- No serious AEs occurred during the Clinical Pharmacology studies. In the Phase III clinical program, similarly low proportions of patients in the Augmentin XR and All Comparators groups experienced serious AEs on-therapy and within 30 days post-therapy, and few serious AEs were of suspected or probable relationship to study medication. The most frequently reported serious AE was pneumonia in both treatment groups. Two serious AEs of diarrhea were reported as being related to Augmentin XR.

- The serious AE profile of Augmentin XR was comparable to that of patients treated with Augmentin 875/125mg, levofloxacin, and clarithromycin comparators.

- Overall, few subjects who received Augmentin XR in the Clinical Pharmacology studies experienced AEs leading to withdrawal. AEs leading to withdrawal occurred infrequently in the controlled and uncontrolled Phase III clinical studies. The most frequently reported AE, diarrhea, led to few withdrawals (0.9%) although this was more frequent than withrawals due to diarrhea in active controls (0.4%).

- The incidence of patients who received Augmentin XR and experienced AEs leading to withdrawal was generally comparable to that of patients treated with Augmentin 875/125mg b.i.d. or patients treated with either levofloxacin or clarithromycin.

- No pregnancies occurred during the Clinical Pharmacology studies and only two occurred in the Phase III clinical program. Each woman delivered a healthy baby girl.

- No remarkable or consistent changes in hematology, clinical chemistry (including liver function) or urinalysis parameters were identified in healthy subjects or in patients who received Augmentin XR in controlled or uncontrolled Phase III clinical studies. In addition, laboratory profiles for Augmentin XR-treated patients did not differ markedly from profiles for patients who received Augmentin 875/125mg, levofloxacin, or clarithromycin.

- No crystals other than those routinely found in the urine were observed at the on-therapy visit in patients treated with Augmentin XR.

- The tolerability profile of Augmentin XR was not altered when administered concomitantly with Maalox® Antacid (simultaneously and two hours apart). No evidence of a drug-drug interaction was noted.

- Augmentin XR was generally well tolerated in patients taking concomitant medications commonly used in — CAP and ABS. The AE profile of the concomitant drug and/or drug class subgroups, where diarrhea, nausea and headache were the most frequent AEs, was consistent with the AE profile of Augmentin XR in the combined controlled clinical studies, although the rate of diarrhea varied. Specifically, there was a significant increase in the rate of diarrhea in the Augmentin XR arm in those patients taking concommittant drugs which have the ability to increase gastric pH (28.6%) as well as those patients who were taking pseudoephedrine (28.0%) as compared to the overall rate of diarrhea for Augmentin XR patients in all controlled clinical trials (18.7%).

- In Clinical Pharmacology studies, headaches were the most frequently reported AEs and occurred more frequently in females than males. Only female subjects reported genital moniliasis, which occurred in 9.7% of the total subject sessions.

- There were no appreciable differences in the AE profiles reported by gender, age, racial origin or country in the Phase III clinical studies. However, the overall proportion of patients reporting AEs was higher in the US compared with the combined non-US centers.

- As with the overall population of patients who received Augmentin XR in the Phase III studies, diarrhea and nausea were the most frequently reported AEs within each demographic subgroup examined.

- The AE and laboratory profiles (hematology, clinical chemistry and urinalysis) of Augmentin XR-treated patients were generally similar for patients with — CAP and ABS. Augmentin XR was generally well tolerated by patients within each indication.

- The profile of serious adverse experiences, including those leading to withdrawal and those associated with death, for the ongoing CAP studies was similar to the profile of the concluded CAP studies (Study 546, Study 556 and an interim analysis of Study 547) with respect to type of serious AE reported and relationship to treatment. Thereby this raised no unique areas of clinical concern.

- There was an increased rate of diarrhea as well as diarrhea and genital moniliasis requiring corrective therapy in the Augmentin XR arm as compared to the other comparators. However, this increased rate did not result in increased serious adverse events or withdrawals secondary to adverse events. The majority of the corrective therapy involved treatment with antidiarrheal medication and very few patients treated with Augmentin XR required more aggressive corrective therapy.

In conclusion, Augmentin XR was safe and generally maintained the safety profile of conventional Augmentin in healthy subjects and in patients treated for [redacted] community acquired pneumonia and acute bacterial sinusitis. There were slightly higher rates of diarrhea and genital moniliasis in the Agumentin XR arm and higher percentages of these patients required corrective therapy, but there were no increases in the rates of serious adverse events or in the drop out rate. In addition, there were higher rates of diarrhea in those patients who were comcomittantly taking pseudoephedrine and medications with the potential to raise gastric pH.

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/s/

Charles Cooper
10/21/02 03:41:29 PM
MEDICAL OFFICER

Initial Augmentin XR review with edits

John Alexander
10/21/02 04:01:05 PM
MEDICAL OFFICER

Dr. Cooper's Review of Initial Submission for Augmentin XR

Janice Soreth
10/21/02 05:21:15 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW OF NDA 50-785 RESUBMISSION: AMOXICILLIN/CLAVULANATE 16:1 (AUGMENTIN XR™)

Date Submitted:	3/29/02
Date Received:	3/30/02
Date Assigned:	3/30/02
Date Action Taken:	9/25/02

Applicant: GlaxoSmithKline
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101-7929
(215)751-3868

Contact Person: Cynthia D'Ambrosio, Ph.D.
(215)751-3468

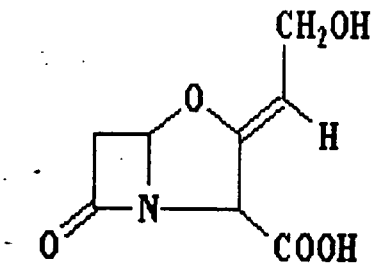
Drug: Proprietary Name: Augmentin XR™
Generic Name: Amoxicillin/Clavulanate 16:1

Chemical Name: (amoxicillin)
4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(2R)-amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, [monosodium salt, (2S, 5R, 6R).

(clavulanate)
clavulanate potassium is potassium (*Z*)-(2 *R* , 5 *R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate

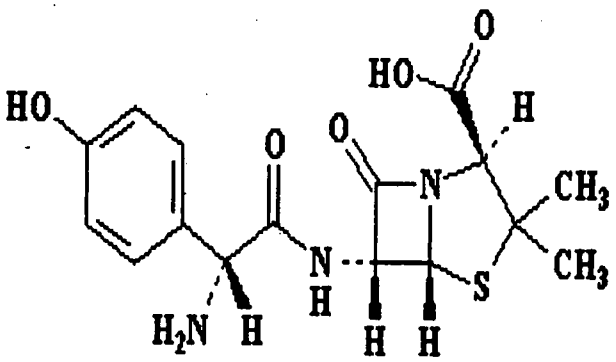
Molecular Structure:

Clavulanic Acid
$C_8H_9NO_5$



Amoxicillin

$C_{16}H_{19}N_3O_5S \cdot 3H_2O$



$\cdot 3H_2O$

Drug Class: Amoxicillin - semi-synthetic penicillin
Clavulanate potassium – naturally occurring beta-lactamase inhibitor isolated from *Streptomyces clavuligerus* and contains a beta-lactam ring

Formulation: Tablet containing 1000 mg of amoxicillin and 62.5 mg of clavulanate

Route of administration: Oral

Related IND: IND ———

Related NDA's: 50-564, 50-575, 50-597, 50-720, 50-725, 50-726, 50-755, ———

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TABLE OF CONTENTS

EXECUTIVE SUMMARY 4
Recommendation on Approvability 4
Recommendation on Phase 4 Studies 4
Summary of Clinical Findings 4
Brief Overview of Clinical Program 4
Efficacy 5
Safety 6
Dosing 6
Labeling Issues 7
CLINICAL REVIEW 8
Community Acquired Pneumonia (CAP) Due to PRSP 8
Definition of Outcome 8
Duration of Treatment 9
Efficacy in Patients with CAP due to PRSP 9
Failures 12
Patients with Residual Symptoms 13
Reasons for Exclusion from PP Analysis 15
Fine Scores (Pneumonia Severity Index) 16
Penicillin Susceptibility of the PRSP Isolates 17
Bacteremia 18
Macrolide Resistance 19
Medical Officer Conclusion/Recommendation: 20
Acute Bacterial Sinusitis (ABS) Due to PRSP 22
Definition of Outcome/ Methodology 22
Reasons for Exclusion from PP Analysis 25
Treatment Duration 26
Efficacy/ Residual Symptoms/ Failures 26
Additional Analysis 28
MIC's of PRSP Isolates Causing ABS 29
Medical Officer Conclusion: 31
PROPOSED LABELING 32
Risk Factors for PRSP 32
Proposed Label 36
Medical Officer Conclusion/Recommendation: 37

EXECUTIVE SUMMARY

Recommendation on Approvability

Based on the review performed on the original NDA submission and the review performed for the NDA re-submission, the applicant has provided substantial evidence of efficacy and safety for Augmentin XR for the indications of community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS). The sponsor's claim of efficacy in infections due to *S. pneumoniae* with a penicillin MIC = 4.0μg/mL is not substantiated because of lack of sufficient data. The sponsor's data do, however, support efficacy in patients with CAP and ABS due to *S. pneumoniae* with a penicillin MIC ≤ 2.0 μg/mL.

