CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-542/S-016
50-754/S-001

MICROBIOLOGY REVIEW

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 1
Consult

NDA # 50-542 (Amoxil Chewable Tablets) **Date Completed: August 17, 2000**
50-754 (Amoxil brand of Amoxicillin)
Labeling Supplement: SLR-016

Sponsor (IND)/Applicant (NDA):
SmithKline Beecham Pharmaceuticals
One Franklin Plaza,
PO Box 7929
Philadelphia, PA 19101

Chem/Ther. Type: Antibiotic

Submissions Reviewed: July 23, 1998

Providing for: Change in the breakpoints for *Streptococcus pneumoniae*

Product Name(s):

Proprietary: amoxicillin

Non-proprietary/USAN: amoxicillin

Compendia: amoxicillin

Code name/number: NA

Chemical name: Amoxicillin:(2S, 5R, 6R)-6-[(R)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid thrihydrate.

Structural formula: See USAN

Molecular formula: $C_{16}H_{19}N_3O_5S.3H_2O$

Dosage form(s): Chewable tablets
Route(s) of administration: Oral

Clinical Microbiological Review

In the clinical microbiological laboratory, *in vitro* susceptibility testing is performed to assess the potential utility of an antimicrobial in the treatment of a pathogen isolated from a specified site of infection. Thus, the association of established breakpoints with clinical outcome is critical in that the values selected must predict a desired outcome.

In order to establish appropriate breakpoints, specific types of data are to be submitted and specific types of analysis are to be performed. They include:

1. Minimum inhibitory concentration and zones of inhibition population distribution profiles of the pathogen(s) under consideration. These data help us describe the association of the susceptibility profile of the clinical isolates and that of the general population.
2. An understanding of the mechanism of resistance found in the target pathogen(s) and their distribution within the population under investigation. Ideally, this data helps us define the population that should not be treated with the antimicrobial and helps define the resistant breakpoint.
3. Pharmacokinetic and pharmacodynamic studies that describes the absorption, distribution, metabolism, and elimination of the drug and the relationship of drug level in target sites to the susceptibility patterns of the pathogen(s) under consideration.
4. Clinical data that describe the association of the susceptibility of the pathogen isolated during the clinical investigation to clinical outcome of the patient, which helps further describe the predictive value of the proposed breakpoints.

In vitro spectrum of activity studies

The applicant provided global and US hospital surveillance data from the Alexander project[1] for the year 1996 and additional data for the year 1997 (Figure 1). The 1996 global surveillance data (n=2160) represents *S. pneumoniae* MIC population distributions for amoxicillin. In addition, the applicant provides US hospital population distributions[2] for amoxicillin (n=79) and for amoxicillin-clavulanate (n=79). The 1997 global surveillance data (n=3248) represents *S. pneumoniae* MIC population distributions for amoxicillin-clavulanate. In addition, a more recent abstract presented at ICAAC was used to further define the MIC population distribution of *S. pneumoniae*.[5]

There are several analyses that need to be performed for the information provided in Figure 1 to understand the significance of the data. The first is the global population distribution for 1996, which suggests that a vast majority of *the S. pneumoniae* isolates (88%) have MICs ≤ 0.5 μg/mL, the current susceptible breakpoint (Table 1). There is a small population of less than 250 isolates with MICs ≥ 1.0 μg/mL and there appears to be an emerging, less susceptible, population of isolates with MICs of 1.0-2.0 μg/mL (Figure 1). A comparison was also made of the 79 US hospital isolates when tested with amoxicillin and amoxicillin-clavulanate. The expected outcome is that both population

distribution profiles should be the same because clavulanate is not a molecule with antimicrobial properties. It is a structural analogue of the beta-lactam antibiotics and functions as a competitive inhibitor of β-lactamase and prevents the hydrolysis of the antibiotic. Although the number of isolates is small, the population distributions look the same for both data sets. It is this reviewers opinion that this comparative data was provided by the applicant to show that no differences exist in the susceptibility profiles of the two formulations (amoxicillin and amoxicillin-clavulanate). Therefore, this would justify the use and acceptance of the 1997 US amoxicillin-clavulanate hospital database as a representation of the susceptibility profile for a more current amoxicillin data set. This data set is interesting because the histogram profile suggest that changes in the susceptibility of *S. pneumoniae* to amoxicillin have occurred as predicted by the 1996 data at MICs of 1.0-2.0 μg/mL. The percentage of isolates with MICs ≥1.0 μg/mL has increased between the years 1996 and 1997. The same is true for the years 1997 and 1998. Table 1 is an attempt to present the susceptibility profile as a cumulative percent of *S. pneumonia* isolates with the MICs defined in that table. The data shows that there has been a gradual increase in isolates with MICs >0.5 μg/mL and that a population with MICs of 8-32 μg/mL has emerged and become more prevalent. On its own, this *in vitro* susceptibility data would suggest that the current breakpoints are appropriate.

Table 1. Distribution of amoxicillin MICs for *Streptococcus pneumonia* for the years 1996, 1997, and 1998.

MICs (μg/mL)	1996 Data set*	1997 Data set**	1998 Data Set
≤0.5	1914/2160 (88.6%)	2441/3248 (75.1%)	1195/1760 (67.9)
1.0	100/2160 (93.2%)	419/3248 (88.0%)	83/1760 (72.6)
2.0	125/2160 (99.0%)	267/3248 (96.2%)	306/1760 (90.0)
4.0	10/2160 (99.5%)	96/3248 (99.2%)	74/1760 (94.2)
8.0	10/2160 (100.0%)	17/3248 (99.7%)	88/1760 (99.2)
16.0	NA	6/3248 (99.9%)	14/1760(100)
32.0	NA	2/3248 (0.06%)	

* Alexander Project: Global amoxicillin MIC population distributions for 2160 *S. pneumonia* isolates. Numerator data is an estimate since actual values were not provided.
** Alexander Project: Global amoxicillin-clavulanate MIC population distributions for 3248 *S. pneumonia* isolates.

Note to reader: The data is found in the NDA submission on page 000017 and is provided as a photocopy in the review. This data will not be available for review in the DFS file.

In addition, is we look at the amoxicillin population distribution using the breakpoints recommended by the applicant for amoxicillin (S≤2.0 μg/mL, I=4.0, and R ≥8.0 μg/mL), we see that the penicillin susceptible and intermediate population will now be considered susceptible to amoxicillin. A portion of the penicillin resistant strains would be considered as intermediate to amoxicillin and the remainder resistant. Further, a small number of isolates (8.2%) that are penicillin resistant will also be incorporated into the amoxicillin susceptible breakpoint.

The published literature was also reviewed to assess the amoxicillin MIC population distribution based on penicillin susceptibility breakpoints (Table 2). This data shows the amoxicillin drug concentration required to inhibit 90% of the bacterial populations that are susceptible, intermediate and resistant to penicillin. The data demonstrate that at least 90% of the penicillin susceptible and intermediate strains will fall in the amoxicillin susceptible category (S≤2.0 μg/mL). This data also suggests that 90% of the penicillin resistant strains will be susceptible to an amoxicillin MIC of 4.0 μg/mL but be classified as intermediate to amoxicillin. In addition, evaluation of the data published by Jacobs[2] demonstrates similarity of the susceptibility profile of *S. pneumonia* to amoxicillin and amoxicillin-clavulanate since the MIC_{90s} for both drugs are the same.

Table 2. Comparison of the *in vitro* MIC activity of amoxicillin for *S. pneumoniae* by population distributions based on penicillin susceptibility.

Agent	MIC_{90} (μg/mL)			Reference
	Pen-S	Pen-I	Pen-R	
Amoxicillin	0.03	1.0	4.0	Jacobs[2]
Amoxicillin-clavulanate	0.03	1.0	4.0	
Amoxicillin	0.13	2.0	4.0	Kaplan[3]
Amoxicillin-clavulanate	NA	NA	NA	
Amoxicillin	0.03	2.0	4.0	Verhaegen[4]
Amoxicillin-clavulanate	NA	NA	NA	

The penicillin breakpoints are S≤0.06 μg/mL, I = 0.12 – 1.0 μg/mL, and R≥2.0 μg/mL.

In a more recent outpatient surveillance study, Jacobs[5] described the susceptibility profile of 1760 *S. pneumoniae* to selected oral agents (Table 1, 1998 data set) . Minimal inhibitory concentration (MIC) studies were performed using NCCLS standardized methods. Using the previously described breakpoints for penicillin (Table 2), 55.3% of strains are considered susceptible, 11.6% are intermediate, and 28.6% are resistant to penicillin. The MIC_{50}/MIC_{90} were 0.03/4.0 (μg/mL). The amoxicillin MIC susceptibility profile was practically identical to that of penicillin in that almost the same percentages of strains were susceptible at the specified MICs. That is, the same percent of strains are susceptible to penicillin and amoxicillin at each MIC evaluated. The amoxicillin MIC_{50}/MIC_{90} are 0.03/2.0 (μg/mL).

Evaluation of this data as before suggests that the if the proposed breakpoints for amoxicillin are used, 90% of the *S. pneumoniae* strains will be susceptible to amoxicillin and they are represented by the penicillin susceptible and intermediate categories. In addition, 4.2% will be intermediate and they are represented by 11.1% of the penicillin resistant population, and 5.8% will be resistant to amoxicillin and they are represented by 0.1% of the penicillin resistant population.

Pharmacokinetics and pharmacodynamic studies

The human pharmacokinetic (PK) parameters of amoxicillin are well established and are provided in the package insert. In addition, the pharmacodynamic (PD) principle that has been proposed for β-lactam antibiotics, as being predictive of successful therapeutic outcome is percentage (>40%) of the dosing interval that drug concentration remains above the MIC_{90} for the pathogen being treated. That is, $T>MIC_{90}$ is >40% dosing interval.

In order to assess the applicability of this principle for amoxicillin, we must:

1. Identify the indications that have been approved for the treatment of *S. pneumoniae*,
2. Identify the approved dosage forms and doses used in the treatment of these indications,
3. Obtain the PK data for the area under the concentration time curve (AUC), and perform the $T>MIC_{90}$ calculation.

The indications and doses approved for amoxicillin were obtained from the product label approved May 16, 2000. The indications listed for the pathogen *S. pneumoniae* are "Ear/Nose/Throat" and "Lower Respiratory Tract" infections. The adult doses recommended are 250mg tid or 500mg bid and 25-mg/kg/day bid or 20-mg/kg/day t.i.d in children for mild to moderate ENT infections. For severe ENT infections or mild/moderate/severe lower respiratory infections or those caused by less susceptible organisms, a dose of 875-mg bid is recommended. For children, the dose is 45-mg/kg/day bid or 40-mg/kg/day tid Thus, PK/PD data needs to be provided with these recommended doses. PK information was provided for the 500-mg tid and 875-mg b.i.d doses.

The applicant provided a summary of the study results for recent PK/PD studies that were conducted with amoxicillin doses of ' ——————— The applicant states that "Time above the MIC = 2 μg/mL was measured for each individual subject plot and a mean for each study was calculated along with corresponding % time above the MIC. Combined data were calculated from the mean values for all subjects from all studies." None of the raw data was provided for this study but the applicant concluded that at a MIC of 2 μg/mL for a dose of ———, the drug concentration would remain above the MIC for 43% (3.45 hours for the tid dosing schedule) of the dosing interval.

The applicant also provided PD calculations for study results obtained with the 875-mg dose. Five independent tablet formulation PK studies were performed and the T>MIC values were presented (See Table 3). These results suggest that the dosing of patients with 875-mg bid will produce amoxicillin drug concentrations that produce T>MIC for more than 40% of the dosing interval for an MIC of ≤2.0 μg/mL for *S. pneumoniae*.

Table 3. Pharmacodynamic results of 5 independent PK studies performed with the 875-mg dose given b.i.d and a *S. pneumoniae* breakpoint of 2.0 μg/mL.

Study	Status	Formulation	# of obs.	T>MIC (h)	T>MIC (%)
25000-362	With food	Tablet	48	5.0	42
25000-491	With food	Tablet	15	4.9	41
25000-433	With food	Tablet	12	4.8	40
25000-360	With food	Tablet	15	3.7	31
2333-058	With food	Tablet	55	4.7	39
Combined data			121	4.8	40

The applicant stated that the PK/PD data would be provided upon request. The fact of the matter is that it should have been provided so that FDA could make its own independent assessment and draw its own conclusions. The conclusions that are inferred from these studies are consistent with the published literature. A review article by Craig and Andes[6] provide information on the time above MIC for various β-lactams against intermediate and resistant *S. pneumoniae*. These data show that at doses of 13.3/mg/kg tid, for penicillin intermediate strains, the T>MIC for 90% of the intermediate strains is 59% of the dosing interval. A similar analysis applied to penicillin resistant strains indicates that the T>MIC for 90% of the strains is 46% of the dosing interval. The authors conclude that data from clinical otitis media trials suggest 80-85% efficacy when one reaches T>MIC >40% of the dosing interval and these observations are supportable by different animal model studies.

It should be noted that the 13.3/mg/kg tid dose is about half of the dose recommended for children in the PI. The data provided will be used to support the argument that the important pharmacodynamic principle for β-lactam antibiotics is T>MIC for at least 40% of the dosing interval. Based on this principle, a susceptible *S. pneumoniae* breakpoint of 2.0 μg/mL for amoxicillin can be supported by the PD argument. The animal data will be reviewed in this context.

Animal model studies

The applicant provided summaries of two experimental animal model studies that were designed to show proof of concept that for β-lactam antibiotics, it is the percentage (>40%) of the dosing interval that a drug concentration remains above the MIC_{90} for the pathogen that is the important pharmacodynamic parameter.

The first study was a lung infection model in the rat that was performed with *S. pneumoniae* isolates that had amoxicillin and amoxicillin-clavulanate MICs of 0.5, 1.0, 2.0, and 4.0 μg/mL. The same strains had penicillin MICs of 1.0, 1.0. 4.0, and 8.0 μg/mL, respectively. Animals were infected intra-bronchially and the amoxicillin-clavulanate dose given as continuous infusion so as to mimic serum concentration-versus-time curves (AUCs) obtained with oral 500-mg tid (amoxicillin) or 875-mg bid (amoxicillin-

clavulanate) doses. Fourteen hours after completion of therapy, the lungs were aseptically removed and enumerated.

The results of the study are reproduced in Table 4. The data demonstrate that untreated control animals had cfu/lung that were reasonable reproducible and the infection well established. The effect of amoxicillin-clavulanate treatment, when administered to produce AUCs similar to the 500-mg and 875-mg dose, clearly show that the antimicrobial produced a therapeutic effect as demonstrated by the reduction of bacteria per lung of animals for *S. pneumoniae* with MICs ≤2.0 μg/mL. Strain 14319 (amoxicillin MIC = 4.0 μg/mL) was not as effectively reduced as were the more susceptible strains.

Table 4. Summary of *S. pneumoniae* bacteriological counts after continuous infusion of amoxicillin-clavulanate to achieve the human serum levels obtained with amoxicillin-clavulanate500/125mg tid and 875/125mg bid.

Isolates	Bacteriological counts (log_{10}cfu/lung ± SD)		
	Amox-clav 500/125mg-tid	Amox-clav 875/125mg bid	Non-treated controls
1320 [a]	2.71±1.43	2.48±0.86	7.07±0.24
APS1 [b]	3.42±0.93	2.88±0.99	6.73±0.67
N1387 [c]	3.78±1.05	3.61±1.01	6.74±0.32
14319 [d]	6.01±0.52	4.590.58±	6.61±0.49

[a] Penicillin MIC 1.0, Amoxicillin MIC 0.5
[b] Penicillin MIC 1.0, Amoxicillin MIC 1.0
[c] Penicillin MIC 4.0, Amoxicillin MIC 2.0
[d] Penicillin MIC 8.0, Amoxicillin MIC 4.0

A neutropenic murine thigh infection model study was also performed with 14 *S. pneumoniae* strains that had MIC ranges from 0.08 to 5.6 μg/mL. Two hours before the start of treatment, the animals were infected, renally impaired and injected SC with amoxicillin tid doses of 0.5, 2.0, 7.0, or 20.0 mg/kg. The intent was to vary the duration of time that serum exceeded the MIC of the infecting strain. Amoxicillin-clavulanate was administered SC at 7mg/kg, tid, to approximate the PK of a 500mg tid dose in man. The author concludes that an excellent correlation between therapeutic efficacy and the duration of time amoxicillin serum levels exceeded the MIC. It was concluded that breakpoints could be estimated from the animal model efficacy data. No data was provided to substantiate these conclusions.

A similar study to the aforementioned was performed with a 12.25 mg/kg amoxicillin-clavulanate total dose designed to mimic the human PK of an 875-mg bid dose. Mice thighs were infected with $10^{6.5\text{-}7.7}$ cfu two hours before twice-daily therapy was instituted. The growth of *S. pneumonia* with differing MIC in the thighs of mice is shown in Figure 2. The affect of therapeutic intervention on the growth of these strains is shown in Figure 3. The data clearly show that with this dosing regimen, organisms with MICs ≤2.0

μg/mL were consistently reduced by 2.7-4.9 $\log_{10}$/thigh 24 hours after infection. The two strains with MICs of 4.0 μg/mL were reduced by 2.0-2.1 $\log_{10}$/thigh 24 hours after infection and the strain with an MIC of 5.6 μg/mL grew by 2 logs. Based on the PK results obtained with the 12.25 mg/kg-amoxicillin dose, it was concluded that a ≥2.7 $\log_{10}$ is expected when amoxicillin levels exceed the MIC for at least 34% of the dosing interval. This data suggests that a susceptible breakpoint of ≤2.0 μg/mL would be appropriate and clearly points to a resistant breakpoint of 5.6 μg/mL. Since 99% reductions (>2 $\log_{10}$ reduction) of the infecting organism were seen when the MIC was 4.0 μg/mL, this would support an intermediate breakpoint of 4.0 μg/mL.

The animal model data that was provided supports the contention that at doses that mimic the human dose of 500-mg tid or 875-mg bid, organisms with MIC of ≤2.0 μg/mL will be reduced to levels that are considered therapeutically acceptable. This animal data supports the proposed susceptible MIC breakpoint of ≤2.0 μg/mL.

Note to reader: The Figures are photocopies of the information conveyed in the NDA (pages 27 and 28) and will not be available when the document is placed in the DFS.

Otitis media clinical Studies

A multi-center, international clinical study was performed during the 1994-1995 respiratory season to assess the efficacy of Augmentin in the treatment of *Streptococcus pneumoniae*. The study was an open label, single treatment group, investigator blinded study to assess the bacteriological and clinical outcome of 917 children with acute otitis media. Treatment was instituted with 40/10mg/kg/day in three divided doses. The results of these studies have been published.[7,8] Of primary interest to this discussion are the clinical outcome results when correlated with amoxicillin and penicillin MICs.

The 1998 report summarizes the microbiological findings on pretherapy middle ear fluid specimens obtained from 917 patients with AOM. Pathogens were isolated from 62% of the patients and of these patients, *Streptococcus pneumoniae* was isolated from 30% resulting in 279 isolates. The specimen collection method included tympanocentesis (241/279), ruptured tympanic membrane (34/279), and tympanostomy tube (4/279). Approximately 243/279 of the *Streptococcus pneumoniae* isolates was susceptible to amoxicillin at ≤0.5 μg/mL. In addition, the penicillin, and amoxicillin susceptibility profile are practically identical as previously discussed. The 1996 report addresses the clinical outcome statistics in relation to the MIC of these isolates. Two sets of data are summarized below to demonstrate the clinical outcomes as measured by the investigators.

In Table 5 the results are presented by clinical response according to penicillin MIC when patients are evaluated at days 12-14. In Table 6 similar analysis is presented when evaluated at days 32 to 38. The data show that at a dose of 40/10-mg/kg/day tid for 10 days, good clinical outcome for penicillin susceptible, intermediate and resistant strains for the US and Europe/Israel are achieved. (Table 5) The Table 6 data continue to show a reasonable outcome as predicted by the PD principle. It needs to be kept in mind that a majority of these strains will be considered susceptible if the breakpoint is set at ≤2.0

μg/mL. Further analysis of this data was provided by the applicant by evaluation of outcome based on amoxicillin MICs. Of interest are the data around the proposed breakpoints. At a MIC of 1.0 μg/mL 16 subjects were enrolled in the study and 15 were considered clinical successes with one failure. For a MIC of 2.0 μg/mL, 6 subjects enrolled and all 6 were clinical successes. For a MIC of 4.0 μg/mL 3 patients were enrolled and 2 were clinical successes. One patient with a MIC of 8 μg/mL was enrolled and the patient was a clinical success.

Table 5. Clinical response of subjects with *Streptococcus pneumoniae* AOM at Days 12 to 14 according to MIC of penicillin.

Clinical Response	No. of Subjects with *Streptococcus pneumoniae*			
	Susceptible	Intermediate	Resistant	Total
United States				
Success	56 (89)*	7 (88)	7 (78)	70
Clinical Failure	7 (11)	0 (0)	1 (11)	8
Unable to determine	0 (0)	1 (13)	1 (11)	2
Total	63 (100)	8 (100)	9 (100)	80
Europe/Israel				
Success	118 (95.9)	49 (96)	13 (93)	180
Clinical Failure	1 (0.8)	0 (0)	1 (7)	2
Unable to determine	4 (3.3)	2 (4)	0 (0)	6
Total	123 (100)	51 (100)	14 (100)	188

* Numbers in parenthesis, percent

Table 6. Clinical response of subjects with *Streptococcus pneumoniae* AOM at Days 32 to 38 according to MIC of penicillin.

Clinical Response	No. of Subjects with *Streptococcus pneumoniae*			
	Susceptible	Intermediate	Resistant	Total
United States				
Success	36 (57)*	5 (63)	4 (44)	45
Clinical Failure	26 (41)	2 (25)	4 (44)	32
Unable to determine	1 (2)	1 (13)	1 (11)	3
Total	63 (100)	8 (100)	9 (100)	80
Europe/Israel				
Success	113 (91.9)	47 (92)	12 (86)	172
Clinical Failure	6 (4.9)	1 (2)	2 (14)	9
Unable to determine	4 (3.3)	3 (6)	0 (0)	7
Total	123 (100)	51 (100)	14 (100)	188

* Numbers in parenthesis, percent

Based on the information provided by the sponsor and the information gathered from the published literature, it is my conclusion that the proposed breakpoints of S ≤2.0 μg/mL, I = 4.0, and R ≥8.0 μg/mL be approved as requested..

/S/

Albert T. Sheldon, Jr. Ph.D.
Team Leader, Microbiology Reviewer

Cc: Original NDA No. 50-542
Microbiologist, HFD-520
File name: N50542s016.doc

SMicro/ATSheldon

DepDir/LGavrilovich

Cc: Original NDA # 50-542
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-520/Smicro/ATSheldon
HFD-520/Micro
HFD-520/MO/
HFD-520/Pharm/
HFD-520/Chem/
HFD-520/CSO/
HFD-520
HFD-502
HFD-635

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[1] The Alexander Project is an international multicenter study that investigated the susceptibility of community acquired lower respiratory tract infections to 16 commercially available antibiotics. The program is supported by a grant from SmithKline Beecham.

[2] Jacobs MR, (1998) Update on Drug-Resistant *Streptococcus pneumoniae* and the Management of Acute Otitis Media. Pediatr Infect Dis J 17(10): 947-952.

[3] Kaplan SL, and EG Mason (1998) Management of Infections Due to Antibiotic Resistant *Streptococcus pneumoniae* Clin Microbiol Rev 11(4):628-644

[4] Verhaegen J, and L Verbist (1998) In vitro activity of 21 β-lactam antibiotics against penicillin susceptible and penicillin resistant *Streptococcus pneumoniae*. JAC 41:381-385.

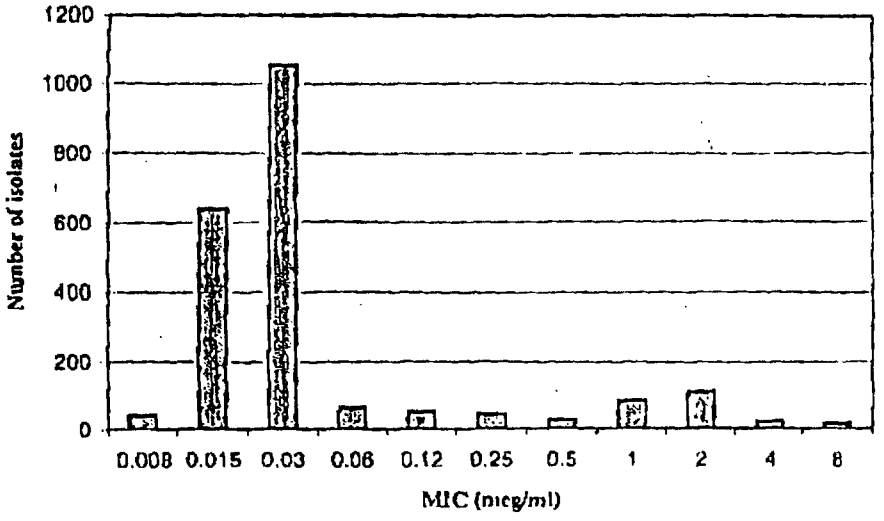
[5] Jacobs MR, et.al. (1999) Susceptibility of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* to Oral agents: Results of a 1998 US Outpatient Surveillance Study. 39th ICAAC

[6] Craig B, and D Andes (1996) Pharmacokinetics and Pharmacodynamics of Antibiotics for Otitis media. Pediatr Infect Dis J 15(10): 944-948.

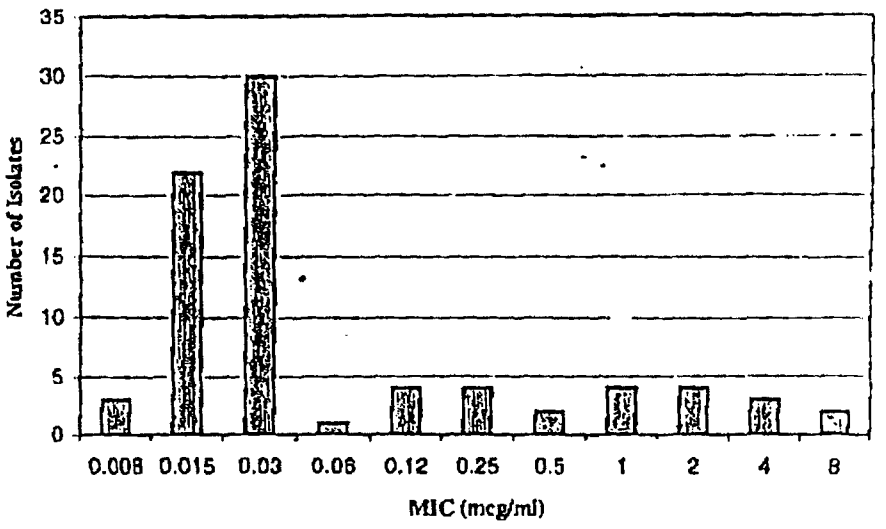
[7] Hoberman A, et. al. (1996) Efficacy of amoxicillin/clavulanate for acute otitis media: relation to *Streptococcus pneumoniae* susceptibility. Pediatr Infect Dis J 15(10): 955-962.

[8] Jacobs MR, et. al. (1998) Prevalence of Antimicrobial-Resistant Pathogens in Middle Ear Fluid: Multinational Study of 917 Children with Acute Otitis Media. Antimicrob Agents Chemother 42(3):589-595.

Distribution of Amoxicillin MICs from Project Alexander
Global *S. pneumoniae* Isolates 1996 (n = 2160)

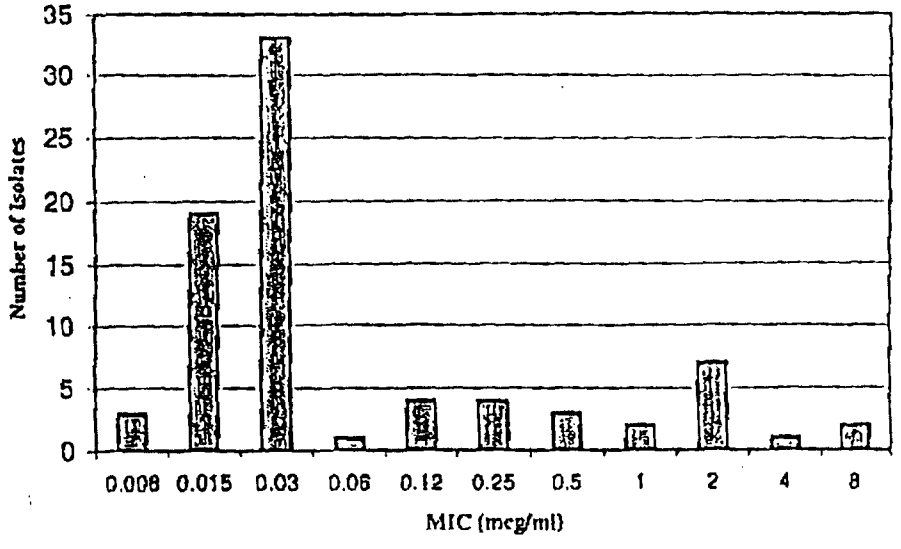


Distribution of Amoxicillin/clavulanate MICs from Project Alexander
U.S. *S. pneumoniae* Isolates 1996 (n = 79)

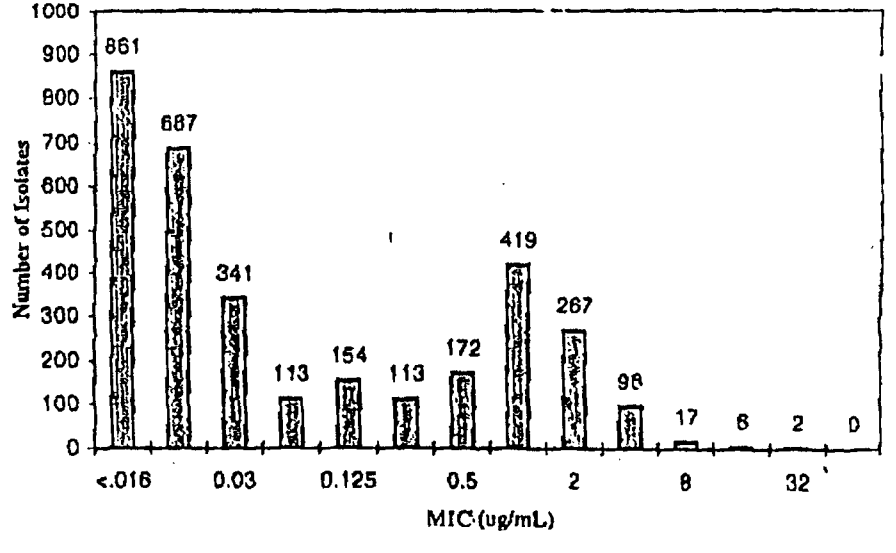


99%

Distribution of Amoxicillin MICs from Project Alexander
U.S. *S. pneumoniae* Isolates 1996 (n = 79)



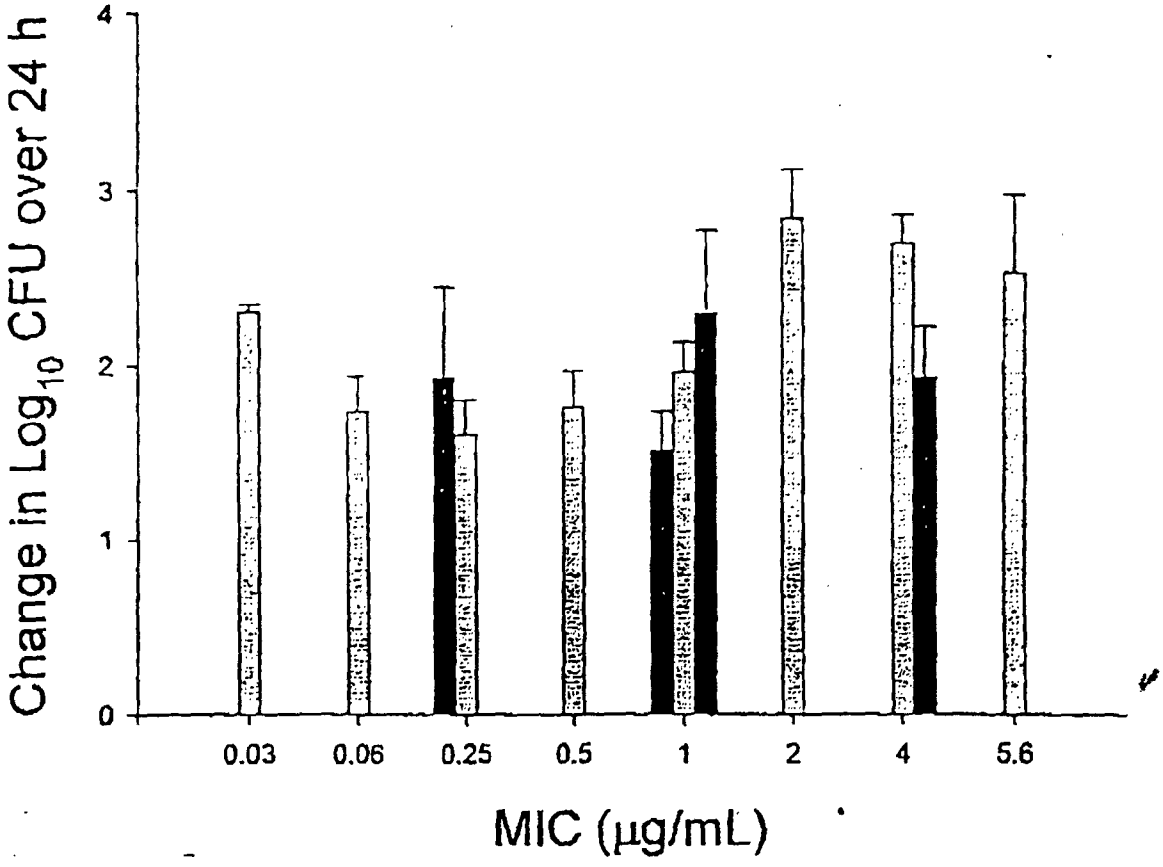
Distribution of Amoxicillin/clavulanic acid MICs from 1997 U.S. *In-vitro*
Hospital study *S. pneumoniae* Isolates (n = 3248)



Data on File SmithKline Beecham Pharmaceuticals.

Figure 2

Growth of various strains of *S. pneumoniae* in thigh muscle of untreated neutropenic mice



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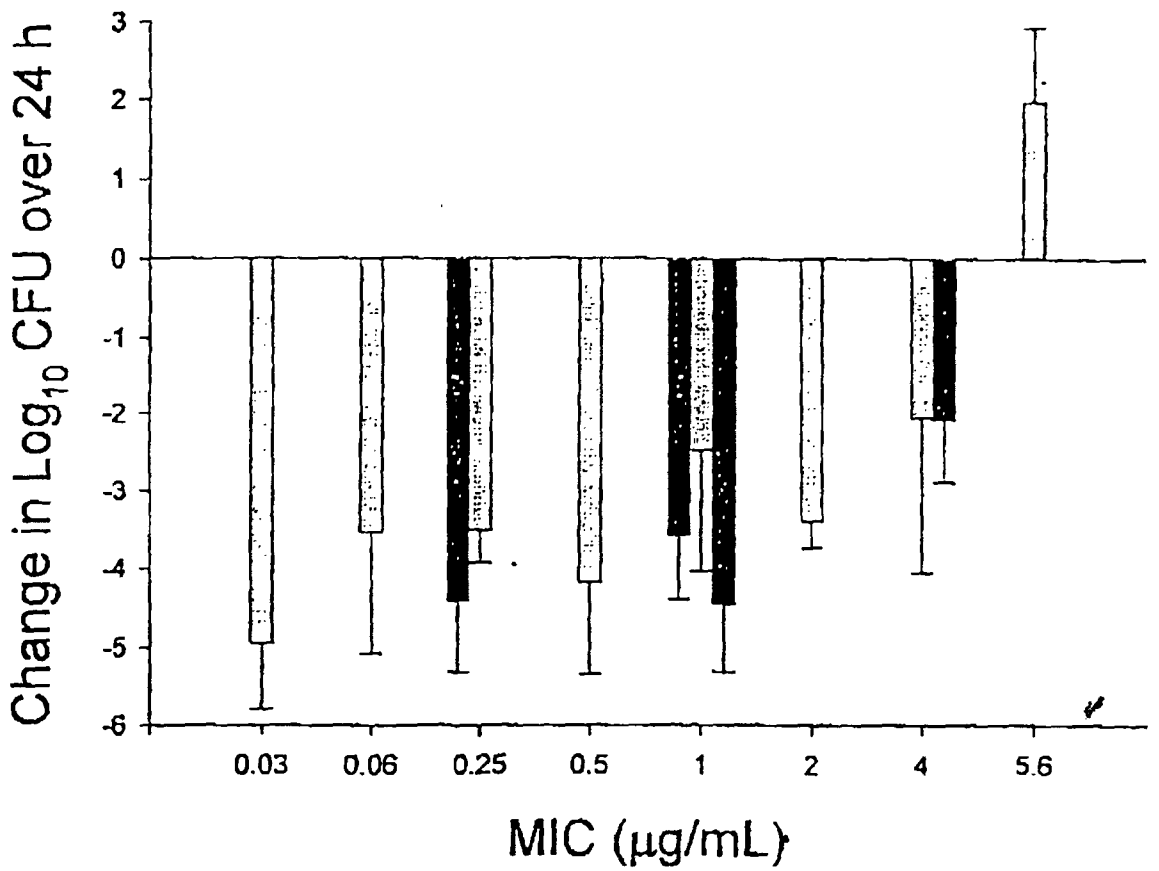
submitted July 23, 1998

000027

Figure 3

Effect of 12.25 mg/kg amoxicillin/clavulanate b.i on numbers of *S. pneumoniae* in thigh muscle of neutropenic mice



NDA 50-542/SLR-016
Submitted July 23, 1998

000028

Division of Anti-Infective Drug Products
Clinical Microbiological Review #2

NDA #50-542 /SLR016 **Date Completed:April 8, 2002**
50-754/SLR001

Sponsor (IND)/Applicant (NDA):
GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929

Chem/Ther. Type: Antibiotic

Submissions Reviewed: Response to Request for Clinical Information Relevant to Breakpoint Determination for *Streptococcus pneumoniae*.

Providing for: The assessment of interpretative criteria for *Streptococcus pneumoniae*.

Product Name(s):

Proprietary: Amoxil®

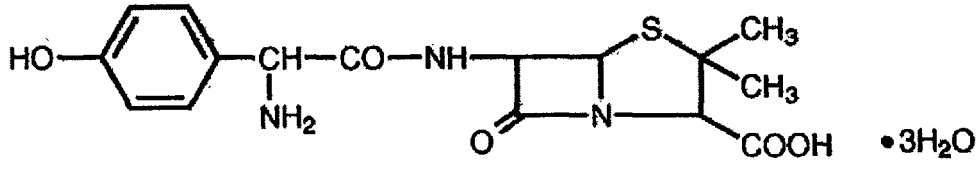
Non-proprietary/USAN: amoxicillin

Compendia: amoxicillin

Code name/number: amoxicillin

Chemical name: 2 *S* ,5 *R* ,6 *R*)-6-[(*R*)-(-)-2-amino-2- (*p* -hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4- thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

Structural formula:



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

Dosage form(s): chewable tablets
Route(s) of administration: oral

Pharmacological Category: antimicrobial, penicillin class

Dispensed: Rx__X____ OTC_____

Initial Submission Dates
Received by CDER:
Received by Reviewer:
Review Completed:

Supplements/Amendments:
Received by CDER: October 15, 2001
Received by Reviewer: October 23, 2001

Related Documents:
NDA 50-542/SLR016 Amoxil (Amoxicillin; 125mg & 250mg.) Chewable Tablets'
NDA 50-754/SLR001 Amoxil (Amoxicillin; 500mg & 875mg.) Oral Tablets
NDA 50-564/SLR034 Augmentin (Amoxicillin/clavulanate; 4:1; 250/125 & 500/125) Oral Tablets
NDA 50-720/SLR006 Augmentin (Amoxicillin/clavulanate; 7:1; 875/125) Oral Tablets
NDA 50-725/SLR001 Augmentin (Amoxicillin/clavulanate; 7:1; 200/28.5 per 5 mL & 400/59.0 per 5 mL) OS
NDA 50-597/SLR027 Augmentin (Amoxicillin/clavulanate; 4:1; 125/31.25 & 250/57.0) Chewable Tablet
NDA 50-726/SLR001 Augmentin (Amoxicillin/clavulanate; 7:1; 200/28.5 & 400/57.0) Chewable Tablet

Remarks:
The October 9, 2001 labeling supplement provides additional clinical summary studies to support a change in the breakpoints of *Streptococcus pneumoniae*. The summary reports are provided in response to a request from the Division of Anti-Infective Drug Products that they be submitted for review in support of the labeling proposal.

Conclusions/Recommendations:

- The breakpoint of S ≤ 2.0 μg/mL (nonmeningitis) is approved when used to define the potential utility of Amoxil and Augmentin dosed at 500mg TID, 875mg BID, 40mg/kg/day TID and 45mg/kg/day BID for the treatment of infections caused by *S. pneumoniae*. The T>MIC of 30-40% of the dosing interval when an MIC of 2.0 g/mL is used can not be justified for the 500mg BID and 250mg TID dosing regimens. Therefore, the microbiology section of the package insert is written to reflect these observations and will read as follows:

  For susceptibility testing of *Streptococcus pneumoniae* from nonmeningitis sources.

Susceptible	≤ 2.0 μg/mL
Intermediate	4.0 μg/mL
Resistant	≥8.0 μg/mL

Clinical studies provided in the June 23, 1998 labeling submission

On June 23, 1998 the applicant submitted a request for a labeling change to the Amoxil (amoxicillin) and Augmentin (amoxicillin/clavulanate) microbiology sections of the package insert. Specifically, they sought to change the *Streptococcus pneumonia* interpretative criteria by moving the breakpoints up two tube dilutions. The request is to move the susceptible breakpoint from ≤ 0.5 to ≤ 2.0 μg/mL and the resistance breakpoint from ≥ 2.0 to ≥ 8.0 μg /mL. It should be noted that these proposed breakpoints, if accepted, would be applicable only to indications other than meningitis. The data submitted by the applicant to support this request included:

1. Minimum inhibitory concentration and zones of inhibition population distribution profiles of the pathogen under consideration.
2. Information on the mechanisms of resistance found in the target pathogen and their distribution within the population under investigation.
3. Pharmacokinetic and pharmacodynamic data that describes the absorption, distribution, metabolism and elimination of the drug and the relationship of drug levels in target sites to the susceptibly patterns of the pathogen under consideration.
4. Clinical data that describes the association of the susceptibility of the pathogen isolated during the clinical investigation to clinical outcome of the patient, which helps further define the predictive value of the proposed breakpoints. The clinical data that was submitted to support the request for higher-breakpoints for both Amoxil® and Augmentin® is a multicenter international clinical study performed during the respiratory season between 1994 and 1995. The study was of open label, single treatment group, investigator blinded trial design and assessed the clinical and bacteriological

outcome of 917 children with acute otitis media. Treatment was Augmentin 40/10mg/kg/day (4:1) tid and not Amoxil. However, since the target pathogen is *S. pneumoniae*, the efficacy of the combination is primarily due to the amoxicillin component of the formulation.

The conclusions reached in Microbiology Review #1 were that the existent **Amoxil** breakpoints be changed to Susceptible ≤.2.0, Intermediate = 4.0 and Resistant ≥ 8.0 mcg/mL as requested by the applicant.

It was also concluded that the **Augmentin** products, that are also the subject of this, review are not approved for the treatment of *Streptococcus pneumonia* and do not warrant breakpoints for a non-existent indication. Clearly, this statement requires clarification because breakpoints for *S. pneumoniae* are currently included in the package insert.

When the Augmentin products were first approved, it was agreed that the combination policy was applicable to the indications section of the package insert but not to the Microbiology section. The reason for this distinction took into consideration the fact that the amoxicillin component of Augmentin would be efficacious, microbiologically, versus *S. pneumoniae* as is Amoxil. So this pathogen was allowed in the second list of the Microbiology section of the package insert. It was not considered unreasonable to include the Amoxil breakpoints in the Augmentin label because Amoxil was approved for the treatment of *S. pneumoniae*.

The first series of reviews performed by Drs. James King and Mercedes Albuerne for these supplements suggested that *S. pneumoniae* [redacted] This policy requires that both product components contribute a clinical effect to the pathogens under investigation. It was argued that only betalactamases producing pathogens met this requirement and are the only pathogens that could be allowed in the product label. Since one of the components of Augmentin is an antibiotic (amoxicillin) and the other a beta-lactamase inhibitor (clavulanate), this effect could not be shown for *S. pneumoniae* because β-lactamases are not a mechanism of resistance found in *S. pneumoniae* isolates. [redacted]

In addition, as the issues of antibiotic resistance began to emerge in the scientific and regulatory communities, the agency decided that we would no longer allow the establishment and inclusion of breakpoints for microorganisms if an indication was not granted. If the Augmentin label is used as an example, we would not set breakpoints for *S. pneumoniae* because this pathogen is not in the indications section of the package insert. However, we would allow *S. pneumoniae* in the second list for the reasons discussed in the next paragraph.

Further, the antimicrobial drug combination policy has recently been reinterpreted within the Center for Drug Evaluation and Research. If it is shown that one of the two components of a drug combination is sufficient to produce a desirable clinical effect, then these are sufficient grounds to allow inclusion of the pathogen into the product label. The most recent example of this interpretation is the Augmentin ES-600 powder for oral suspension. This product was studied for the treatment of *S. pneumoniae* and received approval for the treatment of *S. pneumoniae* in pediatric patients with recurrent or persistent acute otitis media due to *S. pneumoniae* (penicillin MICs ≤ 2.0 μg/mL). Inclusive within this label is the breakpoint for *S. pneumoniae*.

In summary, we have several policies working simultaneously that may produce conflict for drugs approved prior to the implementation of these policies. Cases in point are the Augmentin products with the exception of Augmentin ES-600. As stated earlier, we allowed these products to incorporate the *S. pneumoniae* pathogen into the second list of the package insert and to incorporate breakpoints in the event this product was used in the empiric treatment of pathogens that may or may not carry β-lactamases. This is a logical extension of the use of Augmentin as Amoxil. However, when we try to apply these current policies to old labels, we have conflict as previously described.

These new policies do not produce conflict for drugs approved since the introduction of these policies. Under the new interpretation of the new drug combination policy, the applicant is allowed to investigate the potential utility of amoxicillin/clavulanate versus *S. pneumoniae*. If clinical efficacy is demonstrated, the pathogen will be incorporated into the indications section of the package insert and appropriate breakpoint criteria will be established for the organism. If this pathogen is not approved for inclusion in the indications section of the package insert, but is a pathogen capable of causing infection in one of the indications approved in the package insert, and it meets the algorithm for inclusion into the second list, it will be placed in the second list of the product label as a pathogen that is a candidate for study. However, breakpoints will not be established for this organism. The former example is what we did for Augmentin ES-600.

In summary, the request to change the breakpoints for Augmentin was not a valid request since breakpoints should not exist in the original Augmentin product labels based on our current interpretation of policy. This last statement is based on our current policy of not establishing interpretative criteria for antimicrobial drugs when the pathogen is not approved for inclusion in the indications section of the package insert.

Note: On February 8, 2002 a meeting was held between Drs. Janice Soreth, John Alexander, Albert T. Sheldon, Jr., and Susmita Samanta to discuss the proposed recommendations from the discipline of Microbiology regarding the breakpoints of Augmentin. This meeting focused on the current policy previously described and how best to apply it to the current Augmentin proposal to establish breakpoints for *S. pneumoniae*. In order to address the first issue, that the Augmentin is not indicated for the treatment of *S. pneumoniae*, the argument was presented that the Augmentin label has, by cross reference to Amoxil, the indication for *S. pneumoniae*. Amoxil is approved for the treatment of *S. pneumoniae* and by definition, would be expected to be treatable

with Augmentin. It was further argued that the verbiage found at the end of the Indications and Usage section of the Augmentin label supported this conclusion. The Augmentin label states:

> " While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and (beta)-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and *Augmentin.* (See Microbiology subsection.)"

Thus, the Microbiology reviewer should treat the Augmentin label as having a claim for the treatment of *S. pneumoniae* and the establishment of a breakpoint is now feasible and in compliance with the existent policy. It should be noted that this logic was initially used to include *S. pneunomiae* in the original Augmentin labeling and thus for the incorporation of the existent breakpoints into the product label.

Therefore, the remainder of this review will focus on the evaluation of scientific data provided by the applicant to support the establishment of higher breakpoints than currently exists for Augmentin and Amoxil labels. This evaluation will include the information discussed in Microbiology Review # 1 and the information discussed in this review.

Clinical studies provided in the October 9, 2001 labeling submission

Amoxil® is the brand of amoxicillin manufactured by GlaxoSmithKline in several dosage forms that include capsules, tablets, chewable tablets, and powder for oral suspension. All of these dosage forms can be used to treat the diseases described in the indications section of the package insert. The indications of interest are those that contain the pathogen *Streptococcus pneumoniae* and include "Infections of the ear, nose and throat" (ENT) and "infections of the lower respiratory tract" (LRT). The doses recommended for the treatment of these indications depends on the severity of the infection and the age of the patient as presented in Table 1.

is approved for the treatment of this pathogen for the listed indications. Given this observation, we must now explore whether the doses and dosing intervals investigated provide proof of concept that all doses and dosing intervals listed in Tables 1 and 2 would be effective in the treatment of *S. pneumoniae* with MICs of ≤ 2.0 μg/mL

The information originally reviewed to determine whether the agency needed to change the breakpoints as requested by the applicant included a multi-center international clinical trial that used Augmentin (4:1; 40/10mg/kg/day in three divided doses) as the treatment regimen for acute otitis media due to *S. pneumoniae*. Evaluation of Tables 1 and 2 would suggest that for the treatment of sever otitis media, a dose of 40/10mg/kg/day TID would be appropriate. This clinical data, the in vitro spectrum of activity studies, and the animal model work provided insight regarding the efficacy of amoxicillin versus *S. pneumoniae* and it was concluded in Microbiology Review #1 that the breakpoints proposed were acceptable for Amoxil. However, the original assessment did not take into consideration all of the possible formulations and dosing intervals that could be used to treat *S. pneumoniae*.

During the review of this supplement, the agency became aware of a comparative clinical trial submitted in NDA 50-785 Augmentin XR (amoxicillin/clavulanate; 1000mg:62.5mg (14:1)) that used, as a control, Augmentin (7:1). This randomized, double blind study (BRL-025000/546) compared a new test formulation of Augmentin (16:1) given twice daily with an approved control, Augmentin (7:1) given twice daily. It is the approved control drug that is of interest to these Amoxil and Augmentin supplements. On September 17, 2001 the Medical Team Leader called GlaxoSmithKline and requested that the results of the comparative trial be submitted to the labeling supplements currently under review by the agency. In response to this request, the applicant provided this and additional clinical studies in acute otitis media and respiratory tract infections, which were submitted to the supplement to support the proposed breakpoints.

The information submitted to the labeling supplements on October 9, 2001 include four clinical studies that compare the efficacy of Augmentin (4:1 or 7:1) with other antimicrobials. The studies include two acute otitis media trials, a community acquired pneumoniae trial, and an acute exacerbation of chronic bronchitis trial. They will be reviewed sequentially and then globally from the microbiological perspective to determine whether they support, clinically and microbiologically, the proposed breakpoints. The data will also be evaluated from the pharmacodynamic perspective to determine whether the formulations and dosing intervals studied support the proposed breakpoints for all other formulations and dosing intervals that exist for these products. The last issue is important because the establishment of *S. pneumoniae* breakpoints of 2.0 μg/mL suggests that treatment with any of the Amoxil and Augmentin formulations will be effective for pathogens with an MIC of ≤ 2.0 μg/mL.

Study BRL-025000/496-A single Blind, Randomized, Multicenter Study to Assess the Safety and Efficacy of 5 days of Augmentin q12 h (45/6.4mg/kg/day) Compared with Zithromax q24 (10mg/kg/ on day 1 and 5mg/kg on days 2-5) in the Treatment of Acute Otitis Media in Infants and Children.

This study enrolled 601 pediatric patients and the information provided is basically a very abbreviated summary of the facts thus making it useless in making any regulatory decisions regarding the proposed breakpoints. The applicant states that middle ear fluid for microbiological testing was obtained when clinical failures were observed. The number of patients enrolled in the Augmentin arm was not provided but it is stated that of the failures observed, samples could only be obtained on half due to lack of parental consent to perform tympanocentesis. Of the 5 failures in the 7:1 Augmentin arm for which data is available, all were susceptible to amoxicillin/clavulanate at a MIC of ≤ 0.5 mcg/mL. There are no clinical data to support or negate the proposed pharmacodynamic breakpoint of S ≤ 2.0 mcg/mL.

From the pharmacodynamic perspective, no additional data were provided from the clinical studies. The dose used in this study is consistent with the dose and dosing interval recommended for otitis media in Tables 1 and 2. The dose (45/6.4mg/kg/day) and dosing interval (BID) used is for infections characterized as sever in nature.

Study BRL-025000/509- A Single Blind, Randomized, Multicenter Study to Assess the Bacteriological Efficacy of Augmentin q12 h x 10 days versus Zithromax x 5 days in the Treatment of Acute Otitis Media in Infants and Children.

This study enrolled and treated 118 patients in the Augmentin 7:1 arm and baseline pathogens were identified in 84 (71%) of the patients, of which 37 (44%) were *Streptococcus pneunomiae*. The primary assessment of the data included clinical and bacteriological responses. Bacteriological response was based on tympanocentesis performed prior to therapy and on days 4-6 during therapy with the latter being the primary outcome measure of efficacy. Clinical response was assessed at the end of therapy (days 12-14) and at follow-up (days 22-28).

The clinical and bacteriological response rates for amoxicillin/clavulanate MIC for patients with *S. pneumoniae* are presented in the clinical and bacteriological per protocol (PP) populations respectively in Tables 3 and 4. Visual inspection of the data presented in Table 3 suggests that only three patients had *Streptococcus pneunomiae* with MICs ≥ 2.0 mcg/mL and at EOT (days 12-14), they were all considered clinical successes. This is consistent with the bacteriological assessment (Table 4) where eradication was noted in all three subjects. It should be noted that a bacteriological tympanocentesis sample was obtained while the patient was approximately midway though the course of therapy and it is not clear whether carry over antibiotic would affect isolation of the pathogen. It is interesting that at follow-up (days 22-28), all three patients were considered clinical recurrences. Perhaps this is an expected outcome given the natural history of AOM and risk factors associated with re-exposure (daycare settings, prior antibiotic treatment, etc.). The test of cure used by the FDA is evaluation at

follow-up and application of this criteria would suggest failure of therapy. However, the Division of Anti-infective Drug Product advisory committee has suggested that the agency consider EOT as the appropriate reference point for analysis. The recommendation is based on what we know of the natural history of the disease. If we do so, then all three cases would be clinical successes for microorganism with MICs of 2.0, 4.0, and 8.0 mcg/mL. The evidence is not overwhelming but does trend towards the successful outcome.

Additional clinical and bacteriological information was provided for *S. pneumoniae* isolates from mixed infections at screening (Data not provided). There are two isolates of *S. pneumoniae* that have MICs ≥ 2.0 mcg/mL and both were considered clinical successes at EOT but one was a bacteriological failure (day 4-6). One of the patients was a clinical success at follow-up and one was apparently lost to follow-up.

From the pharmacodynamic perspective, no additional data were provided from the clinical studies. The dose used in this study is consistent with the dose and dosing interval recommended for otitis media in Tables 1 and 2. Again, the dose (45/6.4mg/kg/day) and dosing interval (BID) used is for infections characterized as sever in nature.

Study BRL-025000/546-A Randomized, Double Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Augmentin SR 2000/125mg Twice Daily versus Oral Augmentin 875/125mg Twice Daily for 7 days in the Treatment of Adults with Bacterial Community Acquired pneumonia.

This community acquired pneumonia (CAP) study was submitted in NDA 50-785 for Augmentin XR (amoxicillin/clavulanate, 16:1). The primary efficacy parameter used in the controlled, lower respiratory tract infection CAP study (# 546) was clinical response at test of cure (days 28-35) for the per-protocol population. A total of 261 patients were randomized to receive Augmentin tablets (875/125mg; 7:1). Clinical and bacteriological response rates are reported for 6 patients and are presented in Table 5. Only a single patient was found that provided the information needed to evaluate the efficacy of Augmentin versus *S. pneumoniae* with a MICs ≥ 2.0 mcg/mL. This patient was a clinical and bacteriological success at TOC.

From the pharmacodynamic perspective, no additional data were provided from the clinical studies. The dose used in this study is consistent with the dose and dosing interval recommended for otitis media in Tables 1 and 2. Again, the dose (875/125mg/kg/day) and dosing interval (BID) used is for infections characterized as sever in nature.

Study BRL-025000/070-A Randomized, Double Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320mg Once Daily for 5 days versus Oral Amoxicillin/clavulanate 500/125mg Three Times Daily for Seven Days for the Treatment of Acute Exacerbation of Chronic Bronchitis.

This phase III study was designed to evaluate the efficacy of oral Factive (Gemifloxacin) 320mg given once per day versus Augmentin 500/125mg (4:1) given three times per day for 7 days in patients with AECB. The primary efficacy parameter is clinical response at follow-up (days 14-21). The secondary efficacy parameter is clinical response at EOT (days 9-11) and long term follow-up (days 28-35). Further, secondary response included bacteriological response at EOT, F/U, and long-term F/U. The results for *S. pneumoniae* are presented in Table 6 and it can be seen that only two patients had isolates with amoxicillin MICs of ≥ 2.0 mcg/mL. Both of these subjects had favorable clinical response but were bacteriological failures. One patient had a mixed infection that included *S. pneumoniae* and *Staphylococcus aureus*; both had amoxicillin/clavulanate MICs of 2.0 mcg/mL. At EOT the *S. aureus* was isolated but the *S. pneumoniae* was not and the investigator concluded that this was a bacteriological failure. The second patient had a bacteriological outcome of persistence and was carried forward as a clinical failure. Both patients were deemed clinical successes at EOT and F/U.

From the pharmacodynamic perspective, no additional data were provided from the clinical studies. The dose used in this study is consistent with the dose and dosing interval recommended for otitis media in Tables 1 and 2. Again, the dose (500/125mg/kg/day) and dosing interval (TID) used is for infections characterized as sever in nature.

Summary discussion of clinical data:
The clinical data used to support the proposed breakpoints is limited to studies performed with the Augmentin 4:1 and 7:1 formulations dosed for the treatment of sever infections caused by *S. pneumoniae*. Although the results are limited in total number of observations made with *S. pneumoniae* pathogens with MICs of ≥ 2.0 µg/mL, the data does provide some limited clinical evidence to support the breakpoints of ≤2.0 µg/mL.

The significance of this data and the conclusion must be placed into perspective because the doses and dosing intervals used to support the proposed breakpoints are those used for the treatment of sever infections. There is no clinical or pharmacodynamic evidence to support the breakpoints for doses that would be used for less sever infections as described in Tables 1 and 2. It is this reviewers opinion that the clinical study designs are weighed in favor of the clinical success of Amoxil and Augmentin because only treatments for sever infections caused by *S. pneumoniae* were evaluated. The studies are not designed to provide the evidence necessary to evaluate other doses and dosing intervals used for less sever infections as described in Tables 1 and 2. It is these formulations and dosing intervals that should be characterized to justify the proposed breakpoints. The doses used in these clinical trials are exceptions to the rule and are best case scenarios. Thus we must look to pharmacodynamic evidence to address this issue.

Pharmacokinetic and pharmacodynamic discussions for Amoxicillin

The appropriate time-kill kinetic parameter that characterizes the effect of β-lactam antibiotics is that they kill pathogens in a time dependent manner and not in a concentration dependent manner. That is, β-lactams are capable of killing pathogens at the same rate independent of the concentration of drug present provided the concentration remains above the MIC of the pathogen. Thus, the rate of kill is actually dependent on the time of exposure. For β-lactams, the time that the MIC_{90} of the pathogen remains above the free drug concentration in serum, the better the relationship to survival. For *S. pneumoniae*, it has been determined that if the drug concentration remains above the MIC_{90} for 30-40% of the dosing interval, the better the expected clinical outcome.

The applicant only studied doses and dosing intervals approved for the treatment of severer infections caused by *S. pneumoniae*. It is unclear whether the doses and dosing intervals recommended for mild to moderate or less sever infections produce the desired pharmacodynamic parameter. Therefore, we will attempt to identify and evaluate pharmacodynamic information to determine whether all formulations, doses and dosing intervals are capable of providing T>MIC for 30-40% of the respective dosing intervals when a MIC of 2.0 μg/mL is used. If they do, then we can accept the proposal to raise the breakpoints by two tube dilutions. In order to facilitate this discussion, Biopharmaceutical Reviewers were asked to provide any available pharmacokinetic information that may be available to help in this endeavor.

Dr. Frank Pelsor, Biopharm Team Leader, was able to provide information on the bioavailability relationships of the different formulations and these are presented in Table 7. In addition, the following comments were provided:

1. There is no link (in vivo) to establish the bioavailability relationships among the three oral suspension formulations and four tablet formulations of Augmentin.
2. It is reasonable to expect bioequivalence between the oral suspensions (4:1) and chewable tablets (4:1).
3. Bioequivalence has been demonstrated between the oral suspensions (7:1) and chewable tablets (7:1)
4. A comparison of relevant bioavailability parameters is available for different dosage regimens of the oral tablets.
5. The bioavailability of the oral suspension (14:1) has not been compared to the other Augmentin formulations.

The information provided by Dr. Pelsor suggests that it is reasonable to expect bioequivalence between like doses and dosing intervals. What is not clear is whether the bioavailability between all of the Amoxil and Augmentin formulations when dosed at different dosing intervals is the same. In addition, bioavailability and bioequivalence information does not provide the needed pharmacokinetic characteristics of the Amoxil and Augmentin formulations needed to assess the T>MIC.

As stated before, the T>MIC for *S. pneumoniae* with a MIC of 2.0 μg/mL is 30-40% of the dosing interval. It would appear that there may be reason for concern regarding the T>MIC for the 500/125mg BID and 250/125mg TID dosing regimens. The 500mg BID dose appears to be borderline at less<30% of the dosing interval and the 250 mg TID is clearly below the T>MIC with values of 24 and 25%, respectively. The results represent two independent observations that confirm each other. These studies provide insight into the strategy used by the company to justify the proposed breakpoint. It is now clear why only 875mg BID and 500mg TID data is provided in support of the proposed breakpoint.

Pharmacokinetic/pharmacodynamic calculations presented by Dr. Bill Craig at the National Committee for Clinical Laboratory Standards for amoxicillin suggest that for doses of 500mg TID, the MIC required to produce a T>MIC of 40-50% of the dosing interval is 2.0 μg/mL. For doses of 875mg BID, the MIC required to produce a T>MIC of 40-50% of the dosing interval is 1.0 μg/mL. The applicant original submission also provide a similar argument and concluded that for doses of 875mg BID and 500mg TID the T>MIC of 40 % and 43%, respectively, would be achieved with an MIC of 2.0 μg/mL. Based on the results of this analysis of the available data, it would appear that the breakpoint of ≤ 2.0 μg/mL would be acceptable for doses used to treat sever infections (875mg BID & 500mg TID). The doses used to treat mild to moderate infections also appear to be satisfactory for the treatment of pathogens with an MIC of 2.0 μg/mL. However, it may be questionable to suggest that the 500mg BID and 250mg TID would be adequate to treat pathogens with these MICs.

Summary discussion of pharmacokinetic/pharmacodynamic information:

The pharmacokinetic and pharmacodynamic information used to support the proposed breakpoints of ≤ 2.0 μg/mL suggests that all of the Amoxil and Augmentin regimens may not be appropriate to treat *S. pneumoniae* with MICs of 2.0 μg/mL. The PK/PD information presented was generated using formulations and dosing intervals for the treatment of moderate to sever infections caused by *S. pneumoniae*. The data also suggests that the 500mg BID and 250mg TID regimens may not provide the necessary coverage to treat *S. pneumoniae* isolates with a MIC of 2.0 μg/mL. It is expected that treating infections with higher doses and more frequently will result in T>MIC for the expected times of 30-40% of the dosing interval.

In conclusion, the breakpoints of susceptible ≤ 2.0 μg/mL, intermediate of 4.0 μg/mL, and resistant ≥8.0 μg/mL are approved for individuals receiving dosing regimens other than the available 500mg BID and 250mg TID dosing regimens. In addition, a limitation will be placed in the label which suggests that the approved breakpoints are applicable to *S. pneunomiae* isolates of nonmeningitis origin only.

Summary discussion and recommendations

It will be logical for Amoxil and Augmentin products to have the same label because both product lines have the same active ingredient, regimens and dosing intervals. The

breakpoint of S ≤ 2.0 μg/mL is approved when used to define the potential utility of Amoxil and Augmentin when dosed at 500mg TID and 875mg BID for 10 days in the treatment of infections caused by *S. pneumoniae*. The pediatric doses of 40mg/kg/day TID and 45mg/kg/day BID should be satisfactory in this regard. A note will be added to the package insert stating that doses of 500mg BID, 250mg TID, 20mg/kg/day TID and 25mg/kg/day BID should **not** be used to treat *S. pneumoniae* isolates with an MIC of ≤ 2.0 μg/mL.

The recommended labeling of the Microbiology section of the package insert is as follows:

For susceptibility testing of *Streptococcus pneumoniae* from nonmeningitis sources.

Susceptible	≤ 2.0 μg/mL
Intermediate	4.0 μg/mL
Resistant	≥8.0 μg/mL

Albert T. Sheldon, Jr. Ph.D.
Team Leader, Microbiology Reviewer

Cc: Original NDA No. 50-542
Microbiologist, HFD-520
File name: 50-542#2_SLR016FIN.doc

SMicro/ATSheldon

DepDir/LGavrilovich

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Table 3. Clinical Efficacy of *Streptococcus pneumoniae* Susceptibly (MIC) to Amoxicillin/clavulanate-Patients Treated with Augmentin 45/6.4 mg/kg/day for 10 days (Per Protocol Population)

Amoxicillin/clavulanate MICs (mcg/mL)	Clinical response EOT (days 12-14)				Clinical Response F/U (days 22-28)			
	Success		Failure		Success		Failure	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Total	18/21	86	3/21	14	13/21	62	8/21	38
0.015	1/1	100	0/1	100	1/1	100	0/1	0
0.03	9/10	90	1/10	10	8/10	80	2/10	20
0.06	1/1	100	0/1	0	1/1	100	0/1	0
0.25	0/2	0	2/2	100	0/2	0	2/2	100
0.5	2/2	100	0/2	0	1/2	50	1/2	50
1.0	2/2	100	0/2	0	2/2	100	0/2	0
2.0	1/1	100	0/1	0	0/1	0	1/1	100
4.0	1/1	100	0/1	0	0/1	0	1/1	100
8.0	1/1	100	0/1	0	0/1	0	1/1	100

Table 4. Bacteriological Efficacy of *Streptococcus pneumoniae* