CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-785

MICROBIOLOGY REVIEW(S)

Division of Anti-Infective Drug Products
Clinical Microbiological Review

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DRUG PRODUCT NAME:

Proprietary:	Augmentin —
Nonproprietary/USAN:	amoxicillin /clavulanate potassium, 16:1 ratio
Code Names/#'s:	
Therapeutic Class:	Antimicrobial

PHARMACOLOGICAL CATEGORY: β-lactam/β-lactamase inhibitor combination,
DOSAGE FORM: Tablets
STRENGTHS: 1000/62.5 mg per tablet
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ Rx __ OTC

RELATED DOCUMENTS (if applicable):

IND —
NDAs: 50564, 50575, 50597, 50720, 50725, 50726, 50755 —
DMFs: —

A. BACKGROUND

Augmentin® (amoxicillin/clavulanate potassium) is an approved drug product and has been marketed in the U.S.A. with different formulations for several years. It's safety and efficacy profiles are well characterized. This application provides for the registration of Augmentin —

tablets. Each tablet contains 1000 mg amoxicillin (present as amoxicillin trihydrate and amoxicillin monosodium) and 62.5 mg clavulanic acid (as potassium salt) (16:1 ratio), in two layers- an immediate release layer and a sustained release layer. The proposed dosing regimens are 2000 mg/125 mg amoxicillin/clavulanic acid twice daily for: 10 days for acute bacterial sinusitis (ABS), ——— and 7 to 10 days for community-acquired pneumonia (CAP).

Since this drug product is not a New Molecular Entity this reviewer will only concentrate on discussions surrounding the establishment of new breakpoints and interpretive criteria for in vitro susceptibility testing. The sponsor is only proposing a change in the in vitro susceptibility interpretive criteria for *S. pneumoniae* from the current breakpoints (2=S, 4=I, 8=R μg/mL) to 4=S, 8=I, and 16=R μg/mL. In addition the sponsor is suggesting establishing in vitro susceptibility interpretive criteria for *M. catarrhalis* (≤ 4/2=S, ≥ 8/4=R μg/mL). Since almost all isolates of *M. catarrhalis* are β-lactamase producers and there has not been an indication that this organism is developing antimicrobial resistance to any other antimicrobial agent, performance of a β-lactamase test is sufficient to guide therapy. Therefore establishing in vitro susceptibility testing interpretive criteria is not warranted at the present time and will not be discussed in this review.

B. REMARKS/COMMENTS

In vitro susceptibility testing is performed to assess the potential utility of an antimicrobial in the treatment of a pathogen isolated from a specified site of infection. Association of established susceptibility breakpoints with clinical outcome is critical in that the value selected must predict a successful clinical outcome. In order to establish appropriate breakpoints, the sponsor have submitted the following data:

- In vitro antimicrobial spectrum of activity and MIC frequency distribution of Augmentin® — as it relates to the pathogens indicated in acute bacterial sinusitis, ——— community-acquired pneumonia namely *S. pneumoniae, H. influenzae, H. parainfluenzae, K. pneumoniae, M. catarrhalis, S. pyogenes* and methicillin-susceptible *S. aureus*. These data should help describe the association of the susceptibility profile of the clinical isolates and that of the general population.

- Pharmacokinetic and pharmacodynamic studies that describe serum concentration of Augmentin® — during the dosing interval as it relates to the susceptibility patterns of the pathogen(s) under consideration.

- In vivo animal study to determine the efficacy of Augmentin® — in experimental respiratory tract infections caused by *S. pneumoniae.*

- Clinical efficacy data using Augmentin® — in studies that describe the association of the susceptibility of the pathogen isolated during the clinical investigation to clinical outcome of the patient. These data should help further describe the predictive value of the proposed breakpoints.

1. In Vitro Antimicrobial Spectrum Of Activity

The data presented in this section are from large surveillance studies conducted since 1999. The sponsor states that some studies included isolates collected prior to 1999, but no earlier than 1997. The following is a description of the studies:

Augmentin Global Surveillance Study (AGSS): This major surveillance study was conducted primarily for the purpose of gathering recent susceptibility data for registration of Augmentin — A total of 3,493 *S. pneumoniae* isolates were collected from 63 sites in 13 countries, including 8 countries in Europe. [redacted] [4,5] conducted susceptibility testing and data management.

Alexander Project: This is an ongoing, multicenter, international surveillance study of community-acquired respiratory tract pathogens. A total of 4,300 *S. pneumoniae* isolates were collected from 23 countries and tested in one of the following three central testing laboratories in 1999: [redacted]. Testing was conducted using commercially prepared [redacted] panels from [redacted] and data management was conducted by [redacted] [6].

International Surveillance Study (ISS): This study was conducted in 42 countries and includes data on 3,539 recent isolates of *S. pneumoniae* (1997-2000). Testing was conducted at each site, or at regional central laboratories, using panels from both [redacted] Data collection and management was conducted by [redacted] An initial report based on data from 1997-1999 was issued in February, 2000 [3] and updated with data from 2000 in October 2000 [7].

ALERT: A total of 3,354 *S. pneumoniae* isolates were collected between September 1998 and December 1999 from 43 hospitals within the US. Susceptibility testing was conducted using [redacted] panels [redacted] The majority of hospitals performed MIC testing of the isolates collected in their institution; others were tested by [redacted] [8].

Clinical Microbiology Institute (CMI): Ten clinical microbiology laboratories in major teaching hospitals throughout the US and one center in Canada collected 578 consecutive clinical isolates of *S. pneumoniae* and sent them to CMI (Arthur Barry, Ph.D.) for central testing [2].

Consultants in Anti-Infectives Surveillance and Testing, Inc. (CAST): A total of 552 *S. pneumoniae* isolates were collected from more than 30 sites in the US. All results were processed at the [redacted] [3].

Table 1 and Table 2 show the amoxicillin/clavulanic acid MIC_{50}, MIC_{90}, and MIC range for *S. pneumoniae* tested in the AGSS, Alexander Project, ISS, Alert, CMI, and CAST studies. The range of MIC_{90}s in the US (Table 1) was 1-4 µg/mL. At a presumptive susceptible breakpoint of

2 µg/mL, the percentage of isolates susceptible to amoxicillin/clavulanic acid ranged from 85.2-96%; and at a presumptive susceptible breakpoint of 4 µg/mL, the range was 90.3-98.6%. The MIC_{90} in each study for the isolates from all geographic regions was 2 µg/mL (Table 2), and the percent susceptible ranges at each presumptive breakpoint were as follows: at 2 µg/mL, 92.7-93.7%; and at 4 µg/mL, 96.2-97.2%.

Table 1. In vitro activity of amoxicillin/clavulanic acid against *S. pneumoniae* from surveillance studies – US

Study	No of isolates	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	%Susc @ ≤ 2 µg/mL	% Susc @ ≤4 µg/mL
AGSS 1999 - 2000	648	≤0.015 - ≥32	0.03	4	85.2	90.3
Alexander 1999	1,462	≤0.015 - 16	0.06	4	85.9	90.8
ISS 1997 - 2000	347	0.03 - 8	0.03	2	94.2	96.3
ALERT 1999	3,303	≤0.015 - ≥32	0.03	4	88.1	94.7
CMI 1999[b]	578	≤0.03 - 8	≤0.03	1	93	96.2
CAST 1999	552	≤0.25 - 8	≤0.25	2	96	98.6

[a]Tested as a 2:1 ratio, MICs are expressed in terms of amoxicillin component
[b]Includes 50 isolates from Canada.

Table2. In vitro activity of amoxicillin/clavulanic acid against *S. pneumoniae* from surveillance studies – all geographic regions

Study	No of isolates	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	%Susc @ ≤ 2 µg/mL	%Susc @ ≤ 4 µg/mL
AGSS 1999 - 2000	3,493	≤0.015 - ≥32	0.03	2	93.7	97.2
Alexander 1999	4,300	≤0.015 - 16	0.03	2	92.7	96.2
ISS 1997 - 2000	3,539	≤0.03 - >32	0.03	2	92.9	96.8

[a]Tested as a 2:1 ratio, MICs are expressed in terms of amoxicillin component

The *in vitro* activity of amoxicillin/clavulanic acid against penicillin susceptible, intermediate and resistant *S. pneumoniae* isolated in the US surveillance studies is presented in Table 3. The MIC_{90} and the percent susceptible at each presumptive susceptible breakpoint for each category are presented. The amoxicillin/clavulanic acid MIC_{90} range was 0.03 - 0.25 µg/mL for the penicillin-susceptible isolates, 1-2 µg/mL for the penicillin-intermediate isolates, and 4-8 µg/mL for the penicillin- resistant isolates. As expected, all penicillin-susceptible isolates were susceptible to amoxicillin/clavulanic acid at both presumptive susceptible breakpoints of 2 and 4 µg/mL. At a presumptive susceptible breakpoint of 2 µg/mL, 92.3-100% of the intermediate isolates were susceptible to amoxicillin/clavulanic acid, and at a presumptive susceptible breakpoint of 4 µg/mL, 99.4-100% of isolates were susceptible. At a presumptive susceptible breakpoint of ≤ 2 µg/mL, the percentage of penicillin-resistant isolates susceptible to amoxicillin/clavulanic acid ranged from 41.7-80.2%, and at a presumptive susceptible breakpoint of ≤ 4 µg/mL 64.4-92.8% of isolates were susceptible to amoxicillin/clavulanic acid.

The number of isolates at each MIC and the cumulative percent MIC frequency distribution for amoxicillin/clavulanic acid against *S. pneumoniae* that are resistant to various classes of antimicrobials are presented in Tables 4. The data presented in Table 4 are from all six surveillance studies combined (AGSS, Alexander Project, ISS, Alert, CMI, and CAST) for the US and all geographical regions.

The amoxicillin/clavulanic acid MIC_{90} for *S. pneumoniae* isolates in the US was 4 µg/mL (Table 4). At the sponsor-proposed susceptible breakpoint of 4 µg/mL, 93.9% of the isolates were susceptible to amoxicillin/clavulanic acid while at the current susceptible breakpoint of 2 µg/mL 88.6% of the isolates were susceptible to amoxicillin/clavulanic acid.

The Amoxicillin/clavulanic acid MIC_{90} for *S. pneumoniae* isolates in all geographical regions was of 2 µg/mL. For these isolates, 96.3% were susceptible to amoxicillin/clavulanic acid at the sponsor-proposed susceptible breakpoint while at the current susceptible breakpoint (for Augmentin 4:1, 2.0 µg/mL) 92.1% of the isolates were susceptible to amoxicillin/clavulanic acid.

The MIC_{90} for amoxicillin/clavulanic acid for penicillin-resistant *S. pneumoniae*, from the US was 8 µg/mL (Table 4). For the isolates from the US, 74.4% of the penicillin-resistant isolates were susceptible to amoxicillin/clavulanic acid at the sponsor-proposed susceptible breakpoint while at the current susceptible breakpoint of 2 µg/mL 55% of the isolates were susceptible to amoxicillin/clavulanic acid.

For the penicillin-resistant isolates from all geographic regions (Table 4), the amoxicillin/ clavulanic acid MIC_{90} was 8 µg/mL. For the isolates from all geographic regions, 81.7% of the penicillin-resistant isolates were susceptible to amoxicillin/clavulanic acid at the sponsor-proposed breakpoint (Table 4). Again, only 62.9% of the penicillin-resistant isolates were susceptible to amoxicillin/clavulanic acid at the current susceptible breakpoint (for Augmentin 4:1, 2.0 µg/mL).

For the US erythromycin (macrolide)-resistant *S. pneumoniae* isolates the amoxicillin/clavulanic acid MIC_{90} was 8 µg/mL (Table 4). At the sponsor-proposed susceptible breakpoint, 76.8% of the erythromycin-resistant isolates were susceptible to amoxicillin/clavulanic acid while at the current susceptible breakpoint of 2 µg/mL 66.1% of the isolates were susceptible to amoxicillin/clavulanic acid.

The amoxicillin/clavulanic acid MIC_{90} for the erythromycin-resistant *S. pneumoniae* isolates from all geographic regions was 4 µg/mL (Table 4). At the sponsor-proposed susceptible breakpoint, 90.2% of the erythromycin-resistant isolates from all geographic regions were susceptible to amoxicillin/clavulanic acid. Again, 82.0% of the erythromycin-resistant isolates were susceptible to amoxicillin/clavulanic acid at the current susceptible breakpoint (for Augmentin 4:1).

Table 3. Activity of amoxicillin/ clavulanic acid against *S. pneumoniae* isolated in the US, categorized by penicillin susceptibility.

	Penicillin-Susceptible*				Penicillin-Intermediate*				Penicillin-Resistant*			
	N	MIC_{90}	%S ≤ 2[b]	%S ≤ 4[c]	N	MIC_{90}	%S ≤ 2	%S ≤ 4	N	MIC_{90}	%S ≤ 2	%S ≤ 4
AGSS 1999 - 2000	385	0.06	100	100	86	2	100	100	177	8	45.8	64.4
Alexander 1999	761	0.06	100	100	175	2	98.9	100	526	8	61.2	74.3
ISS 1999 - 2000	186	0.03	100	100	65	1	100	100	96	8	79.2	86.5
ALERT 1999	2,053	0.03	100	100	662	2	92.3	99.4	587	8	41.7	71
CMI 1999[d]	373	0.03	100	100	93	1	100	100	112	8	64.3	80.4
CAST 1999	354	≤0.25	100	100	87	1	100	100	111	4	80.2	92.8

* Penicillin interpretive criteria: Susceptible = ≤ 0.06 µg/mL, Intermediate = 0.12-1.0 µg/mL. Resistant = ≥ 2.0 µg/mL.
[a] *S. pneumoniae* does not produce β-lactamase and, therefore, is susceptible to amoxicillin alone; MICs are expressed in terms of amoxicillin component
[b] Susceptible at ≤ 2/1 µg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio
[c] Susceptible at ≤ 4/2 µg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio
[d] Includes 50 isolates from Canada

Table 4. Frequency distribution of amoxicillin/clavulanic[1] acid MICs (µg/mL) against multidrug resistant *S. pneumoniae* from the combined surveillance studies-US and all geographical regions

Total N Cumulative %	Amoxicillin/clavulanic acid MIC µg/mL										Total
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	
S.pneumoniae-US isolates											
All Isolates	3474[a] 50.79	309 55.31	269 59.24	575[a] 67.65	179 70.26	439 76.68	818 88.64	362 93.93	373 99.39	42[b] 100	6,840
Penicillin-resistant isolates	1[a] 0.06		32 2.05	2 2.18[a]	12 2.92	182 14.25	654 54.95	313 74.42	369 97.39	42[b] 100	1,607
Erythromycin (macrolide)-resistant[2] isolates	69[a] 8.95	33 13.23	30 17.12	28[a] 20.75	30 24.64	69 33.59	251 66.15	82 76.78	159 97.41	20[a] 100	771
TMP/SMX[c] –resistant[3] isolates	217[a] 10.99	81 15.10	77 19.00	70[a] 22.54	65 25.84	208 36.37	632 68.39	262 81.66	324 98.07	38[a] 100	1,974
S.pneumoniae-all geographical regions isolates											
All Isolates	8,933[a] 56.66	932 62.56	657 66.73	918[a] 72.57	414 75.19	925 81.06	1,747 92.14	661 96.33	493 99.46	85[a] 100	15,765
Penicillin-resistant isolates	9[a] 0.29	1 0.32	36 1.49	5[a] 1.65	48 3.20	401 16.18	1,445 62.92	579 81.66	484 97.90	83[b] 100	3,091
Erythromycin (macrolide)-resistant[2] isolates	411[a] 18.54	184 26.84	109 31.75	128[a] 37.53	91 41.63	237 52.32	658 82.00	181 90.17	190 98.74	28[a] 100	2,217
TMP/SMX[c]-resistant[3] isolates	580[a] 13.96	176 18.19	213 23.32	190[a] 27.89	183 32.29	511 44.59	1,340 76.83	468 88.09	422 98.24	73[a] 100	4,156

