime. [See FIGURES 4-7]. These figures verify the data in table 47 which shows high cefotaxime MICs for *K. pneumoniae* strains with SHV-2 and CTX-1, but low MICs for strains with SHV-1 and TEM-1. Ceftibuten had low MICs against strains with all four beta-lactamases. In table 50 cefotaxime showed a high rate of hydrolysis by CTX-1 and SHV-2, while no hydrolysis of ceftibuten could be detected. These data seem to indicate that ceftibuten may be better clinically than cefotaxime against strains containing the CTX-1 or SHV-2 beta-lactamase.

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SYNERGY STUDIES

There were only two studies on this subject. In one paper, ceftibuten which acts primarily at PBP-3 was combined with an orally absorbed penem (SCH 29482) which acts primarily at PBP-2. Synergy was determined by two methods. First, they used a checkerboard agar dilution method, and then the ratio of ceftibuten to SCH 29482 was varied from 2:1 to 8:1. Synergy was defined by a fractional inhibitory concentration (FIC) ≤ 0.5, addition $>0.5-<1$, indifference $>1-<2$, and antagonism >2. They found that the combination was additive for 25% and indifferent for 57% of the gram-positive species, *Haemophilus*, and *Moraxella*. The combination was also indifferent for the anaerobes tested. However, antagonism was found for 80% of the *Serratia* and 30% of the *Citrobacter* and *Enterobacter*. This is probably due to the fact that the penem was a good inducer of the Class I β-lactamases and these β-lactamases will inactivate ceftibuten. The data presented in tables 56 and 57 of this review suggest that ceftibuten is not responsible for the induction of the Class I beta-lactamases, thus in the combination ceftibuten is not inducing the beta-lactamase itself.

In another study (data not shown) using a checkerboard method it was shown that the combination of ceftibuten and isepamicin, an investigational aminoglycoside was synergistic against *Pseudomonas aeruginosa* with an FIC index ranging between

ASSESSMENT OF CROSS-RESISTANCE BETWEEN CEFTIBUTEN AND OTHER ANTIBIOTICS

In one study (data not shown) the investigator found that ceftibuten was active (MICs ≤ 8μg/mL) against 99.1% of the 334 strains that were susceptible to cefuroxime, 78% of the 198 strains that were resistant to cefuroxime, and 52% of the 109 strains that were resistant to cefotaxime.

Another study looked at 2503 clinical isolates over a three year period [Table 63]. Most of these strains were aminoglycoside resistant and many were resistant to other antibiotics as well. Overall ceftibuten was active against 80% of these strains. As shown in Table 64, ceftibuten had the same level of activity (about 80%) against strains that were resistant to gentamicin, tobramycin, amikacin, isepamicin, netilmicin, erythromycin, tetracycline, ciprofloxacin, norfloxacin, ampicillin, cephalothin, cefaclor, and imipenem. Only against cefotaxime-resistant strains did ceftibuten lose some of its activity. The breakdown in this table was based on MIC data, except for erythromycin and tetracycline, where only disk data was available. The susceptibility MIC cut-off of < 16 μg/mL was used to determine the percentage of ceftibuten susceptible strains in all cases. Both of these compounds are hydrolyzed by the chromosomal β-lactamases of *Enterobacter, Citrobacter* and *Serratia*. There were 23.1% of the cefotaxime-resistant strains that were susceptible to ceftibuten. These strains probably contained plasmid-mediated beta-lactamases which hydrolyzed cefotaxime, but not ceftibuten.

Table 63
Isolates treated with ceftibuten

PATHOGEN	STRAINS TESTED	PERCENT OF TOTAL STRAINS
Citrobacter species	114	4.60
Enterobacter species	425	17.00
Escherichia species	504	20.10
Klebsiella species	709	28.30
Proteus species	194	7.80
Providencia species/*P. vulgaris*	138	5.50
Salmonella species/ *Shigella* species	13	0.50
Serratia species	363	14.50
TOTAL STRAINS TESTED	**2503**	**100.00**

Table 64
Cross Resistance between Ceftibuten and other Antibiotics

COMPOUND	NO. STRAINS RESISTANT (OUT OF 2503)	RESISTANCE CRITERIA	% CEFTIBUTEN SUSCEPTIBLE (< 16 MCG/mL)
GENTAMICIN	1494	> 4 μg/mL	76.97
TOBRAMYCIN	1618	> 4 μg/mL	74.41
AMIKACIN	428	> 16 μg/mL	60.51
ISEPAMICIN	142	> 16 μg/mL	59.96
NETILMICIN	1087	> 8 μg/mL	69.55
ERYTHROMYCIN	2434	< 14 MM ZONE	78.27
TETRACYCLINE	1421	< 15 MM ZONE	82.62
CIPROFLOXACIN	53	> 2 μg/mL	64.15
NORFLOXACIN	129	> 2 μg/mL	60.47
AMPICILLIN	2167	> 8 μg/mL	75.45
CEPHALOTHIN	2132	> 8 μg/mL	74.91
CEFOXITIN	1174	> 8 μg/mL	56.47
CEFACLOR	1784	> 8 μg/mL	70.12
IMIPENEM	118	> 4 μg/mL	83.05
CEFOTAXIME	579	> 8 μg/mL	23.14

IN-VIVO ANIMAL PROTECTION STUDIES

The therapeutic efficacy of ceftibuten (CEF) against experimental systemic (intraperitoneal) and local infections (UTI and RTI) in mice was compared with that of cefaclor (CCL) in one study. In the intraperitoneal infection models, ceftibuten had good activity especially against gram-negative bacteria. [See TABLE 65]. Against *E. coli*, *P. mirabilis*, *P. vulgaris*, *E. cloacae*, *S. marcescens*, and *H. influenzae* ED_{50} values were ≤ 0.1 mg/kg while those for cefaclor (CCL) were a lot higher. Against *Klebsiella* infections, ED_{50}s were 1 mg/kg for ceftibuten while those for cefaclor were 8 to 15 mcg/kg. Against gram-positive bacteria, the activity of ceftibuten was similar to that of cefaclor against *S. pyogenes* but significantly less versus *S. pneumoniae* (53 vs 6 mg/kg).

Table 65
Therapeutic efficacy of ceftibuten and Cefaclor on experimental intraperitoneal infection in mice

ORGANISM	CHALLENGE DOSE (CFU/MOUSE)[a]	MUCIN	ED50 (mg/kg/dose)[b]		MIC (μg/mL)[c]	
			CEF	CCL	CEF	CCL
S. aureus Smith	1×10^6	+	64.4	0.052	50	0.78
S. pyogenes C-203	1×10^3	-	1.43	0.71	0.39	0.2
S. pneumoniae Type 1	1×10^3	-	53.7	6.26	3.13	0.78
E. coli EC-14	2×10^5	+	0.080	1.43	0.025	0.78
E. coli SR73 (ABPC-R)	4×10^6	+	0.39	8.96	0.2	12.5
K. pneumoniae SR1	3×10^4	-	0.96	8.11	0.0125	0.39
K. pneumoniae B-54	2×10^4	-	1.02	15.5	<0.006	0.39
P. mirabilis SR434	3×10^6	+	0.092	2.15	0.025	1.56
P. vulgaris CN-329	4×10^5	+	0.069	25.1	0.025	100
E. cloacae SR113	1×10^5	+	0.076	4.59	0.025	3.13
S. marcescens ATCC 13880	2×10^4	+	0.12	105	0.1	100
H. influenzae 88562	2×10^6	+	0.081	0.70	0.025	0.78

[a] Mice were infected intraperitoneally with test organism in 5% mucin or heart infusion broth. Compounds were administered orally at 1 and 5 hours after infection.

[b] ED50 values are expressed as a single dose.

[c] MICs were determined on STA media with an inoculum size of 1×10^6 CFU/mL.
CEF=CEFTIBUTEN; CCL=CEFACLOR

In this same study experiments were performed in which 1) the treatment time was varied [See TABLE 66], 2) the infecting inocula was varied [TABLE 67], and 3) the mice were pretreated with cyclophosphamide to induce neutropenia [TABLE 68]. In the immunocompromised mice, ceftibuten was 10 to 100 times more active than cefaclor in the treatment of infections caused by *E. coli*, *E. cloacae*, and *S. marcescens*.

Table 66
Effect of administration-time on ED50s of ceftibuten and Cefaclor against intraperitoneal infection with *E. coli* EC-14 in mice

ADMINISTRATION TIME (HOURS)	ED50 (MG/KG)	
	CEFTIBUTEN	CEFACLOR
-2	1.52	27.8
-1	0.59	13.6
0	0.13	1.25
1	0.11	0.84
2	0.19	0.99
3	0.14	1.04
4	1.07	2.07

Mice were infected intraperitoneally with 1 x 10^5 CFU/mouse in 5% mucin. Compounds were administered orally as a single dose at the time indicated in the table after infection.

While both compounds did not have significant changes in ED_{50} values with doses given from immediately after infection to 3 hours, the ED_{50} value of ceftibuten administered 4 hours after infection increased 7 times from that of 3 hours after infection. With both compounds the therapeutic efficacy of pre-infection doses was remarkably lower than that in the early stage of infection.

Table 67
Effect of challenge dose on ED50 of ceftibuten and cefaclor against intraperitoneal infection with *E. coli* EC-14 in mice

CHALLENGE DOSE (CFU/MOUSE)	CHALLENGE LD_{50}	ED50 (MG/KG)		RATIO*	
		CEF	CCL	CEF	CCL
1×10^5	5×10^2	0.11	0.81	1.0	1.0
1×10^6	5×10^3	0.13	1.62	1.2	2.0
1×10^7	5×10^4	2.37	4.01	22	5.0

Mice were infected intraperitoneally with test organism in 5% mucin.
Compounds were administered orally at 1 hour after infection.
CEF=CEFTIBUTEN; CCL=CEFACLOR
* Ratio is the ED_{50} at the indicated dose divided by the ED_{50} at the challenge dose of 10^5 CFU/mouse

Major changes were not seen in efficacy of the two drugs when the challenge dose was increased from 10^5 CFU/mouse to 10^6 CFU/mouse, but the therapeutic efficacy of ceftibuten was reduced when the challenge dose was increased to 10^7 CFU/mouse. This same reduction in efficacy was also seen with cefaclor but to a much lesser degree.

Table 68
Therapeutic efficacy of ceftibuten and cefaclor on experimental intraperitoneal infections in neutropenic mice

ORGANISM	CHALLENGE DOSE (CFU/MOUSE)	MUCIN	ED50 (MG/KG/DOSE)		MIC (μG/mL)	
			CEF	CCL	CEF	CCL
E. coli EC-14	2 X 10^3	+	0.23	2.86	0.025	0.78
E. cloacae SR113	3 X 10^4	+	0.18	11.3	0.025	3.13
S. marcescens ATCC 13880	2 X 10^3	+	0.39	333	0.1	100

Neutropenic mice were induced by cyclophosphamide given in a single intraperitoneal dose of 80 mg/kg at 6, 4, and 1 days before infection.
CEF=CEFTIBUTEN; CCL=CEFACLOR

The efficacy of ceftibuten and cefaclor on the infections were lowered to 1/2 to 2/3 of that in normal mice. In all the infections ceftibuten was far superior to cefaclor.

The normal adult dosage for ceftibuten is 400 mg/daily. This dosage is equivalent to about 6mg/kg/day for the average adult of 70 kilograms. Table 65 shows that the ED_{50} for gram-negative intraperitoneal infections is usually $\leq$ 0.1 mg/kg which is 60 times less than the average adult dose. Ceftibuten is, therefore, a good candidate for testing against gram-negative bacteria. Against gram-positive bacteria, except *S. pyogenes*, the ED_{50} values were 50 mg/kg or higher. This indicates that ceftibuten may not work as well against infections caused by gram-positive organisms. It appears from Table 66 that ceftibuten should has no prophylactic effect and does not work as well after the infection has become established and there is a high number of infecting organisms [Table 67]. It appears from Table 28 that ceftibuten may be less effective in immunocompromised patients.

This investigator also studied the efficacy of ceftibuten in the treatment of experimental urinary tract infections. He used both an *E. coli* and a *P. mirabilis* model. [See TABLES 69 and 70].

Table 69
Therapeutic efficacy of ceftibuten and cefaclor on experimental urinary tract infection with *E. coli* EC-14 in mice

DOSE (MG/KG/DOSE)	CEFTIBUTEN		CEFACLOR	
	LOG OF VIABLE CELLS/G	EFFECTIVE/ TESTED	LOG OF VIABLE CELLS/G	EFFECTIVE /TESTED
500			2.72	10/13
150			3.22	14/19
50	≤2.00	12/12	3.98	8/19
15	3.07	13/17	4.78	7/19
5	3.81	10/17	5.57	3/19
1.5	4.88	4/17	7.69	0/12
0.5	5.75	2/17		
CONTROL	8.61	0/22		
ED50	3.23		49.5	
MIC (μg/mL)	0.025		0.78	

MICE WERE INFECTED TRANSURETHRALLY WITH 2 X 10^4 CFU/MOUSE IN 0.125 ML OF HEART INFUSION BROTH. COMPOUNDS WERE ADMINISTERED ORALLY AT 4 AND 7 HOURS AFTER INFECTION AND THEN TWICE A DAY FOR 3 DAYS. THE NUMBER OF ORGANISMS PER GRAM OF KIDNEYS WERE COUNTED AT 4 DAYS POST-INFECTION AND $<10^4$ CFU/G WAS REGARDED AS "EFFECTIVE". ED_{50} VALUES WERE EXPRESSED AS A SINGLE DOSE. MICs WERE DETERMINED BY AGAR DILUTION WITH 10^6 CFU/mL.

Table 70
Therapeutic efficacy of ceftibuten and cefaclor on experimental urinary tract infection with *P. mirabilis* SR434 in mice

DOSE (MG/KG/DOSE)	CEFTIBUTEN		CEFACLOR	
	LOG OF VIABLE CELLS/G	EFFECTIVE/ TESTED	LOG OF VIABLE CELLS/G	EFFECTIVE /TESTED
100			≤2.00	12/12
30			2.47	11/12
10	2.19	11/12	2.58	10/12
3	2.60	10/12	5.77	2/12
1	3.76	7/12	6.96	1/12
0.3	6.42	2/12		
0.1	7.31	0/12		
CONTROL	8.16	0/11		
ED50	0.82		5.44	
MIC (μg/mL)	0.025		1.56	

MICE WERE INFECTED TRANSURETHRALLY WITH 2 X 10^3 CFU/MOUSE IN 0.125 mL OF HEART INFUSION BROTH. COMPOUNDS WERE ADMINISTERED ORALLY AT 6 HOURS AFTER INFECTION AND THEN TWICE A DAY FOR 3 DAYS. THE NUMBER OF ORGANISMS PER GRAM OF KIDNEYS WERE COUNTED AT 4 DAYS POST-INFECTION AND $< 10^4$ CFU/G WAS REGARDED AS "EFFECTIVE". ED_{50} VALUES WERE EXPRESSED AS A SINGLE DOSE. MICs WERE DETERMINED BY AGAR DILUTION WITH 10^6 CFU/mL.

In the *E. coli* model of urinary tract infections ceftibuten was about 7 times superior to cefaclor. In the *P. mirabilis* model of urinary tract infections ceftibuten was about 5 times more effective than cefaclor. The normal adult dose of ceftibuten is only about twice the ED_{50} for *E. coli* in this urinary tract infection model, while the normal dose is about seven times the ED_{50} for *P. mirabilis* in this model. These data suggest that ceftibuten may be effective in urinary tract infections caused by either organism, but may be more effective in infections caused by *P. mirabilis*.

When this investigator studied the activity of ceftibuten and cefaclor in an experimental *Klebsiella* respiratory tract infection model in mice, he found that ceftibuten was about 25 times superior to cefaclor when survival rate was calculated on ED_{50} values. When calculated on the index of eradication rate of the bacterial count in the lungs, ceftibuten was 120 times better than cefaclor. [See TABLE 71]. Once again the ED_{50} was well below the usual adult dose which indicates that ceftibuten may be effective in respiratory tract infections caused by *Klebsiella*.

Table 71

Therapeutic efficacy of ceftibuten and cefaclor on experimental respiratory tract infection with *K. pneumoniae* B-54 in mice

DOSE (MG/KG/DOSE)	CEFTIBUTEN		CEFACLOR	
	SURVIVAL	ERADICATION	SURVIVAL	ERADICATION
500			20/20	11/20
300			20/20	8/20
100			20/20	4/20
30	20/20	19/20	15/20	3/20
10	19/20	12/20	5/20	0/20
3	19/20	8/20	1/20	0/30
1	15/20	6/20		
0.3	1/20	0/20		
0.1	0/10	0/10		
CONTROL	0/28			
ED50	0.69	3.54	16.4	424
MIC (μg/mL)	≤0.006		0.39	

MICE WERE INFECTED WITH AN AEROSOLIZED BACTERIAL SUSPENSION OF 10^9 CFU/mL. COMPOUNDS WERE ADMINISTERED ORALLY AT 4 HOURS AFTER INFECTION AND THEN TWICE A DAY FOR 7 DAYS. THE NUMBER OF ORGANISMS PER GRAM OF LUNGS WERE COUNTED AT 8 DAYS POST-INFECTION AND $< 10^2$ CFU/G WAS REGARDED AS "EFFECTIVE". ED_{50} VALUES WERE EXPRESSED AS A SINGLE DOSE. MICs WERE DETERMINED BY AGAR DILUTION WITH 10^6 CFU/mL.

Another investigator compared the activity of ceftibuten to that of ampicillin and cefixime in an infection model for otitis media in chinchillas [Data not shown]. They used both *S. pneumoniae* and beta-lactamase producing *H. influenzae*. They tested two outcomes: middle-ear sterilization and resolution of the effusion. When *H. influenzae* was the infecting organism both ceftibuten and cefixime resulted in more rapid sterilization of the ear than ampicillin, and ceftibuten but not cefixime was better at eliminating effusion. When *S. pneumoniae* was the infecting organism all groups gave similar results. This study indicates that ceftibuten may be useful in otitis media infections caused by *H. influenzae* and may have some activity in this disease when the pathogen is *S. pneumoniae*.

It appears from these animal model studies that ceftibuten may be effective in systemic infections caused by gram-negative bacteria and may be effective in urinary tract infections caused by *E. coli* or *P. mirabilis*, and in respiratory infections caused by *Klebsiella*. It also appears from animal models that ceftibuten should be effective against otitis media caused by *H. influenzae*.

CLINICAL LABORATORY SUSCEPTIBILITY TEST METHODS

The ultimate purpose of *in vitro* susceptibility tests is to provide a basis for the separation of clinical isolates of pathogens that would likely respond to treatment with the tested antimicrobial from those that would be unlikely to respond. Parameters that are considered in the process of selecting the criteria for susceptibility tests interpretation include human pharmacokinetics, *in vitro* characteristics of the compound, distribution of microorganism susceptibility, and correlation of susceptibility test results with outcome statistics of the disease.

Ceftibuten is about 75 to 90% bioavailable after oral dosing. Maximum plasma concentration following a single 400 milligram dose is μg/mL. The plasma elimination half-life is 2 to 4 hours. The C_{max} at steady-state is about μg/mL after 400 mg twice a day dosing.