The benefits associated with the use of Augmentin XR in patients with CAP or ABS outweigh the risks, thus meeting the regulatory requirements for marketing approval. This product was found to produce higher rates of diarrhea and vaginal candidiasis than comparators; however, this did not result in an increase in serious adverse events or withdrawals due to adverse events. From a clinical perspective, this product has a pharmacokinetic profile consistent with efficacy in the treatment of infections due to pneumococcus with reduced susceptibility to penicillin. Such efficacy was demonstrated in the treatment of CAP and ABS due to pneumococcus with penicillin MIC's ≤2.0μg/mL. Augmentin XR was used in a small number of patients for the treatment of CAP or ABS due to pneumococcus with penicillin MIC's ≥ 4.0 μg/mL; however, the data were not sufficient to support efficacy against organisms with this higher MIC.

It is not recommended that Augmentin XR be approved for the indication of [redacted]. This is because in the [redacted] scientific literature, the role of pneumococcus with reduced susceptibility to penicillin is poorly understood. It is not clear that the use of a drug with such activity confers any additional benefit, and the sponsor did not submit clear data that any such benefit exists. In the context of increased rates of diarrhea and candidiasis and no clear benefit, this indication is not recommended for approval. The original NDA submission included this indication, but an [redacted] indication was not requested in the resubmission.

Recommendation on Phase 4 Studies

It is recommended that the sponsor continue efforts to accumulate additional data on the treatment of CAP and ABS due to pneumococcus with reduced susceptibility to penicillin. Such data could result in a clearer understanding of the benefit of the use of this product over other products including other Augmentin formulations. The accumulation of such data may be accomplished by new or ongoing open-label clinical trials.

Summary of Clinical Findings

Brief Overview of Clinical Program

Augmentin XR is a new formulation of Augmentin that contains both amoxicillin and a beta-lactamase inhibitor (clavulanate) in a ratio of 16:1. The proposed dosage of 2,000 mg amoxicillin/125 mg clavulanate (two tablets) orally twice a day contains substantially more amoxicillin than previous Augmentin formulations and was designed to improve the efficacy of this product in the treatment of pneumococcus with reduced susceptibility to penicillin.

There were a total of ten pivotal phase 3 trials submitted by the applicant to support the safety and efficacy of Augmentin XR. The breakdown of the various clinical trials is as follows:

Four clinical trials of CAP: three blinded, comparative studies (546, 556, 557) and one open label, non-comparative study (547)
Three clinical trials of ABS: one blinded, comparative studies (550) and two open label, non-comparative studies (551, 592)
Two clinical trials of —— two blinded, comparative studies (548, 549)

Six of these trials were submitted as completed studies in the original NDA application, dated December 20, 2000. One trial (Study 547) was also submitted with the original submission as an interim analysis. Those studies were reviewed in detail in the original NDA review and served to establish the safety and efficacy of this product in the treatment of patients with ABS and CAP.

This document reviews the results of new study data as submitted by the applicant in the resubmission which includes studies 557, 592, and a new interim analysis for study 547. The intent of the additional information contained in the resubmission was not to further establish Augmentin XR's efficacy and safety for empiric treatment of CAP and ABS, which had already been established by the original submission. The intent of the additional information contained in the resubmission was to address the specific deficiencies detailed by the FDA in the action letter for the original submission (dated December 12, 2001). These deficiencies include the following:

1. Provide further support for the claim of efficacy in the treatment of CAP and ABS due to pneumococcus with reduced susceptibility to penicillin
2. Identify a target population for treatment
3. Propose new labeling that would enable the clinician to identify the appropriate patient population for treatment with this product.

The following Medical Officer Review contained in this document reviews the additional submitted data as it pertains to the specific deficiencies which lead to the NA action.

In total, 4,144 patients received Augmentin XR in the ten phase 3 clinical trials. These patients were treated with 2,000 mg amoxicillin/125 mg clavulanate (two tablets) orally twice a day for 7-10 days.

Efficacy

Augmentin XR demonstrated efficacy in the treatment of community-acquired pneumonia in one open label, non-comparative study and three blinded, active controlled trials comparing the test drug to three different comparators including: Augmentin 875 BID x 7 days, Augmentin 1000 TID x 7 days, and Augmentin 875 TID x 7-10 days. In the three comparative studies, Augmentin XR showed similar cure rates as measured by clinical and radiologic response. The large open-label study, 547, was performed for the primary purpose of accruing patients with infections due to pneumococcus with reduced susceptibility to penicillin. The majority of such patients were contained in the re-submission from this open label trial. Efficacy was sufficiently demonstrated in patients with CAP who had

penicillin MIC's of 2.0µg/mL. Data were not sufficient to adequately assess efficacy in patients who had isolates with penicillin MIC's of >2.0µg/mL.

Augmentin XR demonstrated efficacy in the treatment of acute bacterial sinusitis based on one active controlled trial and two open-label, non-comparative trials. The one active controlled trial compared Augmentin XR to levofloxacin 500 mg q.d. for ten days. The non-comparative studies also had a treatment duration of 10 days. For the one active controlled trial, the combined clinical-radiological outcome at test of cure was similar for the Augmentin XR and the levofloxacin arms. The open label studies were designed to demonstrate microbiologic efficacy as well as accrue patients with ABS due to pneumococcus with reduced susceptibility to penicillin. The bacteriological efficacy rates of these studies were consistent with the efficacy rate of Augmentin XR in the controlled study. In addition, these open label trials provided the majority of the data which sufficiently demonstrated efficacy in patients with ABS due to pneumococcus with penicillin MIC's of 2.0µg/mL. Data were not sufficient to adequately assess efficacy in patients who had isolates with penicillin MIC's of >2.0µg/mL.

Augmentin XR did not demonstrate efficacy in the treatment of ——————— in patients with infection due to pneumococcus with reduced susceptibility to penicillin. Because of limited numbers of such patients in the two submitted controlled active-comparator clinical trials (548, 549) and because of the lack of scientific evidence in the medical and scientific literature that coverage of such isolates affects outcome in ——— there are insufficient data to support an efficacy claim.

Safety

A prior medical officer review by this author (Chuck Cooper M.D.) provided an integrated review of safety information from phase 1 and phase 3 studies as submitted in the original NDA. A review of new safety data contained in the re-submission performed by medical officer Nasim Moledina M.D. did not result in any changes in the overall assessment of safety for Augmentin XR. Review of the safety data for this drug revealed an increased rate of diarrhea in the Augmentin XR arm as compared to the comparators (including other Augmentin formulations) and an increased rate of vaginal candidiasis. Although these AE's were associated with increased rates of corrective therapy, the types of corrective therapy were not invasive in nature and did not result in increased rates of serious AE's or withdrawals due to AE's.

When considering the additional efficacy of Augmentin XR in the treatment of patients with pneumococcal infection due to isolates with reduced susceptibility to penicillin, the increased rates of non-serious diarrhea and vaginal candidiasis are acceptable.

Dosing

The dosing regimen for the indications of CAP and ABS is 2,000 mg amoxicillin/125 mg clavulanate (two tablets) orally twice a day x 7-10 days for CAP and 10 days for ABS. These are the dosing regimens used in the phase 3 trials of Augmentin XR.

Pre-clinical pharmacokinetic studies involving 55 healthy fed subjects were the basis for the selection of formulation and the dose. This dose/formulation was selected specifically because of it produced an average time above the targeted MIC of 4.0µg/mL that was 49% of the 12 hour dosing interval. Although this average time above the MIC is consistent with adequate antibiotic therapy for

pneumococcal infections, examination of the pharmacokinetic data revealed a variable distribution. There were 5 out of the 55 (9%) subjects for whom the time above an MIC of 4.0μg/mL was between 28 and 32%. There were no data provided in the NDA which assessed the outcome of patients who had infection due to pneumococcus with reduced susceptibility to penicillin and who had a decreased time above the MIC. In addition, there was no data provided on potential differences that might exist between the healthy subjects studied and the ill patients likely to be treated with Augmentin XR. It is possible that the PK profile in patients with CAP could have a different average and/or distribution.

Labeling Issues

In the resubmission, the applicant proposed that [ ]. These criteria were not established or studied in a prospective manner. Review of this proposal revealed that [ ]. Therefore, the applicant's proposed method of targeting an appropriate patient population is not acceptable. Alternative wording to capture the intended treatment population for this product has been developed for the INDICATIONS AND USAGE section.

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CLINICAL REVIEW

The following review is of the Augmentin XR re-submission (dated 3-29-02) which was in response to an FDA Non-Approval letter dated December 12, 2001.

The resubmission includes new data in support of the indications of CAP and ABS caused by PRSP. The new data consists of two new studies (CAP study 557 and ABS study 592 as well as an updated interim report for CAP study 547). The data contained in this re-submission does not alter prior conclusions about overall efficacy and safety as determined from review of the original NDA submission. Instead, the re-submission does specifically address deficiencies identified by FDA after review of the original NDA. The re-submission contains new data to support the claim of efficacy of the treatment of pneumococcal infections with reduced sensitivity to penicillin. It also includes a proposal for how this drug can be marketed in such a way that the appropriate target population is reached.

Community Acquired Pneumonia (CAP) Due to PRSP

In support of an indication for CAP due to PRSP, the sponsor has submitted data from 20 patients with CAP due to PRSP (PCN MIC ≥2.0 μg/mL) who were treated with Augmentin XR. Five of these patients were from the original NDA and 15 are new. These 15 patients were accrued through the ongoing open label, non-comparative Augmentin XR study (Study 547) and from one completed active comparator controlled study (Study 557).

