2. Substantial clinical and microbiological data.

The information necessary to discuss this issue is presented later in this review when discussing the antimicrobial spectrum of activity, and clinical and bacteriological outcome data.

3. Evidence of Efficacy of Augmentin XR in patients with Community acquired pneumonia (CAP) due to penicillin-resistant *Streptococcus pneumoniae* (MICs of 2 or 4), and other organisms

Bacteriological eradication rates, confirmed or presumed at test of cure for key pathogens in clinically evaluable patients from 4 pooled studies of CAP are shown in the following table. One study is non-comparative and the other three are comparative. Fifteen *S. pneumoniae* strains with penicillin MICs of 2 or 4 μg/ml were obtained from infected patients with an eradication rate of 93.3% observed, 14/15 strains eradicated. However it should be noted that only 6 of these strains had a penicillin MIC of 4μg/ml. It should also be noted and will be discussed later in this review that a penicillin MIC of 4 μg/ml can be equivalent to a Augmentin MIC of 8. For all *S. pneumoniae* strains isolated in all indications, an eradication rate of 91% was obtained. Acceptable eradication rates are also demonstrated for *H. influenzae*, *H. parainfluenzae*, *S. aureus* (methicillin susceptible), *M. catarrhalis* and *K. pneumoniae*. Along with good clinical results, these findings support continued inclusion in list one of these organisms for the indications of ABS and CAP but not necessarily PRSP having a penicillin MIC of 4μg/ml.

Bacteriological eradication rates, key pathogens, results from all CAP studies

Number of Pathogens	Pathogens	Eradication Rate (%)
429	All	83.7
172	All *S. pneumoniae*	91.3
15	*S. pneumoniae* with penicillin MIC = 2 or 4 μg/ml [a]	93.3 [b]
102	*H. influenzae*	81.4
45	*H. parainfluenzae*	75.6
30	*S. aureus* (Methicillin susceptible)	76.7
17	*M. catarrhalis*	88.2
13	*K. pneumoniae*	84.6

[a] *S. pneumoniae* strains with penicillin MICs of 2 or 4 μg/ml are considered resistant to penicillin.

[b] 95% confidence interval = 68.1% to 99.8%

4. Evidence of efficacy of Augmentin XR in patients with acute bacterial sinusitis (ABS) due to PRSP and other organisms

Bacteriological eradication rates, confirmed or presumed at test of cure for key pathogens in clinically evaluable patients from 3 pooled studies of ABS are shown in the following table from the applicant's submission of March 29, 2002. Two studies were non-comparative and the other study was comparative. The eradication rate for all *S. pneumoniae* strains (257) was 93% and for *S. pneumoniae* strains (40) with penicillin MICs of 2, 4, 8 or 16, 100% were eradicated. Good eradication rates are also demonstrated for *H. influenzae*, *H. parainfluenzae*, *S. aureus* (methicillin susceptible) and M. *catarrhalis*. Since clinical cure rates were also acceptable, these findings support inclusion in list one for these organisms.

Bacteriological eradication rates, key pathogens, results from all ABS studies

Pathogens	Number of Pathogens	Eradication Rate (%)
All	998	88.3
All *S. pneumoniae*	257	93.4
S. pneumoniae with penicillin MIC = 2 or 4 µg/mL [a]	38	100 [b]
H. influenzae	207	87.4
M. catarrhalis	77	90.9
S. aureus (methicillin susceptible)	35	82.9
K. pneumoniae	34	94.1
H. parainfluenzae	27	85.2

[a] *S. pneumoniae* strains with penicillin MICs of 2 or 4 µg/mL are considered resistant to penicillin.

[b] 95% confidence interval = 90.7% to 100%. Two additional isolates with penicillin MICs of 8 and 16 µg/mL were recovered; both were eradicated.

5. 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).

As indicated in the following proposed indications and usage section of the draft labeling, there is a difference in the intended treatment populations between the presently marketed 7:1 tablets and the proposed extended release tablets. See below, applicants proposed indications and usage section of the package insert and Dosage and administration section. However, other Augmentin products can satisfactorily treat *S. pneumoniae* with a penicillin and Augmentin MIC of 2 µg/ml. There is also, no clinical or microbiological evidence presented to demonstrate that the CAP infected patient populations mentioned below, over 65 years of age, have multiple medical comorbidities, [redacted], alcoholism or immune-suppressive illness can be effectively treated by Augmentin XR. Please see our suggested indications and usage section below

Indications and Usage

Augmentin XR Extended Release Tablets are indicated for the treatment of patients with [redacted]

susceptibility to

Acute bacterial sinusitis or community-acquired pneumonia due to a susceptible strain of *S. pneumoniae* plus a beta-lactamase-producing pathogen can be treated with another *Augmentin* product containing lower daily doses of amoxicillin (i.e., 500 mg q8h or 875 mg q12h).

Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin XR*

Once the results are known, therapy should be adjusted appropriately.

The applicant also proposed the following: "Augmentin Tablets (250 mg or 500 mg) CANNOT be used to provide the same dosages as *Augmentin XR*. This is because *Augmentin* XR contains 62.5 mg of clavulanic acid, while the *Augmentin* 250 mg and 500 mg tablets each contain 125 mg of clavulanic acid. Thus, two *Augmentin* 500 mg tablets are not equivalent to one *Augmentin XR* tablet."

The above statement by the sponsor does not serve to separate Augmentin XR from other Augmentin formulations since sufficient clavulanate is provided in all formulations to inhibit Beta-Lactamases. This formulation is aimed mainly to obtain a higher breakpoint and cover infections caused by *S. pneumoniae* with decreased susceptibility to," Augmentin." *S. pneumoniae* resistance involves changes in binding proteins and not Beta-lactamase and therefore, the concentration of Clavulanate is irrelevant concerning the treatment of *S. pneumoniae*.

6. **The applicant was asked to provide Evidence of Efficacy supporting the Proposed Amoxicillin/Clavulanic Acid Breakpoints against *S. pneumoniae*. This evidence has been provided in the previous discussion above and will be**

expanded in the rest of the review. This evidence leads us to propose the following breakpoints:

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 agar; broth for *S. pneumoniae* and *Haemophilus* species) 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 testing *Klebsiella pneumoniae*:

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

For testing *Streptococcus pneumoniae* [a]:

MIC (µg/mL)	Interpretation
———	Susceptible (S)
———	Intermediate (I)
———	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 testing *Staphylococcus* species and *Haemophilus* species[b]

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]

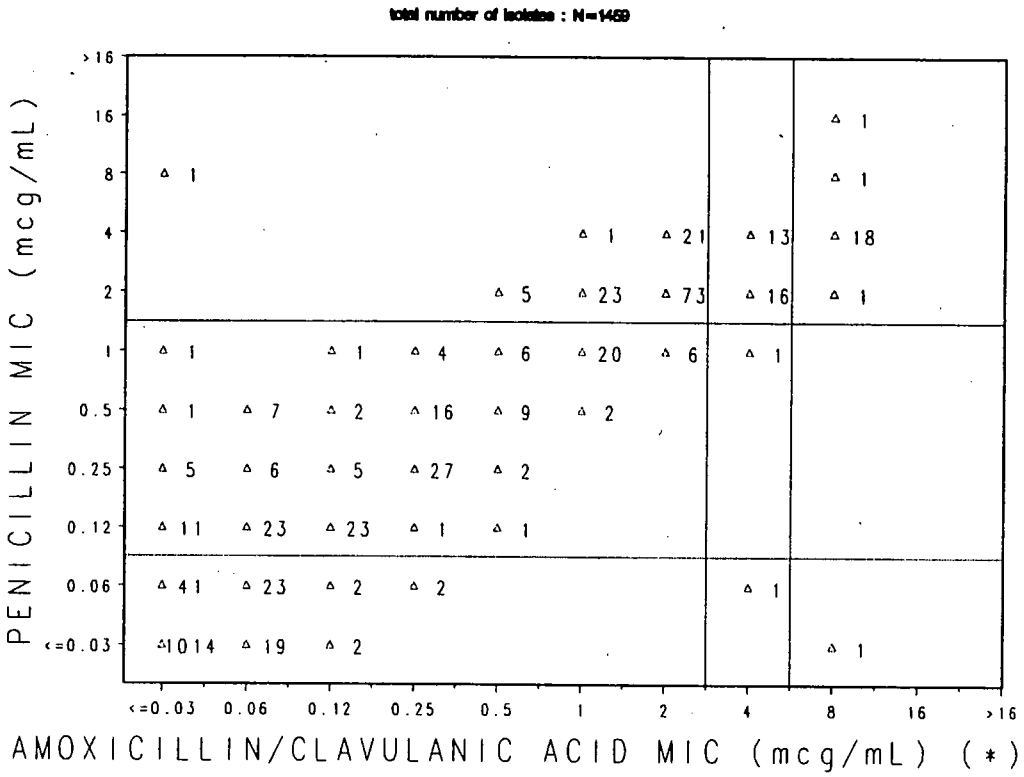
NOTE: Staphylococci, which are resistant to methicillin/oxacillin, must be considered resistant to amoxicillin/clavulanic acid.

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, which 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.

Comparison of Augmentin and Penicillin MICs

The applicant has assumed that penicillin MICs of 2 and 4 are equivalent to Augmentin MICs of 2 and 4 thus equating susceptibility to Augmentin XR to susceptibility to penicillin at 2 and 4 mcg/ml. In order to evaluate whether this is correct, we requested that the sponsor send us a line listing and plot of all *S. pneumoniae* strains clinically isolated by the applicant for whom both penicillin and Augmentin MICs were conducted (isolates from clinical studies over the past 5 years). GSK graciously sent us line listing MIC, susceptibility interpretations and plots from 1459 clinical isolates of *S. pneumoniae* using adult and pediatric clinical trial patients and 1265 isolates using adult patients only. The data submitted came from 26 clinical trials, which involved Augmentin XR, Augmentin ES and Gemifloxacin studies. Results of the plot are shown in the applicant's figure 4 below.

Figure 4: Penicillin MIC vs. Amoxicillin/clavulanic acid MIC for Screening *S. pneumoniae* from GSK Clinical Trials - Adult and Pediatric Studies (Bacteriology Intent-to-Treat Population) – Applying Current Augmentin Breakpoints



(*) NOTE : 2:1 Ratio, Amoxicillin concentration plotted.

From this figure, it can be seen that it is common for isolates to be one or two-fold dilution different when comparing penicillin to Augmentin or Augmentin to penicillin MICs. Although such variation is common for antibiotic MIC determinations, which involve two-fold dilutions, some of the variation here seems to be more than expected from normal assay variation. *S. pneumoniae* isolates with Augmentin MICs of 4 tend to have penicillin MICs of two (13 isolates) or four (16 isolates). However, isolates of *S. pneumoniae* with penicillin isolates of 4 have Augmentin MICs of 2, 4,or 8. The distribution of isolates with a penicillin MIC of 4 indicates a population difference and not random assay variation (21 isolates with a MIC of 2 mcg/ml, 13 isolates with 4 µg/mL and 18 isolates with 8 µg/mL). According to these results, approximately 33% of penicillin isolates with a MIC of 4 in these clinical studies have Augmentin MICs of 8. Typical assay variation is seen for clinical isolates with penicillin MICs of two, giving

corresponding Augmentin MICs of 1 mcg/ml for 23 isolates, 2mcg/ml for 73 isolates and 4 mcg/ml for 16 (12%) isolates. The difference is clearly shown in the table below.

Corresponding number of Augmentin isolates* at various MICs for Penicillin MICs of 2 and 4 µg/ml (*Streptococcus pneumoniae* clinical isolates)

Penicillin MIC	Augmentin MIC: 0.5µg/ml	Augmentin MIC: 1µg/ml	Augmentin MIC: 2µg/ml	Augmentin MIC: 4µg/ml	Augmentin MIC: 8µg/ml
4µg/ml, 53 isolates	0 isolates	1 isolate	21 isolates	13 isolates	18 isolates
2µg/ml 128 isolates	5 isolates	23 isolates	73 isolates	16 isolates	1 isolate

*All *S. pneumoniae* isolates from GSK clinical trials during the past 5 years in which MICs were taken for both Penicillin and Augmentin. Augmentin MICs are given as the Amoxicillin component, clavulanic acid is 1/2 the Amoxicillin value.

The PK/PD information, does not support a Augmentin MIC of 8. There is also insufficient clinical data to support a Augmentin XR breakpoint of 8. An Amoxicillin level of 8 is present in serum less than 32% of the dosing interval which is not considered sufficient time for therapeutic efficacy. (The therapeutic efficacy of beta-lactam antibiotics is related to the percentage of the dosing interval that the antibiotic serum level is above the MIC_{90} for susceptible organisms). Therefore, therapeutic efficacy against a Augmentin MIC of 8 and corresponding penicillin MIC of 4 is questionable.

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PRECLINICAL EFFICACY

In vitro

Mechanism(s) of Action.

There are many marketed Augmentin products that have been reviewed previously at the FDA and therefore, the mechanism of action will not be discussed in this review.

Antimicrobial Spectrum of Activity.

Reviewers comment: The most important change to the microbiology section of the labeling proposed by the applicant involves an increase in the breakpoint from 2 to 4 mcg/ml for Augmentin XR versus *S. pneumoniae.* This change would differentiate Augmentin XR from other Augmentin formulations. Therefore the discussion of the antimicrobial spectrum of activity and clinical microbiological clinical results will concentrate on *S. pneumoniae.*

New data obtained in the Alexander 2000 project are presented in this supplement. These results were obtained since the previous submissions for NDA 50-785 which was reviewed by Dr. S. Altaie (Alexander project of 1999) with completion dates of her reviews being 6-1-2001 and 2-19-2002. The Alexander project is an ongoing international survey, monitoring of susceptibility is being conducted in 23 countries to monitor the susceptibility of community-acquired respiratory tract pathogens. In Alexander 2000, a total of 3,442 *S. pneumoniae* isolates were collected and tested in one of three central laboratories in

A summary of the data for susceptibility testing of *S. pneumoniae* from the 2000 Alexander project is shown in the applicant's Tables 1 & 2 below. Results are interpreted using the current NCCLS guidelines except that Augmentin susceptibility results are also interpreted using the applicant's proposed breakpoint of ≤4 ug/ml. Ninety percent or greater susceptibility is shown to Augmentin, Levofloxacin and Ceftriaxone. The macrolides, 73 and 74%, cefaclor, 57 and 45 % and Trimethoprim/Sulfamethoxazole, 65% display decreased activity against *S. pneumoniae*. Other tested antimicrobials showed intermediate levels of activity. The percentage of Augmentin susceptible strains increased from 91 to 94% in the US samples and from 95-97% in the global sample using the breakpoint of 4 instead of 2. The significance of these differences in the clinical setting is unclear. Susceptibility results are similar from the U.S. and global surveys.

Table 1 Susceptibility of *S. pneumoniae* isolated in the USA: Alexander Project 2000 (n = 1,065)

Antimicrobial	MIC_{90} (mcg/mL)	% Susc.[d]
Penicillin	4	67
Amoxicillin[a]	2	91
Amoxicillin/clavulanic acid[ac]	2	91
Amoxicillin/clavulanic acid[bc]	2	94
Cefaclor	≥128	45
Ceftriaxone	1	96
Cefuroxime	8	74
Azithromycin	16	73
Clarithromycin	8	73
Erythromycin	8	73
Trimethoprim/sulfamethoxazole	8	65
Levofloxacin	1	98

[a] Susceptible breakpoint ≤2 mcg/mL for amoxicillin, and ≤ 2/1 mcg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio; MICs are expressed in terms of amoxicillin component

[b] Susceptible breakpoint ≤ 4/2 mcg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio; MICs are expressed in terms of amoxicillin component

[c] *S. pneumoniae* is a non-beta-lactamase-producing organism and, therefore, is susceptible to amoxicillin alone

[d] Susceptibility based on NCCLS 2002 breakpoints unless indicated otherwise.

Table 2 Susceptibility of *S. pneumoniae* from the global population: Alexander Project 2000 (n = 3,442)

Antimicrobial	MIC_{90} (mcg/mL)	% Susc.[d]
Penicillin	2	71
Amoxicillin[a]	2	95
Amoxicillin/clavulanic acid[ac]	2	95
Amoxicillin/clavulanic acid[bc]	2	97
Cefaclor	≥128	57
Ceftriaxone	1	97
Cefuroxime	8	79
Azithromycin	≥64	74
Clarithromycin	≥64	74
Erythromycin	≥64	73
Trimethoprim/sulfamethoxazole	8	65
Levofloxacin	2	99

[a] Susceptible breakpoint ≤ 2 mcg/mL for amoxicillin, and ≤ 2/1 mcg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio; MICs are expressed in terms of amoxicillin component

[b] Susceptible breakpoint ≤ 4/2 mcg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio; MICs are expressed in terms of amoxicillin component

[c] *S. pneumoniae* is a non-beta-lactamase-producing organism and, therefore, is susceptible to amoxicillin alone

[d] Susceptibility based on NCCLS 2002 breakpoints.

The *in vitro* activity of Augmentin against penicillin susceptible, intermediate and resistant strains isolated from the 2000 Alexander study is shown in Table 3. 100% of the penicillin susceptible and intermediate *S. pneumoniae* isolates were susceptible to Augmentin using breakpoints of 2 or 4 ug/ml. For the penicillin resistant strains, the Augmentin MIC_{90} was 8 ug/ml with percent susceptibilities of 62 and 73 for breakpoints of 2 and 4 respectively for US isolates and 74 and 86 for global isolates. This equates to an ***in vitro*** increase of 18% and 16% in the proportion of PRSP isolates susceptible to the new Augmentin XR formulation when the breakpoint is increased from 2 to 4 in the US and global studies respectively.

Table 3 Activity of amoxicillin/clavulanic acid[a] against *S. pneumoniae* isolated in the Alexander 2000 Project categorized by penicillin susceptibility.

	US (n = 1,064)				All Geographic regions (n = 3,442)			
	N	MIC_{90}	%S ≤ 2[b]	%S ≤ 4[c]	N	MIC_{90}	%S ≤ 2	%S ≤ 4
Penicillin-Susceptible	709	0.03	100%	100%	2,427	0.03	100%	100%
Penicillin-Intermediate	114	1	100%	100%	405	1	100%	100%
Penicillin-Resistant	242	8	62%	73%	610	8	74%	86%

[a] *S. pneumoniae* is a non-beta-lactamase-producing organism and, therefore, is susceptible to amoxicillin alone; MICs are expressed in terms of amoxicillin component

[b] Susceptible at ≤ 2/1 mcg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio

[c] Susceptible at ≤ 4/2 mcg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio

The number of isolates at each MIC and the cumulative percent frequency distribution for Augmentin and comparator agents against *S. pneumoniae* are presented in Tables 4 and 5 for the 2000 Alexander surveillance study. Frequency distributions for Amoxicillin, Augmentin and penicillin were almost identical at all MIC levels, U.S, (Table 4) and all geographic regions (Table 5). Of special interest are the levels around the present and proposed breakpoints. At a breakpoint of 2 mcg/ml, penicillin's cumulative frequency is 89.6%, Augment's 91.4 and amoxicillin's 91.2. At a breakpoint of 4 mcg/ml, penicillin has a slightly higher cumulative frequency, 99.2%, Augmentin and amoxicillin 93.9% (Table 4, US results). Similar results were seen in the global population but percentages were closer together for the three different antibacterials. Since *in vitro* antibacterial activities versus *S. pneumoniae* are almost identical for the three antibacterials, clinical results and PK/PD will be the deciding factors. It is of interest that cumulative MIC frequencies for Clindamycin, Ceftriaxone and Levofloxacin indicated that they have better *in vitro* activity versus *S. pneumoniae* than do Penicillin or Amoxicillin. Augmentin.

Table 4 Frequency distribution of amoxicillin/clavulanic acid and comparator MICs (mcg/mL) for *S. pneumoniae* from the 2000 Alexander surveillance study – US (n = 1,065)

N Cumulative %	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32
Penicillin	512* 48.1%	149 62.1%	48 66.6%	36 70.0%	23 72.1%	27 74.3%	28 77.3	131 89.6%	102 99.2%	6 99.7%	3** 100%	
Amoxicillin	78* 7.32%	581 61.9%	52 66.8%	29 69.5%	26 71.9%	28 74.6%	42 78.5%	135 91.2%	29 93.9%	56 99.2%	6 99.7%	3** 100%
Amox/clav[1]	76* 7.14%	588 62.3%	50 67.0%	35 70.3%	19 72.1%	32 75.1%	39 78.8%	134** 91.4%	27 93.9%	56 99.2%	6 99.7%	3** 100%
Cefaclor						139* 13.1%	342 45.2%	244 68.1%	52 73%	18 74.6%	11 75.7%	259** 100%
Cefprozil				392** 36.8%	298 64.8%	60 70.4%	38 74.0%	15 75.4%	20 77.3%	75 84.3%	96 93.3%	71** 100%
Cefuroxime	14* 1.31%	459 44.4%	143 57.8%	60 63.5%	73 70.3%	25 72.7%	13 73.9%	20 75.8%	117 86.7%	119 97.9%	11 99.0%	11** 100%
Cefdinir	6* 0.56%	31 3.47%	559 56.0%	86 64.0%	71 70.7%	33 73.8%	18 75.5%	10 76.4%	60 82.1%	167 97.7%	18 99.4%	6 100%
Ceftriaxone	294* 27.6%	356 61%	78 68.4%	28 71%	36 74.4%	60 80%	173 96.2%	27 98.8%	9 99.6%	4** 100%		
Erythromycin	7* 0.66%	124 12.3%	624 70.9%	18 72.6%	6 73.1%	1 73.2%	6 73.8%	26 76.2%	69 82.7%	84 90.6%	8 91.4%	92** 100%
Clarithromycin	29* 2.72%	669 65.5%	73 72.4%	4 72.8%	5 73.2%	7 73.9%	9 74.7%	47 79.2%	64 85.2%	63 91.1%	3 91.4%	92** 100%
Azithromycin		23** 2.16%	420 41.6%	325 72.1%	7 72.7%	5 73.2%	6 73.8%	19 75.5%	53 80.5%	91 89.1%	23 91.2%	93** 100%
Clindamycin	9* 0.85%	134 13.4%	800 88.6%	22 90.6%	5 91.1%	4 91.5%	1 91.6%	5 92%	85** 100%			
TMP/SMX[2]			6* 0.56%	180 17.5%	458 60.5%	53 65.4%	48 70.0%	17 71.6%	142 84.9%	125 96.6%	36** 100%	
Levofloxacin				2* 0.19%	3 .47%	325 31.0%	708 97.5%	10 98.4%	17** 100%			

* Isolates reported at this MIC may have MIC values that are lower. ** Isolates reported at this MIC may have MIC values that are higher.

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

[2]TMP/SMX: Trimethoprim/ sulfamethoxazole was tested at a 1: 19 ratio; MICs are expressed in terms of the trimethoprim concentration.

Table 5 Frequency distribution of amoxicillin/clavulanic acid and comparator MICs (mcg/mL) for *S. pneumoniae* from the 2000 Alexander surveillance study – all geographic regions (n = 3,442)

Total N Cumulative%	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32
Penicillin	1,708* 49.6%	525 64.9%	194 70.5%	125 74.1%	94 76.8%	88 79.4%	98 82.3%	354 92.6%	240 99.6%	11 99.9%	5** 100%	
Amoxicillin	221* 6.4%	2,062 66.3%	194 71.9%	109 75.1%	97 77.9%	76 80.1%	122 83.6%	390 94.9%	83 97.3%	73 99.4%	15** 100%	
Amox/clav[1]	221* 6.4%	2,101 67.4%	166 72.2%	126 75.9%	75 78.1%	82 80.5%	122 84.0%	389 95.3%	72 97.4%	75 99.6%	13** 100%	
Cefaclor						481* 14%	1,487 57.2%	572 73.8%	130 77.6%	51 79.1%	36 80.1%	685** 100%
Cefprozil				1,480* 43%	932 70.1%	172 75.1%	112 78.4%	49 79.8%	75 82.0%	209 88.1%	310 97.1%	103** 100%
Cefuroxime	52* 1.5%	1,414 42.6%	656 61.7%	191 67.3%	221 73.7%	113 77.0%	67 79%	52 80.5%	292 89.0%	327 98.5%	38 99.6%	19** 100%
Cefdinir	18* 0.5%	107 3.6%	1,844 57.2%	405 69.0%	200 74.8%	124 78.4%	47 79.8%	34 80.7%	159 85.4%	429 97.8%	64 99.7%	11** 100%
Ceftriaxone	831* 24.1%	1384 64.4%	250 71.6%	125 75.2%	138 79.3%	137 83.2%	456 96.5%	97 99.3%	17 99.8%	7** 100%		
Erythromycin	28* 0.8%	275 8.8%	2107 70.0%	110 73.2%	7 73.4%	5 73.6%	14 74.0%	68 75.9%	162 80.7%	133 84.5%	25 85.2%	508** 100%
Clarithromycin	107* 3.1%	1,648 51.0%	760 73.1%	7 73.3%	9 73.5%	13 73.9%	26 74.7%	120 78.2%	126 81.8%	102 84.8%	21 85.4%	503** 100%
Azithromycin		70* 2.0%	748 23.8%	1,642 71.5%	59 73.2%	10 73.5%	12 73.8%	54 75.4%	123 79.0%	145 83.2%	61 85.0%	518** 100%
Clindamycin	35* 1.0%	351 11.2%	2,336 79.1%	208 85.1%	11 85.4%	5 85.6%	4 85.7%	6 85.9%	486** 100%			
TMP/SMX[2]			14* 0.4%	390 11.7%	1,3385 0.6%	500 65.1%	285 73.4%	134 77.3%	365 87.9%	267 95.7%	149** 100%	
Levofloxacin				2* 0.06%	10 0.35%	1,039 30.5%	2,308 97.6%	40 98.8%	43** 100%			

* Isolates reported at this MIC may have MIC values that are lower. ** Isolates reported at this MIC may have MIC values that are higher

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

[2]TMP-SMX: Trimethoprim/ sulfamethoxazole was tested at a 1: 19 ratio; MICs are expressed in terms of the trimethoprim concentration.

In vitro activity against *H. influenzae* and *M. catarrhalis*.

Augmentin is a mixture of amoxicillin plus the beta-lactamase inhibitor, clavulanic acid. Approximately 25% of all *H. influenzae* clinical isolates are beta-lactamase producers and therefore should remain sensitive to Augmentin. In the 2000 Alexander survey, a MIC_{90} of 1 mcg/ml and a percent susceptibility of 99% were observed at a breakpoint of ≤4 mcg/ml. Ceftriaxone and levofloxacin were more active *in vitro* than Augmentin *versus H. influenzae*, with MIC_{90s} of ≤ 0.015 mcg/ml.

Almost all-clinical isolates of *M. catarrhalis* are beta-lactam producers. Isolates from the 2000 Alexander study had MIC_{90s} of 0.25mcg/ml and 100% susceptibility to Augmentin at a breakpoint of ≤4mcg/ml. Amoxicillin and ampicillin were relatively inactive against *M. catarrhalis* while levofloxacin and ceftriaxone were more active than Augmentin versus *M. catarrhalis* in these *in vitro* studies.

Mechanism(s) of Resistance Studies concerning *S. pneumoniae*:

An *in vitro* study involving the passage of twenty *S. pneumoniae* isolates in the presence of sub-MIC concentrations (0.5 mcg/mL) of antibiotic was conducted. The strains were passed in four different antibiotics for a total of 9 days. Antibiotics tested included Augmentin, Levofloxacin, azithromycin and cefaclor with MICs monitored at baseline and at subsequent passage.

Isolates were grouped according to the following criteria as closely as possible based on the available culture collections:

A. Amoxicillin/clavulanic acid MICs of 2, 4 and 8 mcg/ml

B. Susceptible to beta-lactam agents but azithromycin resistant (strains with known mef and erm resistance mechanisms were included)

C. Susceptible to beta-lactam agents and azithromycin, but Levofloxacin resistant

D. Susceptible to all study agents

E. Resistant to all agents (isolates may have had MICs at or near the NCCLS resistant breakpoint)

Results are shown in the following table, 17. Augmentin showed the least development of resistance and the development was not affected by baseline MIC. Augmentin resistance levels were mainly unchanged and only two of the twenty isolates had a ≥ 4-fold increase in their Augmentin MIC. Azithromycin and Levofloxacin were most effected by repeated exposure to sub-MIC levels of antibiotic. For Azithromycin, twelve strains had a ≥ 4-fold increase in MIC while for Levofloxacin 9 strains had a ≥ 4-fold increase in MIC.

The mechanism(s) of resistance were not studied.

Table 17 Macrodilution MIC (mcg/mL) at baseline and following 9 days of testing in presence of subinhibitory concentrations of antimicrobial agent

Isolate Number	Amox./Clav.		Azithromycin		Cefaclor		Levofloxacin	
	Baseline	Day 9	Baseline	Day 9	Baseline	Day 9	Baseline	Day 9
Group A								
101A								
102A								
103A								
104A								
105A								
106A								
Group B								
107B								
108B								
109B								
110B								
111B								
Group C								
112C								
113C								
114C								
115C								
Group D								
116D								
Group E								
117E								
118E								
119E								
120E								

*Result as of day 7; no growth or contaminated on subsequent days
NT=Not tested (baseline ≥64 mcg/mL)

Development of resistance during the clinical trials

Increases in MICs and decreases in zone sizes for Augmentin and comparators were monitored during the clinical studies. No significant changes were seen in MIC or Zone sizes in isolates from patients comparing results before with those after Augmentin treatment and therefore, resistant strains did not develop in patients treated with Augmentin in these clinical trials. Six strains isolated after treatment with comparators demonstrated significant changes in MIC and/or zone sizes but these were not characterized.

***In vitro* Activity of Augmentin and other antibiotics against *S. pneumoniae* resistant to Penicillin and Erythromycin**

The cumulative *in vitro* activity of Augmentin and other antibiotics against *S. pneumoniae* isolates from the US and all geographic regions resistant to penicillin and macrolide antibiotics were examined as part of the Alexander 2000 survey. Concerning penicillin resistant isolates, the frequency distribution was identical for Amoxicillin and Augmentin. Penicillin was less active than Augmentin and amoxicillin at 2 mcg/ml and slightly more active at 4 and 8 mcg/ml. Levofloxacin and Ceftriaxone were more active than penicillin, amoxicillin or Augmentin on a MIC basis. Data for all geographic regions is shown in table 7 below. Because of the similar MIC frequencies of Penicillin, Amoxicillin, and Augmentin, antibiotic activity and thus breakpoints will depend on clinical results and PK/PD considerations. 85.6% of PRSP were susceptible to Augmentin at a breakpoint of 4 mcg and 73.8 at a breakpoint of 2 mcg/ml. Since frequency distributions are almost identical for Amoxicillin, Augmentin and penicillin, and all 3 have the Beta-lactam ring. Organism cross-resistance on an *in vitro* MIC basis is common when resistance is not based on Beta-lactamase.

Table 7 Frequency distribution of amoxicillin/clavulanic acid and comparator MICs (mcg/mL) for penicillin -resistant *S. pneumoniae* from the 2000 Alexander surveillance study – all geographic regions (N = 610)

N Cumulative %	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32
Penicillin								354 58.0%	240 97.4%	11 99.2%	5** 100%	
Amoxicillin						9 1.48%	59 11.1%	371 72.0%	83 85.6%	73 97.5%	10 99.2%	5** 100%
Amox/clav[2]						11 1.80%	67 12.8%	372 73.8%	72 85.6%	75 97.9%	8 99.2%	5** 100%
Cefaclor						1* 0.2%	1 0.33%	2 0.66%	1 0.82%	1 0.98%	1 1.2%	603** 100%
Cefprozil				1* 0.16%	2 0.49%			2 0.82%	18 3.77%	178 33.0%	308 83.4%	101** 100%
Cefuroxime								5 0.82%	225 36.9%	326 53.4%	36 5.90%	18** 2.95%
Cefdinir			3* 0.49%				2 0.82%	4 1.48%	106 18.9%	420 87.7%	64 98.2%	11** 100%
Ceftriaxone						62* 10.2%	431 80.8%	94 96.2%	17 99%	6** 100%		
Erythromycin	2* 0.33%	25 4.43%	142 27.7%	1 27.9%	1 28.0%	2 28.4%	4 29.0%	47 36.7%	110 54.8%	69 66.1%	3 66.6%	204** 100%
Clarithromycin	6* 0.98%	136 23.3%	27 27.7%	1 27.9%	2 28.2%	5 29.0%	18 32.0%	82 45.4%	81 58.7%	46 66.2%	3 66.7%	203** 100%
Azithromycin		4* 0.68%	48 8.52%	114 27.2%	4 27.9%	1 28.0%	4 28.7%	36 34.6%	92 49.7%	82 63.1%	19 66.2%	206** 100%
Clindamycin	8* 1.31%	56 10.5%	316 62.3%	30 67.2%	2 67.5%	2 67.9%			196** 100%			
TMP/SMX[2]				10* 1.64%	28 6.23%	37 12.3%	44 19.5	14 21.8%	223 58.4%	153 83.4%	101** 100%	
Levofloxacin						215 35.2%	370 95.9%	5 96.7%	20** 100%			

* Isolates reported at this MIC may have MIC values that are lower. ** Isolates reported at this MIC may have MIC values that are higher.

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

[2]TMP/SMX: Trimethoprim/ sulfamethoxazole was tested at a 1: 19 ratio; MICs are expressed in terms of the trimethoprim concentration.

Concerning erythromycin resistant isolates, the *in vitro* MIC frequency distribution was identical for Amoxicillin and Augmentin. Penicillin was less active at 2

mcg/ml and slightly more active at 4 and 8 mcg/ml. Levofloxacin and Ceftriaxone were more active than penicillin, amoxicillin or Augmentin on a MIC basis. Data for all geographic regions is shown in table 9 below. Because of the similar MIC frequencies of Penicillin, Amoxicillin, and Augmentin, antibiotic activity and thus breakpoints will depend on clinical results and PK/PD considerations. 91.8% of erythromycin resistant *S. pneumoniae* were susceptible to Augmentin at a breakpoint of 4 mcg and 85.5% at a breakpoint of 2 mcg/ml. Results from the US concerning Augmentin activity against penicillin and Erythromycin resistant isolates of *S. pneumoniae* from the US were similar to those from all geographic regions but will not be shown.