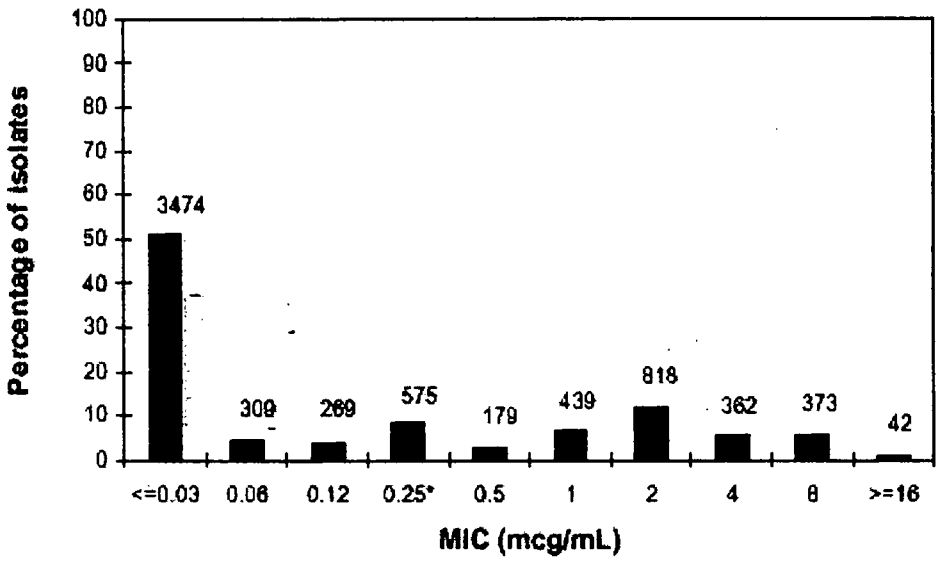
[1] Amoxicillin/ clavulanic acid was tested at a 2: 1 ratio; MICs are expressed in terms of the amoxicillin concentration.
[2] Resistance is defined as erythromycin MIC ≥ 1 µg/mL
[3] Resistance is defined as trimethoprim/sulfamethoxazole MIC ≥ 4/76 µg/mL
[a] Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are lower.
[b] Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are higher.
[c] TMP/ SMX: Trimethoprim/ sulfamethoxazole was tested at a 1: 19 ratio; MICs are expressed in terms of the trimethoprim concentration.

The amoxicillin/clavulanic acid MIC_{90} was 8 µg/mL for the trimethoprim/sulfamethoxazole-resistant *S. pneumoniae* isolates from the US (Table 4). At the sponsor-proposed susceptible breakpoint, 81.7% of the trimethoprim/sulfamethoxazole-resistant *S. pneumoniae* isolates were susceptible to amoxicillin/clavulanic acid while at the current susceptible breakpoint of 2 µg/mL (for Augmentin 4:1) 68.4% of the isolates were susceptible to amoxicillin/clavulanic acid.

The MIC_{90}s for the trimethoprim/sulfamethoxazole-resistant isolates from all geographic regions (Table 4) were identical to those for the US (Table 4). Among the trimethoprim/sulfamethoxazole-resistant isolates from all geographic locations, 88.1% were susceptible to amoxicillin/clavulanic acid at the sponsor-proposed susceptible breakpoint. Again, 76.8% of the erythromycin-resistant isolates were susceptible to amoxicillin/clavulanic acid at the current susceptible breakpoint.

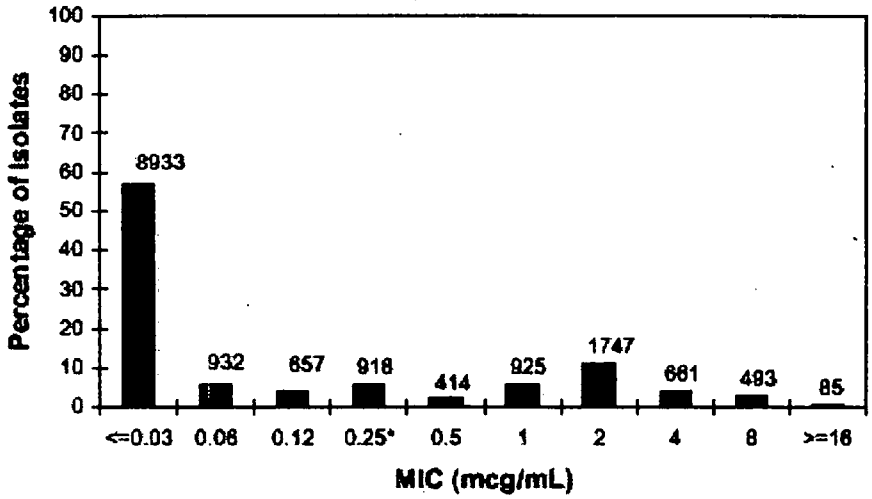
The amoxicillin/clavulanic acid data from Table 4 above are presented below in bar graphs for *S. pneumoniae* from all six surveillance studies combined (AGSS, Alexander Project, ISS, Alert, CMI, and CAST). The data from the US and all geographic regions respectively are presented in Figure 1 and Figure 2. The data for penicillin resistant isolates from the US and all geographic regions respectively are presented in Figure 3 and Figure 4. The data for erythromycin (macrolide)-resistant isolates from the US and all geographic regions are presented in Figure 5 and Figure 6, respectively. The data for trimethoprim/sulfamethoxazole-resistant isolates from the US and all geographic regions respectively are presented in Figure 7 and Figure 8.

Figure 1. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pneumoniae* from surveillance studies - US (n = 6,840)



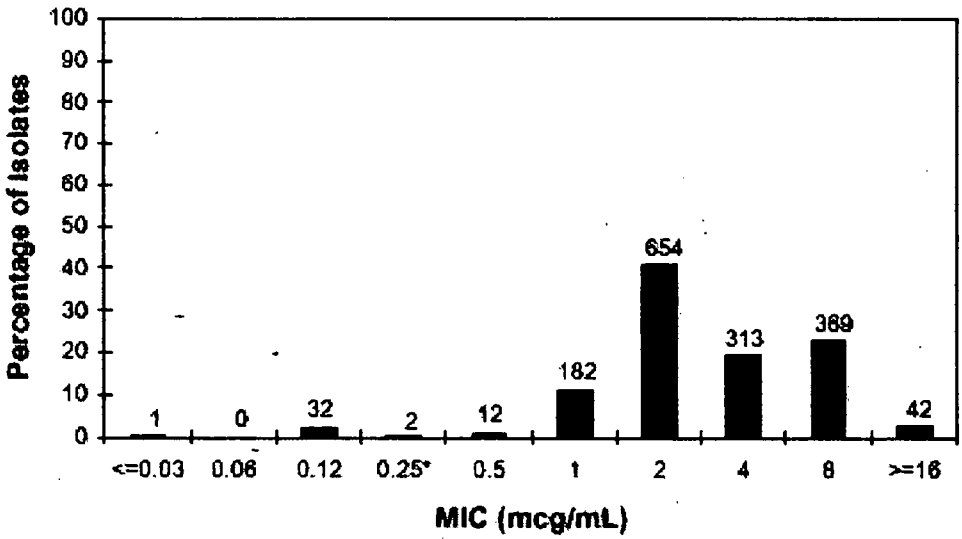
* Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are lower.

Figure 2. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pneumoniae* from surveillance studies – all geographic region (n = 15,765)



* Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are lower

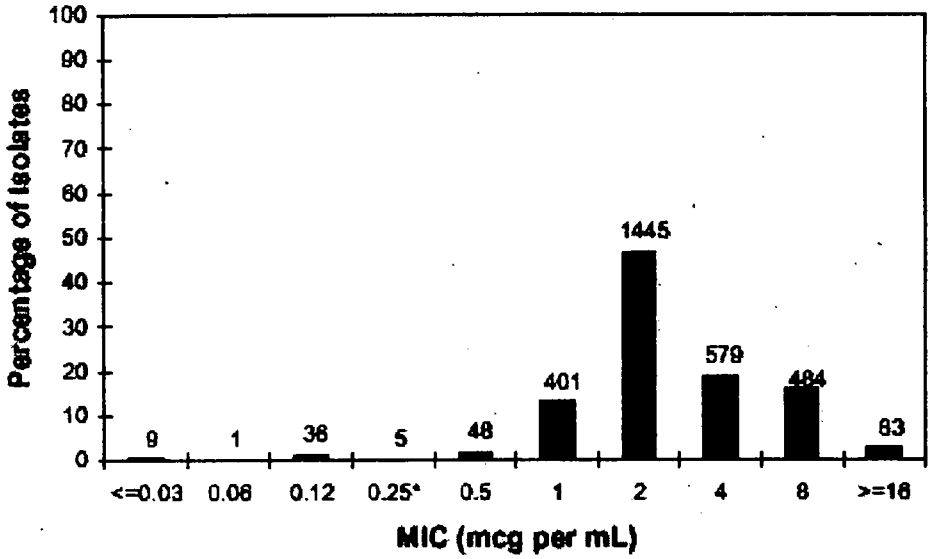
Figure 3. Frequency distribution of amoxicillin/clavulanic acid MICs for penicillin-resistant *S.*



pneumoniae from surveillance studies – US (n = 1,607)

* Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are lower

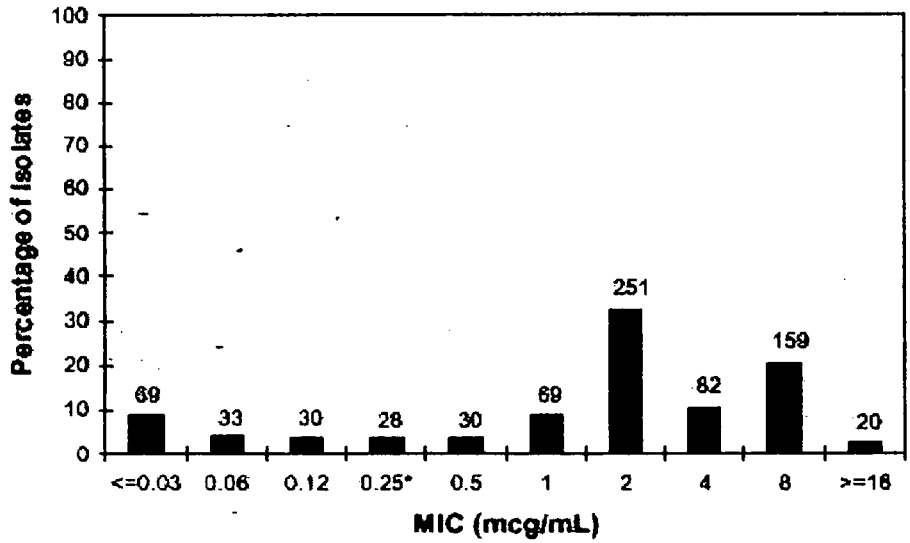
Figure 4. Frequency distribution of amoxicillin/clavulanic acid MICs for penicillin-resistant *S.*



pneumoniae from surveillance studies – all geographic regions (n = 3,091)

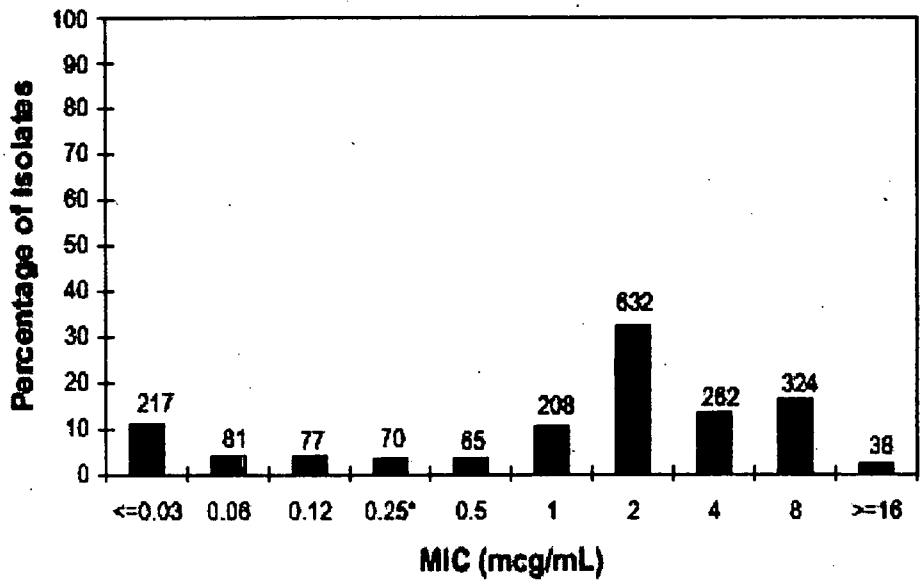
* Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are lower

Figure 5. Frequency distribution of amoxicillin/clavulanic acid MICs for macrolide-resistant (erythromycin MIC =1 mcg/mL) *S. pneumoniae* from surveillance studies– US (n = 771)



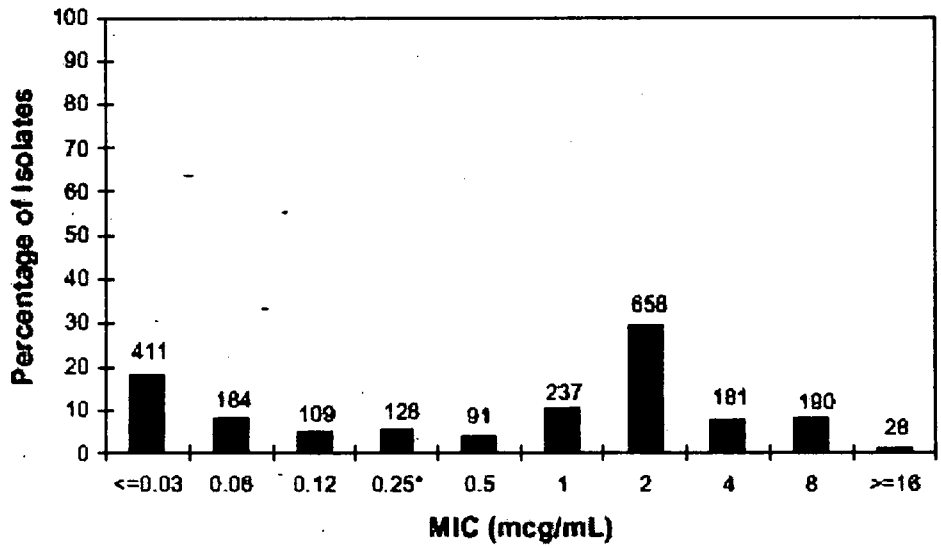
* Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are lower

Figure 6. Frequency distribution of amoxicillin/clavulanic acid MICs for macrolide-resistant (erythromycin MIC =1 mcg/mL) *S. pneumoniae* from surveillance studies- all geographic region (n = 2,217)



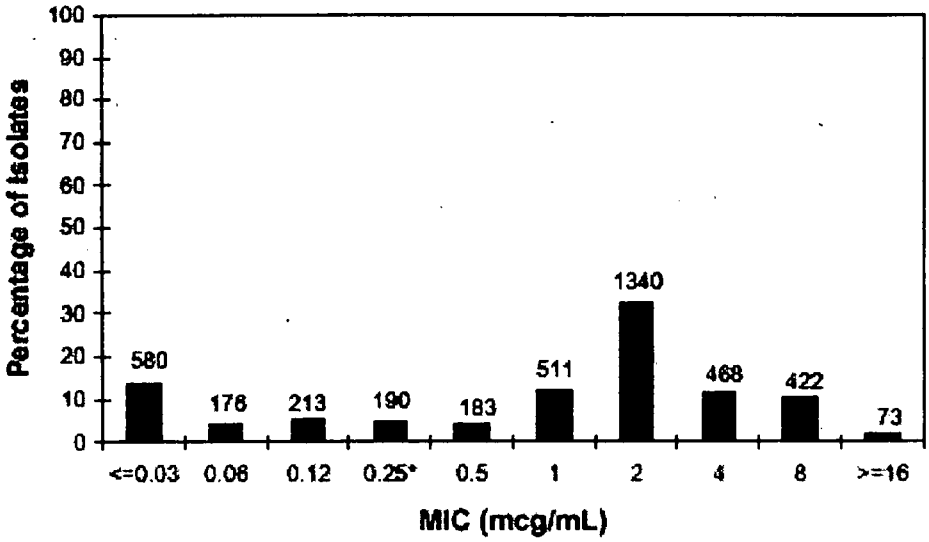
* Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are lower

Figure 7. Frequency distribution of amoxicillin/clavulanic acid MICs for trimethoprim/ sulfamethoxazole-resistant *S. pneumoniae* from surveillance studies –US (n = 1,974)



* Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are lower.