According to its labeling cefaclor produces peak serum concentration of μg/mL within minutes after oral doses of 250 mg, 500 mg and 1 gram, respectively. Serum half-life is 0.6 to 0.9 hours. The serum levels obtained with cefaclor doses of 500 mg and 1 gram are close to those produced with a 400 mg dose of ceftibuten.

Ceftibuten has a mechanism of action that is essentially the same as that of cefaclor. Ceftibuten's *in vitro* spectrum includes most of the organisms susceptible to cefaclor but it is much more stable to most β-lactamases. Since the serum level of ceftibuten after a 400 mg dose is about the same as that of cefaclor's if a 500 mg dose is used; and ceftibuten's *in vitro* spectrum is better than that of cefaclor's, the MIC criteria used for cefaclor and most other cephalosporins should also be used for ceftibuten susceptibility testing. These criteria are as follow:

SUSCEPTIBLE	≤ 8 μg/mL
MODERATELY SUSCEPTIBLE	16 μg/mL
RESISTANT	≥ 32 μg/mL

A multi-laboratory study was performed to determine the ceftibuten MIC quality control guidelines for NCCLS recommended control strains. *Escherichia coli* ATCC 25922 was found to be the only clinically usable strain, having a well defined ceftibuten modal MIC of μg/mL. The results with investigator prepared and common lots of media were essentially identical. The recommended MIC quality control range for ceftibuten will thus be μg/mL. The ceftibuten MIC mode values for *Pseudomonas aeruginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 29213 were μg/mL.

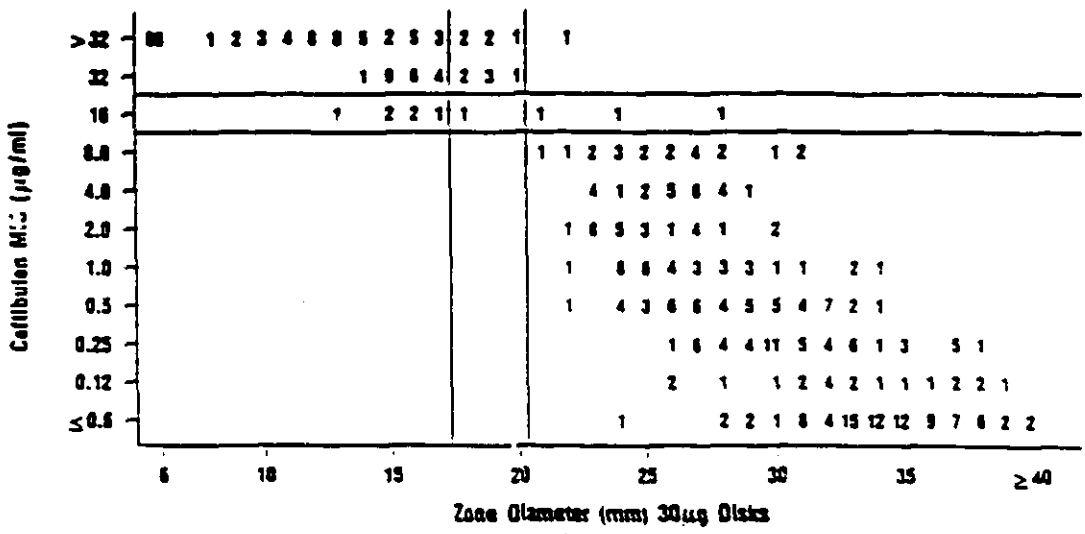
The Clinical Microbiology Institute evaluated the 30-μg ceftibuten disk using 537 strains. Isolates were tested by broth microdilution and disk diffusion tests. Mueller-Hinton broth and microdilution trays were used. The inocula were adjusted to 5 x 10^5 CFU/mL. For *Haemophilus influenzae* isolates, disk diffusion and agar dilution tests were performed with haemophilus test medium. This study found that the majority of the members of the family *Enterobacteriaceae* were susceptible to ceftibuten; median MICs for different species ranged from μg/mL. Only *Enterobacter cloacae, Serratia marcescens,* and *Morganella morganii* had strains with MICs μg/mL. Ceftibuten was inactive against *Pseudomonas aeruginosa* as well as the gram-positive bacilli, enterococci, and *Streptococcus bovis*. Staphylococci were resistant. *Moraxella catarrhalis* isolates were susceptible, as were *Streptococcus pyogenes* isolates and penicillin-susceptible strains of *Streptococcus pneumoniae*. Penicillin-resistant pneumococci were relatively resistant to ceftibuten. *H. influenzae* isolates were all susceptible to ceftibuten. Both β-lactamase producing and non-producing strains of *H. influenzae* were both very susceptible to ceftibuten (MICs μg/mL), but chromosomally mediated ampicillin resistant (β-lactamase negative) strains tended to be less susceptible to ceftibuten (MIC μg/mL). These latter strains of *H. influenzae* and penicillin-susceptible *S. pneumoniae* isolates would be most markedly affected by a one-dilution decrease in the MIC breakpoint from μg/mL to μg/mL. Such a change in breakpoint would be justified only if these types of infections failed to respond to ceftibuten. This has not been observed in the clinical trials and an adjustment of the MIC breakpoints is not needed.

When MICs were correlated to zone diameters, regression analysis provided a correlation coefficient of 0.81 and a regression formula of y=43.7-1.8x (y=zone diameter in millimeters and x=MIC as $\log_2$ + 9 μg/mL). The calculated zone size correlate for an MIC of μg/mL is approximately millimeters. Using the usual millimeter intermediate range gives a resistant category of millimeters. A scattergram was constructed for all species other than *H. influenzae* to evaluate the calculated zone size criteria [See FIGURE 8]. There was only one (0.2%) very major errors (*Enterobacter sakazakii*) and there were 20 (4.2%) minor errors. Strains of *S. pneumoniae* for which the MIC was μg/mL produced very large zones of inhibition that could not be distinguished from zones that were produced by more susceptible strains. An MIC breakpoint of μg/mL would cut through the normally distributed population of MICs and would lead to a greater minor error rate (8.4%-40/478). A separate analysis of disk diffusion tests with 59 *H. influenzae* isolates displayed no interpretive discrepancies. All zones were mm and all MICs were μg/mL. For ampicillin-resistant β-lactamase-negative strains, zones ranged from mm and MICs were μg/mL. There were very few of the ampicillin-resistant strains. It appears that the same criteria can also be used for testing *H. influenzae* on haemophilus test medium. A six laboratory evaluation of susceptibility tests with a 30-μg ceftibuten disk versus *E. coli* ATCC 25922, showed that quality control limits for this organism should be set at zones of mm.

From NDA 50-685

Figure 18

Scattergram Showing Distributions of Ceftibuten Broth Microdilution MICs and Zone Diameters with 30 µg Ceftibuten Disks. Data for 59 *H. influenzae* Isolates are Excluded



In conclusion the following susceptibility cri should be used for ceftibuten:

ZONE SIZE (MM)	MIC (μg/mL)	INTERPRETATION
≤ 17	≥ 32	(R) RESISTANT
18-20	16	(I) INTERMEDIATE
≥ 21	≤ 8	(S) SUSCEPTIBLE

The following quality control criteria have been established using data from a collaborative study:

QC STRAIN	ZONE DIAMETER (MM)	MIC (μg/mL)
E. coli ATCC 25922	29-35	0.12 - 0.5
P. aeruginosa ATCC 27853	--	>32
S. aureus ATCC 29213	--	>32

COMPARISON OF *IN VITRO* SUSCEPTIBILITY WITH CLINICAL OUTCOME

Correlation of susceptibility test results with outcome statistics accumulated during the therapeutic trials of any new antimicrobial agent is flawed by the fact that only infections due to "susceptible" organisms are treated. It is, therefore, difficult to verify resistance criterion with positive data points. This is usually verified by the fact that a too permissive susceptible criterion would lead to the presence of a subset of "susceptible" pathogens from infections that later proved to be clinical and/or bacteriologic failures.

The relationship between susceptibility and bacteriological outcome is shown in Table 72 for zones and Table 73 for MICs. The majority of isolates tested had zone diameters mm or MICs μg/mL. Among these 1158 organisms, the overall bacterial elimination rate was 90%. In the 42 isolates with intermediate zone sizes (18-20 mm), the bacterial elimination rate was also 90% (38/42). These values suggest that the susceptibility cutoff criteria is conservative and patients with susceptible isolates have a high probability of a successful outcome.

Table 72
Relationship between Zone Susceptibility and Bacterial
and Clinical Response
All Ceftibuten Patients

ZONE (mm)	NO.	MICROBIOLOGICAL RESPONSE		CLINICAL RESPONSE	
		ELIMINATED (%)	PERSISTENT (%)	CURE/IMPROVEMENT (%)	FAILURE (%)
15-17	8	7 (88)	1 (12)	8 (100)	–
18-20	42	38 (90)	4 (10)	40 (95)	2 (5)
21-25	244	222 (91)	22 (9)	235 (96)	9 (4)
26-30	392	343 (88)	49 (12)	365 (93)	27 (7)
31-35	230	209 (91)	21 (9)	214 (93)	16 (7)
36-40	65	60 (92)	5 (8)	64 (98)	1 (2)
>40	22	17 (77)	5 (23)	18 (82)	4 (18)
TOTAL 1003					

Table 73
Relationship between MIC Susceptibility and Bacterial
and Clinical Response
All Ceftibuten Patients

MIC (μg/mL)	NO.	MICROBIOLOGICAL RESPONSE		CLINICAL RESPONSE	
		ELIMINATED (%)	PERSISTENT (%)	CURE/IMPROVEMENT (%)	FAILURE (%)
0.025-0.125	44	42 (95)	2 (5)	40 (91)	4 (9)
0.25-1.0	81	76 (94)	5 (6)	78 (96)	3 (4)
1.25-2.0	19	18 (95)	1 (5)	19 (100)	–
4.0-8.0	11	8 (73)	3 (27)	9 (82)	2 (18)
TOTAL 155					

The data for *Streptococcus pneumoniae* is shown in Table 74. Similar excellent bacterial elimination and clinical response was seen for the *S. pneumoniae* as seen with the overall results.

Table 74
Relationship between MIC Susceptibility and Bacterial and Clinical Response
S. pneumoniae

MIC (μg/mL)	NO.	MICROBIOLOGICAL RESPONSE		CLINICAL RESPONSE	
		ELIMINATED (%)	PERSISTENT (%)	CURE/IMPROVEMENT (%)	FAILURE (%)
0.062-0.125	11	11 (100)	–	11 (100)	–
0.25-0.5	8	8 (100)	–	8 (100	–
1.00	2	1 (50)	1 (50)	1 (50)	1 (50)
4.0-8.0	6	4 (67)	2 (33)	4 (67)	2 (33)
TOTAL 27					

There were a total of 131 zones for *S. pneumoniae* isolates. They ranged from millimeters. There were two isolates classified as resistant and both were eliminated. There were 10 isolates classified as intermediate. Three of these 10 isolates persisted. A total of 30 of the 131 isolates persisted. There did not seem to be any trend between zone size and persistence.

There were 38 *Moraxella catarrhalis* isolates tested by disk diffusion methods. The zones ranged from millimeters. Only 5 of the 38 isolates persisted and the ones that persisted were scattered throughout the spectrum of zone sizes.

There were 180 *Escherichia coli* isolates tested by disk diffusion methods. The zone sizes ranged from millimeters. Of these 180 isolates, 21 persisted. The isolates that persisted had zone sizes between millimeters.

There were 40 *Klebsiella pneumoniae* isolates with zone sizes between millimeters. Only one of these isolates persisted and it had a zone diameter of millimeters.

There were 23 *Proteus mirabilis* isolates with zones between millimeters. All 23 isolates were eliminated.

There were 167 isolates of *Haemophilus influenzae* with zone sizes given. These ranged from millimeters. Of these 167 isolates, 17 persisted. There was no correlation between zone size and persistence.

There were 44 isolates of *Haemophilus parainfluenzae* with zone sizes given. These ranged from millimeters. Of these 44 isolates, two persisted; one with a zone of and the other with a zone of millimeters.

There were 251 *Streptococcus pyogenes* isolates with zone diameters determined. The zones ranged from milliliters. Eighteen of these persisted. All but one of the persisting isolates had zones between millimeters. The other isolate that persisted had a zone of milliliters.

There were seven efficacy and safety studies that included 2,325 patients who were treated in the trials with ceftibuten capsules. Of these seven studies, three were positive-controlled, investigator-blind trials in the treatment of lower respiratory tract infections (LRTI) and two were positive-controlled, investigator-blind trials in the treatment of urinary tract infections. A third UTI trial was open-label. One controlled study was in sinusitis, which is not an indication that the applicant is seeking. Of the 2,325 treated patients, 1587 were treated with ceftibuten capsules. Ceftibuten 400 mg QD was administered to 1041 patients in either open-label or positive-controlled, evaluator-blind studies. The mean duration of treatment was 8.7 days. Ceftibuten 200 mg BID was given to 359 patients in positive-controlled, evaluator-blind studies. The mean duration of treatment was 9.6 days. Ceftibuten 300 mg BID was administered to 187 patients in positive-controlled, evaluator-blind studies. The mean duration of treatment was 8.7 days.

The following is a discussion of the data presented by the applicant in their summary of each indication they are requesting:

BRONCHITIS–For patients with bronchitis total bacteriologic elimination rate for ceftibuten 400 mg QD was 116/132 (88%). The elimination rate was 36/44 (82%) for ceftibuten 200 mg BID and was 22/29 (76%) for 300 mg BID. The cefaclor elimination rate was 59/73 (81%) for cefaclor 250 mg TID and 20/30 (67%) for cefaclor 500 mg TID. Ceftibuten given in smaller doses and less often gave equivalent or better elimination rates. The following bacteriologic response was found with these most common isolates:

ORGANISM	200 MG BID	300 MG BID	400 MG QD
H. influenzae	19/21 (90%)	8/11 (73%)	47/50 (94%)
S. pneumoniae	6/10 (60%)	3/6 (50%)	19/27 (70/%)
H. parainfluenzae	12/12 (100%)	0/0	15/16 (94%)
M. catarrhalis	6/8 (75%)	0/0	14/15 (93%)
K. pneumoniae	2/2 (100%)	2/2 (100%)	8/9 (89%)

PNEUMONIA/BRONCHIECTASIS–For patients with pneumonia or bronchiectasis, total bacteriologic elimination rates were as follows: 99/110 (90%) for ceftibuten 200 mg BID, 37/40 (93%) for ceftibuten 300 mg BID, and 57/69 (83%) for cefaclor 500 mg TID. The following bacteriologic response was found with these most common isolates:

ORGANISM	200 MG BID	300 MG BID
S. pneumoniae	28/36 (78%)	12/14 (86%)
H. influenzae	29/31 (94%)	10/10 (100%)
K. pneumoniae	10/10 (100%)	10/10 (100%)
H. parainfluenzae	7/7 (100%)	3/3 (100%)
M. catarrhalis	9/9 (100%)	0/0

Both of these indications were grouped together when discussing patients with beta-lactamase-producing pathogens since there were only a few such patients. Three of four (75%) patients treated with ceftibuten 400 mg QD and 2/4 (50%) of patients treated with cefaclor 500 mg TID had elimination of a beta-lactamase-producing *H. influenzae* from respiratory secretions. Six patients in the ceftibuten 400 mg QD group had a beta-lactamase-producing *Moraxella catarrhalis*; half (3/6) had bacteriologic elimination. One of four (25%) cefaclor 500 mg TID treated patients from whom a beta-lactamase-producing *Moraxella catarrhalis* was isolated had a bacteriological elimination.

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OTITIS MEDIA--One pivotal, controlled, multicenter trial involved 154 patients eligible for efficacy evaluation. It evaluated ceftibuten given in doses of 9 mg/kg for 10 days versus cefaclor 40 mg/kg (divided into 3 doses) for 10 days. Culture documentation of bacteriologic response was not available for the majority of patients because it is undesirable to do repeat tympanocentesis. Overall, 89% of the patients in the ceftibuten group (94/106) and 88% of the patients in the cefaclor group (42/48), had clinically satisfactory results. Prior to treatment, 162 causative pathogens were isolated from the 154 patients. Overall, 88% of the causative pathogens in both the ceftibuten (99/112) and cefaclor (44/50) treatment groups had a clinical cure. Ceftibuten treatment resulted in cures in 97% (33/34) of the cases with *Haemophilus influenzae* as the pathogen compared to 76% (13/17) in the cefaclor group. For *Streptococcus pneumoniae*, ceftibuten gave favorable results in 80% (43/54) of the cases compared to 95% (21/22) for cefaclor. Twelve of 106 patients in the cefibuten group (11%) and six of the 48 patients in the cefaclor group (13%) were failures. Of the 12 ceftibuten failures, 11 (92%) had *S. pneumoniae* as the pathogen. Listed below are the most common pathogens and the number of satisfactory results:

ORGANISM	CEFTIBUTEN	CEFACLOR
H. influenzae	33/34 (97%)	13/17 (76%)
M. catarrhalis	6/6 (100%)	2/2 (100%)
S. pneumoniae	43/54 (80%)	21/22 (95%)
S. pyogenes	12/13 (92%)	7/7 (100%)

Nine ceftibuten-treated patients (3 *H. influenzae* and 6 *M. catarrhalis*) and two cefaclor-treated patients (1 *H. influenzae* and 1 *M. catarrhalis* had infections caused by beta-lactamase producing pathogens. All nine of the ceftibuten-treated patients and one of the two cefaclor-treated patients (*M. catarrhalis*) had a clinical cure or improvement.

PHARYNGITIS--There was one large multicentered trial. A total of 426 patients were eligible for efficacy evaluation. At the five-to-seven day post-treatment visit the infecting organism (*S. pyogenes*) was eliminated in 91% (267/294) of the patients in the ceftibuten group versus 80% (105/132) of the patients in the penicillin V group. At the two-to-three week post-treatment follow-up visit the pathogen remained eliminated in 89% (171/192) of the patients in the ceftibuten group and in 79% (63/80) of the patients in the penicillin V group.

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LABELING (MICROBIOLOGY SECTION)

To be consistent with other current labels the Microbiology Section should be rewritten as follows: [The distribution of organisms between the section that has clinical significance and the one that does not will depend on the Medical Officer's Review].

As with other beta-lactam agents, ceftibuten exerts its bactericidal action by binding to essential target proteins of the bacterial cell wall, leading to inhibition of cell-wall synthesis. Ceftibuten is stable in the presence of most plasmid-mediated beta-lactamases, but it is not stable in the presence of chromosomally-mediated cephalosporinases produced in organisms such as *Bacteroides, Citrobacter, Enterobacter, Morganella,* and *Serratia.*

Ceftibuten has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections at the indicated body sites: (See **INDICATIONS AND USAGE** section.):

Gram-positive aerobes:

Streptococcus pyogenes
Streptococcus pneumoniae (excluding penicillin-resistant strains)

Gram-negative aerobes:

Escherichia coli
Haemophilus influenzae (including beta-lactamase-producing strains)
Haemophilus parainfluenzae
Klebsiella pneumoniae
Klebsiella oxytoca
Moraxella (Branhamella) catarrhalis (including beta-lactamase-producing strains)
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuar...

The following *in vitro* data are available; however, their clinical significance is unknown. Ceftibuten exhibits *in vitro* MICs of 8 μg/mL or less against most strains of the following organisms; however, the safety and efficacy of ceftibuten in treating clinical infections due to these organisms have not been established in adequate and well-controlled trials.