Table 9 Frequency distribution of amoxicillin/clavulanic acid and comparator MICs (mcg/mL) for macrolide-resistant (erythromycin MIC ≥ 1mcg/mL) *S. pneumoniae* from 2000 Alexander surveillance study – all geographic regions (N = 910)

N Cumulative %	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32
Penicillin	132* 14.5%	80 23.3%	65 30.4%	59 36.9%	46 42.0%	29 45.2%	62 52.0%	217 75.8%	206 98.5%	9 99.5%	5** 100%	
Amoxicillin	23* 2.53%	197 24.2%	74 32.3%	45 37.3%	48 42.5%	51 48.1%	67 55.5%	267 84.8%	62 91.6%	63 98.6%	8 99.5%	5** 100%
Amox/clav[1]	18* 1.98%	213 25.4%	65 32.5%	60 39.1%	36 43.1%	56 49.2%	66 56.5%	264 85.5%	57 91.8%	64 98.8%	6 99.5%	5** 100%
Cefaclor						36* 4%	165 22.1%	132 36.6%	56 42.7%	19 44.8%	20 47%	482** 100%
Cefprozil				120* 13.2%	141 28.7%	82 37.7%	54 43.6%	21 45.9%	55 52.0%	118 64.9%	237 91.0%	82** 100%
Cefuroxime	1* 0.11%	105 11.6%	72 19.6%	51 25.2%	87 34.7%	45 39.7%	37 43.7%	29 46.9%	186 67.4%	255 95.4%	30 98.7%	12** 100%
Cefdinir		17* 1.87%	144 17.7%	75 25.9%	88 35.6%	68 43.1%	27 46.0%	23 48.6%	91 58.6%	317 93.4%	54 99.3%	6** 100%
Ceftriaxone	52* 5.71	146 21.8%	86 31.2%	53 37%	68 44.5%	83 53.6%	324 89.2%	80 98%	11 99.2%	7** 100%		
Erythromycin							14 1.54%	68 9.01%	162 26.8%	133 41.4%	25 44.2%	508** 100%
Clarithromycin						12 1.32%	26 4.18%	120 17.4%	126 31.2%	102 42.4%	21 44.7%	503** 100%
Azithromycin						1 0.11%	9 1.10%	53 6.92%	123 20.4%	145 36.4%	61 43.1%	518** 100%
Clindamycin	5* 0.55%	66 7.80%	294 40.1%	35 44.0%	11 45.2%	5 45.7%	4 46.2%	4 46.6%	486** 100%			
TMP/SMX[2]				48 5.27%	135 20.1%	99 31.0%	106 42.6%	44 47.5%	247 74.6%	147 90.8%	84** 100%	
Levofloxacin					2 0.22%	325 35.9%	544 95.7%	14 97.3%	25** 100%			

* Isolates reported at this MIC may have MIC values that are lower. ** Isolates reported at this MIC may have MIC values that are higher

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

[2] TMP/SMX: Trimethoprim/ sulfamethoxazole was tested at a 1: 19 ratio; MICs are expressed in terms of the trimethoprim concentration.

Epidemiological Studies (Published Literature).

In vitro data

Frequency distributions of MIC values for Augmentin were obtained from a variety of studies including the Augmentin Global Surveillance Study, the 2000 Alexander Surveillance Study, the Alert Hospital study, and the 1999 Cast study. The survey frequencies were compared to the MIC frequency distribution of organisms from the Augmentin XR phase III clinical study isolates including CAP, ——— ABS studies. The Augmentin XR results were derived from the intent to treat results. Frequency bar graphs showing the numbers of isolates by MICs were presented for these organisms: *S. pneumoniae, Haemophilus sp.* including *H. influenzae* and *H. parainfluenzae; K.pneumoniae; M. catarrhalis; methicillin susceptible Staphylococcus aureus (MSSA)* and *S. pyogenes.* Frequency graphs were included for the combination of all surveillance studies and for each individual study for each organism (since there was a US and global figure for each study as well as an overall distribution figure, there were at least 8 figures for each organism). Most of the surveillance studies were also presented in the previous Augment XR microbiology reviews(Reviews of Dr. S. Altaie for 50785 with completion dates of 6-1-2001 and 2-19-2002). The MIC frequency distribution of individual organisms in the combined surveillance studies is similar if not identical to the MIC frequency distributions from the combined clinical studies. Therefore, the organisms isolated in the clinical study appear to be representative of the global distribution of organisms at the time of conducting the clinical studies.

In vivo

Pharmacokinetics/Bioavailability (Human and animal).
Animal Prophylactic and Therapeutic Studies.

HUMAN STUDIES

Human pharmacokinetic data are presented and discussed on page 4 of this review. This data appears favorable in that Augmentin levels remain above the proposed breakpoint of 4 mcg/ml for approximately 49% of the dosing interval for total drug and 46%for free drugs.

Reviewers Comment: I have the following concerns. Optimum pharmacokinetics was obtained when the drug was taken at the beginning of a meal. What is the kinetics at other times? The SD might be too large, leading to significant patients with MIC_{90s} at 4 for less than 30% of the dosing interval. The PK reviewer should address these questions. Our breakpoint depends on a true PK/PD profile.

Animal studies

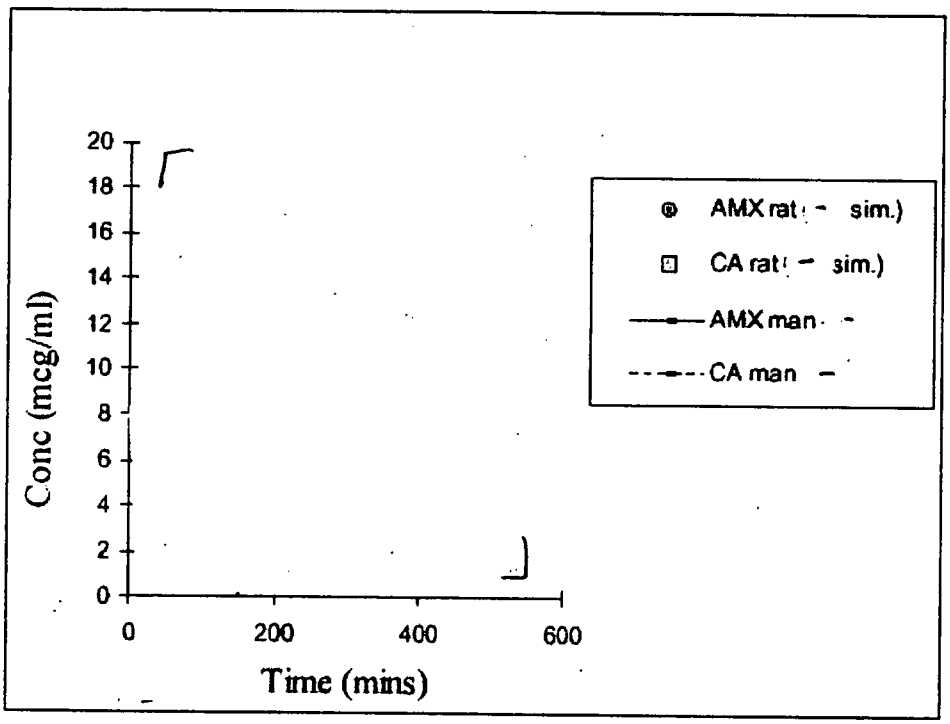
A rat respiratory model was used to examine the efficacy of Augmentin versus 7 strains of *S. pneumoniae* and one strain of *H. influenzae.* The *S. pneumoniae*

strains were chosen to be above and below the applicant's suggested Augmentin XR breakpoint of 4 mcg/ml for *S. pneumoniae*. The infection was seeded intrabronchially. Treatment in the rat was by infusion designed to mimic in rat plasma, human pharmacokinetics following oral administration of 2000/125 BID of Augmentin XR. It is of interest that Augmentin protein binding in rat serum is approximately the same as Augmentin protein binding in humans, 16 and 18% respectively. Dosing in the animals continued for 3 days and 14 hours after cessation of therapy the animals were euthanised and the lungs were removed aseptically for bacteriological assessment

APPEARS THIS WAY
ON ORIGINAL

Amoxicillin and clavulanic acid concentrations in the rats are shown in figure 86 below along with the concentrations in man. As shown in the figure, the actual human and rat simulated concentrations are similar and follow similar kinetics.

Figure 86 Simulated concentrations in rats of amoxicillin/clavulanic acid (XR) in comparison with human concentrations



The efficacy of Augmentin XR versus respiratory infections in the rat caused by 7 isolates of *S. pneumoniae* with different in vitro susceptibilities to Augmentin and one isolate of *H. influenzae* are shown in table 35 below. Bacterial counts were conducted and expressed as cfu/lungs. In all cases there was at least a three-log difference between

the numbers of bacteria in lungs of treated and untreated rats. Therefore, Augmentin XR demonstrated good efficacy in a rat model of respiratory disease caused by 7 strains of *S. pneumoniae* and one strain of *H. influenzae*. MICs for the infecting isolates ranged from 2-8 mcg/ml of Augmentin. Although results are impressive, bacterial counts, not cures, is the end-point for the rat studies while dosing is oral in humans and was IV in rats. Therefore, the relationship of these studies to human results is predictive and suggestive only.

Table 35 Efficacy of Augmentin XR against respiratory tract infections in the rat caused by *S.pneumoniae* and *H. influenzae* with differing *in vitro* susceptibilities

Organism	AMX/CA MIC (mcg/mL**)	Log_{10} cfu/lungs (Mean ± s.d.)	
		Non treated Controls	AUG XR treated
S. pneumoniae			
05010S	2.0/1.0	7.3 ± 0.4	≤1.7*
16001S	4.0/2.0	5.7± 1.2	2.2 ± 0.8*
30005S	4.0/2.0	7.1 ± 0.7	2.3 ± 0.9*
20009S	4.0/2.0	7.1 □ 0.4	2.5 □ 0.9*
05003S	8.0/4.0	6.4 ± 0.6	2.0 ± 0.9*
404053	8.0/4.0	6.8 ± 0.4	3.8 ± 1.4*
47003S	8.0/4.0	6.0 ± 0.3	1.8 ± 0.2*
H. influenzae			
Chesterfield (BLNAR)	4.0/2.0	6.1 ± 0.6	3.1 ± 0.9*

* significantly different to untreated animals $p<0.01$)
** Amoxicillin/clavulanic acid tested in a 2:1 ratio

Other animal models were mentioned in the submission but without as much detail (discussed in detail in the previously mentioned reviews of Dr. S. Altaie). Models

included, a neutropenic mouse thigh model using *S. pneumoniae*, a neutropenic mouse pneumoniae model using *S. pneumoniae*, an immunocompromised rat pneumonia model using strains of *H. influenzae.* In these models, a maximal effect was achieved when the T> MIC was 35-40%. In humans, a MIC of 8 mcg/ml is achieved for less than 35% of the dosing interval. Therefore, these results in animals are analogous to a possible Augmentin susceptibility breakpoint of 4.

CLINICAL EFFICACY

Clinical Microbiology

Disk content Studies.

Disk content studies were not included in this submission because the disk used to interpret susceptibility of the previously approved Augmentin clinical products is used for susceptibility testing of Augmentin XR. The paper disk is impregnated with 20 mcg of Amoxicillin and 10 mcg of clavulanate potassium.

MIC broth/agar dilution comparisons.

Agar dilution methods are not conducted for Augmentin products.

MIC/Disk diffusion Correlation Studies.

Data from the Augmentin global surveillance Study and the Augmentin Phase III studies, all indications were used to generate scattergrams by plotting Log to the base 2 of MIC versus zone of inhibition to determine disk breakpoints.

Plots were presented for *H. influenzae*, *H. parainfluenzae*, *K. pneumoniae* (*Enterobacteriaceae*), and Methicillin susceptible *S. aureus*. In all cases the amount of major and Very major errors was small, ≤ 2.8% leading to proposed zone correlates as follows:

Organism	Zone Size (mm) S	I	R
Haemophilus sp.	≥ 20	–	≤ 19
Staphylococcus sp.	≥ 20	–	≤ 19
Enterobacteriaceae	≥ 18	14-17	≤ 13

Quality Control Studies (MIC and Disk diffusion).

Quality control information was presented and discussed in the previous microbiological reviews for Augmentin XR.