The efficacy of Augmentin XR in the treatment of CAP was demonstrated in two controlled blinded comparative trials submitted the original NDA submission. In one of the studies, Study 546, Augmentin XR was compared to Augmentin 875 and the clinical per protocol cure rates (primary endpoint at TOC) were 86.3% and 91.2% respectively (95% CI -11.0,1.2). In the other study, Study 556, Augmentin XR was compared to Augmentin 1gr[1] and the clinical per protocol cure rates were 91.5% and 93.0 % respectively (95% CI –8.3, 5.4). (Please see MO review of original NDA for detailed review of the studies and secondary endpoints, etc.). Therefore, the focus of this review section will be to address the issue of efficacy in patients with CAP due to PRSP, which was an identified deficiency of the initial submission.

The submitted data includes CRF's for all of these patients, detailed data in the form of SAS transport files, and patient narratives for those patients with PRSP who were enrolled in Study 547. These data were reviewed in detail by the Medical Officer.

Definition of Outcome

The sponsor prospectively defined "clinical failure" of patients with community-acquired pneumonia in such a way as to distinguish between those patients with true failure and those who only had

[1] Augmentin 1 gr is a European approved formulation which contains a total daily dose of 3,000 mg amoxicillin/375 mg clavulanate.

symptomatic sequelae of community acquired pneumonia. The sponsor's definitions of "Success" and "Failure" are included below.

Clinical Success: "Sufficient resolution of the signs and symptoms of CAP for patients who were clinical successes at the end of therapy visit such that no additional antibacterial therapy was indicated for CAP."

Clinical Failure: "Reappearance or deterioration of the signs and symptoms of CAP for patients who were clinical successes at the end of therapy visit such that additional antibacterial therapy was indicated for CAP."

Unable to Determine: "An assessment of clinical outcome could not be made, eg the patient was lost to follow-up or did not consent to clinical examination.

Medical Officer Comment: According to the FDA guidance for antimicrobial drugs development for the treatment of CAP, a "clinical cure" should be defined as "complete resolution of all signs and symptoms or pneumonia and improvement or lack of progression of all abnormalities on chest radiograph as assessed by the 7-21 day test-of-cure visit." The sponsor's definition is slightly different in that it allows for the persistence of symptoms as long as such symptoms do not require re-treatment with additional antibiotics. This is acceptable assuming that the sponsor's TOC visit date is far enough away from the last dose of antibiotic such that recurrences or relapses could be detected.

Duration of Treatment

The duration of exposure for the 20 patients with CAP due to PRSP ranged from 6-11 days. The table below summarizes the number of patients treated for each duration.

Duration of Therapy of PRSP CAP Patients						
Number of days treated	6	7	8	9	10	11
Number of Patients	1*	10**	6	0	0	3

* This patient was a failure who was not compliant with therapy for the first 72 hours
** Two of these patients were failures in the ITT analysis. One was lost to TOC follow up, but was a cure at EOT. The other was a failure because of persisting (although not worsening) symptoms and was not a micro failure.

Efficacy in Patients with CAP due to PRSP

The efficacy of Augmentin [redacted] in patients with CAP due to PRSP is presented in the table below for both the ITT analysis and the PP analysis. In this group of 20 patients with CAP due to PRSP, there were no microbiologically proven failures. The definition of "Bacteriological Success" required that the patient also be a "clinical success." Any patient in this NDA who was determined to be a "Clinical

Failure" was automatically considered to be a presumed "Bacteriological Failure" as well even if repeat cultures were negative or not done.

The following table summarizes the efficacy of this drug according to PCN MIC and PP or ITT analysis. It should be noted that bacteriological outcome incorporated clinical outcome such that clinical failures were automatically categorized as presumptive bacteriological failures. Conversely, clinical successes in the absence of re-culture of the organism were considered to be bacteriological successes.

Efficacy of Augmentin XR for CAP due to PRSP According to MIC's							
		All CAP Studies Combined (546, 547, 556, 557)					
		Augmentin XR Bacteriology ITT			**Augmentin XR Bacteriology PP**		
		n*/N	**(%)**	**95% CI ‡**	***n*/N***	**(%)**	**95% CI ‡**
Penicillin-intermediate resistant *S. pneumoniae* (MIC 0.12-1.0µg/mL)		13/14	(92.9)	68.1, 98.3	13/13	(100)	76.8, 99.8
Penicillin-resistant *S. pneumoniae* (MIC≥2.0µg/mL)		17/20	(85)	62.1, 96.8	14/15	(93)	68.1, 99.8
	MIC= 2.0	13/14¥	(92.9)	68.1, 98.3	10/10	(100)	71.5, 99.7
	MIC= 4.0	4/6†	(66.67)	29.0, 90.1	4/5**	(80)	35.9, 95.7

* *n*/N= number of patients with *S. pneumoniae* eradicated or presumed eradicated/ total number of patients

** The one patient who was a failure (547.376.14972) had an isolate with PCN MIC = 4.0µg/ml and Amox MIC = 8.0 µg/ml. (see "failure" section below for more details). Two other patients with PCN MIC = 4.0 µg/ml who were success also had Amox MIC = 8.0 µg/ml.

¥ The failure in this group (547.437.18569) was non-compliant with study drug for the first 72 hours of therapy (described in more detail in "Failures" section below).

† One of the failures (547.110.18283) in this category also had a second isolate with PCN MIC = 2.0 µg/ml. This patient was included as a failure only in the 4.0 µg/ml category. This and the other ITT failure (547.376.14972) are described in detail in the "Failures" section below.

‡ confidence limits calculated using exact probabilities

Review of all twenty of the PRSP cases revealed that, except for two patients, the TOC visits ranged from 17 to 28 days after the End of Therapy. This would have allowed enough time between

cessation of therapy and the TOC visit to identify recurrences/relapses. There were two patients who were considered ITT failures who did not have a TOC visit (547.110.18283 and 547.437.18569). One of these patients was lost to follow up and did not show up for his TOC visit while the other failed therapy after early medication non-compliance and did not have a TOC visit. The medical officer accepts the sponsor's definition of clinical success and failure as valid.

Failures

Of the twenty patients in this NDA who had CAP due to PRSP, there were three failures according to the ITT analysis. One of these patients was also considered a failure in the PP analysis. The following summaries provide an overview of these thee patients.

Patient 547.110.18283
This HIV positive patient was a 32 year old male inpatient who presented with typical symptoms and findings on exam and chest x-ray for CAP. Information regarding the stage of HIV disease is unavailable. A screening blood culture was positive for S. pneumoniae (PCN MIC=2.0 μg/ml) and sputum culture was positive for S. pneumoniae (PCN MIC= 4.0 μg/ml). The patient did not receive any antibiotics for 28 days prior to study enrollment, and was treated with a 7-day course of study drug with 100% compliance. The only concomitant meds included paracetamol for chest pain due to pneumonia and acyclovir for herpes simplex. An on-therapy blood culture was negative and at the end of therapy, the patient was afebrile and without any signs or symptoms of CAP. Repeat chest x-ray was improved and the patient was considered to be a clinical success at EOT. The patient did not attend the test of cure visit and therefore was not included in the Per Protocol analysis. For the Intent to Treat analysis, this patient had a clinical and bacteriological outcome of "unable to determine" and therefore was assigned a clinical and bacteriological response of "failure."

Patient 547.376.14972
This 65 year old patient with a past history of COPD and smoking presented with mild dyspnea, moderate cough, and pleuritic chest pain. He was found to have an increased WBC, increased temperature of 38.9 degrees C, and progressive infiltrates on the chest x-ray. He did not receive antibiotics 28 days prior to study entry. At screening, a sputum culture grew S. pneumoniae (PCN MIC = 4.0 μg/ml) and K. pneumoniae (amox/clav MIC of 2.0 μg/ml). The patient received a 7-day course of study drug and was 100% compliant. He also received paracetamol for fever and dextromethrophan/ethanol/guaifenesin for cough. At the end of therapy visit, all signs and symptoms had resolved except for a mild persisting cough (there was no sputum production). At the test of cure visit, the patient remained afebrile, however, the mild cough continued and was accompanied by the new presence of purulent sputum. The radiological outcome and response at this time were improved and success, respectively. Although the patient had a recurrence of purulent sputum at this visit, it was reported that a sputum sample was not obtained "due to clinical improvement." For this reason, the bacteriological outcome and response were presumed bacteriological recurrence and failure. Seven days after the end of study treatment, the patient was treated successfully with a 9-day course of oral levofloxacin.

Of microbiological interest, this patient's pneumococcus isolate had a PNC MIC= 4.0 μg/ml and an amoxicillin/clav (Augmentin) MIC = 8.0 μg/ml. When compared to the pharmacokinetic profile of Augmentin XR, this would have resulted in a decrease of the time of above MIC for the dosing interval from 49% (for an amoxicillin MIC of 4.0 μg/ml) to a time of above MIC for the dosing interval of 41% (for an amox MIC of 8.0 μg/ml). There were two other patients who were successes whose isolate had an identical susceptibility pattern as this patient's isolate (557.101.11786 and 557.106.11602). Also, the sponsor reports that paired serum collected from the patient revealed a fourfold increase in antibodies against *M. pneumoniae* thus indicating possible preceding or concurrent mycoplama infection.

Patient 547.437.18569
This 78 year old inpatient with a past history of Crohn's, partial colectomy, and pulmonary embolism presented with a moderate cough, moderate dyspnea, moderate pleuritic chest pain, and mild tachypnea. She had a fever of 39.0 degrees C and a consolidation on chest x-ray consistent with CAP. At screening, a blood culture revealed *S. pneumoniae* with a PCN MIC = 2.0 µg/ml. A trans-tracheal aspirate also grew the same organism (with the same MIC) as well as *P. aeruginosa* with an amox/clav MIC = 16 µg/ml. The patient received therapy for 5-6 days, however, she was not compliant with study medication in the first 72 hours because her nurse lost the medication bottle. The patient was treated with multiple non-antimicrobials for symptomatic relief of cough, chest pain, and fever. At the end of therapy, she was afebrile but had continued moderate cough, tachypnea, dyspnea, and mild pleuritic chest pain. The radiological outcome and response were worse and failure, respectively. A sputum sample was not obtained due to inability to expectorate. The patient was withdrawn due to insufficient therapeutic effect and treated with intravenous ceftriaxone. She remained hospitalized for a total of 22 days. The patient was assigned an outcome of failure at test of cure. After the test of cure visit, the patient was successfully treated with ceftriaxone.

Patients with Residual Symptoms

Of the 17 patients who were included as successes in the ITT analysis, there were 6 who had residual symptoms at the TOC visit, while the remaining 11 experienced complete resolution of symptoms. Several of these patients had pre-existing conditions such as COPD and it is not possible to determine prior baseline underlying symptoms by examination of the submitted data. However, these patients were not febrile and did not require retreatment with other antibiotics thus indicating either resolution to prior baseline or possible residual post-infectious inflammatory symptoms. Details of these patients are included in the table below.

Patients with Clinical/Bacteriological Success and Residual Symptoms at TOC Visit					
Patient	Pre-Exsiting Condition	Baseline Symptoms	Residual signs/ symptoms	Change in symptoms from Study Entry	Organism MIC (PCN MIC)
547.445.18610	Depression, appendectomy	None listed	Mild cough	Improved	2.0
547.450.18613	Chronic bronchitis, tobacco abuse	Diarrhea	Mild cough	Improved	2.0
547.450.18842	Chronic bronchitis, tobacco abuse	Increased ALT	Persisting rales on exam	Rales unchanged, but entry symptoms improved	2.0
547.455.18590	COPD, chronic resp failure, MI	None Listed	Hypoxemia, cough, dyspnea, tachypnea	Improved	2.0
556.008.02211	Acute bronchitis/sinus itis	None Listed	Mild dyspnea, pleuritic chest pain	Dsypnea-no change, pl. cp-improved*	2.0
557.106.11602	Anemia	hypotension	Mild cough	Unchanged**	4.0

* Patient also had cough and tachypnea at entry which were resolved at TOC.
** Patient also had mild tachypnea and moderate pleuritic chest pain which were resolved at TOC.

MEDICAL COMMMENT: Overall, the patients who were categorized as clinical and bacteriological success but who still had residual symptoms were significantly improved from study entry. There was no correlation between the MIC of the organism and likelihood of residual symptoms at the TOC visit. The CRF's did not provide information which allowed adequate assessment of baseline symptoms and it is likely that several of the patients experienced residual symptoms at TOC which were related to underlying conditions (such as COPD, chronic bronchitis, etc.). All of these patients were assessed at TOC at a minimum of 17 days after their last dose of study drug, thus allowing ample time for recurrences/relapses.

Reasons for Exclusion from PP Analysis

Of the twenty patients from this NDA who had CAP due to PRSP, 15 met the criteria for the Per Protocol analysis. The reasons for exclusion for the other 5 patients include the following

PID Excluded from PP analysis	Reason for Exclusion	Outcome	Comments	PCN MIC (µg/mL)
547.110.18283	Visit Compliance (TOC Visit)	Failure (Unable to Determine)	Was lost to follow up; was "success" at EOT visit	2.0 (blood) and 4.0 (sputum)
547.437.18569	Medication Compliance (V1)	Failure	Non-compliance in first 72 hours despite hospitalization (nurse lost medicine bottle)	2.0
547.450.18842	Serious Underlying Disease (V1); Visit Compliance (TOC Visit)	Success	Patient had persisting rales at TOC visit; Newly diagnosed Cardiomyopathy	2.0
547.455.18590	Serious Underlying Disease (V1)	Success	Persisting dyspnea, tachypnea, hypoxia, cough, purulent sputum at TOC (mod. sev.); Ischemic heart disease/COPD/chronic resp. failure	2.0
556.008.02211	Visit Compliance (EOT visit at day 17*)	Success	No additional antibiotics, mild residual dyspnea/ pl. chest pain	2.0

* EOT visit was supposed to be at days 12-14

Fine Scores (Pneumonia Severity Index)

A retrospective analysis of CAP patients in the Augmentin XR Clinical Program, based on modifications to the published Fine criteria, was performed by the sponsor. The Fine criteria, also known as the Pneumonia Severity Index (PSI), were developed by the Pneumonia Outcomes Research Team and has been validated as a predictor of the severity of CAP in individual patients. Patients categorized as Classes I, II, and III are considered to be "non-severe" while those in Classes IV and V are considered to be "severe." The Fine Classes were derived using a computer algorithm based upon clinical review without reference to patient identification numbers, to avoid allocation bias with regard to treatment groups. A blinded review of the baseline ongoing medical history terms as well as baseline signs and symptoms was performed by a physician. The CAP studies in the Augmentin XR Clinical Program were not specifically designed to capture all of the necessary criteria. Items for Fine classification not collected within studies were treated as missing and conservatively, a score of zero for that item was assumed.

The table below summarizes all Modified Fine Scores from PRSP patients in this NDA by Fine Score Classification and by ITT or PP analysis.

FINE SCORES for CAP due to PRSP					
	Non-Severe Disease (number of patients)			Severe Disease (number of patients)	
	I	II	III	IV	V
ITT Analysis	7	8*	1	4*	0
PP Analysis	6	6**	1	2	0
ITT Analysis Totals by Mild vs. Severe	16			4	
PP Analysis Totals by Mild vs. Severe	13			2	

Fine Scores of I, II, III correlate with mild disease, while Fine Scores of IV, V correlate with severe disease.

* One patient with Fine Score of II (547.110.18283) and one patient with Fine Score of IV (547.437.18569) were considered ITT failures because of lost to follow-up and medication non-compliance respectively.

** One patient with a Fine Score of II (547.376.14972) was considered a failure in the PP analysis.

The following table summarizes the number of patients with CAP due to PRSP by MIC and Fine Score.

Fine Scores by MIC of Organism					
	Patients with PRSP PCN MIC=2.0ug/ml				
	Non-Severe Disease			Severe Disease	
	I	II	III	IV	V
ITT	6	4*	0	4†	0
PP	3	3*	0	2	0
	Patients with PRSP PCN MIC=4.0ug/ml				
	Non-Severe Disease			Severe Disease	
	I	II	III	IV	V
ITT	1	4†	1	0	0
PP	1	3	1	0	0

* One patient with a Fine Score of II (547.376.14972) was considered a failure in the PP and ITT analyses.

† One patient with MIC of 2.0 µg/mL and a Fine score of IV (547.437.18569) and one patient with MIC of 4.0µg/mL and a Fine Score of II (547.110.18283) were included as ITT failures but were excluded from PP analysis.

Medical Officer Comment: There were no patients with CAP due to PRSP with an MIC of 4.0 µg/ml who also had a Fine Score indicating Severe Disease. It should be noted that patients with a Fine Score indicating Severe Disease probably should be treated with I.V. antibiotics in an inpatient setting. So the fact that there are no patients with Severe Disease and a PRSP with PCN MIC of 4.0 µg/ml is understandable.

Penicillin Susceptibility of the PRSP Isolates

The penicillin sensitivities of the PRSP isolates ranged from 2.0 µg/ml to 4.0 µg/ml. The sensitivities provided in the SAS transport file for PRSP isolates were labeled as having been determined at the central lab location, rather than at a local lab.

The majority of isolates (20/21) had a MIC for amoxicillin which was within +/- one tube dilution of the MIC for penicillin. Isolates which had a penicillin MIC of 2.0 µg/mL were more likely to have the same MIC for amoxicillin (10/15). In contrast, for those isolates with a penicillin MIC of 4.0µg/mL, there were fewer that also had an amoxicillin MIC of 4.0µg/mL (1/6).

Relationship Between Penicillin MIC and Amoxicillin MIC for PRSP Isolates of CAP Patients			
		Penicillin MIC of PRSP Isolate *	
		2.0 µg/ml	4.0 µg/ml
Amox MIC	1.0 µg/ml	4	0
	2.0 µg/ml	10	2
	4.0 µg/ml	1	1
	8.0 µg/ml	1	3†

*Two patients had more than one isolate. (547.110.18283 had two isolates with PCN/Amox MIC's of 2.0/2.0 and 4.0/2.0 µg/ml; 547.437.18569 had two isolates both with PCN/Amox MIC's of 2.0/2.0 and 2.0/1.0 µg/ml). Both of these patients were ITT failures and were excluded from the PP analysis.

† One of these patients (547.376.14972) was a PP and ITT failure.