Figure 8. Frequency distribution of amoxicillin/clavulanic acid MICs for trimethoprim/ sulfamethoxazole-resistant *S. pneumoniae* from surveillance studies –all geographic regions (n = 4,156)



* Due to the variation in concentration ranges tested among the studies, isolates reported at this MIC might have MIC values that are lower

From frequency distribution tables and bar graphs it is clear that the US and non-US *S. pneumoniae* isolates behave similarly against amoxicillin/clavulanic acid. Whether the isolates are penicillin-resistant or macrolide-resistant or trimethoprim/sulfamethoxazole-resistant the bimodal distribution against amoxicillin/clavulanic acid is similar. The *S. pneumoniae* population distribution seems to be bimodal and the two populations generally split at amoxicillin/clavulanic acid MIC of 1 μg/mL.

2. Pharmacokinetic and Pharmacodynamic Studies

2.1 Human Studies

Three clinical pharmacokinetic studies were conducted with the Augmentin — formulation. Study 553 was a study to determine food effect in 25 patients. Study 558 was a relative bioavailability study in 11 patients and study 583 was a drug-drug interaction study in 19 patients.In these studies the pharmacokinetics of amoxicillin and clavulanate were determined following a single oral administration of Augmentin — at the start of a standard meal. Each subject received two tablets each containing — mg amoxicillin trihydrate and 62.5 mg clavulanate ——— mg —— sodium amoxicillin ——— formulated with — xanthan gum and — citric acid [9,10,11].

Mean pharmacokinetic parameters for amoxicillin following administration of Augmentin — in the three single dose pharmacokinetic studies were pooled and are presented in Table 5. The mean plasma concentration-time profile for amoxicillin suggested the presence of a secondary absorption phase arising from the sustained release component (Figure 9). Maximum plasma concentrations corresponded to the immediate release component and were observed at around 1 to 1.5 hours after dosing. On average, the sustained plasma concentrations resulted in T>MIC for MIC of 4 μg/mL exceeding 49% of the dosing interval. For a MIC of 8 μg/mL, the T>MIC exceeded 35% of the 12-hour dosing interval. Between-subject variability for the amoxicillin component was generally less than 25%.

The mean plasma concentration-time profile and corresponding pharmacokinetic parameters for clavulanate (Figure 10 and Table 5) were consistent with those normally observed following administration of conventional Augmentin.

Table 5. Summary of Pharmacokinetic Parameters [Arithmetic Mean (SD)] for Amoxicillin and Clavulanate following a Single Oral Dose of Augmentin — (2000/125 mg amoxicillin/clavulanate) to Healthy Volunteers [pooled data, n=55]

Parameter (units)	Amoxicillin	Clavulanate
AUC(0-inf) (mcg.h/mL)	71.6 (16.5)	5.29 (1.55)
Cmax (mcg/mL)	17.0 (4.0)	2.05 (0.799)
Tmax (hours)[a]	1.50 —	1.03 —
T1/2 (hours)	1.27 (0.20)	1.03 (0.17)
T>MIC (hours)[b]	5.9 (1.2)	ND[c]
T>MIC (%)[b]	49.4 (10.2)	ND

[a] median (range)
[b] Time above MIC for a MIC of 4 mcg/mL
[c] ND – not determined

Figure 9. Mean plasma concentration-time profile for amoxicillin following oral administration of Augmentin — [pooled data, n=55]

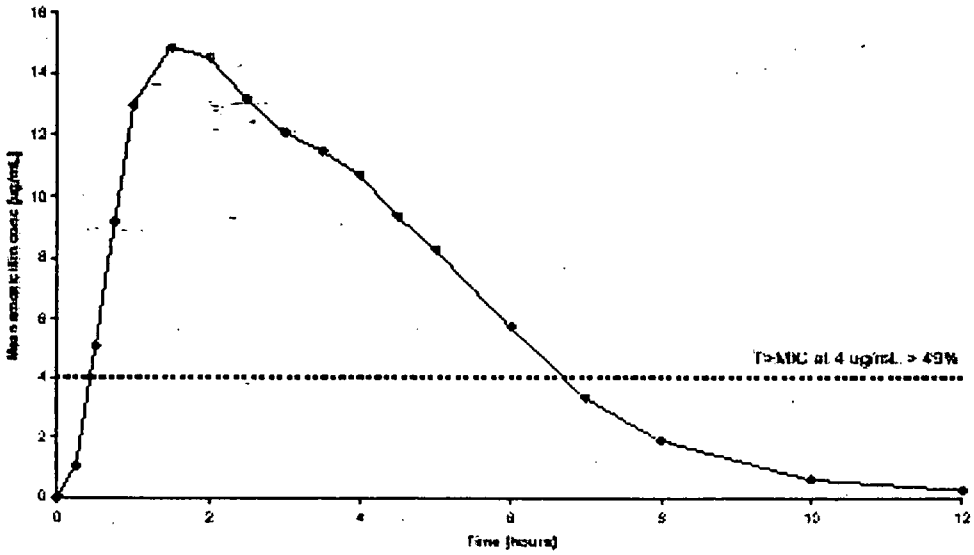
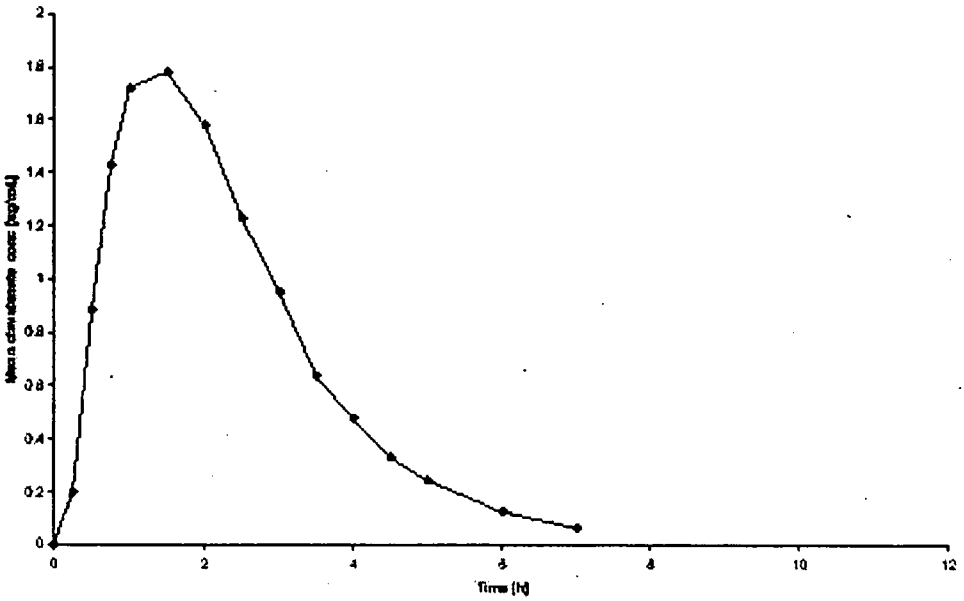


Figure 10. Mean plasma concentration-time profile for clavulanate following oral administration of Augmentin — [pooled data, n=55]



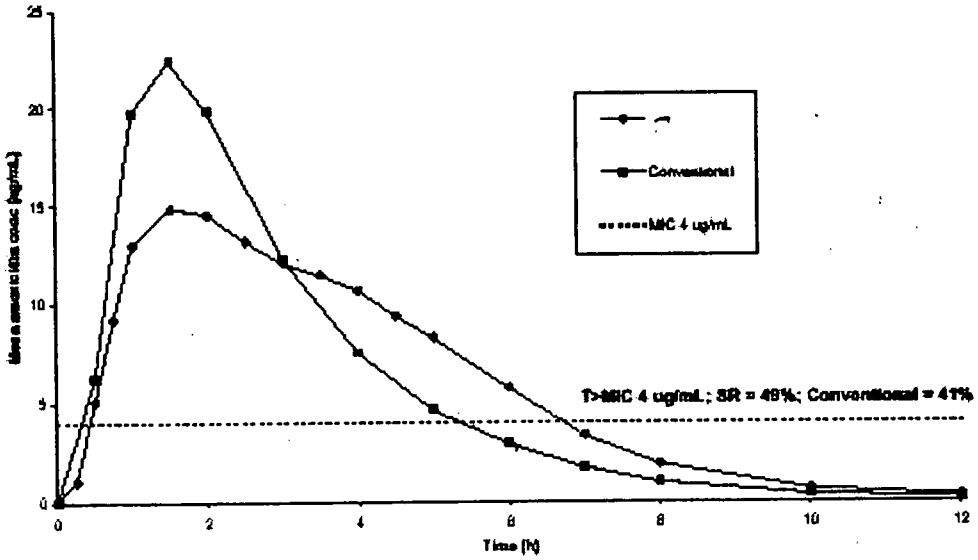
Although the overall plasma concentration-time profile of amoxicillin is extended due to the sustained release component, the underlying elimination is the same as that for immediate release amoxicillin, approximately 1 hour. As with immediate release amoxicillin, plasma concentrations at the end of the dosing interval are negligible. Consistent with the short elimination half-life, notable accumulation would not be predicted following twice daily repeated administration of sustained release Augmentin. This is supported by predicted accumulation ratios based on single dose data of around unity [9].

When the systemic exposure to both amoxicillin and clavulanate is taken into consideration Augmentin — is optimally administered at the start of a meal [9].

Dose proportionality of the sustained release product has not been conducted. However, the sponsor is of the opinion that the sustained release amoxicillin component will exhibit dose proportionality over a similar dose range to the immediate release product.

The sponsor has made a direct comparison of the pharmacokinetics of a dose of Augmentin IR (conventional) equivalent to that of Augmentin — . The direct comparison shows that Augmentin — achieved an amoxicillin T>MIC of 49% for a MIC of 4 µg/mL, where as Augmentin IR achieved an amoxicillin T>MIC of 41% for a MIC of 4 µg/mL (Figure 11) [10].

Figure 11. Mean plasma concentration-time profile for amoxicillin following oral administration of Augmentin — and of conventional Augmentin (625mg) plus 1.5 g amoxicillin



2.2 Animal Studies

Sustained release formulations designed for man are unlikely to demonstrate the same pharmacokinetic characteristics in rats. Thus, for the experiments described below, a method of infusing antibiotics to accurately simulate the concentrations measured in man following therapeutic administration was used. According to the sponsor this provided a better correlation to therapy in man compared with studies using normal animal kinetics [12,13,14,15,16].

The comparative efficacies of Augmentin — Augmentin conventional 7:1 bid and tid, and Augmentin 8:1 tid were examined against experimental lung infections in rats caused by strains of *S. pneumoniae* (recent clinical isolates, with amoxicillin MICs of 2.0, 4.0, and 8.0 µg/mL). Compounds were dosed as continuous infusions designed to stimulate in rat plasma, the concentration-versus-time curve obtained in human serum following oral administration of either 2000/125mg amoxicillin/clavulanate (16:1 bid), 875/125mg amoxicillin/clavulanate (7:1 tid and bid), 1000/125 mg amoxicillin/clavulanate (8:1 tid), and 500/125 mg amoxicillin/clavulanate (4:1 tid). Dosing continued for 3 days and 14h after cessation of therapy the animals were euthanised and the lungs were removed aseptically for bacteriological assessment.
A comparison of concentrations (mean ± standard deviation) of amoxicillin and clavulanate, in the plasma of rats with the actual concentrations of the agents obtained in man after oral administration of therapeutic doses, revealed that in general, the simulated concentrations

measured in rat plasma are similar to the concentrations measured in human plasma. The analyses of these data are presented in the next section of this review.

3. In Vivo Efficacy Studies

3.1 Animal Studies

Table 6 shows the efficacy of amoxicillin/clavulanate dosed to simulate an Augmentin — 2000/125mg 16:1 bid human PK profile (AUG —) in comparison with Augmentin 500/125mg tid (AUG 4:1) against experimental RTI in rats caused by strains of *S. pneumoniae* with amoxicillin MICs of 2.0 and 4.0 µg/mL. The data demonstrate that AUG — was efficacious against both strains of *S. pneumoniae* and that the effect obtained with AUG — administered twice daily, was significantly better than Augmentin 500/125mg AUG 4:1 dosed three times daily [12].

Table 6. Efficacy of Augmentin — and Augmentin 4:1 against RTI caused by *S. pneumoniae* in rats

Strain	Amoxicillin MIC (µg/mL)	$\log_{10}$ cfu/lungs		
		Non-treated Control (NTC)	AUG 4:1	AUG —
S. pneumoniae 05010S	2	7.3±0.4	3.1±1.3*	≤1.7*£
S. pneumoniae 16001S	4	7.0±0.8	4.5±0.8*	2.8 ±1.2*£

*Significantly different from NTC ($p \leq 0.01$)
£Significantly different from AUG 4:1 ($p \leq 0.05$)

Further studies were undertaken comparing the efficacy of Augmentin — with other Augmentin formulations in the rat respiratory tract infection model caused by *S. pneumoniae* strains with amoxicillin MICs of 4.0 and 8.0 µg/mL. For convenience, the agents were referred to as AUG —, AUG 7:1 bid, AUG 7:1 tid and AUG 8:1 tid, respectively. Following infection with *S. pneumoniae* 16001S (amoxicillin MIC = 4.0 µg/mL) bacterial numbers in saline treated infected control animals were 5.7 ± 1.2 $\log_{10}$ cfu/lungs. With the exception of AUG 7:1 bid, all therapies were significantly ($p \leq 0.05$) effective compared with untreated controls. AUG — was significantly better than AUG 7:1 bid (2.2 ± 0.8 Vs 4.5 ± $\log_{10}$ cfu/lungs, $p \leq 0.01$). AUG 7:1 tid and AUG 8:1 tid also showed good effect and bacterial numbers were similar to AUG — (3.0 ± 1.3 and 2.8 ± 0.5 $\log_{10}$ cfu/lungs, respectively; $p > 0.05$).