Anaerobic studies

In vitro or *In vivo* anaerobic studies were not presented as part of this submission. A variety of anaerobes are involved in the etiology of [redacted] but only a few genera that are isolated and considered causes of acute sinusitis. These genera include: Bacteroides, Peptostreptococcus, Fusobacterium and Veillonella. In CAP, anaerobes are almost always isolated as part of mixed infections and are not considered a primary pathogen. Since neither *in vitro* nor *in vivo* studies were presented to demonstrate the activity of Augmentin versus anaerobes, these organisms will not be included in list two of the package insert.

Bacteriological Efficacy
Correlation of Test Results with Outcome Statistics.

Acute Bacterial Sinusitis:

Results are presented from three clinical studies, 550, 551 and 590 but microbiological results were only obtained from two of the studies, 551 and 592.
A summary of combined clinical/radiological, clinical and bacteriological response from the three Sinusitis studies is shown in the applicant's table 20. The three studies 550 show non-inferiority to Levofloxacin for clinical success rates. In the non-comparative studies, 592 and 551, bacteriological success rates of 87.7 and 89% were seen in the ITT population while success rates of 93.1 and 96.4% were observed in the PP population.

Table 20 Summary of Combined Clinical/Radiological, Clinical and Bacteriological Success Rates at Test of Cure: ABS Principal Studies 550, 551 and 592

	Success Rate		
	Augmentin XR % (n/N)	Levofloxacin* % (n/N)	Treatment Difference % (95% CI)**
COMBINED CLINICAL/RADIOLOGICAL RESPONSE			
Clinical PP Population			
550	83.7% (103/123)	84.3% (118/140)	-0.5(-9.4, 8.3)
551	89.7% (628/700)	-	(87.2, 91.8)
592	93.8% (669/713)		(91.7, 95.4)
ITT Population			
550	76.4% (136/178)	83.0% (151/182)	-6.6 (-14.9, 1.7)
551	84.8% (682/804)	-	(82.1, 87.2)
592	87.0% (749/861)		(84.5, 89.1)
CLINICAL RESPONSE			
Clinical PP Population			
550	87.0% (107/123)	88.6% (124/140)	-1.6 (-9.5, 6.4)
551	92.7% (649/700)	-	(90.5, 94.5)
592	94.8% (676/713)		(92.8, 96.3)
ITT Population			
550	82.0% (146/178)	88.5% (161/182)	-6.4 (-13.7, 0.9)
551	87.9% (707/804)	-	(85.4, 90.1)
592	88.4% (761/861)		(86.0, 90.4)
BACTERIOLOGICAL RESPONSE			
Bacteriology ITT Population			
551	87.7% (315/359)	-	(83.8, 90.9)
592	89.0% (414/465)		(85.7, 91.7)
Bacteriology PP Population			
551	93.1% (299/321)	-	(89.7, 95.6)
592	96.4% (373/387)		(93.9, 97.9)

Data Source: Abridged Study 550, Section 11, Tables 11.03a, 11.03b, 11.14a and 11.14b; Abridged Study 551, Section 11, Tables 11.03a, 11.03b, 11.33a, 11.33b, 11.44a and 11.44b; Study 592, Section 11, Tables 11.03a, 11.03b, 11.33a, 11.33b, 11.44a and 11.44b;

* Levofloxacin 500mg once daily for 10 days.

** Non-inferiority limit was prospectively defined as ≥-15% for Study 550. Treatment difference not applicable for Study 551 and Study 592.

Note: Results of the bacteriological assessment for Study 550 are not reported in the ISE due to the small number of patients investigated bacteriologically and the sampling method used (sinus endoscopy or rhinoscopy).

Efficacy of Augmentin XR against resistant pathogens in ABS studies 551 and 592

High rates of cure were observed in patients treated with Augmentin XR infected with penicillin or erythromycin resistant *S. pneumoniae* or beta-lactamase producing *H. influenzae, M. catarrhalis* or *S. aureus* (MSSA). The cure rates in the per protocol and intent to treat populations were virtually identical for both bacteriological and clinical results. Therefore, Augmentin XR is active against resistant organisms, those resistant by virtue of Beta-lactamase production (*H. influenzae, M. catarrhalis* or *S. aureus* (MSSA)) or by virtue of changes in penicillin binding proteins (*S. pneumoniae*) or those resistant to macrolides (*S. pneumoniae*). The difference between these clinical studies and those with previous Augmentin formulations is the finding of a small increase in the number of patients whose infections are caused by PRSP and their clinical and bacteriological cure when treated with Augmentin XR. However since there is no control antibiotic in these

studies, the results are stand-alone results for Augmentin XR. These results show the efficacy of Augmentin XR versus small numbers of patients infected with PRSP but do not compare these results with another antibiotic or Augmentin formulation. Bacteriological and clinical cure rates for these uncontrolled studies of resistant organisms, studies 551 and 592 are shown in tables 21, 23, and 24 below.

Table 21 Rates of Bacteriological Success at Test of Cure by Beta-Lactamase Production: Combined ABS Principal Uncontrolled Studies 551 and 592 (Bacteriology ITT and PP Populations)

		Augmentin XR 2000/125 mg bid			
		Bacteriology PP		Bacteriology ITT	
		n/N	%	*n/N*	%
H. influenzae	beta-Lactamase Positive	29/30	(96.7)	31/34	(91.2)
	beta-Lactamase Negative	134/143	(93.7)	149/172	(86.6)
M. catarrhalis	beta-Lactamase Positive	56/57	(98.2)	62/68	(91.2)
	beta-Lactamase Negative	8/8	(100)	8/9	(88.9)
S. aureus (MSSA)	beta-Lactamase Positive	25/28	(89.3)	26/31	(83.9)
	beta-Lactamase Negative	2/3	(66.7)	3/4	(75.0)

Data Source: ISE Tables 8.G.4.2.11s and 8.G.4.2.12s
n/N = number of successes/ number of beta-lactamase positive or negative isolates.
Note: If a patient had more than one isolate of a specified pathogen with beta-lactamase data, all of the isolates have been included in this table.

Table 23 Rates of Bacteriological Success By *S. pneumoniae* Screening Susceptibility to Penicillin: ABS Studies 551 and 592 Combined (Bacteriology PP and ITT Populations)

	Augmentin XR			
	Bacteriology PP		Bacteriology ITT	
	n/N	(%)	*n/N*	(%)
ABS Studies 551 and 592	N = 232		N = 257	
Susceptible (≤ 0.06 mcg/mL)	160/165	(97.0)	168/183	(91.8)
Intermediate (0.12-1 mcg/mL)	26/27	(96.3)	27/30	(90.0)
Resistant (≥ 2 mcg/mL)	37/37	(100)	40/40	(100)

Data Source: ISE Tables M8.G.4.2.69s, M8.G.4.2.70s
n/N = number of successes/number of susceptible, intermediate or resistant isolates.
N = total number of patients with *S. pneumoniae*. For patients with > 1 isolate, the bacteriological response is counted for each isolate.
NCCLS 2002 breakpoints were applied [1].

Table 24 Rates of Clinical and Bacteriological Success at Test of Cure By *S. pneumoniae* Screening Susceptibility to Erythromycin: Combined ABS Studies 551 and 592 (Bacteriology PP and ITT Populations)

	Augmentin XR			
	Bacteriology PP		Bacteriology ITT	
Susceptibility to Erythromycin	*n/N*	(%)	*n/N*	(%)
CLINICAL EFFICACY				
ABS Studies 551 and 592	N = 232		N = 257	
Susceptible (≤ 0.25 mcg/mL)	165/169	(97.6)	173/188	(92.0)
Intermediate (0.5 mcg/mL)	1/1	(100)	1/1	(100)
Resistant (≥ 1.0 mcg/mL)	57/59	(96.6)	61/64	(95.3)
BACTERIOLOGICAL EFFICACY				
ABS Studies 551 and 592	N = 232		N = 257	
Susceptible (≤ 0.25 mcg/mL)	165/169	(97.6)	173/188	(92.0)
Intermediate (0.5 mcg/mL)	1/1	(100)	1/1	(100)
Resistant (≥ 1.0 mcg/mL)	57/59	(96.6)	61/64	(95.3)

Data Source: ISE Tables M8.G.4.2.3s, M8.G.4.2.4s, M8.G.4.2.71s, M8.G.4.2.72s
n/N = number of successes/number of susceptible or resistant isolates.
N = total number of patients with *S. pneumoniae*. For patients with > 1 isolate, the response is counted for each isolate.
NCCLS 2002 breakpoints were applied [1].

Community Acquired Pneumoniae: Clinical efficacy

Four clinical studies were conducted to evaluate the efficacy of Augmentin XR versus CAP. Three of the studies 546, 556 and 557 had comparators with the primary response evaluated parameter being clinical response, bacteriological response was evaluated as a secondary efficacy endpoint. In the non-controlled study, 547, per patient bacteriological response were the primary endpoint and clinical response was the secondary end-point. In the comparative studies, various Augmentin formulations were used as the comparator, in 546 and 557, Augmentin 875/125 BID and in 556, Augmentin 1000/125 BID was the comparators.

Table 25 is the summary of clinical and bacteriological success rates. . In studies 546 and 557, where Augmentin 875/125 was the comparator, clinical equivalence was demonstrated statistically with high cure rates in both the PP and ITT populations. In study 556, with 1000/125 as the comparator, clinical equivalency was demonstrated. Bacteriological cure rates appeared to be similar but were not analyzed statistically due to the small number of patients. In the non-comparative study, 547, the bacteriological response were the primary endpoint and bacteriological cure rates were 83% in the ITT population and 78% in the PP population.

The numbers of pneumoniae patients infected with PRSP at the proposed breakpoint of 4 or greater was small, 5 patients total.

Table 25- Summary of Clinical and Bacteriological Success Rates at Test of Cure by Treatment and Indication for Patients with Community Acquired Pneumonia

	Success Rate		
	Augmentin XR % (n/N)	Comparator* % (n/N)	Treatment Difference % (95% CI)*
CLINICAL RESPONSE – CAP			
Clinical PP Population			
546	86.3 (176/204)	91.2 (186/204)	-4.9 (-11.0, 1.2)
556	91.5 (108/118)	93.0 (106/114)	-1.5 (-8.3, 5.4)
557	96.0 (121/126)	92.2 (118/128)	3.8 (-1.9, 9.6)
547	85.6 (721/842)	NA	(83.0, 87.9)
ITT Population			
546	78.0 (199/255)	82.6 (214/259)	-4.6 (-11.4, 2.3)
556	81.1 (137/169)	85.7 (150/175)	-4.6 (-12.5, 3.2)
557	88.0 (139/158)	82.6 (133/161)	5.4 (-2.4, 13.1)
547	76.5 (858/1122)	NA	(73.9, 78.9)
BACTERIOLOGICAL RESPONSE – CAP			
Bacteriology PP Population			
546	78.1 (25/32)	84.6 (22/26)	-6.5 (-26.4, 13.4)
556	90.6 (29/32)	84.4 (27/32)	6.3 (-9.9, 22.4)
557	85.0 (17/20)	77.3 (17/22)	7.7 (-15.8, 31.2)
547	83.0 (225/271)	NA	(77.9, 87.2)
Bacteriology ITT Population			
546	69.2 (27/39)	83.3 (25/30)	-14.1 (-33.8, 5.6)
556	84.1 (37/44)	76.6 (36/47)	7.5 (-8.7, 23.7)
557	70.0 (21/30)	66.7 (20/30)	3.3 (-20.2, 26.9)
547	78.1 (267/342)	NA	(73.2, 82.3)

Data Source: Study 546, Section 11, Table 11.04a, Table 11.04b, Table 11.43a and Table 11.43b; Study 547, Section 11, Table 11.06a, Table 11.06b, Table 11.53c and Table 11.53d; Study 556, Section 11, Table 11.04a, Table 11.04b, Table 11.45a and Table 11.45b; Study 557, Section 11, Table 11.04a, Table 11.04b, Table 11.54a and Table 11.54b

* Comparators were Augmentin 875/125mg bid (Study 546), Augmentin 875/125mg tid (Study 557) and Augmentin 1000/125mg tid (Study 556)

** Non-inferiority limit was prospectively defined as ≥-10% for Study 546, and ≥-15% for Study 556. Treatment difference is not applicable for Study 547.

n/N = number of patients with a response of success/ number of patients in the population.