Medical Officer Comment: Based on these data, it appears that for those isolates which have a PCN MIC of 4.0µg/mL, there may be a higher likelihood that the corresponding amoxicillin MIC may be one tube dilution higher. This could potentially be significant because it is possible that Augmentin XR is less effective for those isolates with amoxicillin MIC's at 8.0 µg/mL. There is not enough clinical data at this time to draw a conclusion about efficacy for those isolates which have an amoxicillin or penicillin or amox/clav MIC which is 8.0µg/mL.

Bacteremia

Of the twenty patients with CAP due to PRSP in this NDA, there were four with positive blood cultures.

Two (547.110.18283 and 547.437.18569) from study 547, were ITT failures and are described in detail in the "Failures" section. These two were not proven microbiologic failures. One was lost to follow up at the TOC visit and the other was a clinical failure who was non-compliant with study drug during the first 72 hours.

The other two patients with positive blood cultures were from study 557 (557.101.11786 and 557.106.11602). Both of these patients were Clinical and Bacteriological successes at TOC. They both had *S. pneumoniae* isolates whose PCN MIC was 4.0 µg/ml (central lab), although 557.101.11786 CRF indicates PCN MIC of 2.0 µg/ml from the local lab. These patients had Fine Scores consistent with non-severe disease.

Medical Officer Comment: The amount of data that this NDA accumulated with regard to bacteremic patients was very limited. There were only four such patients and two of them were protocol violators.. It is interesting to note that the other two patients (Study 557) had bacteremia due to a PRSP isolate

with PCN isolate of 4.0 μg/ml but had Fine Scores of I and II. Review of these patients CRF's reveals that the non-severity of their disease was consistent with the calculated Fine scores. This discordance between presence of bacteremia and disease severity seems to indicate that, at least in these two patients, the presence of bacteremia was not an indicator of severity of disease. It most likely represents the spurious incidental finding of intermittent bacteremia which is not uncommon in patients with CAP. For the purposes of examining efficacy in patients with severe CAP due to PRSP, the submitted bacteremic cases were not particularly helpful. It does, however, provide some degree of support for the efficacy of Augmentin XR against PRSP because at least in these two cases, the causative organism can be identified with great certainty.

Macrolide Resistance

The sponsor [redacted]

Review of submitted data regarding macrolide resistance revealed that a significant number of macrolide-resistant isolates were also penicillin resistant. The following table summarizes the number of patients in each study by the *S. pneumoniae* resistance pattern.

Number of Patients Treated with Augmentin XR with CAP due to Resistant *S. pneumoniae*			
	Macrolide Resistant Only (erythromycin MIC≥1.0μg/ml	Penicillin Resistant Only (PCN MIC ≥2.0 μg/ml)	Macrolide and Penicillin Resistant
Study 546 (N=255)	1	1	1
Study 547 (N=1,122)	10	2*	12*†
Study 556 (N=169)	2	0	1
Study 557 (N=158)	2	3	0
Total (N=1704)	15	6	14

* One of these patients was an ITT failure, but was excluded from PP analysis.

† One patient was both an ITT and PP failure. This patient (547.437.18569) had an organism with PCN MIC of 2.0 μg/ml and erythromycin MIC of >32 μg/ml.

Medical Officer Comment: When considering the total N of the four CAP studies (1,704), it is clear that patients with CAP due to a macrolide resistant *S. pneumoniae* are at significantly higher risk for penicillin resistance as well. There are not enough data to determine whether there is any difference in the effectiveness of Augmentin XR against macrolide and penicillin resistant strains in comparison to those strains which are only penicillin resistant.

Medical Officer Conclusion/Recommendation:

Based on review of the submitted data, it can be concluded that Augmentin XR has activity in the treatment of CAP caused by pneumococcus with some degree of resistance to penicillin. Although the total number of isolates is small, it is comparable to that submitted to the FDA in support of the PRSP claim for levofloxacin with respect to the number of PRSP isolates which have an MIC of 2.0 µg/ml. Evidence in support of a claim against organisms with PCN MIC's of 4.0 µg/ml is less strong.

An important difference between this drug and levofloxacin is that for Augmentin XR, the resistance mechanism for PRSP does result in reduction in activity of the study drug. Therefore, the activity of this drug is limited by the degree of the penicillin resistance of an individual isolate. As the penicillin MIC of the PRSP isolate increases, it can be expected that at some point, the efficacy of this drug will decline. For levofloxacin, the degree of penicillin resistance had no impact on the expected levofloxacin efficacy. Therefore, careful consideration has to be given to determining what MIC cut-off will be used to define activity.

Review of this drug's pharamcokinetic profile reveals that the mean time above an MIC of 4.0 µg/mL for amoxicillin is 49% of the dosing interval. Although this is well within the range considered to be necessary for successful treatment, a closer examination of the pharmacokinetic data reveals potential areas for concern. Detailed review of the pharmacokinetic data, which was derived from 55 healthy fed adults, reveals some variability. Five patients total (9%) had time above the MIC of 4.0 µg/mL which was ≤32% of the dosing interval, which could potentially result in decreases in efficacy. Not enough clinical data have been collected in order to conclude that such variability in pharmacokinetics effects efficacy.

In other situations (such as infections due to VRE) there exists a less clear understanding of the significance of the pre-clinical data because of uncertainties regarding treatment effect, emergence of resistance, predictive correlates of efficacy. However, in the case of pneumococcus and penicillin, there exists some understanding of what is necessary for a successful clinical outcome. This drug fulfills the predicted requirements for the successful treatment of CAP due to pneumococcus with a PCN MIC of 2.0 µg/ml. PK studies reveal that this product produces a time above the MIC of 2.0 µg/ml that is 66.7% of the dosing interval which is in excess of what it typically thought necessary (25-40%). In addition, there were fewer numbers of subjects in the PK studies who were found to be at the extreme low end of the exposure curve; there were zero patients with time above the MIC of 2.0 µg/mL for ≤32% of the dosing interval. Because of the difficulty in accumulating sufficient clinical data to prove efficacy, it is necessary to place relatively more weight on pre-clinical data and relatively less weight on actual clinical data. Since *S. pneumoniae*-penicillin is a bug-drug combination for which there is a good understanding of the pharmacodynamics, a greater relative weight placed on this PK/PD data is acceptable. Therefore, it is reasonable to approve this drug in the treatment of CAP due to PRSP with PCN MIC's of up to 2.0 µg/mL, when taking into account the great difficulty in studying this infection.

In this NDA there were three patients with isolates with a PCN MIC of 4.0 µg/ml and amoxicillin MIC of 8.0 µg/ml. One of these was a failure (although not a microbiologically proven failure) while the other two were successes. The two successes both had bacteremia, however, their Fine Scores indicated non-severe disease. The number of isolates are insufficient to identify any clinically significant difference between those PRSP isolates whose penicillin and amoxicillin MIC's are both 4.0 µg/ml

compared to those PRSP isolates whose penicillin MIC is 4.0 μg/ml and amoxicillin MIC is 8.0 μg/ml. This issue is not adequately addressed by the data submitted in this NDA. Because this is a potentially very important point, given the expected decline in drug activity with increasing penicillin or amoxicillin MIC's, a recommendation cannot be made to include in the indication the treatment of such isolates (i.e., any isolate whose penicillin or amoxicillin MIC is ≥4.0 μg/ml).

Acute Bacterial Sinusitis (ABS) Due to PRSP

For this resubmission, the sponsor has submitted data from one additional uncontrolled, open label study, Study 592. The overall efficacy of Augmentin XR in Study 592 was consistent with that found in the prior clinical ABS trials submitted for this NDA. The bacteriology ITT cure rate, which was the primary endpoint, for this open-label non-comparative study was 88.6% (95% CI 85.7, 91.7) which is comparable to that of the prior similar study, 551, which had a bacteriology ITT cure rate of 88.0% (95% CI 84.3, 90.8). Therefore, this review will focus on the issue of efficacy of Augmentin XR for the treatment of ABS due to PRSP.

The original submission contained 10 patients who were found by antral puncture to have ABS caused by PRSP (PCN MIC≥2.0 μg/ml). All of these patients were clinical and bacteriological ITT successes and their case report forms and related data as contained in the SAS transport files were reviewed in the original NDA review. One of these patients (551.049.14850) was not included in the Per Protocol analysis because of a protocol violation (missed EOT visit). However, this patient was a clinical and bacteriological cure at the TOC visit and was included in the ITT analysis. For the purposes of this review, these 10 patients will be included with the new data in the overall assessment of efficacy for ABS due to PRSP.

For this NDA's resubmission, the sponsor has submitted an additional 30 cases of patients with ABS due to PRSP which makes a total of 40 patients with ABS due to PRSP for this NDA. These extra 30 patients were accrued through enrollment in the additional open label non-comparative study, Study 592.

Definition of Outcome/ Methodology

Study 550 was the principal controlled ABS study for this NDA. It was reviewed for the initial NDA submission. This study was primarily a clinical study and did not address the issue of microbiology, except that for a few centers, endoscopically obtained cultures were collected for the purposes of evaluating this technique. From the perspective of the FDA, this technique has not been accepted as an adequate substitute for antral puncture, although it is recognized that there is growing supportive information in the medical literature.

Studies 551 and 592 are the two principal uncontrolled studies and they were designed to assess clinical efficacy in sinusitis patients with bacteria identified at baseline. These studies had bacteriological outcome as the primary focus, but also incorporated clinical outcome in the Bacteriological Response. Current FDA guidances for the collection of bacterial cultures (antral puncture) were followed.

At all centers, sinus puncture of the affected sinus was performed at screening (Visit 1, Day 0) to obtain a sinus sample for bacteriological analysis. For patients who were considered clinical failures of study medication at any time during the study, or clinical recurrences at or prior to the test of cure visit (Visit 4, Day 17-24), the procedure was repeated at the time of failure or recurrence. At selected US centers, prior to performing the sinus puncture as described above at Visit 1, the investigator performed endoscopically directed aspiration of the osteomeatal complex under the middle meatus to obtain a sample for culture.

Bacteriological Response at Test of Cure for Studies 551 and 592

The per patient bacteriological ***response*** (success or failure) at test of cure (Visit 4), determined from the per pathogen bacteriolgical ***outcome*** information on initial and new pathogens, was the primary efficacy variable.

For each initial pathogen identified at the screening visit the per pathogen bacteriological ***outcome*** at test of cure was categorized as follows:

Bacteriological Eradication: The pathogen was eradicated or presumed eradicated at end of therapy and there was a continued absence of the initial pathogen from a repeat sinus culture at test of cure.

Presumed Bacteriological Eradication: The pathogen was eradicated or presumed eradicated at end of therapy and test of cure eradication was presumed if the patient's test of cure clinical outcome was a clinical success and no repeat culture was performed.

Failure: The pathogen was eradicated or presumed eradicated at end of therapy but recurred in a sinus culture at test of cure or the pathogen was persistent at end of therapy.

Presumed Failure: The pathogen was eradicated or presumed eradicated at end of therapy but is presumed to have recurred at test of cure, if the patient's clinical outcome was a clinical recurrence and no repeat sinus culture was performed, or the pathogen was presumed persistent at end of therapy.

Unable to Determine: An assessment of bacteriological outcome could not be made at either end of therapy or test of cure.

MO COMMENT: This definition of the primary efficacy variable incorporated the clinical response. A patient could not be categorized with a bacteriological outcome of "success" unless that patient was also a clinical success as well. So, by definition, all patients who were categorized as bacteriological successes were also clinical successes. Since the majority of patients did not have confirmatory sinus punctures to prove successful bacteriological outcome, it is important to point out that the primary endpoint of these studies was largely driven by the clinical response.

New pathogens identified at test of cure were categorized as follows (a patient must have had a sinus culture at screening):

New Infection: A new pathogen was identified at test of cure in a symptomatic patient requiring additional antibacterial therapy for ABS, i.e., a clinical recurrence.

Colonization: A new organism is identified at test of cure in a non-symptomatic patient who does not require additional antibacterial therapy, i.e., a clinical success.

By study design, no bacteriology was to be performed in clinical successes so colonization should not be detected. However, if an unscheduled sinus culture was performed, the results were still used.

MO COMMENT: It should be pointed out that most patients fell into the category of presumed bacteriological eradication.

The per patient bacteriological ***response*** (success or failure) at test of cure combined information on initial and new pathogens as follows:

> *Success*: All initial pathogens were eradicated or presumed eradicated at test of cure, without any new infection, with or without colonization.
>
> *Failure*: Failure or presumed failure of one or more of the initial pathogens at test of cure, a new infection or an assessment of unable to determine for one or more initial pathogens.

The per patient bacteriological response was only applicable to patients with at least one initial pathogen.

Failures were subcategorized into 'known failures' and failures which were classified as 'unable to determine'. The 'known failures' included patients who had failure or presumed failure of one or more of the initial pathogens at the test of cure visit, or a new infection.

Patients who were bacteriological failures at end of therapy, but who subsequently became protocol violators at the test of cure visit, were included as failures in the Bacteriology PP test of cure population because they satisfied the criteria for being included in the test of cure failure group prior to violating the protocol.

Patients with a test of cure bacteriological outcome of 'unable to determine' for all initial pathogens were excluded from the bacteriological per protocol population at test of cure.

Clinical Response at Test of Cure

Clinical response (success or failure) to study medication at test of cure (Visit 4) was a secondary efficacy variable.

By comparing the signs and symptoms at the end of therapy visit with those observed at the test of cure visit, for patients who were clinical successes at end of therapy, the investigator evaluated each patient's clinical ***outcome.*** (Note: Only those clinical outcomes that were scheduled to have been assessed were used to derive the clinical response at test of cure). A patient's clinical ***response*** at test of cure was then defined as follows:

> *Success*: The patient's clinical outcome at test of cure was 'test of cure clinical success' which was defined as the following:

Sufficient resolution of signs and symptoms of ABS for patients who were clinical successes at the end of therapy visit, such that no additional antibacterial therapy was indicated for ABS.

Failure: The patient's clinical outcome at test of cure was 'clinical recurrence' or 'unable to determine' or the patient's clinical outcome at end of therapy was 'clinical failure' or 'unable to determine'. 'Clinical failure' and 'unable to determine' were defined as the following:

Clinical Failure - Reappearance or deterioration of signs and symptoms of ABS for patients who were clinical successes at the end of therapy visit, such that additional antibacterial therapy was indicated for ABS.

Unable to Determine - An assessment of clinical outcome could not be made (e.g., the patient was lost to follow-up, did not consent to clinical examination).

Patients whose clinical outcome was 'unable to determine' were excluded from the Clinical PP population.

Patients whose clinical response was 'clinical failure' at end of therapy, but who subsequently become protocol violators at test of cure, were included as failures in the Clinical PP test of cure population because they satisfied the criteria for being included in the failure group at test of cure prior to violating the protocol.

Patients whose clinical response was failure at end of therapy, but who subsequently became protocol violators at the test of cure visit were included as failures in the Clinical PP test of cure population because they satisfied the criteria for being included in the test of cure failure group prior to violating the protocol.

MO COMMENT: The medical officer agrees with the method of determination of efficacy.

Reasons for Exclusion from PP Analysis

The following table summarizes the reasons for exclusion from the PP analysis for all patients (three total) with PRSP who were excluded from the Per Protocol Analysis.

All Patients Excluded from PRSP ABS Per Protocol Analysis			
PID Excluded from PP analysis	**Reason for Exclusion**	**Outcome**	**Comments**
551.049.14850	Visit Compliance (late for EOT visit)	Clinical cure, Presumed bacteriological cure	Patient showed up late for EOT visit on day 20
592.002.21802	Visit Compliance (late for TOC visit)	Patient was clinical/micro success	Patient showed up late for TOC visit on day 31
592.006.22039	Visit Compliance (? EOT visit)	Patient was clinical/micro success	SAS dataset is incorrect for visits dates, there is no PV

*The protocol specified windows for end of therapy (Day 12-14) and test of cure (Day 17-24) were extended for the purposes of the efficacy analyses to Day 11-16 and Day 17-28, respectively.

MO COMMENT: These three patients were all determined to be clinical and presumptive bacteriological successes at both EOT and TOC visits. Two patients had visit dates which were outside the pre-specified range. Although these patients were late for pre-specified visits, they were still assessed as successes and it is not likely that the protocol violations in these cases has any significant effect on determination of outcome. The third patient appears to have had incorrect information entered into the SAS dataset from the CRF. The visit dates as recorded in the CRF do not indicate visit non-compliance and are different than those in the SAS dataset.

Treatment Duration

All PRSP patients were treated with approximately the same duration of therapy with 19 patients having received 10 days of therapy and 21 patients having received 11 days of therapy.

Efficacy/ Residual Symptoms/ Failures

The initial NDA submission contained ten patients with ABS due to PRSP. All ten of these patients were clinical and bacteriological successes. The subsequent resubmission contained an additional 30 patients with ABS due to PRSP. The sponsor reported that all 30 of these patients were also clinical and bacteriological successes.

Detailed review was performed by the medical officer of all case report forms and data sets in reference to these patients. The sponsor's submitted report indicates that all patients were clinical and bacteriological successes. These results are summarized in the table below.

Bacteriological Outcome for ITT and PP Populations for Patients with ABS due to PRSP			
	n/N	(%)	95% CI*
Bacteriology ITT	40/40	(100)	91.4, 99.9
Bacteriology PP	37/37	(100)	90.7, 99.9

* confidence limits calculated by Medical Officer using exact probabilities

MO COMMENT: Review of the case report forms revealed that one patient (551.039.06108) was evaluated for the TOC visit 6 days after receiving the last dose of antibiotics. Although this patient was assessed at TOC at day 17 of the study (which is within the 17-24 day TOC window), the visit was too close to the last dose of antibiotic. The FDA guidance for ABS recommends that the TOC visit be done at 1-2 weeks after the last dose to allow for relapses. The exclusion of this patient from the PP analysis, does not effect the overall analysis, because the sponsor inappropriately excluded one patient (592.006.22039) who should have been left in the PP analysis; the overall numbers are unchanged by this.

Review of the case report forms revealed that there were only six out of the 40 patients who had residual symptoms. Five of these patients had residual symptoms which appear to have been mild and significantly improved from enrollment. These patients also had radiographic examinations which were also improved from enrollment. One patient (592.219.19918) had significant residual symptoms at the TOC visit including left facial congestion/fullness, left and right purulent nasal discharge, left nasal cavity purulence, left earache, sore throat, and cough as well as right earache, and change in perception of smell. This patient also had left sinus opacification as seen on sinus x-ray at the TOC visit. These symptoms represent no change from enrollment and the enrollment sinus x-ray was only different in that it had both right and left sinus opacification. This patient was not re-cultured so it is not possible to determine an accurate microbiological outcome. This patient's clinical assessment at the EOT visit did reveal significant improvement in symptoms, so the recurrence of multiple ABS symptoms at TOC represents a relapse. The PCN MIC of this patient's pneumococcus was 2.0 μg/ml. Reclassification of this patient as a clinical and presumptive microbiological failure would result in slight changes in the efficacy rates and 95% CI's which are contained in the table below. The primary effect of this change was to decrease the lower limit of the 95% CI.

Bacteriological Outcome for ITT and PP Populations for Patients with ABS due to PRSP Using Medical Officer's Analysis			
	n/N	(%)	95% CI*
Bacteriology ITT	39/40	(97.5)	87.1, 99.4
Bacteriology PP	36/37	(90)	86.2, 99.4

* confidence limits calculated using exact probabilities

Additional Analysis

There was one investigator who was identified by the MO as having enrolled a disproportionately large percentage of patients with ABS due to PRSP. Review of distribution of enrollment of PRSP patients revealed that Dr. Hendrick enrolled a total of 11 PRSP patients in Study 592 and 3 PRSP patients from Study 551. Although Dr. Hendrick's center was only one out of 83 different centers in study 551 and 56 different centers from Study 592, he accounted for 35% (14/40) of all ABS-PRPS patients in the entire NDA. Dr. Hendrick's center enrolled a total of 111 patients into Studies 551 and 592. The rate of PRSP prevalence for his center was 12.6 % (14/ 111) and this was much higher than for all other centers combined where the PRSP prevalence rate was only 1.6% (26/ 1,609). A DSI inspection has raised questions about the integrity of Dr. Hendrick's data. For these reasons, adjusted summary tables are included below which exclude Dr. Hendrick's data.

None of Dr. Hendrick's patients were excluded from the PP analysis and none of them was considered a failure.

Bacteriological Outcome for ITT and PP Populations for Patients with ABS due to PRSP Using Medical Officer's Analysis and Excluding Dr. Hendrick's Patients			
	n/N	(%)	95% CI*
Bacteriology ITT	25/26	(96.15)	81.02, 99.09
Bacteriology PP	22/23	(95.65)	78.88, 98.97

* confidence intervals calculated using exact probabilities

MO COMMENT: The primary effect of the removal of Dr. Hendrick's patients from the analysis is the widening of the 95% confidence intervals on the efficacy rate.

MIC's of PRSP Isolates Causing ABS

The table below summarizes the range and distribution of MIC's for PRSP isolates in this NDA which caused ABS.

Number of Patients by MIC of *S. pneumoniae* Isolate For ABS Excluding Dr. Hendrick's Patients				
	Penicillin MIC of Isolate			
	2.0 ug/ml	**4.0 ug/ml**	**8.0 ug/ml**	**16.0 ug/ml**
Number of Patients	17*	7	1	1

Relationship Between Penicillin MIC and Amoxicillin MIC for PRSP Isolates of ABS Patients Excluding Dr. Hendrick's Patients					
		Penicillin MIC of PRSP Isolate (ug/ml)			
		2.0	4.0	8.0	16.0
Amox MIC	1.0 ug/ml	2	0	0	0
	2.0 ug/ml	12*	4	0	0
	4.0 ug/ml	3	2	0	0
	8.0 ug/ml	0	1	1	1
	16.0 ug/ml	0	0	0	0

* One patient in this category was reclassified by MO as a failure.

An assessment of residual symptoms according to isolate MIC's was performed for all patients with ABS due to PRSP. The table below summarizes this information.

MIC's of Isolates in Patients with Residual Symptoms in ITT Analysis for ABS Excluding Dr. Hendrick's Data				
	Patients with Residual Symptoms		Patients without Residual Symptoms	
	n/N	(%)	N/N	(%)
PCN MIC = 2.0 µg/ml	4/17*	(23.5)	13/17	(76.5)
PCN MIC = 4.0 µg/ml	2/7	(28.6)	5/7	(71.4)

*One of these patients was re-categorized as a ABS failure by the Medical Officer.

MO COMMENT: Five out of 6 patients with ABS due to PRSP who also had residual symptoms had radiological examinations at TOC which demonstrated marked improvement and were either normal (n=2) or had slight mucosal thickening (n=3). Residual symptoms included tooth pain, nasal obstruction, facial congestion, and halitosis, however, these symptoms were recorded as being improved in severity. Overall, when assessed in the context of a normalized CT scan, these residual symptoms are not suggestive of treatment failure. The sixth patient with residual symptoms was reclassified by the MO as being a failure and this patient had left sinus opacification on radiographic examination which was consistent with his persisting left sided sinus symptoms. Based on review of the case report forms for remaining patients with residual symptoms, the MO concludes that they are appropriately categorized as clinical successes.

Examination of the relationship between PCN MIC and Amox MIC for PRSP isolates recovered from ABS patients in this NDA are summarized in the table below.

Relationship Between Penicillin MIC and Amoxicillin MIC for PRSP Isolates of ABS Patients Excluding Dr. Hendrick's Data					
		Penicillin MIC of PRSP Isolate (µg/ml)			
		2.0	4.0	8.0	16.0
Amox MIC	1.0 µg/ml	2	0	0	0
	2.0 µg/ml	12*	4	0	0
	4.0 µg/ml	3	2	0	0
	8.0 µg/ml	0	1	1	1
	16.0µg/ml	0	0	0	0

* One of these patients was re-categorized as a failure by the MO.

MO COMMENT: There is a general correlation between the amoxicillin and penicillin MIC's but it is not necessarily consistently predictive. Amongst those patients with a penicillin MIC of 2.0 µg/ml, 70.6% (12/17) had the same amoxicillin MIC. Amongst those patients with a penicillin MIC of 4.0 µg/mL, 28.6% (2/7) had the same amoxicillin MIC. None of the 26 patients had more than a one tube dilution difference between the penicillin and amoxicillin MIC's.

Medical Officer Conclusion:

Based on review of the submitted data, it can be concluded that Augmentin XR has efficacy in the treatment of acute bacterial sinusitis as caused by penicillin-resistant pneumococcus with PCN MIC's of 2.0 µg/ml. This is based on the totality of the available data including sufficient numbers of patients with ABS due to PRSP, the expected effectiveness of this drug based on the pharmacokinetic profile, and the very low failure rate.

However, there is not sufficient evidence to demonstrate the efficacy of Augmentin XR in the treatment of acute bacterial sinusitis as caused by penicillin-resistant pneumococcus with PCN MIC's of ≥4.0 µg/mL. There were only nine patients in this NDA who had ABS due to isolates with MIC of ≥4.0 µg/mL. Because of the high placebo rate and modest treatment effect which exists in the treatment of acute bacterial sinusitis, more data is needed to determine the efficacy of Augmentin XR in the treatment of ABS due to pneumococcus with a penicillin MIC of ≥4.0 µg/mL.

It is recommended that this drug be approved for the treatment of ABS due to PRSP only for those patients whose penicillin MIC's are ≤2.0 µg/ml.

PROPOSED LABELING

Risk Factors for PRSP

In the FDA's Non-Approval letter issued for the initial submission and dated December 12, 2001, the Agency noted that the draft labeling does not clearly identify the characteristics of the intended patient population for Augmentin XR™ in contrast to Augmentin 875® (7:1). In the re-submission, the sponsor has addressed this issue by including in their proposed labeling that this drug be used for patients who have possible risk factors for CAP due to PRSP. The risk factors that the sponsor has incorporated in the proposed label are from the American Thoracic Society's Guidelines for the Management of Adults with Community-acquired Pneumonia. [2]

According to the ATS Guidelines, a patient with one or more of the following modifying factors is at increased risk of infection with PRSP:

- Age > 65 years
- Beta-lactam therapy within the past 3 months
- Alcoholism
- Immune-suppressive illness (including therapy with corticosteroids)
- Multiple medical comorbidities
- [redacted]

The sponsor proposes that these criteria will provide readily recognizable patient characteristics to guide the healthcare provider in the selection of empiric therapy.

A retrospective analysis of the CAP patients who fulfilled these ATS criteria was performed by the sponsor. The presence of modifying factors was derived based on a computer algorithm upon clinical review without reference to patient numbers, to avoid allocation bias with regard to treatment groups. A review of the baseline ongoing medical history terms as well as baseline signs and symptoms was performed by a physician. Only information available in the case record (i.e., age, comorbidities, beta-lactam therapy in prior 30 days, concurrent steroid use) was used for this evaluation.

The results of this analysis are summarized in the following tables which were part of the sponsor's re-submission.

[2] American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am. J Respir Crit Care Med* 2001;163: 1730-1754.

Number (%) of Patients with ≥ 1 Modifying Risk Factor for PRSP: Combined CAP Studies 546, 547, 556 and 557 (Clinical PP and ITT Populations)

	Augmentin XR	
	Clinical PP n/N (%)	**Clinical ITT n/N (%)**
All CAP patients	413/1278 (32.3)	593/1704 (34.8)
CAP due to *S. pneumoniae*	43/172 (25.0)	61/214 (28.5)
CAP due to non-PRSP	37/157 (23.6)	52/194 (26.8)
CAP due to PRSP	6/15 (40.0)	9/20 (45.0)

Data Source: Tables 8.G.1.4.106s to 111s
Note: non-PRSP defined as *S. pneumoniae* with penicillin MIC ≤ 1 µg/mL
n/N=number of patients with ≥ 1 Modifying Risk Factor/number of patients in specified group

By applying the ATS criteria, a subset of patients at increased risk for PRSP was identified in the Augmentin XR CAP clinical program. Approximately 30% of patients in the CAP cohort and 40% in the CAP cohort with PRSP had at least one modifying factor for risk of acquiring PRSP.

MO COMMENT: The vast majority of patients with one or more risk factors for PRSP had age ≥65 as their only risk factor. When this risk factor is taken out, the percentage of patients in this NDA who had one or more PRSP risk factors declines drastically. The table below provides a break down of each individual risk factor.

PRSP Risk Factors (ATS Criteria) ITT Population Studies 546, 547, 556, 557 – Sponsor's Analysis				
	Augmentin † (N=1,704)		Augmentin* (N=595)	
	n	(%)	n	(%)
At least 1 ATS Risk Factor for PRSP	684	40.1%	261	43.9
Age ≥65 years old	427	25.1	194	32.6
Greater than 1 Comorbidity	138	8.1	53	8.9
Prior Beta-Lactam Use	118	6.9	53	8.9
Immunosuppressive Therapy	80	4.7	39	6.6
Alcoholism	11	0.6	6	1.0
[redacted]	?		?	

*Includes both Augmentin 875/125mg BID, Augmentin 875/125mg TID and Augmentin 1000/125 TID
† Information not collected.

MO COMMENT: The medical officer's assessment of patients who had prior beta-lactam use is different than that of the sponsor contained in the table above. Many of the patients who were included in the sponsor's analysis received less than 48 hours of antibiotics. Other patients who received more extensive antibiotic therapy were excluded from enrollment. Most of these patients were given one or two doses of antibiotics immediately prior to enrollment in the study. The medical officer disagrees with this assessment and a reanalysis in which all patients were excluded who received <48 hours of antibiotics resulted in a total of only 67 Augmentin XR patients (3.9%) with prior beta-lactam use.

The following table shows clinical response in patients with at least one modifying risk factor for infections due to PRSP.

Clinical Success Rates at Test of Cure in Patients with ≥ 1 Modifying Factors for PRSP (Clinical PP and ITT Populations)

	Augmentin XR n/N (%)	Augmentin Comparators n/N (%)
Clinical PP Population		
All CAP Patients	347/413 (84.0)	159/180 (88.3)
CAP due to *S. pneumoniae*	38/43 (88.4)	13/16 (81.3)
CAP due to non-PRSP	32/37 (86.5)	13/15 (86.7)
CAP due to PRSP	6/6 (100.0)	0/1 (-)
ITT Population		
All CAP Patients	445/593 (75.0)	211/261 (80.8)
CAP due to *S. pneumoniae*	52/61 (85.2)	15/20 (75.0)
CAP due to non-PRSP	45/52 (86.5)	15/18 (83.3)
CAP due to PRSP	7/9 (77.8)	0/2 (-)

Data Source: Tables 8.G.1.4.118s to 123s
Note: non-PRSP defined as *S. pneumoniae* with penicillin MIC ≤ 1 µg/mL
n/N=number of patients with success/number of patients with ≥ 1 Modifying Risk Factor in specified group

In both the Augmentin XR and the Augmentin Comparators group, high clinical response rates were seen in patients who were in the cohort with one or more modifying risk factors for PRSP. In the Clinical PP population, patients with culture-confirmed pneumococcal pneumonia had clinical response rates of 88.4% in the Augmentin XR group and 81.3% in the Augmentin Comparators group. In patients with infections due to PRSP, the clinical response rates remained high in the Augmentin XR group (6/6, 100%; Clinical PP) but there were too few patients to make meaningful comparisons to other subgroups.

MO COMMENT: As pointed out previously, the vast majority of the patients in the table above had age ≥65 as their only risk factor. The following tables give the numbers of PRSP/CAP patients with each modifying risk factor. Of all patients with CAP due to *S. pneumoniae* who had at least one ATS risk factor (n=61), 46 had age ≥65 years as their ATS risk factor. The second table reveals similar findings when considering only at those patients with CAP due to PRSP.

Modifying Factors Associated with Penicillin Resistant Pneumococcal Pneumonia – ATS Criteria CAP Patients with *S. pneumoniae* (Intent To Treat Population) Studies 546, 547, 556, 557 Combined					
		Treatment			
		Augmentin XR (N=214)		Augmentin (N=44)	
		n	(%)	n	(%)
Age ≥ 65	No	168	(78.5)	29	(65.9)
	Yes	46	(21.5)	15	(34.1)
Prior B-lactam use	No	203	(94.9)	40	(90.9)
	Yes	11	(5.1)	4	(9.1)
Alcoholism	No	213	(99.5)	43	(97.7)
	Yes	1	(0.5)	1	(2.3)
Immunosuppressive Illness	No	205	(95.8)	42	(95.5)
	Yes	9	(4.2)	2	(4.5)
Greater than One Comorbidity	No	198	(92.5)	42	(95.5)
	Yes	16	(7.5)	2	(4.5)
At Least One ATS Risk Factor	No	153	(71.5)	24	(54.5)
	Yes	61	(28.5)	20	(45.5)

Modifying Factors Associated with Penicillin Resistant Pneumococcal Pneumonia – ATS Criteria CAP Patients with Penicillin Resistant *S. pneumoniae* (Intent To Treat Population) Studies 546, 547, 556, 557 Combined					
		Treatment			
		Augmentin XR (N=20)		Augmentin Comparator (N=5)	
		n	(%)	n	(%)
Age ≥ 65	No	13	(65.0)	5	(100.0)
	Yes	7	(35.0)	0	(0.0)
Prior B-lactam use	No	17	(85.0)	5	(100.0)
	Yes	3	(15.0)	0	(0.0)
Alcoholism	No	20	(100.0)	4	(80.0)
	Yes	0	(0)	1	(20.0)
Immunosuppressive Illness	No	16	(80.0)	4	(80.0)
	Yes	4	(20.0)	1	(20.0)
Greater than One Comorbidity	No	18	(90.0)	5	(100.0)
	Yes	2	(10.0)	0	(0.0)
At Least One ATS Risk Factor	No	11	(55.0)	3	(60.0)
	Yes	9	(45.0)	2	(40.0)

Proposed Label

In the proposed label, the sponsor specifies the target treatment population as follows:

Community-acquired pneumonia [

]

Acute bacterial sinusitis [

]

MO COMMENT: In summary, it is important to note that there is very little data in the NDA which supports this labeling proposal, and no data were accumulated in a prospective manner.

Medical Officer Conclusion/Recommendation:

The proposed label is problematic for several reasons.

First, the validity of the submitted PRSP risk factor analysis is highly questionable for the following reasons:

1. It was not done in a prospective manner.
2. Not all the necessary information was collected during the course of the NDA (no information is available with regard to one of the most important PRSP risk factors – [redacted]
3. The protocols specifically excluded patients who had some of the risk factors (e.g., multiple co-morbidities, alcoholism, immune suppressive illness).
4. The overall numbers of patients in the identified risk categories (except for age ≥65 years) are extremely small.

Secondly, (and perhaps the most worrisome aspect of the proposed use of this system of ATS risk factors in the labeling) is that it simultaneously selects for those patients who are also most likely to fail therapy with this product: namely, those patients with CAP whose pneumococcal isolate has a PCN MIC ≥4.0 μg/ml. These patients share the exact same ATS risk factors as those patients with an infection due to an isolate whose PCN MIC is 2.0 μg/ml. It can be fully expected that as increasing penicillin resistance occurs in pneumococcal isolates, a growing percentage of patients with these ATS risk factors will fail therapy with this product. Indeed, even at this moment, those patients who present with CAP due to an isolate with higher PCN MIC's (≥4.0 μg/ml) may be at risk for treatment failure.

Thirdly, the proposed use of ATS risk factors for PRSP identifies a group of patients who, according to Fine's criteria, are likely to be sicker and are likely to potentially benefit from I.V. antibiotics as an inpatient rather than oral antibiotics in an outpatient setting, as with this product. The proposed use of the ATS risk factors, if accepted, could potentially grant an implied claim of efficacy in those patients who have more severe disease. This may lead to the inappropriate use of this product in those situations where the patients may actually benefit from more aggressive care in a hospital setting.

Finally, the patient population identified by using the ATS risk factors, may be at increased risk for more serious adverse events as a result of the increased rate of diarrhea caused by this product. There are not sufficient data to prove that the increased diarrhea caused by this product will not result in more serious complications in patients with the ATS risk factors. It could be expected that patients with some of the ATS risk factors (multiple co-morbidities, immune-suppressive illness, age over 65) may be at increased risk for more deleterious complications of diarrhea as caused by this product. Studies of the safety and efficacy of Augmentin XR in patients with these risk factors would have addressed many of these issues, but were not performed.

For the reasons specified above, the current label as proposed by the sponsor is not acceptable.

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/s/

Charles Cooper
10/21/02 03:50:14 PM
MEDICAL OFFICER

MO Review of Resubmission for Augmentin XR with edits

John Alexander
10/21/02 04:02:10 PM
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Dr. Cooper's Efficacy Review of Resubmission

Janice Soreth
10/21/02 05:24:47 PM
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APPEARS THIS WAY
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