Gram-positive aerobes

{The applicant has included no organisms in this list. Any of the two organisms listed in the above list may be placed here if the Medical Officer does not give them as an indication. This reviewer feels that if S. pneumoniae is listed in this section that it should be qualified as penicillin-susceptible strains.}

Gram-negative aerobes

{Once again the applicant has included no organisms for this list. Any of the organisms, except for Haemophilus parainfluenzae for which no in vitro data is included in the NDA, that the Medical Officer does not include from the list above may be transferred to this list.}

{In order to be included in this "in vitro only" list, the more easily obtained and tested organisms must have a minimum of 100 isolates tested and more than one laboratory must have been used and the MIC_{90} for the majority of the studies must be equal to or less than the susceptible breakpoint; there will be very few other species allowed in this list.}

{Ordinarily only organisms recognized as significant pathogens at the body site(s) or in the infection(s) for which clinical efficacy for other pathogens has been established will be listed. This means that organisms such as Neisseria gonorrhoeae, Salmonella species, and Shigella species should not be included since this drug does not have an indication for sexually transmitted diseases or for gastroenteritis.}

NOTE: Ceftibuten is inactive *in vitro* against Enterococci, Staphylococci, or *Acinetobacter, Enterobacter, Flavobacterium, Listeria,* and *Pseudomonas* species. In addition, it shows little *in vitro* activity against most anaerobes, including most species of *Bacteroides*.

SUSCEPTIBILITY TESTING

Susceptibility Tests: ***Diffusion Techniques:*** Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standardized procedure[1] that has been recommended for use with disks to test the susceptibility of organisms to ceftibuten uses the 30-μg ceftibuten disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ceftibuten.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-μg ceftibuten disk should be interpreted according to the following criteria:

Zone diameter	Interpretation
$\geq$ 21	Susceptible (S)
18-20	Moderately Susceptible (MS)
$\leq$ 17	Resistant (R)

A report of "susceptible" implies that an infection due to the strain may be appropriately treated with the dosage of antimicrobial agent recommended for that type of infection and infecting species, unless otherwise contraindicated. A report of "moderately susceptible" indicates that MICs for these isolates approach attainable serum levels and the strain may be inhibited provided higher dosages are used. Response rates may be lower than for susceptible isolates. A report of "resistant" indicates that these strains are not inhibited by the usually achievable systemic concentrations of the tested agent with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms (β-lactamases) are likely and clinical efficacy has not been reliable in treatment studies.

Standardized susceptibility procedures require the use of laboratory control organisms. The 30-μg ceftibuten disk should give the following zone diameters in these laboratory test quality control strains:

Organism	Zone diameter (mm)
Escherichia coli ATCC 25922	29-35

Cephalosporin class disks should not be used to test for susceptibility to ceftibuten.

Dilution Techniques: Use a standardized dilution method[2] (broth, agar, or microdilution) or equivalent with ceftibuten powder. The MIC values obtained should be interpreted according to the following criteria:

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

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard ceftibuten powder should provide the following MIC values:

Organism	MIC range (mcg/mL)
Escherichia coli ATCC 25922	
Pseudomonas aeruginosa ATCC 27853	
Staphylococcus aureus ATCC 29213	

The following references should be added in the REFERENCES section of the labeling:

1. National Committee for Clinical Laboratory Standards, Performance Standard for Antimicrobial Disk Susceptibility Tests - Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS, Villanova, PA, April, 1990.

2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Second Edition. Approved Standard NCCLs Document M7-A4, Vol. 10, No. 8 NCCLS, Villanova, PA , April 1990.

The remainder of the package insert is satisfactory from the microbiology viewpoint.

CONCLUSIONS:

From the microbiology viewpoint the drug should be approved with labeling changes.

Ceftibuten has a carboxyethylidene side chain, which makes it different from most orally absorbed cephems. Ceftibuten has good activity against most gram-negative bacteria. In general it is active against *Escherichia coli, Klebsiella, Proteus, Providencia, Salmonella, Shigella, Haemophilus influenzae,* and *Streptococcus pyogenes*. It has limited activity against *Citrobacter, Enterobacter, Serratia* and *Streptococcus pneumoniae*. It has no activity against staphylococci, enterococci, *Pseudomonas, Acinetobacter, Flavobacterium* and obligately anaerobic bacteria. The drug is stable to most plasmid-mediated beta-lactamases, but is not stable to chromosomal beta-lactamases. It is a poor inhibitor of most plasmid-mediated beta-lactamases. It is a weak inducer of Class I chromosomal beta-lactamases.

NDA 50-685 CEFTIBUTEN CAPSULES

The sponsor should be notified to rewrite the microbiology section of the package insert as follows:

As with other beta-lactam agents, ceftibuten exerts its bactericidal action by binding to essential target proteins of the bacterial cell wall, leading to inhibition of cell-wall synthesis. Ceftibuten is stable in the presence of most plasmid-mediated beta-lactamases, but it is not stable in the presence of chromosomally-mediated cephalosporinases produced in organisms such as *Bacteroides, Citrobacter, Enterobacter, Morganella,* and *Serratia.*

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Moraxella (Branhamella) catarrhalis (including beta-lactamase-producing strains)
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii

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18-20	Moderately Susceptible (MS)
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Organism	Zone diameter (mm)
Escherichia coli ATCC 25922	29-35

Cephalosporin class disks should not be used to test for susceptibility to ceftibuten.

Dilution Techniques: Use a standardized dilution method[2] (broth, agar, or microdilution) or equivalent with ceftibuten powder. The MIC values obtained should be interpreted according to the following criteria:

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

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard ceftibuten powder should provide the following MIC values:

Organism	MIC range (mcg/mL)
Escherichia coli ATCC 25922	
Pseudomonas aeruginosa ATCC 27853	
Staphylococcus aureus ATCC 29213	

NDA 50-685 CEFTIBUTEN CAPSULES

The follcwing references should be added in the REFERENCES section of the labeling:

1. National Committee for Clinical Laboratory Standards, Performance Standard for Antimicrobial Disk Susceptibility Tests - Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS, Villanova, PA, April, 1990.

2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Second Edition. Approved Standard NCCLs Document M7-A4, Vol. 10, No. 8 NCCLS, Villanova, PA , April 1990.

The remainder of the package insert is satisfactory from the microbiology viewpoint.

The rest of the package insert is satisfactory from the microbiology viewpoint.

Peter A. Dionne
Microbiologist, HFD-520
June 29, 1992

This review contains 98 pages

Orig. NDA #50-585
cc:
HFD-473
HFD-635
HFD-502/JWeissenger
HFD-520
HFD-520/Micro/Dionne
HFD-520/MO/Leissa
HFD-520/Pharm/Buko
HFD-520/CSO/Debellas

9/6/92

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/SMicro/ATSheldon

6/18/92
6/23/92
7/1/92

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Microbiology and Drug Control Review Notes #2

SEP 4 1992

NDA # 50-685

Date Completed: September 1, 1992

Sponsor: Schering Corporation
2000 Galloping Hill Road Division
Kenilworth, NJ 07033
Attn: Alexander R. Giaquinto, Ph.D.; V.P. Worldwide Regulatory Affairs
(908) 298-2780

Submission Reviewed: Amendment dated August 21, 1992

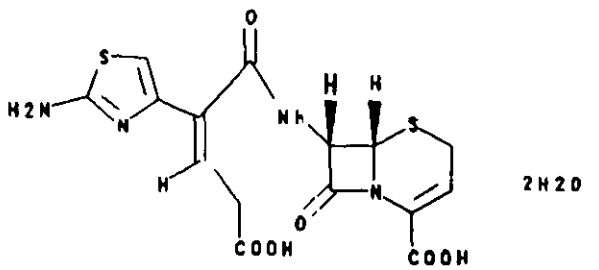
Providing For:
I. Amendment provides answers to deficiencies in Chemistry, Manufacturing and Controls Review #1
II. Draft labels for pouches and boxes of capsules
III. Minor changes and corrections in the method of manufacture and packaging of the drug substance

Names:
Trade: CEDAX™ capsules
Non-Proprietary: ceftibuten capsules
Chemical: (+)-(6R,7R)-7-[(Z)-2-(2-amino-4-thiazoly)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Dosage Form: 200 milligram and 400 milligram capsules

Pharmacological Category: semi-synthetic cephalosporin antibiotic

Structural Formula:



$C_{15}H_{14}N_4O_6S_2 \bullet 2H_2O$
M.W.= 446.43

Related NDA, IND, DMF, Form 5's:
IND IND
NDA 50-686 Ceftibuten for oral suspension;

Initial Submission: Received by CDR: 12/20/91; Received by reviewer: 3/16/92; Reviewed initiated: 4/1/92; Review completed: April 30, 1992

Remarks:

I. Each deficiency is stated and then the applicant's response is given.

Comment 1):

A satisfactory establishment evaluation is needed for the facilities that manufacture and test the new drug substance.

Response:

We understand that FDA inspection of the drug substance manufacturing and testing facilities is planned for October 1992.

Peter Smith of International Programs and Technical Support says that he hopes to be able to schedule an inspection of

Comment 2):

Samples were requested on February 3, 1992 for method validation. Samples were sent to the FDA laboratory on February 12, 1992. Method validation for the new drug substance must still be completed.

Response:

We understand that method validation for the new drug substance is ongoing and we will be notified upon completion.

Method validation work is continuing at our laboratory.

Comment 3):

The tests for heavy metals, residue on ignition, and surface area performed on the new drug substance are not needed. They will not be included in the official monograph for this product. The sponsor may continue to perform these tests as "in house" specifications.

Response:

We will continue to perform these tests as "in-house" specifications.

This response is satisfactory.

Comment 4):

The test for the related substances I (HPLC) will not be included in the official monograph for the new drug substance. Unless present in high amounts or toxic, FDA has been controlling the amount of impurities by using the purity (assay) of the bulk material. The sponsor should continue to perform these tests, however. The structures of these compounds have been determined and they are present in only small amounts under normal storage conditions. The trans compound which is usually the most common one will be controlled by the specific rotation specification. Since the Group X compounds have not been fully characterized and this group is usually the most prominent degradation product they will be tested for in the official monograph.

Response:

We will continue to perform the tests for the related substances I, as requested. We understand that the Group X compounds will be tested for in the official monograph.

This response is satisfactory.

Comment 5):

The test for acetonitrile will not be included in the official monograph for the new drug substance. This is a residual solvent and is present in only very small amounts. The sponsor should continue to perform this test, however.

Response:

We will continue to perform the test for acetonitrile, as requested.

This response is satisfactory.

Comment 6):

The TLC identity test will be the identification method in the official monograph of the new drug substance, since the use of the IR method would require that two different reference standards be established.

Response:

We concur with the use of the TLC identity test method for the official monograph.

This response is satisfactory.

Comment 7):

A crystallinity test should be performed on the new drug substance.

Response:

The USP [695] crystallinity test has been added to the ceftibuten (Sch 39720) drug substance release requirements. Revised specification pages carrying additional acceptance limits for crystallinity are attached (included with this submission).

The new release specifications for the new drug substance are now satisfactory.

Comment 8):

An acceptable EER is needed for the facility that manufactures, processes, packages, and tests the capsules.

Response:

We understand that FDA inspection of our Miami Lakes facility, which is response for the above activities, is planned for October 1992.

An inspection of Schering's Miami Lakes facility should occur in October 1992.

Comment 9):

Method validation for the capsules must be completed by FDA laboratories. The tests for related substances will not be part of the official monograph for this product. The applicant should continue to perform the tests.

Response:

We understand that methods validation by the FDA laboratories is ongoing. We agree to continue to perform the tests for related substances in the capsules.

This response is satisfactory. Method validation in FDA laboratories is ongoing.

Comment 10):

The possibility of heat-sealed polyethylene-paper laminate sheets used to seal the iron oxide in the oxygen absorber used in the packaging of the new drug substance breaking should be addressed. What will the applicant do if this sheet breaks open and the iron oxide in the oxygen absorber gets into the new drug substance?

Response:

The oxygen absorber material is contained in a heat sealed paper/polyethylene lamination that is purchased from an outside supplier. Shionogi takes the paper/polyethylene bags and places them into a secondary perforated polyethylene bag as a precautionary step. These polyethylene bags are placed on the outside of the inner polyethylene bag which contains the drug substance and is tightly sealed. The oxygen absorber does not directly contact the drug substance during shipping/handling and storage. In the unlikely event of spillage, the oxygen absorber would be contained in the secondary polyethylene bag and the drug substance would be protected by the sealed inner poly bag, thereby preventing the oxygen absorber from contacting the active drug substance. Extensive shipping studies from Japan have shown that this package is satisfactory and no oxygen absorber package breakage has occurred.

Diagrams showing how the above packaging is put together and the final packaging configuration have been included in this submission.

The above response is satisfactory. The packaging of the oxygen absorber in the new drug substance packaging is satisfactory.

Comment 11):

The size of the lots should be given for each lot used in the stability studies on the new drug substance. The stability report should also state whether or not production type equipment was used to produce each batch.

Response:

Each batch was produced using equipment which is comparable with respect to type, material, and configuration to that being used for commercial production. This statement and the batch sizes have been added to the first page of the ceftibuten (Sch 39720) drug substance stability report. (This page is included in this submission).

The batch sizes of the stability lots are as follow:

4X803	10.2 kg
4X804	9.5 kg
4Y805	9.3 kg
88ZC03	27.3 kg
88ZC04	56.7 kg
88ZC05	55.5 kg
886006	14.2 kg
886007	14.6 kg
886010	14.0 kg
893004	42.7 kg
893005	46.8 kg
893006	45.7 kg

A typical production batch will yield 150 kg.

This response is satisfactory.

Comment 12):

An expiry of 18 months at -20°C may be used for the new drug substance.

Response:

We concur with this dating period.

Response is satisfactory.

Comment 13):

An expiry of 24 months at 2°C to 25°C may be used for the capsules.

Response:

We concur with this dating period.

Response is satisfactory.

Comment 14):

A satisfactory environmental assessment is needed for this product. The submitted environmental assessment is incomplete and inadequate. The applicant must conduct tests and submit the information requested in the list of deficiencies sent to them.

Response:

A complete Environmental Assessment has been submitted under separate cover on August 14, 1992.

The Environmental Assessment must be reviewed by our Environmental Assessment Officer and found satisfactory. A FONSI for this product must then be written by him before approval.

Comment 15):

The words "brand of" should be deleted from the labels.

Response:

The draft labeling has been revised as requested.

Schering has included labels for a box of 2 x 1 capsules (4 x 1 capsule for the 200 mg capsule); a professional sample of 1 capsule; a bottle of 20 capsules; a bottle of 100 capsules; pouch for the unit dose package; and a box for 40 capsules--unit dose for the 400 mg capsule and the 200 mg capsules. The words"brand of" have been deleted from all these labels.

Comment 16):

The number of capsules in each container should be moved from the left margin of the label to the center of the label and it should read "Contains # capsules" or "# capsules."

Response:

The draft labeling has been revised as requested.

All draft labeling in this submission states "# capsules" in the center of the label.

Comment 17):

The statement "Each capsule contains 200 mg ceftibuten as the dihydrate" should be revised to read "Each capsule contains ceftibuten dihydrate equivalent to 200 mg of ceftibuten.

Response:

The draft labeling has been revised as requested.

The submitted labels have been revised.
The draft container labels are now satisfactory.

Comment 18):

The title of the product in the package insert heading should be listed as follows:

CEDAX
Ceftibuten capsules and
Ceftibuten for oral suspension

Response:

As subsequently requested by the Medical Reviewer, Dr. Leissa, we have separated the combined insert. The heading of each insert will reflect the specific dosage form. In addition, as requested by Dr. Leissa, the Dosage and Administration section of the package insert has been revised to reflect duration of dosing in terms of disease state.

The revised package insert will be submitted under separate cover.

The revised package insert will be reviewed when submitted.

Comment 19):

The inactive ingredients should be listed in the package insert in alphabetical order.

Response:

The package insert has been revised as requested and will be submitted under separate cover.

The revised package insert will be reviewed when submitted.

NDA 50685

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
Microbiological and Drug Control Review Notes

NDA #: 50-685 **REVIEW #:** #6 **REVIEW DATE:** 01-DEC-94

SUBMISSION/TYPE: Amendment dated 09-AUG-94

PROVIDING FOR: Answers to fax received by Schering on July 22, 1994 (From Review #5 dated 27-JUN-94) requesting data on (1) quality control testing of *H. influenzae* ATCC 49247 on Haemophilus Test Media; (2) information on MIC and ceftibuten disk quality control testing of *S. pneumoniae* ATCC 49619.

NAME & ADDRESS OF APPLICANT:

SCHERING CORPORATION
Galloping Hill Road
Kenilworth, NJ 07033

DRUG PRODUCT NAME

Proprietary:	CEDAX®
Nonproprietary/USAN:	Ceftibuten capsules

ANDA Suitability Petition/DESI/Patent Status:

Not Applicable

PHARMACOLOGICAL CATEGORY/INDICATION: Cephalosporin/Antibiotic

DOSAGE FORM:	Capsules
STRENGTHS:	200 and 400 mg/capsule
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	_X_ Rx ___ OTC

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

Chemical Name: (+)-(6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Molecular Formula: $C_{15}H_{14}N_4O_6S_2 \cdot 2H_2O$

Molecular Weight: 446.43

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS: NDA 50-686--ceftibuten for oral suspension

CONSULTS: None

REMARKS/COMMENTS:

{1} Barry et. al. 1992 (1) reported on a five-laboratory collaborative effort to evaluate MIC control limits for two strains of *H. influenzae*. This study involved HTM broth prepared with six lots of Mueller-Hinton broth. Each of the five participants prepared microdilution trays with a different HTM broth medium. The necessary supplements were all from a common source; only the Mueller-Hinton broth base differed. The coordinating facility also prepared broth microdilution trays with a sixth lot of HTM broth medium, and distributed the control lot of trays to all laboratories. The procedures recommended by the National Committee for Clinical Laboratory Standards (NCCLS) were followed. Each participant performed 25 separate microdilution tests with each strain of *H. influenzae*. This included 20 tests with trays prepared by the investigator, using a unique lot of broth and 5 tests with the common lot of broth. In the above study the usual quality control organism *H. influenzae* ATCC 49247, which is beta-lactamase negative, ampicillin-resistant was tested along with *H. influenzae* ATCC 49766 which is ampicillin-susceptible. The following results were obtained for ceftibuten:

	No. of times MIC was recorded
H. influenzae ATCC 49247	0.12-1; 0.25-6; 0.5-86; 1.0-31; 2.0-1
H. influenzae ATCC 49766	≤0.008-1; 0.016-1; 0.03-42; 0.06-77; 0.12-4

Using the mode ± Log_2 dilution the following quality control limits result:

H. influenzae ATCC 49247	0.25-1.0 μg/mL
H. influenzae ATCC 49766	0.03-0.12 μg/mL

In a second study Bale et.al. (2) reported on another collaborative study using *H. influenzae* ATCC 49247. This study design conformed to the NCCLS M23 guideline. The six participant laboratories each received a unique lot of HTM broth in microdilution trays. Each site also processed the organism in a lot of trays common to all laboratories. The total number of MICs contributed from each laboratory was 20 from the unique lot and 5 from the common lot. The following results were obtained for ceftibuten:

	No. of times MIC was recorded
H. influenzae ATCC 49247	[Unique lot] 0.5-118; 1.0-2 [Common lot] 0.5-25; 1.0-5

Using the mode $\pm$ Log_2 dilution the following quality control limits result:

H. influenzae ATCC 49247 0.25-1.0 μg/mL

Barry (3) reported on Quality Control Parameters for Tests with 30 μg ceftibuten disks. Five laboratories each performed 25 separate tests with *H. influenzae* ATCC 49247 and five separate tests with *H. influenzae* ATCC 10211 (used to monitor the growth promoting capabilities of the HTM agars used). Each test involved three different lots of 30 μg ceftibuten disks and a single 10 μg ampicillin disk that was added for control purposes. In addition, each participant performed five tests on a sixth lot of HTM agar common to all participants. The following results were obtained on the unique lots of agar:

Zone	Number of Times each Zone Recorded					
mm	Lab A	Lab B	Lab C	Lab D	Lab E	Total
29		5		4		9
30	2	32	6	9		49
31	16	26	8	18	2	70
32	24	11	13	27	9	84
33	19	1	27	17	24	88
34	5		19		22	46
35	6		2		14	22
36	3				4	7
Total	75	75	75	75	75	375
Mean	32.5	30.6	32.7	31.6	33.7	32.2
SD	1.40	0.87	1.26	1.13	1.16	1.56
Median	32	31	33	32	34	32
Min.	30	29	30	29	31	29
Max.	36	33	35	33	36	36
Range	6	4	5	4	5	7

All Lab Mean	32.2	All Lab Median	32
Average S.D.	1.16	Median of Ranges (MR)	5
± 2 S.D.	29.9-34.5	1/2 MR Rounded up (R)	3
Rounded out	30-35	Median ±1/2 R	29-35

The following results were recorded for the common lot of agar:

Zone	Number of Times each Zone Recorded					
mm	Lab A	Lab B	Lab C	Lab D	Lab E	Total
28		2				2
29		3				3
30	3	6		3	2	14
31	4	4	11	6	6	31
32	7		4	4	3	18
33	1			2	4	7
Total	15	15	15	15	15	75
Mean	31.4	29.8	31.3	31.3	31.6	31.1
SD	0.91	1.01	0.46	0.98	1.06	1.10
Median	32	30	31	31	31	31
Min.	30	28	31	30	30	28
Max.	33	31	32	33	33	33
Range	3	3	1	3	3	5

When using the 10 μg ampicillin disks (each lab tested 30 times) the following zone diameters were obtained: 16mm--2; 17mm-4; 18mm-40; 19mm-49; 20mm-20; 21mm-21; 22mm-12; 23mm--2. The NCCLS control limits are 13-21 mm, therefore, 90.7% of the zones are within limits. When testing *H. influenzae* ATCC 10211 the median zone size obtained by each laboratory varied from 29 to 36 mm with the overall mean of 35 mm. This indicated that all lots of media tested supported growth. The mean zone size for the three different disk lots varied from 31.4 to 32.2 mm, which showed that all three lots were equivalent.

The quality control limits for the 30 μg ceftibuten disk should be listed as follows:

H. influenzae ATCC 49247 29-35 mm

The NCCLS committee accepted the recommendation for MIC quality control values, with ATCC 49247 of 0.25 to 1.0 μg/mL. They did not vote on the values for disk testing and these data will be presented again in January.

{2} Schering's response is "Since we did not recommend testing of *S. pneumoniae* to the NCCLS, we did not present data for quality control testing of *S. pneumoniae* ATCC 49619. In fact, we do not have this data, since we do not feel it is needed."

Since the drug will be in the package insert with a claim for *S. pneumoniae* (penicillin-sensitive isolates only) this information is not needed at the present time. If this organism's claim is expanded in the future via a supplement the above information will be needed along with separate breakpoints.

REFERENCES

1. Barry, A.L., J.H. Jorgensen, D.J. Hardy, S.D. Allen, and C.N. Baker. 1992. *Haemophilus influenzae* ATCC 49766, an Alternative Quality Control Strain for Monitoring Broth Microdilution Susceptibility Tests with Selected β-Lactams. J. Clin. Microbiol. 30:2033-2037.

2. Bale, M.J., R.N. Jones, M.E. Erwin, F.P.Koontz, E.H.Gerlach, P.R.Murray, and J.A. Washington. 1991. MIC Quality Control Guidelines for *Haemophilus* Susceptibility Tests Using Cefdinir (FK482), Cefepime, Cefetamet, Cefpirome, Ceftibuten, Fleroxacin, Temafloxacin, Clarithromycin, RP59500 and Trospectromycin. Submitted to: Journal of Clinical Microbiology, August, 1991.

3. Barry, A.L. 1991. Disk Diffusion Susceptibility Tests for *Haemophilus influenzae* Isolates.

CONCLUSIONS AND RECOMMENDATIONS:

1. The foliowing quality control ranges should be added to the package insert for *Haemophilus influenzae* ATCC 49247 tested on Haemophilus Test Media:

   MICs 0.25 -1.0 μg/mL Zone Size 29-35 mm

   Since NCCLS list limits for *H. influenzae* ATCC 49766 only in cases where *H. influenzae* ATCC 49247 is not satisfactory, it should not be listed for ceftibuten.

   Since in the Clinical Trials for this drug there were no isolates with MIC values ≥ 2 μg/mL or zone diameters of ≤ 28 mm, only a suspectable breakpoint can be determined for *H. influenzae*. NCCLS approved these criteria in June 1994. This will be indicated in the Susceptibility Testing section of the labeling.

2. At the present time data on MIC and ceftibuten disk quality control testing of *Streptococcus pneumoniae* ATCC 49619 is not needed.

   Since this drug is indicated only for penicillin-sensitive strains of *S. pneumoniae*, susceptibility only has to be determined for penicillin. The statement "Isolates of pneumococci with oxacillin zone sizes of ≥ 20 mm are susceptible (MIC ≤0.06 μg/mL) to penicillin and can be considered susceptible to ceftibuten for approved indications. Testing of ceftibuten against penicillin-intermediate or penicillin-resistant isolates is not recommended. Reliable interpretive criteria for ceftibuten are not currently available." This statement was approved for ceftibuten by NCCLS in June 1994.

3. The Environmental Assessment for this product was reviewed by Dr. Tsu and found satisfactory in March 1994. A FONSI has been rewritten for the product..

4. The zone diameter quality control range for *E. coli* ATCC 25922 should be revised from 29-35 mm to 27-35 mm. The old criteria only included 86.5% of the data from the six laboratory evaluation. In general, at least 95% of common and test lot values should be included in the proposed range. The new range includes 98% of the values. The range of 27-35 was approved by NCCLS in June 1994.

5. Method validation for this product has been completed and a monograph has been written and is ready for publication [see Review #5].

6. A satisfactory Establishment Evaluation for all facilities was received 3/17/94. A Final Update Request that all sites remained acceptable was received 8/3/94. Since this Update expired 10/3/94, another Final Update Request was filed on 11/22/94--a 10 day letter was sent to ORL district (for the Miami Lakes site) on 11/28/94. An acceptable response was received dated 12/14/94.

FROM THE MICROBIOLOGICAL AND CHEMISTRY MANUFACTURING CONTROL VIEWPOINT THIS PRODUCT SHOULD BE APPROVED WITH THE FOLLOWING CHANGES IN THE LABELING:

The MICROBIOLOGY section of the label should be written as follows:

> Ceftibuten exerts its bactericidal action by binding to essential target proteins of the bacterial cell wall, leading to inhibition of cell-wall synthesis.
>
> Ceftibuten is stable in the presence of most plasmid-mediated beta-lactamases, but it is not stable in the presence of chromosomally-mediated cephalosporinases produced in organisms such as *Bacteroides, Citrobacter, Enterobacter, Morganella,* and *Serratia*. Ceftibuten should not be used against strains resistant to beta-lactams due to general mechanisms such as permeability or penicillin-binding protein changes (*e. g.*, such as found in penicillin-resistant *S. pneumoniae*).

Ceftibuten has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections at the indicated body sites: (See **INDICATIONS AND USAGE** section.):

Gram-positive aerobes:

Streptococcus pneumoniae (penicillin-sensitive strains only)
Streptococcus pyogenes

NOTE: Ceftibuten is inactive against methicillin-resistant staphylococci.

Gram-negative aerobes:

Haemophilus influenzae (including β-lactamase-producing strains)

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

Ceftibuten exhibits *in vitro* MICs of 8 μg/mL or less against most strains of the following organisms; however, the safety and efficacy of ceftibuten in treating clinical infections due to these organisms have not been established in adequate and well-controlled trials.

Gram-negative aerobes:

Moraxella catarrhalis (including β-lactamase producing strains)

NOTE: Ceftibuten is inactive *in vitro* against Enterococci, Staphylococci, or *Acinetobacter, Bordetella, Campylobacter, Enterobacter, Enterococcus, Flavobacterium, Hafnia, Listeria, Pseudomonas, Staphylococcus,* and *Streptococcus* (except *pneumoniae* and *pyogenes*) species. In addition, it shows little *in vitro* activity against most anaerobes, including most species of *Bacteroides*.

SUSCEPTIBILITY TESTING

Dilution Techniques: Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[1] (broth, agar, or microdilution) or equivalent with ceftibuten powder. The MIC values obtained should be interpreted according to the following criteria for aerobic organisms other than *Haemophilus, Neisseria gonorrhoeae,* and *Streptococcus pneumoniae*:

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

A report of "susceptible" implies that an infection due to the strain may be appropriately treated with the dosage of antimicrobial agent recommended for that type of infection and infecting species, unless otherwise contraindicated. A report of "intermediate" indicates that the result should be considered equivocal, and, if the organism is not fully susceptible to alternative, clinically feasible drug, the test should be repeated. This category implies 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 that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that these strains are not inhibited by the usually achievable systemic concentrations of the tested agent with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms (β-lactamases) are likely and clinical efficacy has not been reliable in treatment studies.

The following interpretive criteria should be used when testing *Haemophilus* species using Haemophilus Test Media (HTM):

MIC (μg/mL)	Interpretation
≤ 2	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

Ceftibuten does not have an indication for *Neisseria gonorrhoea* and no testing criteria for this organism has been determined.

Ceftibuten is indicated for penicillin-sensitive only strains of *S. pneumoniae*. *S. pneumoniae* should be tested using an oxacillin disk. Isolates of pneumococci with oxacillin zone sizes of ≥20 mm are susceptible (MIC ≤ 0.06 μg/mL) to penicillin and can be considered susceptible to ceftibuten. Testing of ceftibuten against penicillin-intermediate or penicillin resistant isolates is not recommended. Reliable interpretive criteria for ceftibuten are not currently available.

Standardized susceptibility procedures require the use of laboratory control microorganisms. Standard ceftibuten powder should provide the following MIC values:

Organism	MIC range (μg/mL)
Escherichia coli ATCC 25922	
Haemophilus infleunzae ATCC 49274	

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters provide estimates of the susceptibility of bacteria to antimicrobial agents. One such standardized procedure[2] that has been recommended for use with disks to test the susceptibility of organisms to ceftibuten uses the 30-μg ceftibuten disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ceftibuten.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-μg ceftibuten disk should be interpreted according to the following criteria for aerobic organisms other than *Haemophilus*, *Neisseria gonorrhoeae*, and *Streptococcus pneumoniae*:

Zone diameter (mm)	Interpretation
$\geq$ 21	(S) Susceptible
18-20	(I) Intermediate
$\leq$ 17	(R) Resistant

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

The following interpretive criteria should be used when testing *Haemophilus* species using Haemophilus Test Media (HTM):

Zone diameter (mm)	Interpretation
$\geq$ 28	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

As with standardized dilution techniques diffusion methods require use of laboratory control microorganisms. The 30-μg ceftibuten disk should provide the following zone diameters in these laboratory quality control strains:

Organism	Zone diameter (mm)
Escherichia coli ATCC 25922	27-35
Haemophilus influenzae ATCC 49247	29-35

Cephalosporin class disks should not be used to test for susceptibility to ceftibuten.

The following references should be added to the REFERENCES section of the labeling:

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically--Third Edition. Approved Standard NCCLS Document M7-A3 , Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards, Performance Standard for Antimicrobial Disk Susceptibility Tests--Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

The remainder of the package insert is satisfactory from the microbiology viewpoint and CMC viewpoint.

As per review #3 dated June 21, 1993, the following organisms have been deleted from the label since only one or two studies were reported and usually only ten or fewer strains were included in each study:

Streptococcus C
Streptococcus G
Brucella

Haemophilus parainfluenzae has been deleted due to no *in vitro* studies being performed.

Neisseria has been deleted since this drug does not have an indication for sexually transmitted diseases.

Morganella should be listed as *Morganella morganii* since most studies were performed on this species and we now list only species in the package insert. Since this product will not be approved for UTI this organism should be deleted anyway.

Since this product is only being approved for otitis media and pharyngitis the following organisms should be deleted since they are not usually found in the above diseases:

Citrobacter diversus
Citrobacter freundii
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia liquefaciens
Serratia marcescens

Peter A. Dionne
Review Microbiologist

cc: Orig. NDA 50-685
HFD-502
HFD-520/Division File
HFD-520/MO/Leissa
HFD-520/Pharm/Buko
HFD-520/CSO/Debellas
HFD-520/Micro/Dionne/12/01/94

Concurrence Only:
HFD-520/ActingDir/LGavrilovich
HFD-520/SMicro/ATSheldon

JUN 8 1994

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Comments on Proposed Monographs

NDA #: 50-685 **REVIEW #:** #5 **REVIEW DATE:** 01-JUN-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
CORRESPONDENCE	19-MAY-94	23-MAY-94	23-MAY-94

NAME & ADDRESS OF APPLICANT:

SCHERING CORPORATION
Galloping Hill Road
Kenilworth, NJ 07033

DRUG PRODUCT NAME
Proprietary: CEDAX®
Nonproprietary/USAN: Ceftibuten capsules

ANDA Suitability Petition/DESI/Patent Status:

Not Applicable

PHARMACOLOGICAL CATEGORY/INDICATION:
Cephalosporin/Antibiotic

DOSAGE FORM: Capsules
STRENGTHS: 200 and 400 mg/capsule
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _____ OTC

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

Chemical Name: (+)-(6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Molecular Formula: $C_{15}H_{14}N_4O_6S_2 \bullet 2H_2O$

Molecular Weight: 446.43

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS: NDA 50-686--ceftibuten for oral suspension

CONSULTS: None

REMARKS/COMMENTS:

Schering is submitting comments on the proposed monographs for these products. These monographs were sent to them on February 22, 1994. Each of the comments is listed and then our response to it.

Page 1--2.a.xx--Correction in chemical name "(2-amino-4-thiazolyl)", the final "l" was missing in thiazolyl.

Response: Correction has been made.

Page 1--3.a.xxx--Assume word "designed" in third sentence was intended to be "designated".

Response: Assumption is correct. Correction has been made.

Page 2--4.b.xxx--The potency factor given of 1.148 is not that of the ceftibuten master standard as stated. The correct value for the master standard is 1.138. However, the value for the ceftibuten working standard is 1.148.

Response: Value has been corrected to 1.138.

Page 3--6.b--The dissolution medium volume should be 1000 mL, not 900 mL.

Response: All of FDA's dissolution testing is performed in volumes of 900 mL. The containers used would be too full if 1000 mL is used. Schering may use 1000 mL if the apparatus they use has containers large enough.

Page 4--c.xx.iii--This paragraph list "water as the blank". The blank should be the dissolution medium of 0.05 M potassium phosphate buffer, pH 7.0.

Response: The blank has been changed to 0.05M potassium phosphate buffer, pH 7.0.

The absorbance maximum should be 263 nanometers, not 260 nanometers as given.

Response: The monograph says absorbance maximum of approximately 260 nanometers. Since 263 nanometers is approximately 260 nanometers this statement will remain as is.

The spectrophotometer cell path length is not given. Our 200 mg and 400 mg capsules require the use of 0.1 and 0.05 cm path length UV cells. Thus, we suggest that the following sentence be added. "The path length of the spectrophotometer cell should be selected so that the absorbance of the standard is between 0.5 and 1.0 AU."

Response: The requested statement has been added.

Page 5--iv--The number 900 in the calculation should be changed to 1000.

Response: Since we are using 900 mL not 1000 mL (see response above) this value will stay as 900.

Page 7-d--The 8th sentence requires that the sample solution be spotted at positions 2 and 3. Should this be 2 and 4? The standard was also spotted at position 3 and thus as written the standard and sample are both spotted at position 3.

Response: This has been corrected to positions 2 and 4.

Page 9-3.b--Suggest that the requirement for constant temperature be written to clearly state that the temperature control is for the column, "...using an over or water bath capable of maintaining the column at a constant operating temperature between 30°C and 40°C, ...",

Response. The suggested statement has been added.

Page 16--443.1xx--The word "foams" should be "forms".

Response: The correction has been made.

Page 17-(i) Preparation of sample solution.

The proposed sample preparation for capsules is significantly different from the procedure we submitted. A comparison is given below:

FDA Proposed	Schering-Plough Submitted
1 intact capsule extracted with 150 mL and diluted to 200 mL Dilute further to 0.2 mg/mL.	Pool 10 capsules contents and accurately weigh an amount equivalent to 100 mg of ceftibuten and extract with 75 mL. Dilute to 100 mL and further dilute to 0.2 mg/mL.

Comment: With respect to concentration, the FDA proposal is equivalent for the 200 mg capsule, however, for the 400 mg capsule the FDA procedure would result in the initial extraction solution being twice as concentrated as that which we validated.

The FDA proposal uses an intact capsule and the method has not been validated by Schering-Plough to extract from intact capsules.

We do not believe that the use of one capsule is sufficient to be representative of the potency of the batch.

Recognizing that the FDA would prefer to provide a more generally written method in the CFR than we have previously submitted, we would like to suggest the following replace the first two sentences.

(i) Preparation of Sample Solution. Transfer, as completely as possible, the contents of ten capsules to a suitable tared container, determine the average content weight per capsule, and mix the combined contents. Transfer an accurately weighed quantity of the powder, equivalent to about 100 mg of ceftibuten, into a 100 mL volumetric flask. Mix with 75 mL of potassium phosphate buffer, pH 7.0 (described in §442.XX (b)(1)(A)).

Response: We usually do not like to assay only part of a mixture of the contents of a sample of capsules, but in this case due to the fact that the solubility of the drug in the buffer is about 4 mg/mL, it appears that this will have to be done. In order to keep solutions below 4 mg/mL a very large amount of buffer would be needed for the initial solution if the whole mixture of capsule contents was used. The sample preparation has been changed as written above. This will also require that the calculations be altered to read as follows:

(ii) Calculations. Calculate the ceftibuten content as follows:

$$\text{Milligrams of ceftibuten per capsule} = \frac{A_U \times P_S \times W_{con} \times d}{A_S \times W_{sam} \times 1000}$$

where:

- A_U = **Area of the ceftibuten peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);**
- A_S = **Area of the ceftibuten peak in the chromatogram of the ceftibuten working standard;**
- P_S = **Ceftibuten activity in the ceftibuten working standard solution in micrograms per milliliter;**
- W_{con} = **Average weight of the contents of the capsules;**
- W_{sam} = **Weight of the sample used; and**
- d = **Dilution factor of the sample.**

Page 20-(i) Preparation of Sample Solution

The solubility of ceftibuten in the phosphate buffer, pH 7.0 is about 4 mg/mL. The sample preparation as written could allow one to select a volumetric size for the initial sample extraction that would give a solution having a concentration close to or greater than the solubility limit. Thus, we would like to suggest that the first half of the second sentence be revised to,: "Transfer a 5.0-milliliter portion of the suspension into an appropriately sized volumetric flask that will provide an initial concentration of about 1 mg/mL and quantitatively dilute stepwise.."