Bacterial numbers isolated from the lungs of control animals infected with *S. pneumoniae* 30005S (Amoxicillin MIC = 4.0 µg/mL) were 7.1 ± 0.7 $\log_{10}$ cfu/lungs. AUG —, AUG 7:1 tid and AUG 8:1 tid produced a marked effect and a 4.5-5 log reduction in bacterial numbers, compared with saline treated animals, was obtained (2.3 ± 0.9, 2.1 ± 0.7, and 2.7 ± 1.3 $\log_{10}$ cfu/lungs, respectively; $p \leq 0.01$). AUG 7:1 bid produced a marginal effect with counts < 1 log

lower than saline treated controls (5.6 ± 1.3 and 5.7 ± 0.8 log $_{10}$ cfu/lungs, respectively; $p \leq 0.01$). AUG ⟵ was significantly ($p \leq 0.01$) more effective than AUG 7:1 bid.

AUG ⟵ was efficacious against infection caused by *S. pneumoniae* 20009S (amoxicillin MIC = 4.0 µg/mL) producing approximately 4.5 log reduction in bacterial numbers compared with saline treated controls (2.5 ± 0.9 and 7.1 ± 0.4 log $_{10}$ cfu/lungs, respectively; $p \leq 0.01$). The effect obtained with AUG ⟵ was similar ($p > 0.05$) to that seen with AUG 7:1 tid and AUG 8:1 tid (3.2 ± 0.4 and 3.3 ± 0.7 log $_{10}$ cfu/lungs, respectively). In contrast, AUG ⟵ was significantly ($p \leq 0.01$) more effective than AUG 7:1 bid (5.2 ± 0.7 log $_{10}$ cfu/lungs).

In summary, amoxicillin/clavulanate dosed to simulate a Augmentin ⟵ human pharmacokinetic profile (2000/125mg 16:1 bid) was highly effective against all three strains of *S. pneumoniae* having in vitro MIC of 4.0 µg/mL to amoxicillin. Further, the effect obtained with ⟵ was similar to 875/125mg amoxicillin/clavulanate (7:1 tid), 1000/125mg amoxicillin/ clavulanate (8:1 tid) and significantly more effective than 875/125mg amoxicillin/clavulanate (7:1 bid).

Following infection with *S. pneumoniae* 05003S (amoxicillin MIC=8.0 µg/mL) bacterial numbers in saline treated infected control animals were 6.4 ± 0.6 log $_{10}$ cfu/lungs. With the exception of AUG 7:1 bid, all therapies were significantly ($p \leq 0.01$) effective compared with saline treated controls. AUG ⟵ was significantly better than AUG 7:1 bid, AUG 8:1 tid and AUG 7:1 tid (2.0 ± 0.9, 6.3 ± 0.7 and 4.9 ± 0.5 and 5.2 ± 0.8 log $_{10}$ cfu/lungs, respectively, $p \leq 0.01$).

Bacterial numbers isolated from the lungs of animals infected with *S. pneumoniae* 404053 (amoxicillin MIC=8.0µg/mL) were 6.8 ± 0.4 log $_{10}$ cfu/lungs. AUG ⟵, was effective and produced approximately 3-log reduction in bacterial numbers (3.75 ±1.4 log $_{10}$ cfu/lungs, $p \leq 0.01$). The effect achieved with ⟵ was better than the effects achieved with AUG 7:1 bid, AUG 7:1 tid, and AUG 8:1 tid (6.4 ± 0.7, 6.6 ± 1.3, and 6.4 ± 0.6 log $_{10}$ cfu/lungs respectively, $p \leq 0.01$), all of which had similar ($p \geq 0.05$) bacterial counts to saline treated controls.

Augmentin ⟵ was effective against infection caused by *S. pneumoniae* 47003S (amoxicillin MIC = 8.0 µg/mL) and approximately 4-log reduction in bacterial numbers was obtained compared with saline treated controls (1.8 ± 0.2 and 6.0 ± 0.3 log $_{10}$ cfu/lungs respectively, $p \leq 0.01$). AUG 7:1 bid, AUG 8:1 tid, and AUG 7:1 tid produced poor effects and were significantly less effective ($p \leq 0.01$) than AUG ⟵ (5.5 ± 0.42, 4.7 ± 0.7, and 4.9 ± 0.4 log$_{10}$ cfu/lungs respectively).

To summarize, amoxicillin/clavulanate dosed to simulate an Augmentin ⟵ human pharmacokinetic profile (2000/125mg 16:1 bid) was effective against all three strains of *S. pneumoniae* having amoxicillin MIC of 8.0 µg/mL. Further, AUG ⟵ showed statistically significant improvements over 875/125mg amoxicillin/clavulanate (7:1 tid), 1000g/125mg amoxicillin/ clavulanate (8:1 tid), and 875/125mg amoxicillin/clavulanate (7:1 bid).

The time for which concentrations are above the MIC (T>MIC) is the pharmacodynamic parameter which has been demonstrated to correlate most closely with efficacy for beta-lactam antibiotics [17]. For amoxicillin it has been demonstrated that a value of approximately 35-40% correlates with a good clinical and bacteriological outcome. The T>MIC values for the Augmentin formulations simulated in these studies are shown in Table 7 and these data reflect the efficacy seen against the strains of *S. pneumoniae* tested with amoxicillin MICs of 2.0-8.0 µg/mL.

Table 7. Time above MIC for simulated amoxicillin/clavulanate doses

		T>MIC* for an MIC (µg/mL) of:		
Dose	**Frequency**	**2**	**4**	**8**
AUG —	Bid	15.4 (64%)	12.0 (50%)	9.1 (38%)
AUG 7:1	Bid	9.6 (40%)	7.2 (30%)	4.3 (18%)
AUG 7:1	Tid	14.4 (60%)	10.8 (45%)	6.5 (27%)
AUG 8:1	Tid	16.2 (68%)	11.5 (48%)	7.4 (31%)

* T>MIC, h/24h (% of 24h)

1.2 Human Studies

The clinical program to evaluate the efficacy of Augmentin — in the treatment of ABS, CAP — consists of five randomized, double blind, controlled clinical studies (Studies 550, 546, 556, 548 and 549). The primary efficacy parameter in the controlled ABS study (Study 550) was combined clinical and radiological response at test of cure. The primary efficacy parameter in the controlled lower respiratory tract infection (LRTI) studies (CAP Studies 546 and 556, — Studies 548 and 549) was clinical response at test of cure.

In addition to the controlled studies, a single uncontrolled Phase III ABS study (Study 551) and the prospectively planned interim analysis from a single uncontrolled Phase III CAP study (Study 547) are also included. The primary efficacy parameter in these uncontrolled studies was per patient bacteriological response (success or failure) at test of cure.

To provide further support for the proof of efficacy of Augmentin — in the treatment of upper respiratory tract infections due to penicillin resistant *S. pneumoniae*, data from an uncontrolled clinical study with Augmentin ES (14:1) suspension conducted in pediatric patients with acute

otitis media (AOM) due to penicillin resistant *S. pneumoniae* (Study 536) have been combined with data from ABS Study 551, (as agreed at the 17 June 1999 and 06 June 2000 meetings between SB and the Division). Study 536 is being used to support the amoxicillin/clavulanic acid breakpoints for *S. pneumoniae* for Augmentin — Data from Study 536 are also used in the Integrated Summary of Efficacy to support efficacy against PRSP.

The sponsor states that the data from Study 536 are considered supportive for efficacy against PRSP and the breakpoint determination for Augmentin — because the T>MIC for an MIC of 4.0 µg/mL following oral administration of Augmentin ES suspension (46.0% ± 10.4%) in pediatric patients (at a dose of 90/6.4mg/kg/day) is similar to values obtained following oral administration of Augmentin — to adults (49.0% ± 10.2%). Therefore, at an MIC of 4 µg/mL, the predicted efficacy from the pharmacodynamic profile of Augmentin ES would be similar to Augmentin — formulation [9,10,11] and thus the bacteriological outcome in the pediatric AOM study 536 may be considered as supportive of the efficacy of Augmentin —

Four patient populations were defined for the analysis of clinical, combined clinical and radiological (ABS Study 550) and bacteriological efficacy as follows:

- **ITT:** All randomized/enrolled (uncontrolled studies) patients who took at least one dose of study medication.
- **Clinical PP:** This population excluded patients who violated any aspect of the protocol to an extent that may affect treatment efficacy. The Clinical PP population was a subset of the ITT population.
- **Bacteriology ITT:** All randomized/enrolled (uncontrolled studies) patients who took at least one dose of study medication and had at least one pre-therapy pathogen identified at screening (in CAP studies this had to be non-atypical pathogen).
- **Bacteriology PP:** This population excluded patients who violated any aspect of the protocol to an extent that may affect treatment efficacy. The Bacteriology PP population was a subset of the Bacteriology ITT population, i.e. all patients in this population had at least one pre-therapy pathogen identified at screening (in CAP studies this had to be non-atypical pathogen).

Clinical response at test of cure, which was based on the resolution of clinical signs and symptoms of the disease under study, was determined from the following clinical outcomes:

- **Clinical Success:** Sufficient resolution of signs and symptoms of the disease under study for patients who were clinical successes at the end of therapy visit, such that no additional antibacterial therapy was required.
- **Clinical Recurrence:** Reappearance or worsening of signs and symptoms of the disease under study for patients who were clinical successes at the end of therapy, such that additional antibacterial therapy was required.
- **Unable to Determine:** An assessment of clinical outcome could not be made (e.g., the patient was lost to follow-up).

Patients whose clinical outcome was "unable to determine" were to be excluded from the PP population. Therefore, a response of failure in the PP analysis consisted of outcomes of clinical failure at end of therapy or clinical recurrence at test of cure. In the ITT analysis, patients with a clinical outcome of "unable to determine" at end of therapy were carried forward to test of cure as failures, as were outcomes of clinical failure at end of therapy. Patients who were clinical failures at end of therapy, but who subsequently became protocol violators at the test of cure visit were included as failures in the test of cure PP population because they satisfied the criteria for being included in the test of cure failure group prior to violating the protocol.

For the primary endpoint of ABS Study 550, an independent assessor (e.g., radiologist) assessed the patient's radiological outcome based upon the comparison of the sinus X-ray (Water's view) or coronal CAT scan performed at the preliminary visit and at the test of cure visit (or at time of withdrawal) according to the following categories:

- **Improved:** Improvement or resolution of radiological signs of ABS
- **Unchanged:** No improvement in the baseline radiological signs of ABS
- **Worse:** Worsening of the baseline radiological signs of ABS, or the appearance of new radiological signs of ABS.
- **Unable to Determine:** A valid assessment of radiological outcome could not be made (e.g., the patient was lost to follow up)

From these categories the combined clinical and radiological response was defined as:

- **Success:** The clinical response at test of cure was "success" and the radiological outcome was "improved" or "unchanged."
- **Failure:** The clinical outcome at end of therapy was "Failure" or the clinical outcome at test of cure was "Recurrence" and/or the radiological outcome at test of cure was "Worse"
- **Unable to Determine:** Either the clinical outcome at end of therapy or test of cure was "Unable to Determine" and the radiological outcome at test of cure was "Improved", "Unchanged" or "Unable to Determine" or the clinical outcome at test of cure was "Success" and the radiological outcome was "Unable to Determine"

The sponsor evaluated bacteriological response after the patient had completed the study. For each initial pathogen identified in an evaluable sputum sample, sinus culture or invasive respiratory sample at the screening visit, the per pathogen bacteriological outcome at end of therapy was categorized as follows:

- **Bacteriological Eradication:** The elimination of the initial pathogen from an evaluable repeat sputum sample, sinus culture or invasive respiratory sample taken at end of therapy.
- **Presumed Bacteriological Eradication:** In the absence of a repeat sputum sample, sinus culture or invasive respiratory sample, or if the repeat sputum sample, sinus culture or invasive respiratory sample did not meet the evaluability criteria, eradication was presumed if the patient's clinical outcome was a clinical success.
- **Bacteriological Persistence:** Presence of the original pathogen in an evaluable repeat sputum sample, sinus culture or invasive respiratory sample at end of therapy.

- **Presumed Bacteriological Persistence:** In the absence of a repeat sputum sample, sinus culture or invasive respiratory sample, or if the repeat sputum sample, sinus culture or invasive respiratory sample did not meet the evaluability criteria, persistence was presumed if the patient's clinical outcome was a clinical failure.
- **Unable to Determine:** An assessment of bacteriological outcome could not be made.

For each initial pathogen identified at the Screening visit, which was eradicated or presumed eradicated at the end of therapy visit, the test of cure bacteriological outcome was categorized as follows:

- **Bacteriological Eradication:** The continued absence of the initial pathogen at test of cure.
- **Presumed Bacteriological Eradication:** Inability to obtain a repeat sputum, sinus culture or invasive respiratory sample because of clinical improvement. The patient was a clinical success at the test of cure visit.
- **Bacteriological Failure:** The pathogen was eradicated or presumed eradicated at the end of therapy but recurred in an appropriate respiratory sample at test of cure, or the pathogen was persistent at end of therapy.
- **Presumed Bacteriological Failure:** No repeat sputum, sinus culture or invasive respiratory sample was obtained and the patient was a clinical recurrence.
- **Unable to Determine:** An assessment of bacteriological outcome could not be made at either end of therapy or test of cure.

New pathogens identified at test of cure were categorized as follows:

- **New Infection:** A new pathogen was identified at test of cure in a symptomatic patient requiring additional antibacterial therapy for the disease under study, i.e., a clinical recurrence.
- **Colonization:** A new pathogen was identified at test of cure in a non-symptomatic patient who did not require additional antibacterial therapy for the disease under study, i.e., a test of cure clinical success.

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

- **Success:** All initial pathogens were eradicated or presumed eradicated at the test of cure assessment, without any new infections, with or without colonization.
- **Failure:** Failure or presumed failure of one or more of the initial pathogens at the test of cure assessment, a new infection, an assessment of "unable to determine" for one or more initial pathogens, or the bacteriological response at the end of therapy visit was "failure".

Patients with one or more initial pathogen outcomes of "unable to determine" were excluded from the Bacteriology PP population. Patients who were bacteriological failures at end of therapy, but who subsequently became protocol violators at the test of cure visit, were to be included as failures in the PP population at test of cure because they had satisfied the criteria for being included in the test of cure failure group prior to violating the protocol.

3.2.1. Summary of Clinical and Bacteriological Response by Indication

3.2.1.1. Acute Bacterial Sinusitis

Clinical Efficacy

Among Bacteriology ITT patients in all geographic regions who were treated with Augmentin — for ABS in Study 551, the most common individual pathogen isolated was *S. pneumoniae* (112 isolates). The majority (96.4%) of amoxicillin/clavulanic acid MICs for *S. pneumoniae* were ≤ 2.0 µg/mL, with the exception of four isolates with an MIC of 8.0 µg/mL.