Bacteremic patients in CAP combined studies, Clinical and bacteriological responses

Results for bacteremic patients are shown in the applicant's Table 26 below. Results indicate that cure rates are still high but, somewhat lower rates of success rates than in the non-bacteremic patients. However, rates are also lower for the comparators and the clinical significance of these findings are unknown. In the combined CAP studies, there were a total of 66 bacteremic patients in the bacteriological PP populations: 50 in the Augmentin XR group and 16 in the comparator group. In the combined CAP studies, in

the XR group, 33/39, 84.6% were clinical and bacteriological success at test of cure in the bacteriological PP population. In the comparators, with positive cultures for *S. pneumoniae*, 11/12 (91.7% were clinical and bacteriological successes at the test of cure in the bacteriological PP populations. In the ITT group, cure rates were 71.7% in the XR treated and 70.6% in the comparator group. Therefore, in treating this group of patients, XR is equivalent to other Augmentin formulations using less drug in either the clinical or bacteriological cure of S. *pneumoniae*.

Table 26 Clinical and Bacteriological Response at Test of Cure for Bacteremic Patients in Combined CAP Studies- All Geographic Regions (Bacteriology PP and ITT Populations)

Patients*	Studies 546, 547, 556 and 557 Treatment Group			
	Augmentin XR 2000/125 mg bid		Comparator	
	n/N	(%)	n/N	(%)
CLINICAL RESPONSE				
Bacteriology PP Test of Cure Population	N = 355		N = 80	
All Isolates				
Success	41/50	(82.0)	15/16	(93.8)
Failure	9/50	(18.0)	1/16	(6.3)
S. pneumoniae				
Success	33/39	(84.6)	11/12	(91.7)
Failure	6/39	(15.4)	1/12	(8.3)
Bacteriology ITT Population	N = 455		N = 107	
All isolates				
Success	47/69	(68.1)	16/22	(72.7)
Failure	13/69	(18.8)	3/22	(13.6)
Unable to determine	9/69	(13.0)	3/22	(13.6)
S. pneumoniae				
Success	38/53	(71.7)	12/17	(70.6)
Failure	9/53	(17.0)	3/17	(17.6)
Unable to determine	6/53	(11.3)	2/17	(11.8)
BACTERIOLOGICAL RESPONSE				
Bacteriology PP Test of Cure Population	N = 355		N = 80	
All isolates				
Eradication	41/50	(82.0)	15/16	(93.8)
Failure	9/50	(18.0)	1/16	(6.3)
S. pneumoniae				
Success	33/39	(84.6)	11/12	(91.7)
Failure	6/39	(15.4)	1/12	(8.3)
Bacteriology ITT Population	N = 455		N = 107	
All isolates				
Eradication	47/69	(68.1)	16/22	(72.7)
Failure	12/69	(17.4)	2/22	(9.1)
Unable to determine	10/69	(14.5)	4/22	(18.2)
S. pneumoniae				
Success	38/53	(71.7)	12/17	(70.6)
Failure	9/53	(17.0)	2/17	(11.8)
Unable to determine	6/53	(11.3)	3/17	(17.6)

Data Source: 2.2.09(a)s, 2.2.09(b)s, 2.2.09(c)s, 2.2.09(d)s, 2.2.11(a)s, 2.2.11(b)s, 2.2.11(c)s, 2.2.11(d)s
n/N = number of successes/number of susceptible, intermediate or resistant isolates
N = total number of patients
Comparators were Augmentin 875/125mg bid (Study 546), Augmentin 875/125mg tid (Study 557) and Augmentin 1000/125mg tid (Study 556)
* Bacteremic status was assessed from the screening blood culture

Clinical and Bacteriological efficacy for resistant organisms, CAP studies

From the combined CAP Augmentin XR group, PRSP clinical and bacteriological cure rates were compared for penicillin S, I, and R strains. -Per Protocol, 14/15 R isolates were clinical and microbiological successes while in the ITT population, 17/22 were successfully treated.. The success rate was equivalent to the success rates for patent's whose *S. pneumoniae* was judged to be susceptible or intermediate (12/12 intermediate isolates were successfully treated PP and 13/14 in the ITT population). This compares to the susceptible population where 140/155 in the PP and 164/192 in the ITT populations were cured. . See table 27 below.

Table 27 Rates of Clinical and Bacteriological Success at Test of Cure by *S. pneumoniae* Screening Susceptibility to Penicillin: Combined CAP Studies (Bacteriology PP and ITT Populations)

	Studies 546, 547, 556 and 557 Pooled Augmentin XR 2000/125mg bid			
	Bacteriology PP		Bacteriology ITT	
	n/N	(%)	*n/N*	(%)
CLINICAL EFFICACY				
CAP (Studies 546, 547, 556, 557)	N = 172		N = 214	
Susceptible	140/155	(90.3)	164/192	(85.4)
Intermediate	12/12	(100)	13/14	(92.9)
Resistant	14/15	(93.3)	17/22	(77.3)
BACTERIOLOGICAL EFFICACY				
CAP (Studies 546, 547, 556,557)	N = 172		N = 214	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 28 Rates of Clinical Success At Test of Cure By *S. pneumoniae* Screening Susceptibility to Other Antimicrobial Agents: CAP Studies Combined (Bacteriology PP and ITT Populations)

Table 29 Rates of Bacteriological Success At Test of Cure By *S. pneumoniae* Screening Susceptibility to Other Antimicrobial Agents: CAP Studies Combined (Bacteriology PP and ITT Populations)

	Studies 546, 547, 556 and 557 Pooled Augmentin XR 2000/125mg bid	
	Bacteriology PP *n/N* (%)	Bacteriology ITT *n/N* (%)
S. pneumoniae	N = 172	N = 214
Susceptibility to Erythromycin		
Susceptible (≤ 0.25 mcg/ml)	149/163 (91.4)	170/198 (85.9)
Intermediate (0.5 mcg/mL)	0	0
Resistant (≥ 1.0 mcg/mL)	16/19 (84.2)	22/30 (73.3)
Susceptibility to TMP/SMX		
Susceptible (≤ 0.5/9.5 mcg/ml)	117/132 (88.6)	139/166 (83.7)
Intermediate (1/19-2/38 mcg/mL)	22/22 (100)	24/25 (96.0)
Resistant (≥ 4/76 mcg/mL)	26/28 (92.9)	29/37 (78.4)
Susceptibility to Cefuroxime		
Susceptible (≤ 1 mcg/ml)	149/165 (90.3)	173/204 (84.8)
Intermediate (2 mcg/mL)	1/1 (100)	1/1 (100)
Resistant (≥ 4 mcg/mL)	15/16 (93.8)	18/23 (78.3)

Data Source: ISE Tables M8.G.1.4.71s, M8.G.1.4.72s, M8.G.1.4.73s, M8.G.1.4.74s, M8.G.1.4.75s and M8.G.1.4,76s.
n/N = number of clinical successes/ number of susceptible, intermediate or resistant isolates.
N = total number of patients with *S. pneumoniae*. For patients with > 1 isolate, the bacteriological response is counted for each isolate.
TMP/SMX = Trimethoprim/Sulfamethoxazole.
NCCLS 2002 breakpoints were applied [1].

Clinical and bacteriological efficacy against Beta-Lactamase Producing Pathogens

Beta-Lactamase producing microorganisms involved include *H. influenzae, H. parainfluenzae, M. catarrhalis* and *methicillin-susceptible S. aureus.* Clinical and bacteriological outcomes are seen in the applicant's Tables 30 and 31 below. Bacteriological cure rates ranged from 72% for *H. parainfluenzae* to 86.7% for *M. catarrhalis*. Clinical cure rates ranged from 74.93.8%. results are seen in the sponsor's tables 30 and 31 below.

Table 30 Rates of Clinical Success at Test of Cure by Beta-Lactamase Production: CAP Studies Combined (Bacteriology PP and ITT Populations)

Bacteriology Population		CAP Studies Combined 546, 547, 556 and 557			
		Augmentin XR 2000/125 mg bid			
		PP		ITT	
		n/N	%	*n/N*	%
H. influenzae	beta-Lactamase Positive	15/16	(93.8)	16/19	(84.2)
	beta-Lactamase Negative	72/86	(83.7)	86/109	(78.9)
H. parainfluenzae	beta-Lactamase Positive	3/3	(100)	3/3	(100)
	beta-Lactamase Negative	32/43	(74.4)	43/57	(75.4)
M. catarrhalis	beta-Lactamase Positive	13/15	(86.7)	15/18	(83.3)
	beta-Lactamase Negative	2/2	(100)	3/3	(100)
S. aureus (MSSA)	beta-Lactamase Positive	20/26	(76.9)	24/34	(70.6)
	beta-Lactamase Negative	4/4	(100)	5/5	(100)

Data Source: ISE Tables M8.G.1.4.19s and M8.G.1.4.20s.
n/N = number of successes/ number of beta-lactamase positive or negative isolates.
Note: If a patient had more than one isolate of a specified pathogen with beta-lactamase data, all of the isolates have been included in this table.

Table 31 Rates of Bacteriological Success at Test of Cure by Beta-Lactamase Production: CAP Studies Combined (Bacteriology PP and ITT Populations)

Bacteriology Population		CAP Studies Combined 546, 547, 556 and 557			
		Augmentin XR 2000/125 mg bid			
		PP		ITT	
		n/N	%	*n/N*	%
H. influenzae	beta-Lactamase Positive	15/16	(93.8)	16/19	(84.2)
	beta-Lactamase Negative	68/86	(79.1)	81/109	(74.3)
H. parainfluenzae	beta-Lactamase Positive	3/3	(100)	3/3	(100)
	beta-Lactamase Negative	31/43	(72.1)	41/57	(71.9)
M. catarrhalis	beta-Lactamase Positive	13/15	(86.7)	15/18	(83.3)
	beta-Lactamase Negative	2/2	(100)	3/3	(100)
S. aureus (MSSA)	beta-Lactamase Positive	19/26	(73.1)	21/34	(61.8)
	beta-Lactamase Negative	4/4	(100)	5/5	(100)

Data Source: ISE Tables M8.G.1.4.87s and M8.G.1.4.88s
n/N = number of clinical successes/ number of beta-lactamase positive or negative isolates.
Note: If a patient had more than one isolate of a specified pathogen with beta-lactamase data, all of the isolates have been included in this table.

Overall bacteriological outcomes

Overall bacteriological outcomes, all pathogens from the ABS and CAP studies separated and combined are shown in tables 32 below.
Efficacy rates in the ABS studies were high for all organisms, 87.1 for *MSSA* to 98% for *M. catarrhalis*. In the CAP studies efficacy rates varied from 75.6% for *H. parainfluenzae* to 91.3 % for *S. pneumoniae*.

Table 32 Pre-Therapy Pathogens Eradicated or Presumed Eradicated at the Test of Cure Visit in Clinical Studies Supporting the Efficacy of Augmentin XR (Bacteriology PP Population)

Indication All Pathogens**	Augmentin XR n/N	 (%)	Comparator Drug n/N	 (%)
ABS Studies 551 and 592				
S. pneumoniae	228/232	(98.3)	n/a	n/a
H. influenzae	164/174	(94.3)	n/a	n/a
M. catarrhalis	64/65	(98.5)	n/a	n/a
MSSA	27/31*	(87.1)	n/a	n/a
CAP (Studies 546, 547, 556 and 557)				
S. pneumoniae	157/172	(91.3)	32/36	(88.9)
H. influenzae	83/102	(81.4)	19/24	(79.2)
H. parainfluenzae	34/45	(75.6)	8/9*	(88.9)
MSSA	23/30*	(76.7)	1/2	(50.0)
M. catarrhalis	15/17	(88.2)	2/3	(66.7)
K. pneumoniae	11/13	(84.6)	2/2	(100)

Data Source: ISE Tables M8.G.1.4.27s and M8.G.4.2.27s.

Comparators were Augmentin 875/125mg bid (Study 546) Augmentin 875/125mg tid (Study 556) and Augmentin 1000/125mg tid (Study 556) for CAP studies

*One isolate from each of these pathogens had bacteriological outcomes of "unable to determine" at Test of Cure (One MSSA isolate with an MIC of 1 mcg/mL (ABS Studies), one MSSA isolate with an MIC of 1 mcg/mL (CAP studies), and one isolate of *H. parainfluenzae* with an MIC of 0.5 mcg/mL (CAP Studies))

** Some patients may have had more than one causative pathogen at screening.

n/N = number of patients with the pathogen eradicated or presumed eradicated / number of patients with the pathogen.

Clinical success and Bacteriological Eradication rates at the test of cure visit for PRSP combining all indications for respiratory track infections.

Clinical success and Bacteriological Eradication rates at the test of cure visit for PRSP are shown in the sponsor's Table 33 below. Cure rates are shown versus different MICs of PRSP. Clinical and bacteriological outcomes were high and identical for clinical and bacteriological, 98.2% at Test of Cure in the PP population and 92.3% bacteriological cure rate. Although, 3 of the isolates were from —— the table gives useful information. Both clinical and bacteriological eradication rates were high at all MICs for PRSP including isolates with penicillin MICs of 2 and 4. Cure rates were high 100% at an MIC of 2 and 94.1% at an MIC of 4 (however, the numbers of cases at 4µg/ml for S. pneumoniae were small). There were too few isolates at 8 and 16 ug, only one, to make conclusions at these resistance levels.

Table 33 Clinical Success and Bacteriological Eradication at the Test of Cure Visit: PRSP All Indications Combined (RTI) (Bacteriology PP and ITT Populations)

	Augmentin XR Treated Patients Bacteriology PP/ITT Population (TOC)			
Clinical Response-Success	**TOC Success-PP**		**TOC Success-ITT**	
***S. pneumoniae* Penicillin MIC (mcg/mL)**	**n/N**	**(%)**	**n/N**	**(%)**
Overall versus PRSP	54/55	(98.2)	60/65	(92.3)
2	36/36	(100)	42/45	(93.3)
4	16/17	(94.1)	16/18	(88.9)
8	1/1	(100)	1/1	(100)
16	1/1	(100)	1/1	(100)
Bacteriological Outcome-Total Eradication	**TOC Success-PP**		**TOC Success-ITT**	
***S. pneumoniae* Penicillin (mcg/mL)**	**n/N**	**(%)**	**n/N**	**(%)**
Overall versus PRSP	54/55	(98.2)	60/65	(92.3)
2	36/36	(100)	42/45	(93.3)
4	16/17	(94.1)	16/18	(88.9)
8	1/1	(100)	1/1	(100)
16	1/1	(100)	1/1	(100)

Data Source: Tables 5.5.01as, 5.5.01bs, 5.5.03as and 5.5.03bs
n/N = number of successes (eradicated) /number of isolates at the specified MIC
Note: Total eradication = known eradication + presumed eradication

Isolates Approvable from the microbiological point of view:

As discussed in the text of this review sufficient microbiological data has been supplied to support the following applicant's list of organisms for list one of the package insert. *S. pneumoniae*, isolates with Augmentin MICs of — μ/ml. Breakpoints are not normally given for *M. catarrhalis*. Therefore, *M. catarhalis* will be eliminated from the breakpoint portion of the final label.

For *Streptococcus pneumoniae*, isolates should be included with Augmentin MICs —

Concerning the organisms for list two of the package insert where the safety and effectiveness of Amoxicillin/clavulanic acid has not been established in adequate and well controlled clinical trials, there are several criteria that are used by reviewing microbiologist to determine inclusion in this list of organisms. One of which is that such organisms are common pathogens in the indication(s) approved and listed in the Indications and Usage section. *Streptococcus pyogenes* is a cause of acute bacterial sinusitis and is allowed in the second list. Although labeling for other Augmentin products include anaerobes, the applicant should provide evidence of Augmentin activity versus recent clinical isolates. Of anaerobes to include at least one hundred recent clinical isolates from a broad geographic distribution. Since this was not done, anaerobes will not be included in the list 2 of the package insert.

Interpretive criteria established for Augmentin .

For testing *Streptococcus pneumoniae*:

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

* Intermediate strains of *S. pneumoniae* might be clinically susceptible to Augmentin XR

[redacted] should be removed from the susceptibility MIC interpretations as they are universally producers of beta-lactamase and are not tested versus other antibiotics to which they are sensitive.

Zone correlates should not be used for Augmentin versus *S. pneumoniae* as those with zones less than or equal to 19 would have to be tested for susceptibility to 4 mcg of Augmentin by MIC. This would take a total assay and isolation times of 4-5 days and would be confusing.

References to treatment of PRSP strains with penicillin MICs of 4 mcg should be removed because the correlation between Augmentin and penicillin MICs at 4 mcg is not good enough to prevent the treatment of infected patients with Augmentin MICs of 8 to *S. pneumoniae*.

The following microbiology section of the Augmentin XR label is proposed and was presented at the project team meeting of September 12, 2002. It is possible that further changes will occur as part of the negotiations between GSK and the agency.

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 XR* 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 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 (all known strains are β-lactamase producing)

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

Aerobic Gram-positive Microorganisms

Streptococcus pyogenes

NOTE: *S. pyogenes* does not produce β-lactamase, and therefore, is 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 agar; broth for *S. pneumoniae* and *Haemophilus* species) 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 testing *Klebsiella pneumoniae*:

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

For testing *Streptococcus pneumoniae*[a]:

MIC (µg/mL)	Interpretation
—	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 testing *Staphylococcus* species and *Haemophilus* species[b] :

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 which 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 to 16
Escherichia coli ATCC 25922	2 to 8
Haemophilus influenzae[d] ATCC 49247	2 to 16
Staphylococcus aureus ATCC 29213	0.12 to 0.5
Streptococcus pneumoniae[e] ATCC 49619	0.03 to 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 testing *Klebsiella pneumonia*:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
14 – 17	Intermediate (I)
≤ 13	Resistant (R)

For testing *Staphylococcus* and *Haemophilus*[f] species:

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

For testing *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 plus 10 µg clavulanate potassium) disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 35218	17 to 22
Escherichia coli ATCC 25922	18 to 24
Staphylococcus aureus ATCC 25923	28 to 36
Haemophilus influenzae[h] ATCC 49247	15 to 23

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

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ON ORIGINAL

Joel Unowsky
Microbiology Reviewer

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Microbiologist, HFD-520
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Smicro/ATSheldon
RD#1 initialed 8/19/02 ATS
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DepDir/LGavrilovich

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HFD-473
HFD-520/DepDir/LGavrilovich
HFD-520/Smicro/ATSheldon
HFD-520/Micro/JUnowsky
HFD-520/MO/CCooper
HFD-520/Pharm/TPeters
HFD-520/Chem/SPagay
HFD-520/CSO/SSusmita
HFD-520
HFD-502
HFD-635

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Division of Anti-Infective Drug Products
Clinical Microbiological Review
Final Package Insert
Microbiology section

NDA # 50785 **Date Completed:** September 27, 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

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: April 5, 2002, and information addendum Sept 20, 2002,
Review Completed: September 27, 2002

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 microbiology review number 3 for NDA 50-785 (attached as an appendix.) That review includes our rationale for and proposed microbiology section of the package insert for Augmentin XR™. Based on our discussions with the project team, GSK and further data submitted by GSK, several changes have been made to our proposed version of the package insert. The changes made and the reasons for those changes will be the subject of this review:

1.Further data were submitted concerning the activity of Augmentin versus anaerobes, allowing us to conclude that several anaerobes could be included in list two of the package insert.

2. The observation that *S. pneumoniae* isolates from pneumoniae patients with penicillin MICs of 4 can have Augmentin MICs of 8 µg/ml and therefore not be treatable by Augmentin.

3.The opinion of our clinical colleagues: the small numbers of pneumoniae patients infected with *S. pneumoniae* having either penicillin or Augmentin MICs of 4µg/ml are not sufficient to prove that *S. pneumonia* infected patients with an MIC of 4µg/ml can be cured with Augmentin XR treatment.

Anaerobes and Acute Bacterial Sinusitis

Anaerobes are not the primary cause of ABS being responsible for only 6-10% of cases. The most prominent organisms being *Bacteroides*, *Peptostreptococcus* and *Fusobacterium spp.* In CAP, anaerobes are normally present in mixed infections and not considered the primary pathogen. The presence of anaerobes in ABS allows us to include them in list two of the package insert. Recently GSK provided us with sufficient numbers

of recent *in vitro* susceptibility test results both from the US and world-wide to justify including anaerobes in list two of the PI. The MIC results are shown in the Applicant's Tables 51 for all geographic regions and for the US in Table 50 below. Important results for consideration, include MIC_{90s} for *Bacteroides fragilis* of 4 µg/ml, 0.25 µg/ml for *Fusobacterium nucleatum* and, 0.50 µg/ml for *Peptostreptococcus micros* and *P. magnus.*

Table 51 ***In vitro*** **activity of amoxicillin/clavulanic acid[a] against anaerobic organisms - all geographic regions**

Organism	No of isolates	MIC Range (mcg/mL)	MIC50 (mcg/mL)	MIC90 (mcg/mL)	%Susc ≤ 4 (mcg/mL)
Prevotella species	259	0.125 - 4	0.12	1	100
B. fragilis	259	≤0.125 - 32	0.5	4	94.6
F. nucleatum	144	0.03 - 1	0.12	0.25	100
E. corrodens	70	0.06 - 2	0.5	1	100
P. magnus	90	0.125 - 1	0.25	0.5	100
P. micros	142	0.03 - 2	0.12	0.5	100
P. anaerobius	83	0.03 - 32	0.25	8	84.3
Porphyromonas species	119	0.03 - 0.5	0.125	0.12	100

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

Table 50 *In vitro* **activity of amoxicillin/clavulanic acid[a] against anaerobic organism - US**

Organism	No of isolates	MIC Range (mcg/mL)	MIC50 (mcg/mL)	MIC90 (mcg/mL)	%Sens ≤ 4 (mcg/mL)
Prevotella species	85	≤0.125 - 4	0.25	2	100
B. fragilis	101	0.25 - 32	0.5	4	97
F. nucleatum	111	≤0.125-1	≤0.12	≤0.12	100
E. corrodens	62	0.06 - 1	0.5	1	100
P. magnus	58	≤0.125 - 1	0.25	0.5	100
P. micros	68	≤0.125 - 2	≤0.12	0.25	100
P. anaerobius	52	≤0.125 - 32	0.25	16	75
Porphyromonas species	59	≤0.125 - 0.5	≤0.12	≤0.12	100

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

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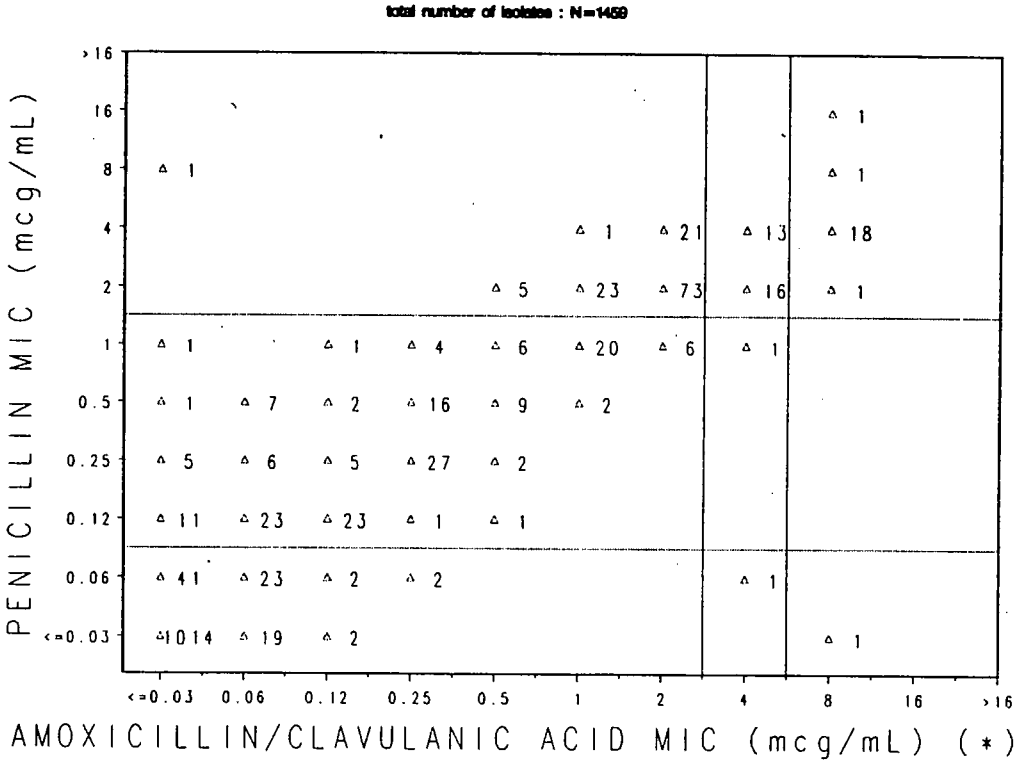
The applicant has presented a penicillin MIC as equal to a Augmentin MIC, i.e., a Augmentin MIC of 2 µg/ml as equal to a Penicillin MIC of 2 µg/ml and a Penicillin MIC of 4 µg/ml as equal to a Augmentin MIC of 4 µg/ml. In order to evaluate these assumptions we conducted the analysis that follows and found that although a penicillin MIC of 2 µg/ml equals a Augmentin MIC of 2 µg/ml, within normal assay error, this was not true for MICs of 4 µg/ml. For Penicillin MICs of 4 µg/ml, Augmentin MICs of 8 µg/ml were observed in over 30% of the isolates. This would be confusing to clinicians and clinical laboratories alike. This analysis is shown below as extracted from Augmentin microbiology review # 3.

Analysis of S. pneumoniae isolates with Penicillin MICs of 4 µg/mL Comparison of Augmentin and Penicillin MICs

The applicant has assumed that penicillin MICs of 2 and 4 are equivalent to Augmentin MICs of 2 and 4 thus equating susceptibility to Augmentin XR to susceptibility to penicillin at 2 and 4 µg/ml. In order to evaluate whether this is correct, we requested that the sponsor send us a line listing and plot of all *S. pneumoniae* strains clinically isolated by the applicant for whom both penicillin and Augmentin MICs were conducted (isolates from clinical studies over the past 5 years). GSK graciously sent us line listing MIC, susceptibility interpretations and plots from 1459 clinical isolates of *S. pneumoniae* using adult and pediatric clinical trial patients and 1265 isolates using adult patients only. The data submitted came from 26 clinical trials, which involved Augmentin XR, Augmentin ES and Gemifloxacin studies. Results of the plot are shown in the applicant's figure 4 below.

Figure 4: **Penicillin MIC vs. Amoxicillin/clavulanic acid MIC for Screening *S. pneumoniae* from GSK Clinical Trials - Adult and Pediatric Studies (Bacteriology Intent-to-Treat Population) – Applying Current Augmentin Breakpoints**



(*) NOTE : 2:1 Ratio, Amoxicillin concentration plotted.

From this figure, it can be seen that it is common for isolates to be one or two-fold dilution different when comparing penicillin to Augmentin or Augmentin to penicillin MICs. Although such variation is common for antibiotic MIC determinations, which involve two-fold dilutions, some of the variation here seems to be more than expected from normal assay variation. *S. pneumoniae* isolates with Augmentin MICs of 4 µg/ml tend to have penicillin MICs of two (13 isolates) or four (16 isolates). However, isolates of *S. pneumoniae* with penicillin isolates of 4 have Augmentin MICs of 2, 4,or 8. The distribution of isolates with a penicillin MIC of 4 indicates a population difference and not random assay variation (21 isolates with a MIC of 2 mcg/ml, 13 isolates with 4 µg/mL and 18 isolates with 8 µg/mL). According to these results, approximately 33% of penicillin isolates with a MIC of 4 in these clinical studies have Augmentin MICs of 8. Typical assay variation is seen for clinical isolates with penicillin MICs of two, giving

corresponding Augmentin MICs of 1 µg/ml for 23 isolates, 2 µg/ml for 73 isolates and 4 mcg/ml for 16 (12%) isolates. The difference is clearly shown in the table below.

Corresponding number of Augmentin isolates* at various MICs for Penicillin MICs of 2 and 4 µg/ml (*Streptococcus pneumoniae* clinical isolates)

Penicillin MIC	Augmentin MIC: 0.5µg/ml	Augmentin MIC: 1µg/ml	Augmentin MIC: 2µg/ml	Augmentin MIC: 4µg/ml	Augmentin MIC: 8µg/ml
4µg/ml, 53 isolates	0 isolates	1 isolate	21 isolates	13 isolates	18 isolates
2µg/ml 128 isolates	5 isolates	23 isolates	73 isolates	16 isolates	1 isolate

*All *S. pneumoniae* isolates from GSK clinical trials during the past 5 years in which MICs were taken for both Penicillin and Augmentin. Augmentin MICs are given as the Amoxicillin component, clavulanic acid is 1/2 the Amoxicillin value.

Clinical data:
Breakpoints based on animal studies and Pk/PD are predictive only and as stated in Review # 3 would support a susceptible *S. pneumoniae* breakpoint of 4.0 µg/mL for Augmentin. However, clinical results and biostatistics constitute the final proof of a breakpoint. Concerning Augmentin XR, the statistical and medical reviewers did not feel that there were sufficient numbers of clinical cases presented to have confidence that a pneumoniae patient infected with *S. pneumoniae* having an Augmentin or penicillin MIC of 4.0 µg/mL would be assured of being cured. The medical and statistical evidence will not be presented here as that is the responsibility of those reviewers.

It is also necessary that the breakpoints presented in the Microbiology section of the package insertbe compatible with information in the indications and usage section of the package insert. Breakpoints in the microbiology section of the package insert can not be higher than the MICs of pathogens for which proof of clinical efficacy was demonstrated. This would result in the Microbiology section of the package insert granting approval for *S. pneumoniae* pathogens with higher Augmentin and penicillin MICs than was actually demonstrated in the clinical data as described below for the indications and usage section of the Augmentin XR package insert. The breakpoints given should be compatible with information in the indications and usage section of the package insert. Especially when dealing with indications for the treatment of resistant pathogens. See below for the final approved indications and usage section of the Augmentin XR package insert.

"Indications and Usage

Augmentin XR Extended Release Tablets are indicated for the treatment of patients with community-acquired pneumonia or acute bacterial sinusitis due to confirmed, or

suspected β-lactamase-producing pathogens (i.e., *H. influenzae*, *M. catarrhalis*, *H. parainfluenzae*, *K. pneumoniae*, or methicillin-susceptible *S. aureus*) and *S. pneumoniae* with reduced susceptibility to penicillin (i.e., penicillin MICs = 2 µg/mL). *Augmentin XR* is not indicated for the treatment of infections due to *S. pneumoniae* with penicillin MIC ≥4 µg/mL. Data are limited with regard to infections due to *S. pneumoniae* with penicillin MICs ≥4 µg/ml (See CLINICAL STUDIES Section).

Of the common epidemiological risk factors for patients with resistant pneumococcal infections, only age >65 years was studied. Patients with other common risk factors for resistant pneumococcal infections (e.g., alcoholism, immune-suppressive illness, and presence of multiple co-morbid conditions) were not studied.

In patients with community-acquired pneumonia in whom penicillin-resistant *S. pneumoniae* is suspected, bacteriological studies should be performed to determine the causative organisms and their susceptibility when *Augmentin XR* is prescribed. Once the results are known, therapy should be adjusted appropriately.

Acute bacterial sinusitis or community-acquired pneumonia due to a penicillin-susceptible strain of *S. pneumoniae* plus a beta-lactamase-producing pathogen can be treated with another *Augmentin* product containing lower daily doses of amoxicillin (i.e., 500 mg q8h or 875 mg q12h). Acute bacterial sinusitis or community-acquired pneumonia due to *S. pneumoniae* alone can be treated with Amoxicillin

Clinical Outcome for CAP due to *S. pneumoniae*						
Penicillin MIC of *S. pneumoniae* Isolates	**Intent To Treat**			**Clinically Evaluable**		
	n*/N	**%**	**95% CI ‡**	***n*/N***	**%**	**95% CI ‡**
All *S. pneumoniae*	184/214	86.0	--	157/172	91.3	--
MIC ≥2.0 µg/ml**	17/20	85.0	62.1, 96.8	14/15	93.3	68.1, 99.8
MIC = 2.0 µg/ml	13/14	92.9	66.1, 99.8	10/10	100	69.2, 100
MIC = 4.0 µg/ml	4/6	66.7	22.3, 95.7	4/5	80.0	28.4, 99.5

* *n*/N= patients with pathogen eradicated or presumed eradicated/ total number of patients

‡ Confidence limits calculated using exact probabilities

** *S. pneumoniae* strains with penicillin MICs of ≥2 µg/mL are considered resistant to penicillin."

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Based on the previous discussion, the final product label for the Microbiology section is as follows:

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 XR* 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 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 (all known strains are β-lactamase producing)

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

Amoxicillin/clavulanic acid exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2.0 μg/mL or less against most (≥90%) strains of *Streptococcus pyogenes* and MICs of 4.0 μg/mL or less against most (≥90%) strains of the anaerobic bacteria listed below.

Aerobic Gram-positive Microorganisms

Streptococcus pyogenes

Anaerobic Microorganisms

Bacteroides fragilis (including β-lactamase producing strains)

Fusobacterium nucleatum (including β-lactamase producing strains)
Peptostreptococcus magnus
Peptostreptococcus micros

NOTE: *S. pyogenes, P. magnus* and *P. micros* 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 agar; broth for *S. pneumoniae* and *Haemophilus* species) 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 testing *Klebsiella pneumoniae*:

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

For testing *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 testing *Staphylococcus* species and *Haemophilus* species[b] :

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 which 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 to 16
Escherichia coli ATCC 25922	2 to 8
Haemophilus influenzae[d] ATCC 49247	2 to 16
Staphylococcus aureus ATCC 29213	0.12 to 0.5
Streptococcus pneumoniae[e] ATCC 49619	0.03 to 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 testing *Klebsiella pneumoniae*:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
14 – 17	Intermediate (I)
≤ 13	Resistant (R)

For testing *Staphylococcus* and *Haemophilus*[f] species:

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

For testing *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 plus 10 µg clavulanate potassium) disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 35218	17 to 22

Escherichia coli ATCC 25922	18 to 24
Staphylococcus aureus ATCC 25923	28 to 36
Haemophilus influenzae[h] ATCC 49247	15 to 23

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

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Cc: Original NDA No. 50,785
Microbiologist, HFD-520
File name: N50785

SMicro/ATSheldon
RD Initialed 9/26/02 ATS
Final Initialed 9/27/01 ATS
DepDir/LGavrilovich

Cc: Original NDA # 50,785
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HFD-520/DepDir/LGavrilovich
HFD-520/Smicro/ATSheldon
HFD-520/Micro/JUnowsky
HFD-520/MO/CCooper
HFD-520/Pharm/TPeters
HFD-520/Chem/SPagay
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