Response: Revision has been made as requested.

CONCLUSIONS & RECOMMENDATIONS:

The mongraph will be published with the above revisions when the product is approved.

Peter A. Dionne

Peter A. Dionne
Review Microbiologist

cc: Orig. NDA 50-685
HFD-520/Division File
HFD-520/MO/Leissa
HFD-520/Pharm/Buko
HFD-520/CSO/Debellas
HFD-520/Micro/Dionne/06/01/94

Concurrence Only:
HFD-520/ActingDir/LGavrilovich
HFD-520/SMicro/ATSheldon
AS 6/8/94

6/8/94

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

NDA #: 50-685 **REVIEW #:** 4 **REVIEW DATE:** 11-24-93

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	11-02-93	11-04-93	11-04-93

NAME & ADDRESS OF APPLICANT: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

DRUG PRODUCT NAME

Proprietary:	CEDAX® Capsules
Nonproprietary/USAN:	Ceftibuten
Code Name/#'s:	Sch 39720
Chemical Type/ Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status:
Not applicable

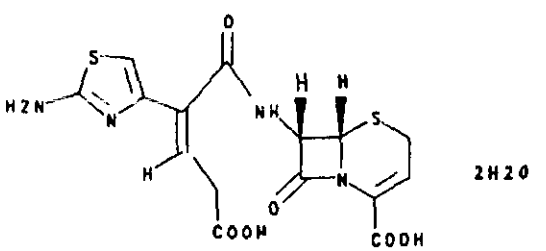
PHARMACOLOGICAL CATEGORY/INDICATION: CEPHALOSPORIN ANTIBIOTIC

DOSAGE FORM:	CAPSULES
STRENGTHS:	400 MILLIGRAMS/CAPSULE
ROUTE OF ADMINISTRATION:	ORAL
DISPENSED:	X Rx _____OTC

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

Chemical Name: (+)-(6R,7R)-7-[(Z)-2-(2-amino-4-thiazoly)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Structural Formula:



$C_{15}H_{14}N_4O_6S_2 \bullet 2H_2O$
M.W.= 446.43

SUPPORTING DOCUMENTS:

DMF
6/8/10, Type I DMF for facility in To support production of 3-Alcohol synthesis. Reference authorized by letter dated 02/26/93, signed by
DMF
6/8/10, Type I DMF for facility in Via To support production as an alternate site of 3-Alcohol synthesis. Reference authorized by letter dated 02/26/93, signed by President.
DMF
Type I DMF to support production of 3-Alcohol synthesis. Reference authorized by letter dated 01/12/93, signed by President.
DMF
Type I DMF for facility to be used in synthesis of thiazoline an intermediate supplied to used to produce 3-Alcohol. Reference authorized by letter dated 01/11/93, signed by Plant Manager.

RELATED DOCUMENTS:
IND
IND
NDA 50-686 Ceftibuten for oral suspension; PENDING

CONSULTS: AMENDMENT TO ENVIRONMENTAL ASSESSMENT sent to Dr. Vincent 11/08/93

REMARKS/COMMENTS: In this amendment Schering provides for alternative sourcing for the 3-Alcohol (Compound VII) used in the synthesis of ceftibuten drug substance at which supplies the new drug substance to Schering. Some minor changes are made in the synthesis based on the alternative sources. The submission gives a detailed summary and explanation of the changes with the changes highlighted on replacement pages in the synthesis description.

Equivalency reports are included showing that the 3-Alcohol VII prepared at and at is equivalent to that prepared at An equivalency report comparing ceftibuten prepared from 3-Alcohol and ceftibuten prepared from 3-Alcohol made at is submitted.

CONCLUSIONS & RECOMMENDATIONS:

The changes made in this amendment are approvable.

The application is not approvable for manufacturing and controls under section 507 of the Act. Specific items which are not approvable are identified below:

1. Method Validation must still be completed for this application. This may be completed post-approval.

2. A satisfactory establishment inspection is still needed for the facility in Kenilworth, New Jersey.

3. The amendment to the Environmental Assessment must be reviewed by Dr. Vincent and found satisfactory.

Peter A. Dionne
Review Microbiologist

This review contains 15 pages

cc: Orig. NDA 50-685
HFD-473
HFD-635
HFD-502
HFD-520/Division File
HFD-520/Micro/Dionne
HFD-520/MO/Leissa
HFD-520/Pharm/Buko
HFD-520/CSO/Debellas

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/SMicro/ATSheldon
TS 11/30/93

E. A. memo

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 10 1992

FROM: Environmental Assessment Officer HFD-102

SUBJECT: Environmental Concerns--NDA 50-685 (50-686) Cedax (ceftiben) Capsules.

TO: Harold Silver HFD-520

Schering-Plough Corp.

Please transmit the following to the firm:

1. Your environmental assessment for NDA 50-685 may not be used to comply with the regulatory requirements for NDA 50-686. A separate environmental assessment is needed for NDA 50-686.

2. Item 5. Please move "appendix A" to the main body of the environmental assessment.

3. Item 7. You must provide the actual test reports for review. You have failed to provide the appropriate environmental fate tests and therefore the environmental assessment is not adequate at 21 CFR 25.22(b).

4. Item 8. You have failed to provide the appropriate environmental effects tests and therefore the environmental assessment is not adequate at 21 CFR 25.22(b).

5. Item 11. You must include as an alternative "no action" or not approvable.

6. Item 15. You have failed to submit item 15 of the environmental assessment as defined by the regulation at 21 CFR 25.31a(a).

CC: Original NDA 50685
EA File 50685
Division File/HFD-520
Supervisory Chemist/HFD-520
Reader File HFD-102

F/T 3/ 10 /92

NDA 50685
NDA 50686

Dr. Alexander Giaquinto
Vice President
Regulatory Affairs
Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

1 1 1992

Dear Dr. Giaquinto:

Reference is made to your NDA's 50685 and 50686 for ceftibuten capsules and suspension, respectively, submitted on December 21, 1991 pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act.

Reference is also made to a telephone conversation we had following the Division of Anti-Infective Drug Products' recent 45-day meeting regarding these submissions. In that conversation you and I agreed that the Division would file both of these applications, but that the reviews and action decisions on the two applications would not be undertaken concurrently. That is, the Division would proceed with the review of the capsule formulation application and issue an action letter on that application based on the findings in that review. Subsequent to that review, the Division would begin its review of the suspension application.

As we discussed, the Division does not believe presently that the data submitted in support of the acute otitis media claim in the suspension application are adequate for an unrestricted labeling claim. Therefore, as we agreed, if at the time the Division is ready to make its final action decision on the suspension application, there have been no further data submitted to the suspension application to support the efficacy claim in acute otitis media, a final decision will, nonetheless, be made, and, if approvable for other indication(s), an approval letter for the suspension application will be issued without the indication of acute otitis media. However, if Schering is able to submit further efficacy data concerning acute otitis media prior to the time the division starts its review of that indication, then the application may be amended and the data will be reviewed prior to a final action decision on the suspension application. Otherwise, if the suspension application is approvable for other indication(s), an approval decision will be made, and further data concerning acute otitis media will have to be submitted as an efficacy supplement to the then approved suspension NDA.

If this is not your understanding of our agreement, please do not hesitate to contact me or Mr. Carmen DeBellas at (301) 443-4310 or (301) 443-6797.

Yours sincerely,

MML 3/10/92

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Orig NDA 50685
Orig NDA 50686
HFD-520
HFD-520/SMD/Albuerne
HFD-520/RMO/Leissa
HFD-520/SPharm/Osterberg
HFD-520/SMicro/Sheldon
HFD-520/SChem/DeCamp
HFD-520/SCSO/Bona
HFD-520/CSO/DeBellas
HFD-501/Burlington

NDA 50-685

Douglas B. Given, M.D., Ph.D.
Vice President
U.S. Regulatory Affairs
Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

JAN 7 1992

Dear Dr. Given:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cedax (ceftibuten) Capsules

Date of Application: December 20, 1991

Date of Receipt: December 23, 1991

Our Reference Number: NDA 50-685

Unless we find the application not acceptable for filing, the filing date will be February 23, 1992.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning the NDA, please contact Mr. Carmen DeBellas, Project Manager at 301-443-6797.

Sincerly yours,

JBona 1/6/92

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

cc:
ORIG. NDA 50-685
HFD-520
HFD-520/MO/ELeissa 1/6/92
HFD-520/PHARM/[redacted] (1/7/92)
HFD-520/MICRO/HSilver
HFD-521/PMS/CDeBellas 1/6/92
SJohnson/1/3/92
F/T: 1/3/92

TELEPHONE MEMORANDA, ELECTRONIC MAIL, AND MEETINGS WITH APPLICANT INCLUDING AMENDMENTS SUBMITTED RELATING TO THE REVIEW OF

NDA 50-685

GENERIC DRUG NAME: Ceftibuten
TRADE DRUG NAME REQUESTED: CEDAX®
DATE: February 3, 1993
RELATED IND's/NDA's: IND
IND
NDA 50-686 - suspension (pending review)

APPLICANT: Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
(908) 298-2793

SCHERING-PLOUGH REPRESENTATIVES CONTACTED DURING REVIEW:

Ed Barry - Project Manager, Clinical Systems
Mike Buska - Associate, Regulatory Affairs
Jean-Jacques Garaud, M.D. - Senior Director, Anti-Infectives
Alexander Giaquinto, M.D. -
Ann Kilian - MRA Manager, Anti-Infectives
Douglass Given, M.D. - Vice President, U.S. Regulatory Affairs
William Huang, Ph.D. - Manager, Biostatistics
Robert Kammer, M.D. - Clinical Research
Joseph Lamendola, Ph.D. - Senior Project Director
Barbara Matlosz - Director, Regulatory Affairs
Bridget Neigel - Systems Analyst, Research Information Services
Amy Rubin - Manager, Regulatory Affairs
Louise Schenfele - Supervisor, Clinical Data Management
Mary Treuhaft, Ph.D. - Assoc. Director, Regulatory Affairs
Harold Wolkoff, Ph.D. - Senior Vice President, Development Operations

NOTE: When All-in-1 was used for communication with the applicant's representatives, messages were sent to Rubin, Treuhaft, Matlosz, Kammer, and Given. On 8/3/92, Matlosz was deleted from this list and Lamendola was included instead. On 8/19/92, Given was removed and Drs. Giaquinto and Garaud were added.

THIS DOCUMENT IS SEPARATED INTO 2 SECTIONS. THE FIRST SECTION DESCRIBES VERBAL (MEETINGS & TELEPHONE CONTACTS) AS WELL AS ALL-IN-1 COMMUNICATIONS WITH THE APPLICANT, WHILE THE SECOND SECOND SECTION DESCRIBES WRITTEN COMMUNICATIONS (FAX & CLINICAL AMENDMENTS) SUBMITTED BY THE APPLICANT.

*****TELEPHONE MEMORANDA, ELECTRONIC MAIL, AND MEETINGS*****

December 20, 1991:
Contact: Treuhaft

Dr. Treuhaft called to inform me that the NDA was being sent. In addition, she wanted to know if an orientation session would be helpful. Also, what "support" I might need during the review.

She requested that the deadline for their Safety Update be extended to 6-8 months, instead of 4 months as specified in the regulations. Their rationale was that they would be submitting approximately 300 additional

safety patients as well as new analysis of the safety data, which had been recommended by an outside consulting group, and they believe that it would be difficult for them to be ready by that time. Likewise, they felt it would simplify things if they would be able, for future purposes, to submit the IND and NDA Safety Updates within the same time period. The anniversary for the capsules is June and for the suspension it is August.

I spoke to Drs. Lumpkin and Albuerne about these issues. We agreed that the Safety Update could be extended to 6 months. I emphasized that it was in their interest to have this information to us as soon as possible, since if we had completed our review quickly, and this information was not available, they risked receiving a nonapprovable letter. I also requested that all safety update information should be included in the NDA Safety Update; nothing should be included in the IND Annual Report safety update and not in the NDA Safety Update. She acknowledged these points.

In addition, we agreed that an "orientation session" would be helpful. I recommended that at this meeting, they "walk me through" one or two indications to show me where the data can be found in the NDA. With regard to "support" services, I informed Dr. Treuhaft that the review process would be beneficial if I had access to a laser printer; specifically, a HP LaserJet III. I told her that I did not have access to one at this time. She said that she would look into this.

January 6, 1992:
Contact: Treuhaft

Dr. Treuhaft called to inquire whether I had received the NDA. I responded that I had and that I had found certain patient profiles which were possibly lacking. She told me that she would look into them. In addition, we discussed computer support, in particular, spread sheets of the clinical data, such as Lotus 1-2-3.

January 7, 1992:
Contact: Rubin

Ms. Rubin called back to update me on the possible missing data in the patient profiles. The specifics follow:

NDA 50-685 - Center I88-111-4, patient : data is complete.
NDA 50-685 - Center I87-325-9, patient page 3108 was missing. NDA 50-685 - Center I87-234-2, patient data is complete.
NDA 50-685 - Center I87-236-1, patient data is complete.
NDA 50-685 - Center I88-230-4, patient only one sheet presented. She confirmed that these pages were missing
NDA 50-685 - Center C87-069-1, patient data is complete.
NDA 50-685 - Center I87-326-7, patient data is complete.
NDA 50-685 - Center I87-326-24, patient : data is complete.
NDA 50-686 - Center C87-112-11, patient data is complete.
NDA 50-686 - Center I88-112-1, patient data is complete.

In addition, I asked Ms. Rubin about a statement in the cover letter regarding the Environmental Assessment (EA) requirement. They referred to a conversation with Dr. Al Sheldon, Supervisory Microbiologist, where it was proposed that an interim EA report would be submitted. He was asked whether or not the Division would agree to this.

MO Comment: I asked Dr. Sheldon if he recalled the conversation. He said that he did and had told them that they could submit an interim EA report, but they would be taking a risk with this approach if they had not submitted the EA within a reasonable review time period. In addition, he recalled strongly recommending that they speak to Mr. Phil Vincent of the FDA about the requirements for this.

I asked Ms. Rubin if Dr. Vincent had been contacted. She responded that she did not know but would look into this.

January 9, 1992:
Contact: Treuhaft

I called Dr. Treuhaft to find out what treatment and dosing a specific patient had received. This was for Center I87-234-04, patient [redacted]. The patient profile did not specify this information.

Furthermore, I requested that a better system be developed to help find the data in the volumes. I noted that currently it was very difficult to find specific line-listings. She said she would work on this.

I reiterated that the applicant should contact Mr. Phil Vincent concerning the Environmental Assessment requirements.

January 13, 1992:
Contact: Rubin

Ms. Rubin called to follow-up on the 1/9/92 telephone conversation. I requested that a detailed Table of Contents be sent as well as an electronic copy if possible. In addition, for I87-234-04, patient [redacted] she told me the patient received both ceftibuten and cefaclor, concomitantly. Specific dosing is unknown.

January 13, 1992:
Telecon: Treuhaft, Huang, Barry
FDA representatives: Ana Szarfman, M.D.
Paul Seckler (management information services)

I requested that the applicant provide an electronic copy of the data base as well as computer hardware. I specified that this was only a request and that they did not need to agree to these requests. Specifically, I requested Lotus 123 and Paradox, a computer with ample RAM, a HP LaserJet Printer III, the clinical summaries in WordPerfect, as well as PC Tools and Lotus Magellan. The representatives agreed to provide this. They said that they would need to assure that this was feasible and would get back to me.

I also spoke with Dr. Treuhaft about the submitted Overall Table of Contents. I told here that it was still not "user friendly" with regard to finding tables, etc. She said they would work on this.

January 22, 1992:
Contact: Treuhaft

Dr. Treuhaft called to inform me that the computer would be sent in about one week. She also informed me that my previous request for better organization of the Table of Contents would be honored as well as they could. Yet, they believed this could take too long. They offered

to organize better the TOC for the efficacy and safety data. I asked them to do whatever they could.

In further discussions, I remarked how my counting of their patient profiles with regard to their evaluability and nonevaluability differed significantly from what was provided on the patient profiles. She said she would look into this.

January 23, 1992:
Contact: Treuhaft

Dr. Treuhaft called to inquire about the differences in numbers as we had discussed the previous day. I prepared a comparison sheet which I faxed to her.

January 24, 1992:
Contact: Treuhaft

Dr. Treuhaft and I discussed how the Table of Contents could be better organized. In addition, I asked that the *in vitro* microbiology for clinical isolates of *H. influenzae* and *M. catarrhalis* relative to β-lactamase activity as well as PCN susceptibility for *S. pneumoniae* be submitted.

January 27, 1992:
Contact: Rubin

Ms. Rubin called to discuss my needs with regard to organization of the Table of Contents for the NDA. She also faxed me a sample sheet of the proposed organization. We agreed to this organization.

January 29, 1992:
Contact: Treuhaft

I asked Ms. Treuhaft to officially submit to the NDA copies of all substantive faxes sent to me.

February 4, 1992:
MEETING WITH SCHERING-PLOUGH REPRESENTATIVES:
Huang, Kammer, Matlosz, Schenfele, Treuhaft

Presentation of format and organization of NDA. I was told that few pathogens had β-lactamase tested. I asked that a data for all isolates that underwent β-lactamase be submitted as this was missing in the NDA.

During this meeting I asked Dr. Kammer why the pneumonia indication wasn't being pursued as a much data on 200 mg p.o. b.i.d. pneumonia patients were submitted in the NDA. He responded that "the 200 mg b.i.d. dose doesn't work in pneumonia," and this is why Schering is conducting 300 mg b.i.d. studies.

February 5, 1992:
Contact: Treuhaft

I requested that the applicant provide a list of all patients in the LRTI studies who had the inclusion criterion in the CRF, "Did the baseline sputum contain >25 WBC and <10 epis/LPF?" answered "no." I also requested that the applicant ask the US investigators to submit sputa Gram's stain results from there medical records.

Ms. Treuhaft agreed to look into these requests.

MEETING WITH SCHERING-PLOUGH REPRESENTATIVES:
Ed Barry and Bridget Neigel

They installed the computer and provided an orientation session on Paradox and Lotus files.

February 6, 1992:
Contact: Buska

In response to a previous question, I responded that the format for the Safety Update should include data from the NDA, data since the NDA, and a combined safety profile.

I asked why a 200 mg capsule was requested when all adult studies are for 400 mg q.d. dosing?

I asked, if the 400 mg AECB and bronchitis indication were not considered approvable from the Division's assessment, would Schering request 200 mg b.i.d. dosing using data from their other studies?

February 7, 1992:
Contact: Matlosz

I repeated the conversation I had with Mike Buska yesterday. In addition, I asked whether Schering's definition of "valid" was the same as their "efficacy" population and whether this also correlated with "evaluable." Did "valid" at any time ever include the "expanded efficacy" population?

Contact: Treuhaft

Ms. Treuhaft called to tell me that the reason for the 200 mg capsule is for dosing in renal insufficiency. I then asked about 100 mg dosing for severe renal insufficiency. I was told that they would recommend the administration of suspension in this situation.

She responded that "valid" = "efficacy" = "evaluable." As far as she knows, there are no circumstances where "valid" includes "expanded efficacy."

Contact: Treuhaft, Kammer

Schering wants 400 mg q.d. and not 200 mg b.i.d. dosing for . In their opinion, 400 mg q.d. dosing is superior. They would prefer submitting data from on-going 400 mg trials than accept 200 mg b.i.d. dosing.

February 10, 1992:
Telecon with: Given, Kammer, Treuhaft, Ryman, and Rubin
FDA: Leissa, DeBellas, and Silver

Called to tell Schering that in light of the 45-Day Meeting, the Division had determined that the NDA was fileable. In addition, I told them that:
1) otitis media was not fileable,
2) the Division would review AECB/bronchitis patients but did not feel that review of pneumonia data was needed,

3) they need to stick to their inspection dates,
4) they need to get their environmental assessment done and to call Phil Vincent,
5) we need to see β-lactamase for LRTI, and
6) we need sputa verification for LRTI.

They expressed great concerns about not having otitis media in the final package and they were concerned that otitis media would not be available, as an indication, at the time of their launch.

February 12, 1992:
Contact: Kammer, Treuhaft

I called to ask, in the ADE section, specifically for diarrhea patients, why they were described as having diarrhea of "50 secs" duration. I was told that this was an error and that really this duration was for the each event and not the total duration. I requested that I be provided this corrected information.

February 14, 1992:
Telecon with: Wolkoff, Given, Kammer, Matlosz, Rubin, Treuhaft
FDA representatives: Lumpkin, Leissa, DeBellas

We discussed why the DAIDP considered the otitis media indication nonfilable. In addition, we discussed how they could proceed with new studies to garner the claim. We suggested that they might want to consider withdrawing the suspension NDA at this time and proceed with filing.

February 26, 1992:
Contact: Barry

I called and asked their permission that MIS be allowed to install antiviral software on the loaner PC. He gave verbal approval and I asked that a letter to this effect be sent to Dave Moss. He agreed to this request.

February 28, 1992:
Contact: Treuhaft

I called to ask about an apparent contraindication. In the capsule NDA, in the appendix that lists all the differences between similar protocols, for C88-044, it stated that unlike I88-111, I88-217, and I88-327, an exclusion criterion of no prior anti-infective therapy within the previous two weeks was included. However, when I looked at the protocol provided with the NDA, this exclusion criterion was absent. I asked Dr. Treuhaft whether I had the original or revised protocol. Furthermore, I would like to know where to see all protocol revisions for all studies.

Dr. Treuhaft was surprised to find out that the otitis media studies were being filed. I explained to her that the Division had agreed to file the otitis media indication for the suspension with the understanding that the capsule and suspension would be unlinked and that the capsule would be reviewed first and an action taken on it. Then, the Division would review and take action on the suspension with the understanding that the Division would accept a major clinical amendment for the otitis media indication.

March 5, 1992:
Contact: Given

Dr. Given called to tell me that they anticipated submission of the new otitis media indication data in October. He asked whether I would like to see both an ISE and ISS for this information. I told him that at this point I didn't feel that the revised ISE would be necessary (which would include information from the already submitted otitis media studies) but that I would want an updated ISS.

March 10, 1992:
Contact: Kammer, Treuhaft

I was called to let me know that for the C88-044 protocol, the one in the NDA was not the revised one. In the revised protocol, an exclusion criterion of "no antimicrobial therapy for 72 hours prior to enrollment" was included. Dr. Kammer told me that no patients had been enrolled prior to the revised protocol. They are checking to make sure that I have all the revised protocols for the different indications.

March 11, 1992:
Contact: Treuhaft

I called to ask the applicant to identify the role of the following concomitant medications which I was unfamiliar with: Aescin, Aralen, Broncho-vaxom, Dexpanethol, Dipirona, Dipyrone, GTN, Natamycin(e), and Paracetamol.

March 16, 1992:
All-in-1: Treuhaft (via Schering All-in-1 E-mail)

I asked Dr. Treuhaft whether patient I8732509021, who had a primary diagnosis of "bronchitis" and a secondary diagnosis of "bronchiectasis," shouldn't really be listed as the latter diagnosis.

In addition, I asked how the clinicians assessed entry diagnoses; whether the investigators made these determinations themselves or whether or not specific diagnostic criteria supplied.

March 18, 1992:
Contact: Treuhaft

I was told that the applicant anticipated the Gram's stain results for domestic evaluable patients would be available in May and not before. Since the capsule is to be reviewed first, I asked that separate revised labeling for it (excluding the suspension) be submitted.

March 23, 1992:
Contact: Kammer, Treuhaft

The Schering representatives called to follow-up on my questions of 3/16/92. It was agreed that patient I8732509021 was more appropriately listed as AECB, having had bronchiectasis in the past and having undergone bronchotomy. This patient responded quickly to therapy with complete resolution of sputum which would be "uncharacteristic" of a patient with bronchiectasis.

With regard to how specific diagnoses were established, it turns out that for the majority of the "bronchitis" patients, the investigators did not specify how these diagnoses were determined and only noted

"bronchitis" on the CRF. Dr. Kammer said that he and Dr. Jackson went through the case report forms and made the determination of "acute bronchitis" and "AECB" depending on whether a patient had a history of "chronic" pulmonary disease (e.g., history of either chronic asthma, chronic bronchitis, emphysema, COPD, etc.).

For pneumonia, some patients were classified with this despite a negative baseline CXR on the basis of signs & symptoms "consistent with" pneumonia (e.g., signs of consolidation).

March 26, 1992:
Contact: Treuhaft

I called Dr. Treuhaft and told her that I was concerned that I wouldn't receive the Gram stain results for the evaluable domestic (C88-044) patients until May. I noted that if Schering limited this to ONLY the evaluable bronchitis patients (n=73), that it should be easier (excluding the pneumonia and bronchiectasis patients). Dr. Treuhaft said that she would encourage her clinical people to expedite this process.

After looking at the data, I became aware that there were patients who were "misrandomized" and some were listed as SAFETY population while others were listed as EXCLUDED. I asked that this discrepancy be explained.

March 30, 1992:
All-in-1: Schering

I requested that Dr. Treuhaft ask the Schering statisticians to reanalyze appendiceal tables C-4 and C-8 in volume 8.61 with acute bacterial bronchitis and tracheitis as one group and AECB as the other.

Contact: Barry

It became apparent that the some of the Paradox and Lotus files had numeric-type data logged in as alphanumeric data. I asked that new electronic files be sent with these changed to numeric ones.

March 31, 1992:
All-in-1: Schering

I asked Schering to reevaluate 5 patients from the US study who had "bronchitis," but had baseline CXR's consistent with pneumonia. I asked them to explain why the 5 shouldn't be considered pneumonia patients.

April 7, 1992:
Contact: Treuhaft

I asked that Schering provide the patients' laboratory AE's in Paradox and Lotus files.

I also asked about study C88044, center 44, where of the 20 patients enrolled, 17 were considered evaluable for "clinical efficacy" while all 17 were misrandomized. I asked what "misrandomized" meant. Was the blind broken?

Telecon: Kammer, Treuhaft

We discussed the 5 pts. (all C88044) addressed on 3/31/91: After this discussion, the reviewer changed the diagnoses for two patients to pneumonia (-38004 and -04162) and another to lung abscess (-11103).

April 9, 1992:
All-in-1: Schering

I requested that Dr. Kammer review the case report forms for 22 additional patients who had baseline CXR's consistent with pneumonia despite being diagnosed with "bronchitis" or "tracheitis." They are:
C88044-04112, -44116
I88111-02017, -02101, -02102, -02104, -02105, -02106, -02107, -02108, -02109, -02111, -02112, -02113, -02114
I88217-07111, -08110, -09113, -17104, -18102, -21102, -23105

April 13, 1992:
All-in-1: Schering

I asked that the applicant to explain the 28 LRTI isolates (from 27 patients) which were listed as either "R,S, or I," but where zone size data were missing. Conversely, there were 25 (24 patients) isolates which did not include the cefaclor zone data.

All-in-1: Schering

I asked that the applicant explain how the term "pathogen" was defined. I gave an example where two patients grew *P. aeruginosa* at baseline but in one circumstance, under the FZXREAS field ("further exclusion reason") it stated, "NO PATHOGEN ISOLATED PRETHERAPY" while for the other, it stated, "PATHOGEN NOT SUSCEPTIBLE."

April 14, 1992:
All-in-1: Schering

I asked that the applicant explain the meaning of blood cultures where a result of "normal flora" was listed.

April 15, 1992:
All-in-1: Schering

I requested that the applicant explain why only 15/102 "bronchitis" failures were listed as having received concurrent anti-infective therapy following their "failure." In light of this low reporting, I noted that this raised concerns for me - whether concurrent therapies for <u>all</u> patients were adequately reported in the data base.

I also wanted to know how clinical outcomes were determined. Were these determined by the investigators or by the Schering monitors?

April 16, 1992:
All-in-1: Schering

I asked the applicant for more information regarding centers I88-111-02 and I88-217-17, where the investigators dispensed the drug themselves. I wanted to know who maintained the randomization codes there and whether the investigators remained blinded.

All-in-1: Schering

I responded to the April 16 FAX, which was a response to my April 1 request for information. I asked for additional information as their response was incomplete.

April 20, 1992:
Telecon: Kammer, Treuhaft, Rubin

The applicant's representatives called to answer some of the questions I had posed over the previous weeks:

1) Blood cultures marked as "normal flora" meant "sterile."

2) Patients from C88-044, center 44, where 17/20 were misrandomized, the blind was not broken. Patients were accidentally given the assignment of pneumonia patients, of which there were none, but still were treated with the appropriate dose of study drug for "bronchitis."

3) Pathogen was defined by the applicant as a "susceptible" bacterial isolate where the Schering monitor considered a "pathogen." Gram stain findings and quantity of growth were not used to make this determination. Thus, "pathogen" was determined by Schering monitors, not by the investigator.
He told me, that if, for example, a patient with a purulent sputum grew *H. influenzae* and *E. coli* at baseline, then the former would be considered a pathogen and the latter a contaminant/colonizer. If, on the other hand, another patient with a purulent sputum grew *E. coli* alone, this isolate would be considered a pathogen.

April 22, 1992:
Telecon: Treuhaft, Rubin, Barry, Huang, Schenfele

We discussed the electronic laboratory files. It was agreed that this would include all ceftibuten patients with abnormalities. If a patient didn't have any laboratory values out of the normal range, then these data wouldn't be submitted. It was agreed that these files would be submitted for Paradox only.

> ***Medical Officer's Comment:*** In fact, when these files were submitted, they did contain all laboratory data.

I was told that the patients who had a "R", "S", or "I", but no zone value accompanying these was due to the fact that the investigator did not write the actual value on the CRF.

All-in-1: Schering

I recommended, in light of the Draft Policy Statement, if Schering wanted *K. pneumoniae* and *H. parainfluenzae* included in the Indications & Usage section of labeling for the "bronchitis" treatment indication, that they submit literature/expert opinion supportive of their inclusion in the label.

All-in-1: Schering

I asked Schering to comment on patient I8821709125, as one example of other patients. This patient was identified as having an EOT response of "cure" and an F/U response of "unknown." However, the patient

clearly had signs & symptoms recorded on day +7 AND received ofloxacin on day +6 for "bronchitis."

April 23, 1992:
All-in-1: Schering

After identifying 56 "bronchitis" patients from C88-044 *et al*, who were identified by the applicant with an extended follow-up response of "unknown," but were evaluated by investigators between days +7-+14, I asked that the applicant submit all case report forms for all patients in study C88-044 who received either cefaclor 250 mg p.o. t.i.d. or ceftibuten 400 mg. p.o. q.d. I identified a total of 352 patients this could affect. I received verbal permission for this request from Dr. Gavrilovich.

April 27, 1992:
Telecon: Kammer, Treuhaft

We discussed how clinical outcomes were assessed. Dr. Kammer said that this was always determined by the study investigator. Changes to clinical outcome were never done without the investigators concurrence.

I was told that all concomitant medications listed in the case report forms were included in the current NDA database. I was told that the reason that so few treatment failures were listed as receiving anti-infectives was that the "investigators considered the patients withdrawn from the study" at the time as a failure and therefore new therapies were not listed.

I told Drs. Kammer and Treuhaft that I would use the case report forms the Division had requested to spot check data for concurrence and to analyze the patients who had extended follow-up visits but had a response of "unknown."

They told me that the reason that there were some 50-60 patients who were seen between day +7-+14, but did not receive a extended follow-up assessment is because they thought that I was interested only in the extended follow-ups for bacteriologically-evaluable patients.

April 28, 1992:
All-in-1: Schering

I inquired about a discrepancy in days of therapy and doses of therapy. For example, one patient, C8804404151, received one day of therapy and "4.5 doses." Another patient, C8804404153, received 14 days of therapy and a total of "4.5 doses."

April 29, 1992:
All-in-1: Schering

I inquired about the extended clinical response for C8804424106. This individual was assigned an extended clinical response of "sustained cure." Yet, there is no documentation that this patient was seen beyond day +3. Extended clinical response was defined, by the applicant, as a visit between days +7-+14. I asked the applicant to explain this.

April 30, 1992:
All-in-1: Schering

I had a question about patient C8804430102 who apparently received 5 days, 5 doses of ceftibuten 400 mg q.d., but is listed as "D/C NON-COMPLIANCE." I asked that they explain why this patient would be considered "non-compliant."

All-in-1: Schering

I asked a question concerning patient C8804431103 who had an adverse event listing of URINARY TRACT INFECTION. However, no other information was provided, such as day of onset, culture result, etc. I asked them to provide this information, if available.

All-in-1: Schering

Patient C8804432107 had an "adverse event" of "increased therapeutic response." I asked what this meant.

May 8, 1992:
Telecon: Kammer, Treuhaft

The applicant's representatives called me to discuss some questions I had previously asked. There were:

1) A total of 6 patients were listed as having received oxygen.

2) Patient C8804432107 had an "adverse event" of "increased therapeutic response." This meant that the patient had taken 20 capsules in 4 days.

3) Patient C8804430102 apparently received 5 days, 5 doses of ceftibuten, but was listed as "D/C NON-COMPLIANCE." The reason for this was that the patient was unable to meet follow-up visits. I acknowledged this but then asked why this would keep the patient from being evaluable for the first five days. Dr. Kammer said that he would have to look at the CRF again to seen if there were any reasons why the patient should be excluded from clinical efficacy analysis.

4) Patient C8804431103 had an "adverse event" listing of URINARY TRACT INFECTION. Apparently this was a concurrent infection which began before enrollment. The urine had 10-14 WBC's and RBC's/LPF, but a urine culture wasn't obtained.

5) Patient C8804424106, assigned an extended clinical response of "sustained cure," did not have documentation of a visit beyond day +3. Dr. Kammer informed me that the patient's "comment" section cited clinical cure (no sputum) was obtained on day +13. However, I pointed out to Dr. Kammer that in the patient profile, a date was not provided with this comment. Yet, I agreed to accept this as a valid posttherapy follow-up visit.

6) Patient, C8804404151, who received one day of therapy which was "4.5 doses," and C8804404153, received 14 days of therapy which was also "4.5 doses." The applicant told me that indeed these were mistakes. Actually, these should have been 1 dose and 14 doses, respectively.

May 19, 1992:
All-in-1: Schering

I asked what happened to investigators Rumans, Westblom, Citron, and Corona, in C88-044, who did not apparently enroll any patients.

May 20, 1992:
All-in-1: Schering

I asked for a date (day +?) for the comment on the last page of C8804407111's patient profile which suggests a successful extended therapy response when the last day of assessment I could find is day +3.

May 21, 1992:
Contact: Rubin

I was called by Schering concerning investigators Rumans, Westblom, Citron, and Corona. I was referred to page 43 of volume 8.3 of the NDA which describes the centers that did not enroll patients.

May 28, 1992:
Telecon: Reidenberg, Treuhaft

I was called by Schering to answer my May 20, All-in-1 message. Following in-depth review of C8804407111's physician's chart, in contrast to the case report form, it was apparent that this patient was NOT a sustained cure at F/U, but was a clinical relapse instead. The patient was placed on Keftab® and steroid inhaler on day +14 for worsening sputum and shortness of breath. The culture at that time grew *Citrobacter diversus*.

Furthermore, I was told that a patient's end-of-therapy response was always determined by the investigator, while the extended posttherapy response was either determined by the investigator or the Schering study monitor - more often by Schering - on a *post hoc* basis. I asked that I be provided a list of patients who had extended clinical responses assigned by Schering instead of by the investigator.

All-in-1: Schering

Patient C8804407112, like C8804424106 (see above), had a sustained clinical response of cure without a date for the comment. I asked that this date (day +?) be provided.

June 1, 1992:
Contact: Treuhaft

She updated me on pending issues:

1) "Bronchitis" CRF's should be sent this week.

2) Gram's stain data should be sent out this week.

3) The applicant has chosen to go back and reassign extended follow-up responses for those patients who were not assigned one initially. I responded that I have already done this myself. This reassessment will be submitted within the next 1-2 weeks.

4) She said that they are going to submit additional information that has come to light since the NDA was submitted (i.e., reanalysis of the submitted data that was NOT initially apparent in their initial analysis).

5) The Safety Update for the capsule will be submitted at the end of June.

6) Electronic files for laboratory data are still being prepared.

Other information during this discussion...

1) In light of the DRAFT Division Policy Statement, Schering is interested in retaining *K. pneumoniae* and *H. parainfluenzae* in their "bronchitis" label. I recommended that they submit literature references and "expert" opinion to support this.

June 4, 1992:
Telecon: Treuhaft, Reidenberg, Rubin

I was told that C8804407112, who had a sustained clinical response of cure, that the date for the associated comment was day +13. (See 5/28/92 Telecon.)

June 11, 1992:
Contact: Rubin

Schering responded to my request for more information regarding centers I88-111-02 and I88-217-17, where the investigators apparently dispensed the drug themselves. I wanted to know who maintained the randomization codes there and whether the investigators remained blinded.

Ms. Rubin responded that the first center was NOT dispensed by the investigator but by other members of the staff. At the second center, Dr. Zurcher, did know the randomization codes but sub-investigators didn't. I asked if he clinically assessed any of the patients. She said that she would find out.

June 15, 1992:
MEETING WITH SCHERING-PLOUGH REPRESENTATIVES:
Kammer, Reidenberg, Treuhaft
FDA REPRESENTATIVES: Albrecht, Leissa, DeBellas

Schering had requested this meeting to discuss the submission of their otitis media clinical amendment scheduled for October as well as progress with the "bronchitis" indication to date.

Following the meeting, Dr. Kammer discussed with me the CXR findings for the 22 patients I had previously identified with baseline radiographs suggestive of pneumonia despite a diagnosis of "bronchitis." (See 4/9/92.) During this discussion, it was determined that the following 9 patients were misdiagnosed as "bronchitis" and actually had pneumonia: C8804404112, C8804444116, I8811102101, I8811102108, I8811102111, I8811102112, I8821708110, I8821718102, and I88217233105.

June 18, 1992:
All-in-1: Schering

I raised the following questions:

(1) I8811102017: excluded due to "misrandomization." Was the blind broken?

(2) I8821705105: received chloramphenicol ophthalmic soln. for eye infection. I requested more information.

(3) I8811102111: had an "adverse event" of "infection." Requested more info.

(4) I8821701112: had an "adverse event" of "fever." Requested more info.

(5) I8821705102: had an "adverse event" of "fungal infection." Also had "cutaneous infection with staphylococcus." Requested more info. for both conditions.

(6) I asked about a discrepancy in days of therapy and doses received for ceftibuten 400 mg q.d. - e.g., there are international patients listed as either receiving 5 doses - 5 days. In addition, there are other patients listed as receiving 10 doses - 5 days.

All-in-1: Schering

I inquired about patient I8811104103 who did not have "clinical signs & symptoms" provided on the patient profile. I asked that this information be provided, if possible.

June 22, 1992:
All-in-1: Schering

I had specific requests/questions:

(1) I need the COMMENT dates (i.e., day +4) for patients I8811103106, I8811103107, I8811103109, and I8811103110.

(2) I8821701002 is a clinical failure. But there are no signs & symptoms to corroborate this.

(3) I8821705103 is missing microbiology data on the case report form which can be found in Paradox.

(4) I8821705104, a "bronchitis" patient, appears to have had pneumonia. I asked that this be confirmed.

(5) I8821709103. The CXR "COMMENT" appears to be a statement concerning the patient's clinical status. I asked that the CXR information be corrected.

(6) I8821709111. Based on data provided in the patient profile, I asked whether this patient should be listed as having had a concurrent UTI or not.

June 24, 1992:
All-in-1: Schering

I asked the following questions:

(1) Patients in I88217, center 14, were excluded due to "misrandomization." Was the blind broken.

(2) I8821714010 states that pt. received 22 doses of cefaclor in 2 days. I requested an explanation.

(3) I asked for the missing CXR information for I8821717101.

(4) I8821723108 died of pneumonia on day +31. I asked if they could determine when (day +?) this patient began to experience signs & symptoms of pneumonia.

(5) I8821723108 received 52 doses of cefaclor in 12 days. I asked them to confirm this.

(6) I asked for the COMMENT dates for patients I8832701104 and I8832703102.

(7) I asked for follow-up to the 6/11/92 telephone conversation concerning dispensing of medication at two centers.

In light of problems I was having with connecting to Schering's All-in-1, they had recommended that a DATALINE be installed here (a direct telephone link between Schering and the PC in my office). Following consultation with Dave Moss, I informed Schering that a DATALINE would not be appropriate. I asked them to consider MCImail instead as recommended by Dave Moss.

All-in-1: Schering

After reviewing the case report forms recently submitted, I noted that there were a significant number of comments that had been left out of the patient profiles. Indeed, the comment section in the patient profile listed, "none recorded in database."

June 29, 1992:
Telecon: Kammer, Rubin

The Schering representatives called to respond to my All-in-1 messages of June 18 and 22:

(1) I8811102017: Although it wasn't noted in the patient profile, this patient actually received ceftibuten 200 mg p.o b.i.d. Still, the blind was not broken.

(2) I8821705105: received chloramphenicol ophthalmic soln. for an eye infection. Further data is pending.

(3) I8811102111: had an "adverse event" of "infection." This was a parasitic infection of concurrent ascariasis and strongyloidiasis - both severe.

(4) I8821701112: had an "adverse event" of "fever." Following further information, it turned out that this was due to infectious mononucleosis ("glandular fever") confirmed by a (+) monospot test.

(5) I8821705102: had an "adverse event" of "fungal infection." This turned out to be thrush. Also had "cutaneous infection with staphylococcus." Information for this is still pending.

(6) I had asked about a discrepancy in days of therapy and doses received for ceftibuten 400 mg q.d. Apparently some centers dispensed 100 mg capsules while others dispensed 200 mg capsules. They told me

that they were sending the specifics. I asked if bioequivalence had been established between the 100 mg and 200 mg capsule. They said that it had.

(7) I asked for the baseline clinical signs & symptoms for patient I8811104103. These are still pending.

(8) The COMMENT dates (e.g., day +7) for patients I8811103106, I8811103107, I8811103109, and I8811103110 are being sent.

(9) I8821701002 is a clinical failure. But there are no signs & symptoms to corroborate this. I asked that these be submitted. Dr. Kammer responded that this patient had not improved by day 5 and that an anti-infective drug was subsequently prescribed.

(10) I8821705103 appears to be missing microbiology data on the case report form which is present in Paradox. They told me that this was an apparent error in the Paradox data base.

(11) I8821705104, a "bronchitis" patient, appears to have had pneumonia. I asked that this be confirmed. The CXR was read as ABNL but "not clinically significant" at baseline. Dr. Kammer could not explain the follow-up CXR comment of "some improvement in the left base."

(12) I8821709103. The CXR "COMMENT" appears to be a statement concerning the patient's clinical status. I asked that the CXR information be corrected. Additional comment information states that "patient improved subsequent to gyrase inhibitor."

(13) I8821709111. Based on data in the patient profile, I asked whether this patient had a concurrent UTI or not. Dr. Kammer responded that the first urine culture (6/28) grew 10^4 CFU/mL of *S. albus* and *E. coli*. Following anti-infective therapy, the same organisms were isolated from urine in the same concentrations.

(14) Concerning I88111, center 2, the PI assessed all the patients but the subinvestigators (other physicians) dispensed the medication.

(15) With regard to center 17 of I88217, the PI did not "evaluate" the patients although he did examine some of them. The subinvestigators made assessments on all patients.

July 1, 1992:
Telecon: Kammer, Rubin

Schering called in response to the queries of my June 24 All-in-1 message:

(1) Patients in I88217, center 14, were excluded due to "misrandomization." This entailed not using the randomization procedure. However, it did not appear that the blind was broken.

(2) I8821714010 actually received 22 doses of cefaclor in 8 days.

(3) I had asked for additional CXR information missing for pt. I8821717101. This is still pending.

(4) I8821723108 died of pneumonia of day +31. I asked if they could determine when this patient represented with pneumonia. He stated that this information is still pending.

(5) I8821723108 actually received 34 doses of cefaclor in 12 days.

(6) I had asked for the COMMENT dates for patients I8832701104 and I8832703102. He responded that they would have to ask the study sites this.

July 2, 1992:
All-in-1: Schering

I had questions/requests in response to Schering's 6/30 correspondence:

1) I asked for a list of all the patients in the NDA who received 100 mg capsules.

2) I asked for the location in the NDA of the data demonstrating bioequivalence between the 100 mg and the 200-400 mg capsules.

3) Patients I8821701107 and I8821701108: I was informed that they actually received cefaclor, not ceftibuten. I asked for the source of this information including the corrected doses.

July 6, 1992:
All-in-1: Schering

I asked Schering to send me the COMMENT pages for the "excluded" patients in I88217, center 14. These had been omitted by the applicant in their clinical amendment of COMMENT pages.

July 7, 1992:
All-in-1: Schering

In light of discrepancies between the COMMENT page of the CRF and the Patient Profile, I requested a copy of the entire CRF for patient I8832701106.

July 21, 1992:
Telecon: Kammer, Rubin

I requested the following:

1) Formal submission of the CXR reports for the 22 patients Dr. Kammer and I had previously discussed.

2) Proposed dosage duration which is not specified in their labeling.

3) The COMMENT pages for all patients in the NDA; as previously requested.

4) The corrected total doses of drug administered to all patients in the NDA.

August 10, 1992:
All-in-1: Schering

I requested the status for numerous centers in the UTI studies where there was no explanation whether they had enrolled patients or not.

August 12, 1992:
All-in-1: Schering

I requested that the applicant reevaluate the total doses administered and total days of therapy, since significant discrepancies still exist, i.e., "valid" patients who received ceftibuten 400 mg q.d. for "5" days yet received "10 doses," which would be a PROTOCOL VIOLATION, if true.

Contact: Lamendola

I told Dr. Lamendola that the electronic copy of the UTI VITALS file is missing entries which had been present in the patient profiles.

August 17, 1992:
All-in-1: Schering

Pt C8706902009 from the UTI study, according to the Patient Profile, grew *K. pneumoniae*. However, according to the Comment page of the CRF, the patient actually grew *K. oxytoca*. I asked that the applicant review this discrepancy.

Contact: Treuhaft

Dr. Treuhaft called to tell me that the *corrected* LRTI dosings would be sent on Wednesday. She did not know when the corrected UTI dosing would be done. Furthermore, she told me that the UTI data base is in the *process of* being reviewed for errors and should be done by the end of the week. As far as they can tell, at this time, only the "vitals" file of the UTI database had been corrupted, but they are evaluating this further. I requested that the corrected "vitals" file be sent within the next 2 days.

All-in-1: Schering

I asked about C8706903036. Here, the entire comment on the comment page of the CRF washed crossed out. I asked why and how this happened. (The comment states that the patient received posttherapy anti-infective therapy.)

August 18, 1992:
All-in-1: Schering

Pt C8706901020 is identified as having received TMP/SMX in the Patient Profile. *However*, on the Comment page of the CRF it states that the patient received ceftibuten. I asked Schering to explain this discrepancy.

All-in-1: Schering

C8706905018 is mentioned as having developed severe diarrhea on day 8 of ceftibuten therapy from the patient profile. However, in the CRF comment pages it specifies that this patient developed *C. difficile* diarrhea (?colitis) and received Flagyl. I asked the applicant how this information came to be omitted from the Original NDA.

August 19, 1992:
All-in-1: Schering

I8732603006, a valid patient who received TMP-SMX for UTI, grew *E. coli* at baseline that was "susceptible" to TMP/SMX and subsequently failed.

However, according to the Comment section of the CRF, the patient grew a "resistant" pathogen. The patient should have been considered a nonevaluable failure. I asked the applicant to explain this discrepancy.

Telecon: Garaud, Treuhaft, Rubin

Schering called to introduce Dr. Garaud and to inform me that they are putting together a task force to answer reviewer's requests on a more timely basis. According to Dr. Garaud, in his opinion, in the past Schering had been too slow in responding to my requests. Yet, he told me that it would take some time to get this "up and running." I told them that I would be taking vacation for 2 weeks.

August 20, 1992:
All-in-1: Schering

Following receipt of a FAX containing the details for centers in the UTI studies not accounted for, I requested that the applicant submit the CRF's for the 24 patients who were not submitted to the NDA; namely, the efficacy data. (Safety data were submitted with the Safety Update in June.)

Telecon: Rubin, Kilian

Schering called to respond to E-mail messages:

1) I asked about C8706903036 whose entire comment on the comment page of the CRF was crossed out. I was told that the comment was erased by the investigator which shouldn't have occurred. However, the patient did not take the ampicillin during the follow-up visit as prescribed.

2) C8706901020 is identified as receiving TMP/SMX in the Patient Profile. However, on the Comment page of the CRF it states that the patient received ceftibuten. They acknowledged that this was an error and the patient did receive ceftibuten 400 mg qd x 10 doses.

3) Ms. Kilan said that they had reviewed the database and believe that I8732603006 is the only patient with a discrepancy of zone susceptibility and MIC susceptibility. I noted that there still remained many more such patients (e.g., I8732603013), with this same discrepancy. She said she would go back and reevaluate the database.

4) C8706902009 from the UTI study, grew *K. oxytoca*, not *K. pneumoniae*, as stated in the Patient Profile.

August 21, 1992:
All-in-1: Schering

In response to the faxed LRTI revised corrected doses, I requested confirmation on dosing for additional patients. I also requested that Schering send me the CRF's for C8706905018, who had *C. difficile* diarrhea, which wasn't reported, and I8732603006, where there was a mix-up between the reporting of zones and MIC's.

All-in-1: Schering

I asked the applicant to confirm the susceptibilities reported for I8732603011.

September 15, 1992:
Contact: Rubin

During this telephone call, Ms. Rubin told me that she was planning on submitting revised DRAFT labeling by the beginning of October. I asked that this be submitted by the end of next week instead.

Contact: Barry

I called to inform Mr. Barry that there appeared to be data missing from the NEW vitals file. He said he would look into this.

September 16, 1992:
Contact: Barry

He called to confirm our previous discussion of yesterday that data was indeed missing from the vitals electronic file. He said he would send a corrected file ASAP.

September 17, 1992:
All-in-1: Schering

I requested that the applicant submit the corrected "total doses" of study drug administered for the patients in studies I87247, centers 02 (16 patients) and 03 (8 patients).

September 26, 1992:
All-in-1: Schering

I reminded the applicant of my 6/24/92 request that I receive all the COMMENT pages for all the patients from clinical studies submitted in the NDA. As far as I can tell, they haven't fully complied with this request.

I also requested that a new InfoCard to connect to their All-in-1 network be provided. The one I have currently malfunctions.

September 28, 1992:
Contact: Lamendola

Dr. Lamendola asked why I was revisiting the bronchitis indication. I told him that from the Division's initial analysis, from a review standpoint, we were experiencing difficulties with regard to there lacking significant "evaluable" LRTI numbers. I told him that I was evaluating different dosing regimens used in bronchitis as supportive of the 400 mg q.d. dosing requested in proposed labeling.

September 29, 1992:
Contact: Lamendola

Dr. Lamendola called to ask if I had received the InfoCard. I told him I had. He asked if I could shed more light on yesterday's comment concerning the "numbe s" difficulties with bronchitis. I discussed this with him. He said that he would like to arrange a meeting with me to go over this in greater detail. I told him that I did not feel that a meeting was needed at this time, but that certainly a meeting at some time would be most appropriate. I told him that I am very busy continuing my review and that I would discourage a meeting at this time. He said that he would relay this information to Drs. Garaud and Kammer and that they might be calling me back for a telecon. I agreed to this.

September 30, 1992:
Telecon: Kammer, Reidenberg, Treuhaft, Lamendola

I received a follow-up telephone call from Schering's regulatory group - in response to the telephone call I had with them recently where I let them know that the Division was revisiting bronchitis at the 200 mg b.i.d. dose. During the previous telephone call I told them that the Agency was revisiting bronchitis due to insufficient numbers on which to meet the 95% confidence interval approach for the 400 mg qd dosing.

During this telecon, Schering asked whether I was using the pneumonia data as supportive of bronchitis. I said that in light of previous conversations with them where I was told by Dr. Kammer that they believe that "the 200 mg b.i.d. does doesn't work in pneumonia," and since they are currently performing 300 mg b.i.d. pneumonia studies, I said that this did not appear to be a reasonable extrapolation. Dr. Kammer said that he doesn't believe this to be the case - that 200 mg b.i.d pneumonia DOES work. I asked him that if he believes that 200 mg does work in pneumonia, why aren't they asking for the pneumonia indication and conversely why are they pursuing 300 mg b.i.d. pneumonia studies? He responded that Schering probably will NOT pursue a pneumonia indication and will drop the 300 mg b.i.d. studies. I asked why they would do this. He said that "marketing" thinks the label would be "too confusing" if it had more than one dosing regimen. (Yet, Schering currently is pursuing a 300 mg b.i.d. bronchitis study because of concerns with pneumococcus.)

Dr. Kammer emphasized that Schering has had an understanding with the Agency that the pneumonia patients would be used as supportive of bronchitis. I responded that I would pass their concern on within the Division.

In addition, Dr. Kammer asked if they could sit down with me and go over our differences, patient-by-patient, where we disagree. I responded that was a possibility for the future.

They asked for a meeting, but I told them that this would be premature and that this would be more appropriate at a later time.

October 4, 1992:
All-in-1: Schering

I asked for documentation for the changes made for three patients in the 9/30/92 clinical amendment containing numerous "reassessments" of patients.

October 9, 1992:
Contact: Rubin

Following review of the "pneumonia" patient corrections, I asked why so many patients had been missed. Why so many "pneumonia" patients DID NOT have pneumonia. She replied that she would get back to me on this.

October 29, 1992:
Contact: Schenfele

I called Ms. Schenfele to ask about what appeared to be discrepancies in the laboratory data base including the list of corrections given to me by Dr. Kammer on 10/27/92 at the Advisory Committee. From our conversation it was apparent that a misunderstanding had taken place and

that the way the corrections were described to me were misleading. In light of these errors to the data base, I asked that the applicant submit corrected laboratory files for both UTI and LRTI.

November 2, 1992:
Contact: Treuhaft

Dr. Treuhaft called to express her concern that there have been communication problems between Schering and me. We discussed these. It was agreed that I would make a concerted effort to use All-in-1 as my major method of communication.

All-in-1: Schering

In light of the pages of corrections to the pharyngitis data base, I requested that corrected electronic suspension files be submitted.

November 30, 1992:
All-in-1: Schering

I asked about a patient in the UTI studies, I8712807003, who died of gangrene of the leg. In the adverse reaction section of the patient profile, it states that this patient developed pneumonia on the last day of therapy. However, there is not mention of pneumonia in the CRF. I asked them to explain this discrepancy.

Telecon: Garaud, Kammer, Reidenberg, Treuhaft.

During a conversation concerning an IND protocol, I was asked where the Division's review stood. I told them that the Division continues to have problems with the bronchitis indication as well as problems with the complicated UTI indication. The major problem was meeting the 95% confidence interval approach. Furthermore, I told them that at this point in time the Division anticipates an action with regard to NDA 50-685 by the end of the year.

December 23, 1992:
All-in-1: Schering

I informed Schering that the Division will not be sending an action letter on CEDAX capsules before the end of the year.

January 8, 1993:
Contact: Treuhaft

I called to enquire what ceftibuten formulations/batch numbers had been used in the following UTI studies: I87326 (centers 2,5) and I87232 (1-4). For the LRTI studies: all centers for I87107, I87223, I87233, I87234, and I87236; I87325, center 1-6. I could not find this information in the NDA submission.

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AMENDMENTS RELATED TO CAPSULE NDA REVIEW

January 7, 1992:
NDA 50-685 - Center I87-325-9, patient [redacted] page 3108 was missing. It was faxed to me.

January 8, 1992:
I received faxed sheets for NDA 50-685 - Center I88-230-4, patient [redacted], which were missing.

January 15, 1992:
Received electronic disks of Overall Table of Contents.

January 16, 1992:
Received paper submission of Overall Table of Contents.

January 29, 1992:
Received FAX regarding microbiology questions regarding *H. influenzae* and *M. catarrhalis* and β-lactamase activity as well as PCN-susceptible and PCN-resistant *S. pneumoniae*.

A second FAX contained four patient profiles missed in the original submission. These were for center I88-230-4; patients

February 4, 1992:
Received 1/28/92 submission with proposal concerning submission of electronic files.

February 5, 1992:
Received 1/27/92 submission of revised Table of Contents for appendices with added volume numbers.

February 6, 1992:
Received FAX from Amy Rubin regarding revised tables for Volumes 8.1 for both NDA's. Officially submitted to NDA on 2/13/92.

February 11, 1992:
Received FAX from Ed Barry concerning PARADOX tutorial

February 12, 1992:
Received FAX from Bridget Neigel concerning Lotus 123 files.

February 18, 1992:
Received 2/10/92 submission with replacement pages for 4 patient profiles and replacement pages for application summary.

March 5, 1992:
Received "floppy" disks from Schering with electronic files for LRTI indication which I loaded.

March 10, 1992:
Received 3/3/92 submission information concerning Gram's stain in LRTI studies and β-lactamase activity for select clinical organisms.

March 18, 1992:
Received 3/12/92 submission with additional missing Table of Contents pages.

March 23, 1992:
Received a manual with more description of how to use Lotus Magellan program.

March 26, 1992:
Floppy disc containing revised TOC files.

March 30, 1992:
Received 3/30/92 submission with list of β-lactamase (+) and (-) isolates for LRTI.

April 1, 1992:
Received 3/25/92 submission with descriptions for 8 concurrent drugs that I was unfamiliar with.

April 7, 1992:
Received 4/6/92 submission containing new LRTI Lotus and Paradox files with numeric fields. I noted that for the NSIGNS file, there were 12,318 entries. In contrast, for the old SIGNS file there were 12,395 files. I requested a explanation for this discrepancy.

I received April 1 submission which contained further explanation for those pediatric patients who were excluded.

April 16, 1992:
Received 4/16/92 FAX which was a response to my request for information of April 1.

April 27, 1992:
Received 4/22/92 submission which included reanalysis of baseline symptoms according to underlying diagnosis.

April 29, 1992:
Received 4/27/92 submission which contained the revised labeling for the capsule alone. This included the WordPerfect version of this on diskette.

April 30, 1992:
Received 4/27/92 submission which supplied the diskettes for both capsule and suspension NDA's, containing NDA summary information in WordPerfect (i.e., pharmacology, pharmacokinetics).

Received 4/28/92 submission with the corrected β-lactamase data for clinical isolates in the LRTI study.

May 7, 1992:
Received 5/4/92 submission with diskette containing revised numeric version "investigator assessment of day of resolution" file (NIADR).

May 18, 1992:
Received 5/18/92 submission with a copy of the final protocol submitted for C88044 et al. Documentation of exclusion criterion where no concurrent anti-infective was permitted within 72 hours prior to enrollment.

June 2, 1992:
Received 5/21/92 submission with request for meeting between Schering and Division to discuss various issues.

Received 5/22/92 submission with CORRECTED (without pediatric dosing) electronic version of annotated and unannotated package insert for capsule alone.

June 5, 1992:
Received 6/2/92 submission with CRF's of evaluable patients from C88-044 as well as CRF's for "clinical efficacy" patients who had extended clinical responses assigned later.

June 11, 1992:
Received 5/29/92 submission with proposal for the content and format of the otitis media amendment.

Received 6/3/92 submission with source documentation for domestic "valid" LRTI Gram's stain results.

Received 6/3/92 submission with additional computer support as well as diskettes containing ADE's and Paradox macros.

June 24, 1992:
Received 6/23/92 submission with diskettes containing new "lab" and "range" files, including scripts.

June 26, 1992:
Received fax with the interpretative criteria used for urinalyses.

July 1, 1992:
Received 6/30/92, submission with COMMENT pages for bronchitis patients from international studies (I88111, I88217, & I88327).

July 2, 1992:
Received 7/1/92 submission containing the Safety Update.

Received 6/30/92 submission containing information discussed in telecon of 6/29.

July 13, 1992:
Received 7/8/92 submission containing the COMMENT pages for the excluded patients in I88217, center 14.

July 16, 1992:
Received 7/8/92 submission containing X-ray comments for I88-111-02, patients 108, 111, and 113.

Received FAX of applicant's changes to patient profiles following review of the COMMENT pages for the international patients.

July 20, 1992:
Received 7/16/92 submission containing some follow-up responses to my 6/18/92 and 6/24/92 E-mails.

Received 7/17/92 submission containing COMMENT pages of CRF's for all the pneumonia/bronchiectasis patients in C88044 et al, C87001 et al, and I88230 (except 200 BID ceftibuten and 500 TID cefaclor; see 7/28/92 below). (3 volumes.)

July 24, 1992:
Received 7/23/92 submission containing electronic files (WordPerfect, Lotus, and Paradox) of the UTI files.

Received 7/20/92 submission containing applicant's formal analysis of the discordant comments.

July 24, 1992:
Received 7/24/92 submission containing COMMENT pages of CRF's for 200 BID ceftibuten and 500 TID cefaclor pts with pneumonia or bronchiectasis from C87001 and 188230. (2 volumes.)

July 31, 1992:
Received 7/29/92 submission containing COMMENT pages of CRF's for UTI studies. (4 volumes.)

Received 7/31/92 fax with confirmation of the CXR reassessments per the 4/9/92 All-in-1 request.

August 8, 1992:
Received 8/4/92 submission containing CXR summaries documenting change in diagnosis from "bronchitis" to pneumonia.

August 12, 1992:
Received 8/11/92 fax containing the corrected total doses for the patients in the LRTI study.

August 20, 1992:
Received 8/14/92 Environmental Assessment submitted.

Received 8/19/92 FAX containing information on the missing UTI centers.

August 21, 1992:
Received 8/21/92 FAX containing the revised corrected total doses for the patients in the LRTI study.

August 25, 1992:
Received 8/25/92 FAX containing responses to some of my previous All-in-1 queries, i.e, corrected doses for LRTI, etc.

September 15, 1992:
Received 8/26/92 submission in response to my August 10, 17, and 18 E-mail.

Received 8/27/92 submission containing new Paradox scripts.

Received 8/31/92 submission containing CRF's for C87069, centers 2 and 3, and two patients of interest, C8706905018 and I8732603006. (2 volumes)

Received 9/2/92 submission containing Dr. Robert McCabe's response to questions concerning patient C8706905018; the patient with probable *C. difficile* diarrhea.

Received 9/9/92 submission containing minutes of FDA-Schering meeting of 6/15/92.

Received 9/10/92 submission containing responses to 6/22/92 E-mail requests for additional information.

Received 9/10/92 submission containing responses corrected doses for UTI patients.

Received 9/11/92 submission containing diskettes with corrected Paradox files, including a discussion of the causes for these discrepancies.

September 16, 1992:
Received FAX containing revised dosage and administration section.

September 18, 1992:
Received 9/17/92 submission containing diskette with additional corrected Paradox files and scripts.

Received 9/18/92 FAX containing total doses for the patients in I87247, centers 2 and 3.

September 25, 1992:
Received 9/24/92 submission containing revised proposed labeling. The 200 mg capsule has been deleted.

October 1, 1992:
Received 9/25/92 submission containing diskette with revised proposed labeling.

Received 9/30/92 submission containing a list of "corrections" for bronchitis.

October 5, 1992:
Received 10/2/92 submission containing a list of "corrections" for pneumonia.

October 6, 1992:
Received 10/2/92 submission containing the applicant's responses to comments from the Biopharmaceutics Division.

October 8, 1992:
Received 10/8/92 FAX containing applicant's responses for the three patients I had questions about in the "corrections" submission of 10/4/92.

October 14, 1992:
Received 10/13/92 submission containing corrected LRTI files (with diskette) and new Paradox scripts.

October 27, 1992:
At the Advisory Committee meeting, Dr. Kammer provided me with a sheet of paper with corrections to the Laboratory database.

October 29, 1992:
Received 10/23/92 submission containing revised Paradox scripts on diskette.

November 2, 1992:
Received 10/30/92 submission containing corrected Paradox script for one submitted 11/23/92.

November 13, 1992:
Received 11/6/92 submission containing a corrected page for the applicant's proposed label where *K. pneumoniae* was inadvertently deleted from the bronchitis portion of the INDICATIONS & USAGE section.

November 20, 1992:
Received 11/18/92 submission containing corrected lab and ranges files for UTI and LRTI.

January 7, 1993:
Received FAX containing listing of countries where ceftibuten is approved including the doses and indications.

Received FAX containing clinical formulation information.

January 14, 1993:
Received 1/12/93 letter and diskette containing an electronic copy of the applicant's NDA summary (e.g., overall safety).

Received 1/13/93 & 1/14/93 faxes containing missing formulations used in clinical trials.

Brad Leissa, M.D.
Medical Officer / HFD-520

Concurrence Only:
HFD-520/DivDir/Lumpkin
HFD-520/SMO/Albrecht 2/5/93

cc: Orig. NDA
HFD-340
HFD-520
HFD-520/DepDir/Gavrilovich
HFD-520/MO/Leissa
HFD-520/Pharm/Buko
HFD-520/Micro/Dionne
HFD-520/CSO/DeBellas
WP51\FILES\CEDAX\NDA\MEMO-685.FDA
2/3/93

MAR 4 1992

MEDICAL OFFICER'S
MEETING MINUTES & TELEPHONE MEMORANDA
NDA 50-685

BETWEEN:

SPONSOR - Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
(908) 298-2793

FDA REPRESENTATIVE - Brad Leissa, Med. Officer, DAIDP

GENERIC DRUG NAME: Ceftibuten capsules
TRADE DRUG NAME: Cedax®
DRUG CLASS: "Third-generation" cephalosporin for oral administration
RELATED NDA: Ceftibuten suspension, NDA 50-686
RELATED IND's:

MEETING PARTICIPANTS (**February 4, 1992**) -
William Huang, Ph.D. - Manager, Biostatistics
Robert Kammer, M.D., - Director, Anti-Infective Clinical Research
Barbara Matlosz - Director, Regulatory Affairs
Louise Schenfele - Supervisor, Clinical Data Management
Mary Treuhaft, Ph.D. - Assoc. Director, Regulatory Affairs

TELECON PARTICIPANTS (**February 10, 1992**) -
Douglas Givens, M.D., - Vice President, U.S. Regulatory Affairs
Hans Reimann, Ph.D., - Assoc. Director, Regulatory Affairs
Amy Rubin - Manager, Regulatory Affairs
Robert Kammer, Mary Treuhaft

TELECON PARTICIPANTS (**February 12, 1992**) -
Robert Kammer, Mary Treuhaft

TELECON PARTICIPANTS (**February 14, 1992**) -
SCHERING-PLOUGH:
Harold Wolkoff - Senior Vice President, Development Operations
Givens, Kammer, Matlosz, Treuhaft, Rubin

FDA: Lumpkin, Leissa, DeBellas

BACKGROUND: Ceftibuten is a "third-generation" oral cephalosporin available in both capsule and suspension formulations. The NDA was received December 23, 1991. It is currently under review. Indications being sought in the NDA include acute bronchitis and AECB,

in adults, as well as otitis media and pharyngitis/tonsillitis in children. We have agreed to file the NDA.

COMMUNICATIONS: During the February 4, 1992, the NDA orientation session, the following questions were raised by the applicant. The responses were discussed with the applicant during the three separate telephone conversations:

QUESTION #1: With regard to the on-going development of the otitis media indication, what are the required number of evaluable organisms for the microbiology as well as the numbers of β-lactamase pathogens? What is required of the 2nd study?

Currently, there are two "active" otitis media studies in addition to the two already submitted with the NDA:

STUDIES SUBMITTED TO THE NDA:
a) **C88-082:** A clinical/microbiology study comparing ceftibuten with cefaclor. It is a domestic study with a 2:1 randomization. There are 14 centers with 47 "evaluable" ceftibuten patients and 16 "evaluable" cefaclor recipients.

b) **I88-115:** A clinical/microbiology study comparing ceftibuten and cefaclor as well. This is an international study also with a 2:1 randomization. There are 11 centers and 59 "evaluable" ceftibuten patients and 32 "evaluable" cefaclor recipients.

Combining the microbiology from the two studies presently in the NDA, according to Dr. Kammer, there are 35 "evaluable" *H. influenzae* (of those tested, only three ceftibuten treated pathogens were β-lactamase positive), eight *M. catarrhalis* ("most" were β-lactamase positive), and 54 *S. pneumoniae*.

"ACTIVE" STUDIES:
a) **C90-886:** This is a clinical/microbiology study comparing ceftibuten with cefaclor. It is a domestic study with a 1:1 randomization schedule. There are 5 centers. To date there are 44 patients enrolled with 70% evaluability. They plan on opening new centers in South America as soon as the winter season begins there.

b) **C90-037:** This is a clinical (microbiology recommended but not required) study comparing ceftibuten with Augmentin®. It is a U.S. study with 1:1 randomization. There are 20 sites with enrollment not yet begun.

Dr. Kammer said that he anticipated that study C90-037 would have

65 evaluable patients/arm and approximately an 87% "success" rate for both arms. Assuming these numbers to be realized, using the 95% confidence interval approach the following is seen: (my calculations)

Without correction factor: {-0.116, 0.116}
With correction factor*: {-0.146, 0.146}
(*See discussion of correction factor below.)

I responded that this appeared appropriate.

With regard to microbiology, according to the Division's Policy Statement on otitis media, we request microbiology for at least 10 *M. catarrhalis*, 30 *H. influenzae*, and 30 *S. pneumoniae*. In addition, although not specified in the Policy Statement, we would like to see at least 10 β-lactamase (+) *H. influenzae* and 9 β-lactamase (+) *M. catarrhalis*.

We agreed to the following strategy in keeping with the Policy Statement:

STUDY #1 (the large clinical study) could be C90-037 or a continuation of C88-082 as a clinical study (keeping in mind that the patients who had already undergone tympanocentesis would be looked at separately). I added that, since this is primarily a clinical study, we would expect very "tight" clinical definitions and evaluations including tympanometry and good posttherapy follow-up. The clinical portion of either study must use domestic populations. We would expect the statistical analysis to hold-up under the 95% confidence interval approach.

STUDY #2 (the microbiology study) could be the assembled from the evaluable microbiology data in studies C88-082, I88-115, as well as C90-886 (assuming comparability of the protocols). Where foreign microorganisms are used, the sponsor must show that the results are comparable to pathogens treated in the U.S. population. We cautioned them that they needed more β-lactamase positive *H. influenzae* and more *M. catarrhalis* for this indication. Otherwise, they might have restricted labeling.

I told Dr. Givens that in light of our 45-day meeting, we would refuse to file the otitis media indication. He expressed great concern about this and responded that the DAIDP has known all along that they were planning on submitting a major amendment for this indication. He told me that he would be calling the Division in the next few days to discuss this.

Medical Officer's Comment: Ms. Matlosz was surprised at our decision to refuse to file the otitis media indication, since according to "their statistical analysis," they did

have two adequate and well controlled studies.

Following this conversation, I calculated the 95% confidence intervals using their "success" and evaluability rates rates at end-of-therapy and at posttherapy follow-up. Looking at both C88-082 and I88-115 separately, the following confidence intervals are generated (with or without the correction factor):

95% CONFIDENCE INTERVAL WITH AND WITHOUT CORRECTION FACTOR FOR OTITIS MEDIA STUDIES IN NDA 50-686
(Assessment at end-of-therapy)

		C88-082		I88-115	
		Success Rate	Evaluable Patients	Success Rate	Evaluable Patients
CEFTIBUTEN		85%	47	92%	59
CEFACLOR		75%	16	94%	32
95% C.I.	W/C.F.*	{-0.22, 0.42}		{-0.18, 0.14}	
	NO C.F.†	{-0.14, 0.34}		{-0.13, 0.09}	

* USING THE CORRECTION FACTOR (the standard 95% CI calculation with the correction factor:

"$\pm$ 0.5 * $(1/n_1 + 1/n_2)$"

† WITHOUT THE CORRECTION FACTOR

Note: By the 1-3 day posttherapy visit, for C88-082, there were 7 ceftibuten failures and 4 for cefaclor. In I88-115, there were 5 ceftibuten failures and 2 for cefaclor.

95% CONFIDENCE INTERVAL WITH AND WITHOUT CORRECTION FACTOR FOR OTITIS MEDIA STUDIES IN NDA 50-686
(Cumulative assessment at posttherapy follow-up)

		C88-082		I88-115	
		Success Rate	Evaluable Patients	Success Rate	Evaluable Patients
CEFTIBUTEN		61%	44	91%	53
CEFACLOR		44%	16	86%	28
95% C.I.	W/C.F.*	{-0.20, 0.54}		{-0.15, 0.25}	
	NO C.F.†	{-0.11, 0.45}		{-0.1, 0.2}	

* USING THE CORRECTION FACTOR (the standard 95% CI calculation with the correction factor:
"+ 0.5 * $(1/n_1 + 1/n_2)$"
† WITHOUT THE CORRECTION FACTOR
Note: The success rates listed above are determined including the failures from end-of-therapy. For C88-082, there were 10 ceftibuten relapses and 5 for cefaclor by the 2-4 week posttherapy follow-up visit. For I88-115, respective numbers were 0 ceftibuten relapses and 2 for cefaclor.

Using the 95% confidence interval approach, with the correction factor noted above and the end-of-therapy responses, neither study meets the Division's requirement of an adequate study. If one does not include the correction factor, only C88-082 is an adequate study.

Likewise, if one looks at the cumulative success rates at posttherapy follow-up, using the correction factor, only C88-082 is adequate. Without the correction factor, both are adequate.

Yet, there were only 16 evaluable cefaclor patients in the C88-082 trial and this assumes that our assessment of the outcomes and evaluabilities coincide with the applicant's. I discussed this with Dr. Harkins, of biostatistics, who feels that the correction factor should be used in all cases even with 1:1 randomization studies.

On February 14, 1992, the Division discussed the otitis media studies in depth. We agreed with how future studies should proceed. In addition, the issue was raised whether the applicant

should withdrawal the suspension NDA at this time if they did not want it approved with only pharyngitis. Dr. Wolkoff responded that he would have discuss this further within the Company. We asked that they get back to us by COB, February 18, 1992, the filing date.

QUESTION #2: What does the Division require of an applicant to garner a sinusitis indication? How should the applicant proceed?

Currently, they have an on-going comparative study, C89-135, ceftibuten, 400 mg p.o. q.d., vs. Augmentin® 500 mg p.o. t.i.d. This is a domestic clinical/microbiology study with a 2:1 randomization schedule. To date they have performed 217 aspirations. Only 35 baseline aspirates were positive (25 ceftibuten and 10 Augmentin®).

The Division's Policy Statement regarding the sinusitis treatment indication requires that there be a large clinical study and a smaller clinical/microbiology study (a minimum of 90 microbiologically evaluable patients).

We agreed that STUDY #1 should be a new clinical study with "tight" clinical definitions and evaluations including sinus X-rays. We would not accept continuation of C89-135 and a subsequent intent-to-treat analysis of that data, since an intent-to-treat analysis would include those patients with known negative cultures AND would include a therapeutic modality.

STUDY #2 could entail a continuation of C89-135 as an open noncomparative trial to accrue the requisite numbers of evaluable pathogens. These numbers would be similar to the microbiology numbers discussed above for otitis media.

The conversations ended amicably.

Brad Leissa

Brad Leissa, M.D.
Medical Officer / HFD-520

Concurrence Only:
HFD-520/DivDir/Lumpkin
HFD-520/SMO/Albuerne MDA 2/27/92

cc: Orig. NDA
HFA-224
HFD-520
HFD-520/MO/Leissa
HFD-520/Pharm/Euko
HFD-520/Micro/Silver
HFD-713/Biostats/Harkins
HFD-520/CSO/DeBellas
CEDAX\WP\MEET1
2/14/92; 2/27/92

MWM 3/4/92

Subsequent to this conversation, I spoke further w/ Dr A. Giaquinto of Schering. We agreed to "de-couple" the susp + oral solid dosage form NDA's. We would proceed now to review fully the solid oral NDA + come to completion in its following action on that NDA. We would commence review of the susp. NDA. By at the time we were ready to take action on the susp NDA, there were not adequate clinic data, The application would be acted upon only for the pharyngitis indication - This was acceptable to both Division + Applicant.

4 Mar 92

END

MD

J.H.M. RESEARCH &DEVELOPMENT, INC. 5776 SECOND STREET,N.E. WASH. DC 20011