The clinical success rate at the test of cure in all geographic regions for patients with ABS caused by *S. pneumoniae* was 92.0%. All four isolates of *S. pneumoniae* with amoxicillin/ clavulanic acid MICs of 8.0 µg/mL were associated with clinical success.

Similar clinical success rates were observed among Bacteriology ITT patients in the US with ABS caused by *S. pneumoniae* (90.9%).

A summary of clinical efficacy at test of cure by amoxicillin/clavulanic acid MICs is presented in Table 8 for *S. pneumoniae* in the Bacteriology ITT population for patients treated with Augmentin — for ABS, for all geographical regions combined and for the US.

Bacteriological Outcome

As few patients underwent repeat sinus puncture, bacteriological outcome in most cases was based on clinical outcome. Therefore, bacteriological outcome results are similar to the clinical results. The overall bacteriological eradication rate for patients in all geographic regions with ABS caused by *S. pneumoniae*, was 92.9%. All four *S. pneumoniae* isolates with a MIC of 8.0 µg/mL were eradicated.

Similar bacteriological eradication rates were observed among Bacteriology ITT patients in the US with ABS caused by *S. pneumoniae* (90.9%).

A summary of bacteriological outcome at test of cure by amoxicillin/clavulanic acid MICs is presented in Table 9 for *S. pneumoniae* in the Bacteriology ITT population for patients treated with Augmentin —for ABS, for all geographical regions combined and for the US.

Table 8. Clinical Efficacy at Test of Cure by Amoxicillin/Clavulanic Acid MICs - Patients with Acute Bacterial Sinusitis (Bacteriology ITT Population)

	Augmentin — (10 days) (All geographical regions)						Augmentin — (10 days) (US)					
	Success		Failure		Unable To Determine**		Success		Failure		Unable to Determine**	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	103/112	(92.0)	4/112	(3.6)	5/112	(4.5)	40/44	(90.9)	3/44	(6.8)	1/44	(2.3)
≤ 0.015	14/16	(87.5)	1/16	(6.3)	1/16	(6.3)	5/6	(83.3)	0/6		1/6	(16.7)
0.03	64/69	(92.8)	2/64	(2.9)	3/69	(4.3)	19/21	(90.5)	2/21	(9.5)	0/21	
0.06	6/6	(100)	0/6		0/6		3/3	(100)	0/3		0/3	
0.12	4/4	(100)	0/4		0/4		2/2	(100)	0/2		0/2	
0.25	2/3	(66.7)	0/3		1/3	(33.3)	1/1	(100)	0/1		0/1	
0.5	2/2	(100)	0/2		0/2		2/2	(100)	0/2		0/2	
1	2/3	(66.7)	1/3	(33.3)	0/3		0/1		1/1	(100)	0/1	
2	5/5	(100)	0/5		0/5		4/4	(100)	0/4		0/4	
8	4/4	(100)	0/4		0/4		4/4	(100)	0/4		0/4	

* n/ N= number of patients with a specified response/ number of patients with a pathogen with the specified MIC.
** Unable to Determine includes Unable to Determine and missing outcomes at End of Therapy and Test of Cure.
[b] µg/ mL. Amoxicillin/ clavulanic acid was tested at a 2: 1 ratio; MICs are expressed in terms of the amoxicillin concentration.

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Table 9. Bacteriological Outcome at Test of Cure by Amoxicillin/Clavulanic Acid MICs - Patients with Acute Bacterial Sinusitis (Bacteriology ITT Population)

	Augmentin — (10 days) (All geographical regions)						Augmentin — (10 days) (US)					
	Success		Failure		Unable To Determine**		Success		Failure		Unable to Determine**	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	104/112	(92.9)	3/112	(2.7)	5/112	(4.5)	40/44	(90.9)	3/44	(6.8)	1/44	(2.3)
≤ 0.015	15/16	(93.8)	0/15		1/15	(6.3)	5/6	(83.3)	0/6		1/6	(16.7)
0.03	64/69	(92.8)	2/69	(2.9)	3/69	(4.3)	19/21	(90.5)	2/21	(9.5)	0/21	
0.06	6/6	(100)	0/6		0/6		3/3	(100)	0/3		0/3	
0.12	4/4	(100)	0/4		0/4		2/2	(100)	0/2		0/2	
0.25	2/3	(66.7)	0/3		1/3	(33.3)	1/1	(100)	0/1		0/1	
0.5	2/2	(100)	0/2		0/2		2/2	(100)	0/2		0/2	
1	2/3	(66.7)	1/3	(33.3)	0/3		0/1		1/1	(100)	0/1	
2	5/5	(100)	0/5		0/5		4/4	(100)	0/4		0/4	
8	4/4	(100)	0/4		0/4		4/4	(100)	0/4		0/4	

* n/ N= number of patients with a specified response/ number of patients with a pathogen with the specified MIC.
** Unable to Determine includes Unable to Determine and missing outcomes at End of Therapy and Test of Cure.
[b] Amoxicillin/ clavulanic acid was tested at a 2: 1 ratio; MICs are expressed in terms of the amoxicillin concentration.

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3.2.1.2 Community Acquired Pneumonia

Clinical Efficacy

Among Bacteriology PP patients who were treated with Augmentin – for CAP, the most commonly isolated pathogen was *S. pneumoniae* (82 isolates). MICs to amoxicillin/clavulanic acid were ≤ 2.0 µg/mL for most of these isolates except for two from the US region, one each with MICs of 4.0 µg/mL and 8.0 µg/mL.

The clinical success rate for patients in the Bacteriology PP population with CAP caused by *S. pneumoniae* for all geographic regions was 91.5%. The *S. pneumoniae* isolate with a MIC of 4.0 µg/mL was a clinical success. The *S. pneumoniae* isolate with a MIC of 8.0 µg/mL was part of a polymicrobial infection with *K. pneumoniae*, and was a clinical failure and presumed bacteriological failure at the test of cure visit. Clinical success rates among Bacteriology PP patients in the US with CAP were lower (80.0%) for *S. pneumoniae.*

A summary of clinical efficacy at test of cure by amoxicillin/clavulanic acid MICs is presented in Table 10 for *S. pneumoniae* in the Bacteriology PP population for patients treated with Augmentin – for CAP, for all geographical regions combined and for the US.

Table 10. Clinical Efficacy at Test of Cure by Amoxicillin/Clavulanic Acid MICs - Patients with Community Acquired Pneumonia (Bacteriology PP Population)

	Augmentin — (All geographical regions)[a]				Augmentin – (US)[a]			
	Success		Failure		Success		Failure	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	75/82	(91.5)	7/82	(8.5)	16/20	(80.0)	4/20	(20.0)
≤ 0.015	12/13	(92.3)	1/13	(7.7)	4/5	(80.0)	1/5	(20.0)
0.03	51/56	(91.1)	5/56	(8.9)	7/9	(77.8)	2/9	(22.2)
0.06	5/5	(100)	0/5		2/2	(100)	0/2	
0.12	2/2	(100)	0/2					
0.25	1/1	(100)	0/1					
0.5	1/1	(100)	0/1					
2	2/2	(100)	0/2		2/2	(100)	0/2	
4	1/1	(100)	0/1		1/1	(100)	0/1	
8	0/1		1/1	(100)	0/1		1/1	(100)

* n/N = number of patients with a specified response/number of patients with a pathogen with the specified MIC.
[a] Studies 546, 547 and 556.
[b] Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.

Bacteriological Outcome

Bacteriological eradication rates in all geographic regions combined were 91.5% for patients with CAP caused by *S. pneumoniae.* Two *S. pneumoniae* isolates from patients in the

Bacteriology PP population with CAP had an amoxicillin/clavulanic acid MIC of ≥ 4.0 µg/mL. One of the *S. pneumoniae* isolates (MIC = 4.0 µg/mL) was eradicated, and the other isolate (MIC = 8.0 µg/mL) was part of a polymicrobial infection with *K. pneumoniae*, and was a presumed bacteriological failure at the test of cure visit. Bacteriological eradication rates among Bacteriology PP patients in the US with CAP were lower (80.0%) for *S. pneumoniae.*

A summary of bacteriological outcome at test of cure by amoxicillin/clavulanic acid MICs is presented in Table 11 for *S. pneumoniae* in the Bacteriology PP population for patients treated with Augmentin — for CAP, for all geographical regions combined and for the US.

Table 11. Bacteriological Outcome at Test of Cure by Amoxicillin/Clavulanic Acid MICs - Patients with Community Acquired Pneumonia (Bacteriology PP Population)

	Augmentin — (All geographical regions)[a]				Augmentin — (US)[a]			
	Success		Failure		Success		Failure	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	75/82	(91.5)	7/82	(8.5)	16/20	(80.0)	4/20	(20.0)
≤ 0.015	12/13	(92.3)	1/13	(7.7)	4/5	(80.0)	1/5	(20.0)
0.03	51/56	(91.1)	5/56	(8.9)	7/9	(77.8)	2/9	(22.2)
0.06	5/5	(100)	0/5		2/2	(100)	0/2	
0.12	2/2	(100)	0/2					
0.25	1/1	(100)	0/1					
0.5	1/1	(100)	0/1					
2	2/2	(100)	0/2		2/2	(100)	0/2	
4	1/1	(100)	0/1		1/1	(100)	0/1	
8	0/1		1/1	(100)	0/1		1/1	(100)

* n/N = number of patients with a specified response/number of patients with a pathogen with the specified MIC.
[a] Studies 546, 547 and 556.
[b] Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.

Bacteremic Patients

Among Bacteriology PP patients who were treated with Augmentin — for bacteremic CAP, the most commonly isolated pathogen was *S. pneumoniae* (13 isolates). The clinical success rate for the Bacteriology PP population at test of cure in all geographic regions for isolates of *S. pneumoniae* obtained from bacteremic CAP patients was 84.6% (11/13). Bacteriological eradication rates for Bacteriology PP patients with bacteremic CAP were identical to the clinical success rates.

A summary of clinical efficacy/bacteriological eradication rate at test of cure by amoxicillin/clavulanic acid MICs is presented in Table 12 for *S. pneumoniae* in the Bacteriology PP population for patients treated with Augmentin — for bacteremic CAP, for all geographical regions combined and for the US.

Table 12. Clinical Efficacy/Bacteriological Outcome at Test of Cure by Amoxicillin/Clavulanic Acid MICs - Patients with Bacteremic Community Acquired Pneumonia (Bacteriology PP Population)

	Augmentin — (All geographical regions)[a]				Augmentin — (US)[a]			
	Success		Failure		Success		Failure	
S. pneumoniae amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Clinical Efficacy								
Total	11/13	(84.6)	2/13	(15.4)	1/1	(100)	0/1	
≤ 0.015	1/1	(100)	0/1		1/1	(100)	0/1	
0.03	10/12	(83.3)	2/12	(16.7)				
Bacteriological Outcome								
Total	11/13	(84.6)	2/13	(15.4)	1/1	(100)	0/1	
≤ 0.015	1/1	(100)	0/1		1/1	(100)	0/1	
0.03	10/12	(83.3)	2/12	(16.7)				

* n/N = number of patients with a specified response/number of patients with a pathogen with the specified MIC.
[a] Studies 546, 547 and 556.
[b] Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.

3.2.1.3. —

Clinical Efficacy

There were 20 isolates of *S. pneumoniae* recovered from the Bacteriology PP patients in all geographic regions who were treated with Augmentin — for —. The majority of MICs for amoxicillin/clavulanic acid were less than 2.0 µg/mL. Clinical success rate in the Bacteriology PP population at test of cure for all geographic regions was 90.0%. The clinical success rate for *S. pneumoniae* isolates in the US region (75.0%) was lower than in all geographic regions combined, however it should be noted that only eight isolates of *S. pneumoniae* were obtained from US patients with — There was only one *S. pneumoniae* isolated, which had amoxicillin/clavulanic acid MIC of 4.0 µg/mL. This isolate was obtained from a US patient, and was associated with clinical success.

A summary of clinical efficacy at test of cure by amoxicillin/clavulanic acid MICs is presented in Table 13 for *S. pneumoniae* in the Bacteriology PP population for patients treated with Augmentin — for —, for all geographical regions combined and for the US.

Bacteriological Outcome

Bacteriological eradication rate in Bacteriology PP patients in all geographic regions for patients with *S. pneumoniae* was 90.0%. One isolate of *S. pneumoniae* had an amoxicillin/clavulanic acid MIC of 4.0 µg/mL, and was a bacteriological success. In the US Bacteriological eradication rate in Bacteriology PP patients with — were lower (6/8, 75.0%) for *S. pneumoniae.*

A summary of bacteriological outcome at test of cure by amoxicillin/clavulanic acid MICs is presented in Table 14 for *S. pneumoniae* in the Bacteriology PP population for patients treated with Augmentin — for —— for all geographical regions combined and for the US.

Table 13. Clinical Efficacy at Test of Cure by Amoxicillin/Clavulanic Acid MICs - Patients with ———————— (Bacteriology PP Population)

	Augmentin — (7 Days)[a] (All geographical regions)				Augmentin — (7 Days)[a] (US)			
	Success		Failure		Success		Failure	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	18/20	(90.0)	2/20	(10.0)	6/8	(75.0)	2/8	(25.0)
≤ 0.015	2/2	(100)	0/2					
0.03	11/11	(100)	0/11		2/2	(100)	0/2	
0.12	0/1		1/1	(100)	0/1		1/1	(100)
0.25	1/2	(50.0)	1/2	(50.0)	1/2	(50.0)	1/2	(50.0)
0.5	1/1	(100)	0/1					
2	2/2	(100)	0/2		2/2	(100)	0/2	
4	1/1	(100)	0/1		1/1	(100)	0/1	

* n/N = number of patients with a specified response/number of patients with a pathogen with the specified MIC.
[a] Studies 548 and 549 combined
[b] Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.

3.2.1.4. Upper Respiratory Tract Infections

Clinical Efficacy in Patients with *S. pneumoniae*

Among Bacteriology PP patients with upper respiratory tract infections (URTIs) who were treated with Augmentin — for ABS or Augmentin ES (14:1) pediatric suspension for AOM, 247 isolates of *S. pneumoniae* were reported in all geographic regions, and 109 isolates were reported in the US region. MICs to amoxicillin/clavulanic acid were observed in the range of ≤ 0.015 to 8.0 µg/mL.

The total clinical success rate for patients in the Bacteriology PP population with URTIs caused by *S. pneumoniae* in all geographic regions was 93.5%. Among these isolates, four had amoxicillin/clavulanic acid MICs of 4.0 µg/mL. Nine isolates had amoxicillin/clavulanic acid MICs of 8.0 µg/mL. All of the *S. pneumoniae* isolates with a MIC of 4.0 µg/mL were associated with clinical success. Eight of nine isolates (88.9%) with a MIC of 8.0 µg/mL were associated with clinical success. The single *S. pneumoniae* failure came from AOM Study 536. This patient was infected with *S. pneumoniae* and *H. influenzae* at screening. A second tympanocentesis showed eradication of *H. influenzae* and persistence of *S. pneumoniae* at the on therapy visit. Therefore, the patient was classified as a clinical failure at the end of therapy.

Table 14. Bacteriological Outcome at Test of Cure by Amoxicillin/Clavulanic Acid MICs - Patients with ——— (Bacteriology PP Population)

	Augmentin — (7 days)[a] (All geographical regions)						Augmentin — (7 days)[a] (US)					
	Eradication**		Failure**		Unable To Determine		Eradication**		Failure**		Unable to Determine	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	18/20	(90.0)	0/20		2/20	(10.0)	6/8	(75.0)	0/8		2/8	(25.0)
≤ 0.015	2/2	(100)	0/2		0/2							
0.03	11/11	(100)	0/11		0/11		2/2	(100)	0/2		0/2	
0.12	0/1		0/1		1/1	(100)	0/1		0/1		1/1	(100)
0.25	1/2	(50.0)	0/2		1/2	(50.0)	1/2	(50.0)	0/2		1/2	(50.0)
0.5	1/1	(100)	0/1		0/1							
2	2/2	(100)	0/2		0/2		2/2	(100)	0/2		0/2	
4	1/1	(100)	0/1		0/1		1/1	(100)	0/1		0/1	

* n/ N= number of patients with a specified response/ number of patients with a pathogen with the specified MIC.
** Eradication = total eradication (eradication + presumed eradication); Failure = total failure (failure + presumed failure).
a. Studies 548 and 549 combined
b. Amoxicillin/ clavulanic acid was tested at a 2: 1 ratio; MICs are expressed in terms of the amoxicillin concentration.

A similar clinical success rate was observed among Bacteriology PP patients in the US with *S. pneumoniae* as the causative pathogen (90.8%). The single isolate of *S. pneumoniae* with an MIC of 4.0 µg/mL was a clinical success. Seven of eight isolates with a MIC of 8.0 µg/mL (87.5%) were associated with clinical success.

A summary of clinical efficacy by *S. pneumoniae* susceptibility to amoxicillin/clavulanic acid, by MIC, in the Bacteriology PP population for patients treated with Augmentin — (16:1) or Augmentin ES (14:1) for URTIs, for all geographical regions combined and for the US is presented in Table 15.

Table 15. Clinical Efficacy by Screening Pathogen *(S. pneumoniae)* Susceptibility (MIC) to Amoxicillin/Clavulanic Acid: Patients with Upper Respiratory Tract Infections (Bacteriology PP Population)

	Augmentin — (10 Days)[a] (All geographical regions)				Augmentin — (10 Days)[a] (US)			
	Success		Failure		Success		Failure	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	231/247	(93.5)	16/247	(6.5)	99/109	(90.8)	10/109	(9.2)
≤ 0.015	16/17	(94.1)	1/17	(5.9)	5/5	(100)	0/5	
0.03	134/141	(95.0)	7/141	(5.0)	54/60	(90.0)	6/60	(10.0)
0.06	16/16	(100)	0/16		8/8	(100)	0/8	
0.12	9/9	(100)	0/9		4/4	(100)	0/4	
0.25	13/15	(86.7)	2/15	(13.3)	2/2	(100)	0/2	
0.5	4/4	(100)	0/4		4/4	(100)	0/4	
1	4/5	(80.0)	1/5	(20.0)	1/2	(50.0)	1/2	(50.0)
2	23/27	(85.2)	4/27	(14.8)	13/15	(86.7)	2/15	(13.3)
4	4/4	(100)	0/4		1/1	(100)	0/1	
8	8/9	(88.9)	1/9	(11.1)	7/8	(87.5)	1/8	(12.5)

* n/N = number of patients with a specified response/number of patients with a pathogen with the specified MIC.
[a] Studies 551 and 536 combined. Study 551 utilized Augmentin — 2000/125 mg bid. Study 536 utilized Augmentin (14:1) pediatric suspension, 90mg/kg/day in divided doses q12h every 12 hours.
[b] Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.

The range of MIC values observed in the URTI Bacteriology ITT population was similar to the PP population. The clinical success rate in the Bacteriology ITT population for all geographic regions was 84.5%, lower than the PP population. A similar difference was observed in the US region.

Bacteriological Outcome in Patients with *S. pneumoniae*

The total bacteriological eradication rate among the Bacteriology PP population for patients in all geographic regions with URTIs caused by *S. pneumoniae* was 97.6%. All four *S. pneumoniae* isolates with a MIC of 4.0 µg/mL were eradicated. Seven of the nine (77.8%) *S. pneumoniae* isolates with an amoxicillin/clavulanic acid MIC of 8.0 µg/mL were also eradicated.

In the US region, the total bacteriological eradication rate for URTIs with *S. pneumoniae* as the causative pathogen was 95.4%. The single isolate of *S. pneumoniae* with an MIC of 4.0 µg/mL was eradicated, and six of eight isolates with an MIC of 8.0 µg/mL were also eradicated (75.0%).

Both bacteriological failures occurred in AOM Study 536. One patient had *H. influenzae* and *S. pneumoniae* at screening. A second tympanocentesis showed eradication of *H. influenzae* and persistence of *S. pneumoniae* at the on therapy visit. The second bacteriological failure, a patient infected with *S. pneumoniae* alone, failed bacteriologically at the on-therapy visit (outcome of persistence for *S. pneumoniae* at the second tympanocentesis), but was a clinical success at the end of therapy (outcome of improvement).

A summary of bacteriological outcome by *S. pneumoniae* susceptibility to amoxicillin/clavulanic acid, by MIC, in the Bacteriology PP population for patients treated with Augmentin — (16:1) or Augmentin ES (14:1) for URTIs, for all geographical regions combined and for the US, is presented in Table 16.

Table 16. Bacteriology Outcome by Screening Pathogen *(S. pneumoniae)* Susceptibility (MIC) to Amoxicillin/Clavulanic Acid: Patients with Upper Respiratory Tract Infections (Bacteriology PP Population)

	Augmentin — (10 Days)[a] (All geographical regions)				**Augmentin — (10 Days)[a] (US)**			
	Eradication**		**Failure**		**Eradication****		**Failure**	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	241/247	(97.6)	6/247	(2.4)	104/109	(95.4)	5/109	(4.6)
≤ 0.015	17/17	(100)	0/17		5/5	(100)	0/5	
0.03	139/141	(98.6)	2/141	(1.4)	59/60	(98.3)	1/60	(1.7)
0.06	16/16	(100)	0/16		8/8	(100)	0/8	
0.12	9/9	(100)	0/9		4/4	(100)	0/4	
0.25	15/15	(100)	0/15		2/2	(100)	0/2	
0.5	4/4	(100)	0/4		4/4	(100)	0/4	
1	4/5	(80.0)	1/5	(20.0)	1/2	(50.0)	1/2	(50.0)
2	26/27	(96.3)	1/27	(3.7)	14/15	(93.3)	1/15	(6.7)
4	4/4	(100)	0/4		1/1	(100)	0/1	
8	7/9	(77.8)	2/9	(22.2)	6/8	(75.0)	2/8	(25.0)

* n/N = number of patients with a specified response/number of patients with a pathogen with the specified MIC.
** Eradication = total eradication (eradication + presumed eradication); Failure = total failure (failure + presumed failure).
[a] Studies 551 and 536 combined. Study 551 utilized Augmentin — 2000/125 mg bid. Study 536 utilized Augmentin (14:1) pediatric suspension, 90mg/kg/day in divided doses q12h every 12 hours.
[b] Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.

Bacteriological eradication rates for *S. pneumoniae* in the URTI Bacteriology ITT population were lower than the PP population. The eradication rates were92.3% and 90.5% for the all geographic and US regions, respectively.

3.2.1.5. Lower Respiratory Tract Infections

Clinical Efficacy

Among Bacteriology PP patients who were treated with Augmentin — for a lower respiratory tract infection (LRTI; CAP — studies combined) *S. pneumoniae* was most commonly isolated pathogens in all geographic regions (102 isolates). Amoxicillin/clavulanic acid MICs ranged from ≤ 0.015 to 8.0 µg/mL for these isolates.

The clinical success rate in all geographic regions for patients with LRTIs caused by *S. pneumoniae* was 91.2% (Bacteriology PP population). In the US region, the clinical success rate for patients with isolates of *S. pneumoniae* was lower (78.6%) than the rate for patients in all geographic regions.

The amoxicillin/clavulanic acid MICs for these pathogens were generally ≤ 2.0 µg/mL. Two isolates of *S. pneumoniae* had a MIC of 4.0 µg/mL, both of which were a clinical success. One isolate of *S. pneumoniae* (part of a polymicrobial infection with *K. pneumoniae*) had a MIC of 8.0 µg/mL and was presumed eradicated at end of therapy due to clinical success. However, the patient was a clinical failure at test of cure; therefore, both *S. pneumoniae* and *K. pneumoniae* were presumed to have recurred at test of cure.

A summary of clinical efficacy at test of cure by *S. pneumoniae* susceptibility to amoxicillin/ clavulanic acid, by MIC, in the Bacteriology PP population, for patients treated with Augmentin — for LRTIs, for all geographical regions combined and for the US, is presented in Table 17.

Bacteriological Outcome

Overall, the bacteriological eradication rates and MIC values were very similar to the clinical results. In the PP population, the bacteriological eradication rate in all geographic regions for patients with LRTIs caused by *S. pneumoniae* was 91.2%. In the US region, bacteriological eradication rate for patients with isolates of *S. pneumoniae* was lower (78.6%) than the rate for patients in all geographic regions.

Two isolates of *S. pneumoniae* had a MIC of 4.0 µg/mL, both of which were eradicated. One isolate of *S. pneumoniae* (part of a polymicrobial infection with *K. pneumoniae*) had a MIC of 8.0 µg/mL and was presumed eradicated at end of therapy due to clinical success. However, the patient was a clinical failure at test of cure; therefore, both *S. pneumoniae* and *K. pneumoniae* were presumed to have recurred at test of cure, which led to a bacteriological outcome of failure.

A summary of bacteriological outcome at test of cure by *S. pneumoniae* susceptibility to amoxicillin/clavulanic acid, by MIC, in the Bacteriology PP population for patients treated with Augmentin — for LRTIs, for all geographical regions combined and for the US is presented in Table 18.

Table 17. Clinical Efficacy at Test of Cure by Screening Pathogen *(S. pneumoniae)* Susceptibility (MIC) to Amoxicillin/Clavulanic Acid: Patients with Lower Respiratory Tract Infections (Bacteriology PP Population)

	Augmentin — (All geographical regions)[a]				Augmentin — (US)[a]			
	Success		Failure		Success		Failure	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (μg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	93/102	(91.2)	9/102	(8.8)	22/28	(78.6)	6/28	(21.4)
≤ 0.015	14/15	(93.3)	1/15	(6.7)	4/5	(80.0)	1/5	(20.0)
0.03	62/67	(92.5)	5/67	(7.5)	9/11	(81.8)	2/11	(18.2)
0.06	5/5	(100)	0/5		2/2	(100)	0/2	
0.12	2/3	(66.7)	1/3	(33.3)	0/1		1/1	(100)
0.25	2/3	(66.7)	1/3	(33.3)	1/2	(50.0)	1/2	(50.0)
0.5	2/2	(100)	0/2					
2	4/4	(100)	0/4		4/4	(100)	0/4	
4	2/2	(100)	0/2		2/2	(100)	0/2	
8	0/1		1/1	(100)	0/1		1/1	(100)

* n/N = number of patients with a specified response/number of patients with a pathogen with the specified MIC.
[a] Includes: Studies 546, 547, 548, 549 and 556.
[b] Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.

3.2.1.6. LRTI and URTI Combined

Clinical Response

In order to obtain an overall view of the clinical efficacy and bacteriological outcome of Augmentin — against *S. pneumoniae*, data from the Phase III studies and Study 536 (from Augmentin 14:1) were combined (i.e., Studies 546, 547, 548, 549, 551, 556 and 536). Among Bacteriology PP patients in all geographic regions who were treated with Augmentin — for a respiratory tract infection (RTI) the most commonly isolated pathogen was *S. pneumoniae* (349 isolates). Amoxicillin/clavulanic acid MICs against *S. pneumoniae* ranged from ≤ 0.015 μg/mL to 8.0 μg/mL.

The total clinical success rate for patients with RTIs caused by *S. pneumoniae* (including Study 536) was 92.8%. Clinical success rates in the US region were generally similar to the global assessment.

The amoxicillin/clavulanic acid MICs against *S. pneumoniae* were generally ≤ 2.0 μg/mL. All of the six isolates of *S. pneumoniae* with an amoxicillin/clavulanic acid MIC of 4.0 μg/mL were associated with clinical success. Of ten *S. pneumoniae* isolates with a MIC of 8.0 μg/mL, eight were associated with clinical success (80.0%). As described in previous sections (CAP and LRTI), one *S. pneumoniae* failure (CAP Study 547) was part of a co-infection with *K. pneumoniae*. Both pathogens were associated with clinical success at end of therapy, with outcomes of presumed eradication. At test of cure, however, the patient was a clinical failure, so both pathogens were presumed to have recurred.

Table 18. Bacteriological Outcome at Test of Cure by Amoxicillin/Clavulanic Acid MICs - Patients with Lower Respiratory Tract Infections (Bacteriology PP Population)

	Augmentin — (All geographical regions)[a]						Augmentin — (US)[a]					
	Eradication**		Failure**		Unable To Determine		Eradication**		Failure**		Unable to Determine	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	93/102	(91.2)	7/102	(6.9)	2/102	(2.0)	22/28	(78.6)	4/28	(14.3)	2/28	(7.1)
≤ 0.015	14/15	(93.3)	1/15	(6.7)	0/15		4/5	(80.0)	1/5	(20.0)	0/5	
0.03	62/67	(92.5)	5/67	(7.5)	0/67		9/11	(81.8)	2/11	(18.2)	0/11	
0.12	2/3	(66.7)	0/3		1/3	(33.3)	0/1		0/1		1/1	(100)
0.25	2/3	(66.7)	0/3		1/3	(33.3)	1/2	(50.0)	0/2		1/2	(50.0)
0.5	2/2	(100)	0/2		0/2							
2	4/4	(100)	0/4		0/4		4/4	(100)	0/4		0/4	
4	2/2	(100)	0/2		0/2		2/2	(100)	0/2		0/2	
8	1/0		1/1	(100)	0/1		0/1		1/1	(100)	0/1	

* n/ N= number of patients with a specified response/ number of patients with a pathogen with the specified MIC.
** Eradication = total eradication (eradication + presumed eradication); Failure = total failure (failure + presumed failure).
a. Studies 546, 547, 548, 549, and 556 combined
b. Amoxicillin/ clavulanic acid was tested at a 2: 1 ratio; MICs are expressed in terms of the amoxicillin concentration.

The second *S. pneumoniae* failure came from AOM Study 536. This patient was infected with *S. pneumoniae* and *H. influenzae* at screening and withdrew from the study at the on therapy visit due to insufficient therapeutic effect. The patient was therefore classified as a clinical failure at the end of therapy.

A summary of clinical efficacy at test of cure, by amoxicillin/clavulanic acid MICs against *S. pneumoniae,* in the Bacteriology PP population for patients treated with Augmentin — for a RTI, for all geographical regions combined and the US, is presented in Table 19.

Table 19. Clinical Efficacy at Test of Cure by Screening Pathogen *(S. pneumoniae)* Susceptibility (MIC) to Amoxicillin/Clavulanic Acid: Patients with Respiratory Tract Infections (Bacteriology PP Population)

	Augmentin — (All geographical regions)[a]				Augmentin — (US)[a]			
	Success		Failure		Success		Failure	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	324/349	(92.8)	25/349	(7.2)	121/137	(88.3)	16/137	(11.7)
≤ 0.015	30/32	(93.8)	2/32	(6.3)	9/10	(90.0)	1/10	(10.0)
0.03	196/208	(94.2)	12/208	(5.8)	63/71	(88.7)	8/71	(11.3)
0.06	21/21	(100)	0/21		10/10	(100)	0/10	
0.12	11/12	(91.7)	1/12	(8.3)	4/5	(80.0)	1/5	(20.0)
0.25	15/18	(83.3)	3/18	(16.7)	3/4	(75.0)	1/4	(25.0)
0.5	6/6	(100)	0/6		4/4	(100)	0/4	
1	4/5	(80.0)	1/5	(20.0)	1/2	(50.0)	1/2	(50.0)
2	27/31	(87.1)	4/31	(12.9)	17/19	(89.5)	2/19	(10.5)
4	6/6	(100)	0/6		3/3	(100)	0/3	
8	8/10	(80.0)	2/10	(20.0)	7/9	(77.8)	2/9	(22.2)

* n/N = number of patients with a specified response/number of patients with a pathogen with the specified MIC.
[a] Includes: Studies 546, 547, 548, 549, 551, 556 and 536 (*S. pneumoniae* only) combined
[b] Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.

Bacteriological Outcome

Bacteriological eradication rate in all geographic regions was 95.7 % for patients with RTIs caused by *S. pneumoniae.* Six isolates of *S. pneumoniae* reported a MIC of 4.0 µg/mL, all of which were eradicated. Seven of ten *S. pneumoniae* isolates (70.0%) with a MIC of 8.0 µg/mL were eradicated. One *S. pneumoniae* failure (CAP Study 547) was part of a co-infection with *K. pneumoniae,* as described in this section under Clinical Efficacy. The two other bacteriological failures were from AOM Study 536. One patient had *H. influenzae* and *S. pneumoniae* at screening. A second tympanocentesis showed eradication of *H. influenzae* and persistence of *S. pneumoniae* at the on therapy visit. The patient withdrew from the study at the on therapy visit and was subsequently classified as a clinical failure at the end of therapy. The second bacteriological failure from Study 536, a patient infected with *S. pneumoniae* alone, failed bacteriologically at the on-therapy visit (outcome of persistence for *S. pneumoniae* at the second tympanocentesis), but was a clinical success at the end of therapy (outcome of improvement).

A summary of bacteriological outcome at test of cure, by amoxicillin/clavulanic acid MICs against *S. pneumoniae,* in the Bacteriology PP population for patients treated with Augmentin — for a RTI, for all geographical regions combined and the US, is presented in Table 20.

Table 20. Bacteriological Outcome at Test of Cure by Amoxicillin/Clavulanic Acid MICs - Patients with Respiratory Tract Infections (Bacteriology PP Population)

	Augmentin — (All geographical regions)[a]						Augmentin — (US)[a]					
	Eradication**		Failure**		Unable To Determine		Eradication**		Failure**		Unable to Determine	
S. pneumoniae alone or in mixed cultures amoxicillin/clavulanic acid MIC (µg/mL)[b]	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)	n/N*	(%)
Total	334/349	(95.7)	13/349	(3.7)	2/349	(0.6)	126/137	(92.0)	9/137	(6.6)	2/137	(1.5)
≤ 0.015	31/32	(96.9)	1/32	(3.1)	0/32		9/10	(90.0)	1/10	(10.0)	0/10	
0.03	201/208	(96.6)	7/208	(3.4)	0/208		68/71	(95.8)	3/71	(4.2)	0/71	
0.06	21/21	(100)	0/21		0/21		10/10	(100)	0/10		0/10	
0.12	11/12	(91.7)	0/12		1/12	(8.3)	4/5	(80.0)	0/5		1/5	(20.0)
0.25	17/18	(94.4)	0/18		1/18	(5.6)	3/4	(75.0)	0/4		1/4	(25.0)
0.5	6/6	(100)	0/6		0/6		4/4	(100)	0/4		0/4	
1	4/5	(80.0)	1/5	(20.0)	0/5		1/2	(50.0)	1/2	(50.0)	0/2	
2	30/31	(96.8)	1/31	(3.2)	0/31		18/19	(94.7)	1/19	(5.3)	0/19	
4	6/6	(100)	0/6		0/6		3/3	(100)	0/3		0/3	
8	7/10	(70.0)	3/10	(30.0)	0/10		6/9	(66.7)	3/9	(33.3)	0/9	

* n/ N= number of patients with a specified response/ number of patients with a pathogen with the specified MIC.
** Eradication = total eradication (eradication + presumed eradication); Failure = total failure (failure + presumed failure).
a. Studies 546, 547, 548, 549, 551, 556, and 536 (*S. pneumoniae* only) combined
b. Amoxicillin/ clavulanic acid was tested at a 2: 1 ratio; MICs are expressed in terms of the amoxicillin concentration.

4. Breakpoint Determination

Amoxicillin/clavulanic acid is a previously approved drug product. Therefore, interpretive criteria for in vitro susceptibility testing exist for all the approved microorganisms for which clinical efficacy was demonstrated. Under this application the sponsor is only requesting a change in the in vitro susceptibility testing interpretive criteria for *S. pneumoniae* against amoxicillin/clavulanic acid. Thus, this reviewer will only discuss the in vitro susceptibility interpretive criteria for *S. pneumoniae* against amoxicillin/clavulanic acid.

Table 1 and Table 2 show the amoxicillin/clavulanic acid MIC_{50}, MIC_{90}, and MIC range for *S. pneumoniae* tested in the AGSS, Alexander Project, ISS, Alert, CMI, and CAST studies. The range of MIC_{90}s in the US (Table 1) was 1.0 - 4.0 µg/mL. At a susceptible breakpoint of 2.0 µg/mL, the percentage of isolates susceptible to amoxicillin/clavulanic acid ranged from 85.2-96%; and at a susceptible breakpoint of 4.0 µg/mL, the range was 90.3-98.6%. The MIC_{90} in each study for the isolates from all geographic regions was 2.0 µg/mL (Table 2), and the percent susceptible ranges at each breakpoint were as follows: at 2.0 µg/mL, 92.7-93.7%; and at 4.0 µg/mL, 96.2-97.2%. The amoxicillin/clavulanic acid MIC_{90} range was 0.03 - 0.25 µg/mL for the penicillin-susceptible isolates, 1.0 - 2.0 µg/mL for the penicillin-intermediate isolates, and 4.0 - 8.0 µg/mL for the penicillin-resistant isolates. As expected, all penicillin-susceptible isolates were susceptible to amoxicillin/clavulanic acid. At a susceptible breakpoint of 2.0 µg/mL, 92.3-100% of the intermediate isolates were susceptible to amoxicillin/clavulanic acid, and at a susceptible breakpoint of 4.0 µg/mL, 99.4-100% of isolates were susceptible. At a susceptible breakpoint of $\leq$ 2.0 µg/mL, the percentage of penicillin-resistant isolates susceptible to amoxicillin/clavulanic acid ranged from 41.7-80.2%, and at $\leq$ 4.0 µg/mL 64.4-92.8% of isolates were susceptible to amoxicillin/clavulanic acid.

From the combined clinical trials the number of *S. pneumoniae* isolates and the cumulative percent MIC frequency distribution for amoxicillin/clavulanic acid in the Bacteriology ITT population from patients treated with Augmentin — for respiratory tract infections in the US and in all geographic regions is presented in Table 21. The MIC_{90} for amoxicillin/clavulanic acid was 2.0 µg/mL *S. pneumoniae* isolates in the US. The MIC_{90} for amoxicillin/clavulanic acid was 0.5 µg/mL for the *S. pneumoniae* isolates in all geographic regions.

Table 21. Frequency distribution of amoxicillin/clavulanic acid MICs (µg/ mL)* for *S. pneumoniae* from phase III clinical studies – US (n = 98), all geographical regions (n= 287)

Total N Cumulative %	≤0.015	0.03	0.06	0.12	0.25	0.5	1.0	2.0	4.0	8.0
S. pneumoniae- US isolates										
	12 12.24	46 59.18	10 69.39	4 73.47	3 76.53	3 79.59	2 81.63	11 92.86	2 94.90	5 100
S. pneumoniae- all geographical isolates										
	39 13.59	185 78.05	17 83.97	8 86.76	7 89.20	5 90.94	4 92.33	13 96.86	4 98.26	5 100

* Amox/ clav: Amoxicillin/ clavulanic acid was tested at a 2: 1 ratio; MICs are expressed in terms of the amoxicillin concentration.

The frequency distribution histograms for the US and global clinical isolates recovered from clinical studies (Figures 12 and 13) are very similar to the frequency distribution histograms from the in vitro surveillance studies presented earlier in this review.

Figure 12. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pneumoniae* from Clinical Studies - US (N=98)

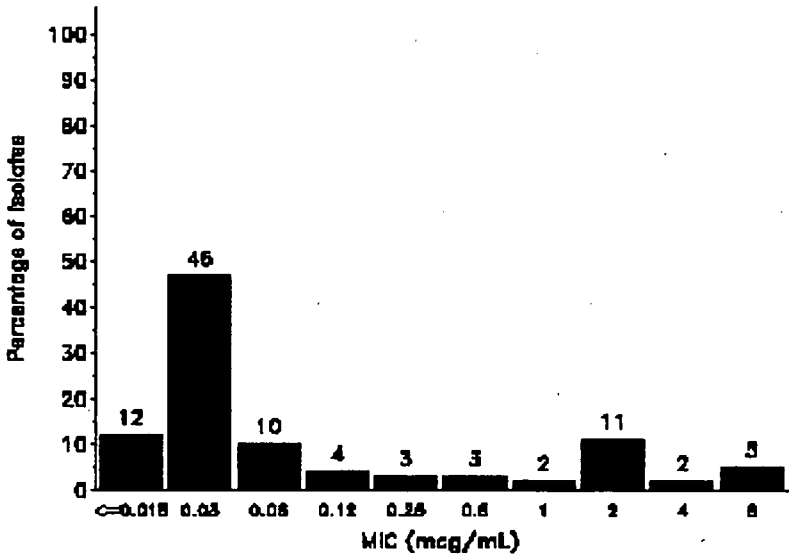
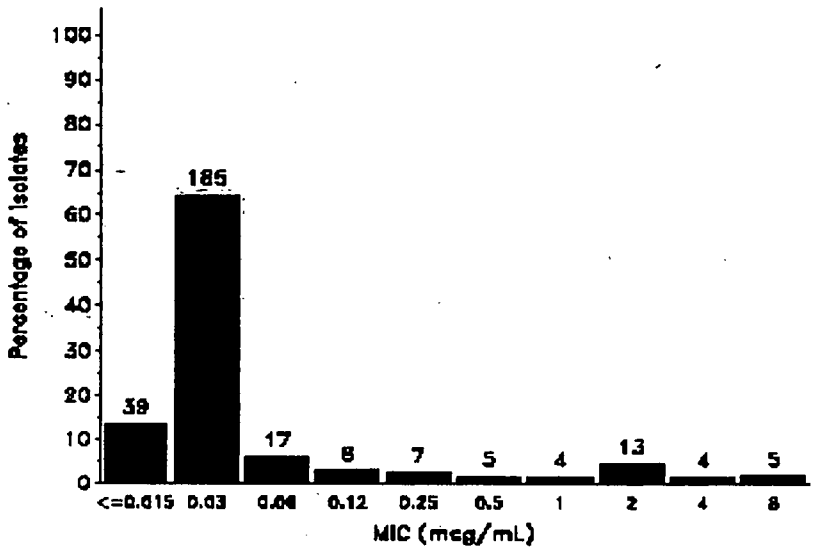


Figure 13. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pneumoniae* from Clinical studies- all geographic regions (N=287)



Pharmacodynamic studies in the neutropenic Murine thigh model and Murine respiratory tract infection model have demonstrated that, for *S. pneumoniae*, the T>MIC required for maximal efficacy is approximately 35-40%.

The sponsor-submitted PK studies indicate that the mean T>MIC for an amoxicillin MIC of 4.0 μg/mL is approximately 49%. Using the same methodology T>MIC for an amoxicillin MIC of 2.0 μg/mL is approximately 57% of the dosing interval. With this information this reviewer believes that the PK/PD data would probably support a MIC breakpoint of 2.0 μg/mL.

The clinical studies that would have been the proof of concept resulted in 13 patients at TOC visit with isolates that had amox/clav MICs of ≥ 4.0 μg/mL (nine with MICs of 8 and four with MICs of 4 μg/mL) (see Table 1 in the addendum to tis review dated 9-6-01). Six out of the nine (66.7%) patients with isolates having amox/clav MICs of 8.0 μg/mL failed clinically at the TOC and one out of the four (25%) patients with isolates having MICs of 4.0 μg/mL also failed clinically at the TOC. This resulted in a clinical success rate of 9/13, 69% for all patients with isolates that had amox/clav MICs of ≥ 4.0 μg/mL. The successful clinical response rate for patients with *S. pneumoniae* isolates with amox/clav MICs of 2.0 μg/mL was18/27, 66.7% and for patients with amox/clav MICs of < 2.0 μg/mL (i.e. ≤ 1.0 μg/mL) was 178/204, 87%. When one combines these two populations, the successful clinical response rate for patients with *S. pneumoniae* isolates with amox/clav MICs of ≤ 2 μg/mL was 196/231, 84.8% which is an acceptable rate.

In summary, when this reviewer takes into consideration the PK/PD findings and the clinical outcomes from the clinical trials the susceptible breakpoint seems to fall on ≤ 2.0 μg/mL. If one chooses the MIC of ≤ 2.0 μg/mL for the susceptible breakpoint then MICs of 4.0 and ≥ 8.0 μg/mL would be the obvious intermediate and resistant breakpoints respectively.

5. Recommended labeling

Based on the above review the microbiology subsection of the product insert should read as follows:

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by (beta)-lactamases and, therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a (beta)-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of (beta)-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated (beta)-lactamases frequently responsible for transferred drug resistance.

clavulanic acid in *Augmentin* protects amoxicillin from degradation by (beta)-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other (beta)-lactam

antibiotics.

Microbiology:

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and, therefore, the spectrum of activity does not include organisms, which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance.

The clavulanic acid component in Augmentin — protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics.

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic Gram-positive microorganisms

Streptococcus pneumoniae (including isolates with penicillin MICs ≤ 2.0 μg/mL)
Staphylococcus aureus (including β-lactamase producing strains)

Note: Staphylococci, which are resistant to methicillin/oxacillin, must be considered resistant to amoxicillin/clavulanic acid.

Aerobic Gram-negative microorganisms

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

The following *in vitro* data are available, **but their clinical significance is unknown**.

Aerobic Gram-positive microorganisms

Streptococcus pyogenes

NOTE: *S. pyogenes* do not produce β-lactamase and, therefore, are susceptible to amoxicillin alone. Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to *S. pyogenes*.

Susceptibility Testing

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure[1,2]. Standardized procedures are based on a dilution method (broth) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to the following criteria:

For

MIC (µg/mL)	Interpretation
≤ 8/4	Susceptible (S)
16/8	Intermediate (I)
≥ 32/16	Resistant (R)

For *Streptococcus pneumoniae*[a]

MIC (µg/mL)	Interpretation
≤ 2/1	Susceptible (S)
4/2	Intermediate (I)
≥ 8/4	Resistant (R)

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5 % lysed horse blood.[2]

For *Staphylococcus* species and *Haemophilus*

MIC (µg/mL)	Interpretation
≤ 4/2	Susceptible (S)
≥ 8/4	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Test Medium (HTM)[2]

NOTE: Staphylococci, which are resistant to methicillin/oxacillin, must be considered resistant to amoxicillin/clavulanic acid.

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

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard amoxicillin/clavulanate potassium powder should provide the following MIC values:

Microorganism	MIC range (µg/mL)[c]
Escherichia coli ATCC 35218	4-16
Escherichia coli ATCC 25922	2-8
Haemophilus influenzae[d] ATCC 49247	2-16
Staphylococcus aureus ATCC 29213	0.12-0.5
Streptococcus pneumoniae[e] ATCC 49619	0.03-0.12

[c] Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

[d] This quality control range is applicable to *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM[2]

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg of amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg amoxicillin/clavulanate potassium (20-µg amoxicillin plus 10-µg clavulanate potassium) disk should be interpreted according to the following criteria:

For —

Zone diameter (mm)	Interpretation
≥ 18	Susceptible (S)
— 14-17	Intermediate (I)
≤ 13	Resistant (R)

For *Staphylococcus* species and *H.* —

Zone diameter (mm)	Interpretation
≥ 20	Susceptible (S)
≤ 19	Resistant (R)

[f] These zone diameter standards are applicable only to tests conducted with *Haemophilus* spp. using HTM[2].

NOTE: Staphylococci, which are resistant to methicillin/oxacillin, must be considered — resistant to amoxicillin/clavulanic acid.

NOTE: β-lactamase negative, ampicillin-resistant *H. influenzae* strains must be considered resistant to amoxicillin/clavulanic acid.

For *Streptococcus pneumoniae*

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

[g] These zone diameter standards for *S. pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2[2].

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for amoxicillin/ clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg amoxicillin/clavulanate potassium (20 µg amoxicillin plus10 µg clavulanate potassium) disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 35218	—
Escherichia coli ATCC 25922	—
Haemophilus influenzae[h] ATCC 49247	15-23
Staphylococcus aureus ATCC 25923	28-36

[h] This quality control limit applies only to tests conducted with *H. influenzae* ATCC 49247 using HTM[2].

References:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2. NCCLS, Wayne, PA, Jan. 2000.
2 National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing – — . Informational — Standard — No. 1. NCCLS, Wayne, PA, Jan —
3. National Committee for Clinical Laboratory Standards. Performance Standard for Antimicrobial Disk Susceptibility Tests – Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1. NCCLS, Wayne, PA, Jan. 2000.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY section of the package insert. These revisions are found on pages 40-45 of this review. The sponsor should be notified of the needed changes in the product insert.

Sousan Sayahtaheri Altaie, Ph.D.
Clinical Microbiology Review Officer

Orig. NDA 50755
HFD-520/Division File
HFD-520/MO/C. Cooper
HFD-520/BioStat/ T. Valappil
HFD-520/PharmTox /K. Seethaller
HFD-520/Biopharm TL/ J. Zheng
HFD-520/Micro/S.S. Altaie
HFD-520/Chem/S. Pagay
HFD-520/PM/S. Samanta

Concurrence Only:
HFD-520/Dep. Dir./L. Gavrilovich
HFD-520/TL Micro/A. T. Sheldon
RD Initialed 8/15/01 ATS
Final Initialed 9/11/01 ATS

REFERENCES

1. BRL-025000/RSD-101720/1. International surveillance study: Augmentin report. Bouchillon, S., S. Farooqui. 17 February, 2000.

2. SB-265805/RSD-1010VM/1. In vitro activity of gemifloxacin (SB-265805) against contemporary clinical bacterial isolates from eleven North American medical centers, and assessment of disk test interpretive criteria. P. Fuchs, A. Barry and S. Brown. 24 June 1999.

3. BRL-25000/RSD-1017JS/1. *In vitro* Activity of Penicillin, Amoxicillin and Amoxicillin/clavulanic acid Against Recent (1999) Clinical Isolates of *Streptococcus pneumoniae* from the United States: Consultants in Anti-Infectives Surveillance and Testing, Inc.. Butler, D., and C. Stewart. 9 March, 2000.

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5. BRL-025000/RSD-1017P5/1. Augmentin Global Surveillance Study: Global Results. L. Koeth. November 2000.

6. BRL-025000/RSD-1017P9/1. Amoxicillin/clavulanic acid in vitro activity against RTI pathogens from the 1999 Alexander Project . C. Jakielaszek, J.Finlay, L. Miller. October 2000.

7. BRL-025000/RSD-1017PF/1. Augmentin Report: International Surveillance Study. S. Bouchillon. October 2000.

8. BRL-025000/RSD-1017PB/1. Susceptibility of *Streptococcus pneumoniae* in 1998/1999: Results of a Hospital Based Study. L. Koeth. May 2000.

9. BRL-025000/RSD-1018M9/2. An open, randomised, balanced, three period, single dose crossover study to investigate the effect of food on the bioavailability of sustained release oral Augmentin in healthy male and female volunteers. M. McDonagh, M. Davy, O. Dewitt, N. Bird, I. Khan, C. Kaye, S. Perry. September 2000.

10. BRL-025000/RSD-10163X/1. An open, randomised, four part crossover study to investigate the relative bioavailability of three new sustained release — formulations of Augmentin in comparison to the standard immediate release (IR) formulation of Augmentin in healthy volunteers. M. McDonagh, N. Bird, T. Montague, O. Dewit, C. Kaye, M. Davy. January 2000.

11. BRL-25000/RSD-1018M7/1. An open, randomised, three way crossover study to investigate the effect of Maalox on the bioavailability of sustained release oral Augmentin® (BRL

25000) in healthy male and female volunteers. M. McDonagh, N. Bird, C. Kaye, M. Davy. In Preparation.

12. BRL-025000/RSD-101CKK/1. Efficacy of simulated human serum concentrations of Augmentin — (16:1) in comparison with those of Augmentin 4:1 against experimental respiratory tract infections caused by strains of Streptococcus pneumoniae (AMX MIC 2.0 and 4.0 mcg/mL). V. Berry, J. Satterfield, C. Singley, G. Woodnutt. October 2000.

13. BRL-025000/RSD-1017PP/1. Efficacy of simulated serum concentrations of Augmentin — (16:1), augmentin 7:1 bid and tid, Augmentin 8:1 tid, azithromycin and levofloxacin against experimental respiratory tract infections caused by strains of *Streptococcus pneumoniae* (AMX .MIC 4.0 mcg/mL). Valerie Berry, Jennifer Satterfield, Christine Singley, Gary Woodnutt. June 2000

14. BRL- 025000/RSD-1017/PR. Efficacy of simulated serum concentrations of Augmentin — (16:1), augmentin 7:1 bid and tid, Augmentin 8:1 tid, azithromycin and levofloxacin against experimental respiratory tract infections caused by strains of *Streptococcus pneumoniae* (AMX .MIC 8.0 mcg/mL). Valerie Berry, Jennifer Satterfield, Christine Singley, Gary Woodnutt. October 2000.

15. BRL-025000/RSD-1017PV/1. Efficacy of Augmentin — (16:1), augmentin 7:1 bid and tid, Augmentin 8:1 tid, azithromycin and levofloxacin against experimental respiratory tract infections caused by strains *H. influenzae* (BLA+ and BLNAR). Valerie Berry, Jennifer satterfield, Christine Singley, Gary Woodnutt. October 2000.

17. General/PUB-1005FF/1. WILLIAM CRAIG. 1998. Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial dosing of Mice and Men.. *Clinical Infectious Diseases,* **26,** 1-12.

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Sousan Altaies
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MICROBIOLOGIST

Lillian Gavrilovich
11/29/01 03:13:07 PM
MEDICAL OFFICER

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Division of Anti-Infective Drug Products
Clinical Microbiological Review
Resubmission

NDA # 50785 **Date Completed:** August 16, 2002

Applicant: GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, Pa 19101-792

Chem/Ther. Type: Antimicrobial, β-Lactam/βLactam inhibitor combination, Extended and normal Release formulation

Submission Reviewed: Re-submission of NDA 50-785 as a complete response to the DAIDP Action Letter of December 12, 2001.

Providing for: Treatment of Acute Bacterial Sinusitis and Community Acquired Pneumonia.

Product Name(s):

Proprietary: Augmentin XR™

Non-proprietary/USAN: amoxicillin/clavulanate potassium, 16:1 ratio

Dosage form: Extended Release Tablet 1000/62.5 mg per tablet, two tablets given BID

Route of administration: Oral

Pharmacological Category: β-lactam/β-lactamase inhibitor

Dispensed: Rx

Initial Submission Dates

Received by CDER: 12-21-00
Received by Reviewer: 1-10-01
Review Completed: 9-11-01

Supplements/Amendments:

Received by CDER: March 29, 2002
Received by Reviewer:
Review Completed:

Related Documents:

IND ——
NDA: 50564, 50575, 50597, 50720, 50725, 50726, 50755, ——, 50542, 50754 and numerous amendments to the IND and NDAs.
DMFs: —— **and** ——

Remarks:

Reference is made to the applicant's NDA submission for XR™ (amoxicillin/clavulanate potassium) Extended Release Tablets (NDA 50-785), originally submitted to our division on December 21, 2000, the addendum submitted 8-25-01 and to our action letter of December 12, 2001, which concluded that the NDA was non-approvable. A meeting was held on March 8, 2002 and a teleconference on March 21, 2002 between representatives of GSK and DAIDP for the purpose of formulating specific questions concerning needed information and a format for re-submission of this NDA. Questions that pertain to the microbiological reviewer include the following:

- Information on the time above the MIC based on free amoxicillin concentrations. (Percentage of the dosing interval that free drug concentration remains above the MIC_{90} at the suggested breakpoint)
- Substantial additional clinical and microbiological data
- Evidence of Efficacy of Augmentin XR in patients with community acquired pneumonia (CAP) due to penicillin-resistant *Streptococcus pneumoniae* (PRSP)
- Evidence of efficacy of Augmentin XR in patients with acute bacterial sinusitis due to PRSP as well as beta-lactamase producing *H. influenzae* and *M. catarrhalis*
- Draft Labeling identifying the characteristics of the intended patient populations for Augmentin XR Extended Release Tablet, in contrast to those for Augmentin Tablets (7:1 formulation)

- Evidence of Efficacy Supporting the Proposed Amoxicillin/Clavulanic Acid Breakpoints against *S. pneumoniae.*

It should be noted that the applicant has withdrawn the request for the indication,

This review will concentrate on those points discussed above in the resubmitted NDA. I will not repeat a discussion of the general properties of Augmentin XR because they were discussed in the previous clinical microbiology reviews of Augmentin XR. Previous reviews were conducted by Dr. S. Altaie (previous reviews of 50,785, by Dr. S. Altaie with completion dates of 6-1-2001 and 2-19-2002) as well as reviews concerning other Augmentin products.

Conclusions/Recommendations:

From the viewpoint of clinical microbiology, It appears that the applicant has provided sufficient evidence for approval of the two indications, Community Acquired Pneumonia (CAP) and Acute Bacterial Sinusitis (ABS). Concerning specific organisms, patient populations infected with *S. pneumonia* demonstrating reduced susceptibility to Augmentin XR (Augmentin MICs ≤ 4) and beta-lactamase producing *H. influenzae, H. parainfluenzae and M. catarrhalis*. These conclusions are based on evidence demonstrating sufficient time (46%) of the dosing interval above the applicant's suggested Augment MIC breakpoint of 4 μg/mL (It will have to be demonstrated and verified by our PK reviewer that the standard deviations in the PK studies are small enough to provide confidence that a significant patient population will not have percent of the dosing interval ≤ 30). A large portion of the data submitted by the applicant studied the ability of Augmentin XR to cure patients and eradicate *Streptococcus pneumoniae* with various MICs to penicillin including special emphasis on PRSP-those isolates having MICs of ≥ 2 μg/ml. The ITT population for CAP had 22 PRSP organism (penicillin MICs of 2-4 μg/ml) infected patients with 77.3% cures observed in the ITT population and 93% cures observed in the PP population (Table 27). In acute bacterial sinusitis, 40 PRSP organisms (penicillin MICs of 2-4 μg/ml) were isolated from infected patients with Augmentin XR demonstrating bacteriological cures in all 40 patients, the ITT population (Table 23) and 37/37 in the PP populations.
Pharmacokinetics/pharmacodynamics of the new formulation showed different PK/PD properties compared to the currently approved Augmentin 7:1 formulation, higher peaks sustained over a longer time-period. Total clinical and bacteriological results from all CAP and ABS clinical studies are shown in Table 33 (see p. 40 of this review), at the proposed Augmentin breakpoint of 4μg/mL, 16/17, PP and 16/18, ITT patients infected with *S. pneumoniae* show clinical and bacteriological cure. Five of these patients were diagnosed with CAP and the others with ABS. Only 2 patients with pneumoniae were infected with a *S. pneumoniae* having a penicillin MIC of 4μg/ml (both cured) and 3 patients were infected with *S. pneumoniae* isolates having a penicillin MIC of 2μg/ml (

2/3) were cured clinically and microbiologically. Assay variation for Augmentin MICs around the penicillin MIC of 4μg/ml, make it questionable that all patients infected with *S. pneumoniae* isolates with a breakpoint of 4μg/mL for penicillin can be effectively treated with Augmentin XR. At a penicillin MIC of 4, 33% of *S. pneumoniae* clinical isolates had Augmentin MICs of 8 μg/mL. **Because of the small number of clinical cases and non-linearity of MICs, we can not recommend treatment of *S. pneumoniae* patients having penicillin MICs ≥ 4 μg/mL.**

Detailed analysis of points presented by GlaxoSmithKline:

1. Information on time above MIC based on free amoxicillin concentrations

The applicant's table of mean (±SD) pharmacokinetic parameters, reproduced below indicates that Augmentin XR given to healthy volunteers BID results in blood levels of total amoxicillin remain above 4 μg/ml for approximately 50% of the dosing interval. William Craig has demonstrated that for beta-lactam antibiotics, a time period of 40% or more of the dosing interval above a given antibiotic MIC will result in a positive therapeutic result for that dose of antibiotic. However these optimum levels of amoxicillin were only obtained if the Augmentin was given alone at the start of a standard meal. It should also be noted that this data was generated from total, not free drug. The same conclusions can be made from free drug but the percent of the dosing interval above a MIC of 4μg/ml is 46%, not 49% of the dosing interval. The applicant provided the following pharmacokinetic information

Mean (SD) Pharmacokinetic Parameters for Amoxicillin and Clavulanate Following Oral Administration of *Augmentin XR* (2000/125 mg) to Healthy Adult Volunteers [n=55]

Parameter (units)	Amoxicillin	Clavulanate
AUC(0-inf) (μg.h/mL)	71.6 (16.5)	5.29 (1.55)
C_{max} (μg/mL)	17.0 (4.0)	2.05 (0.80)
T_{max} (hours)†	1.50 [redacted]	1.03 [redacted]
$T_{1/2}$ (hours)	1.27 (0.20)	1.03 (0.17)
T> 4 μg/mL (hours)	5.9 (1.2)	ND
T> 4 μg/mL (% dosing interval)	49.4 (10.2)	ND

† median (range)
ND – not determined

APPEARS THIS WAY
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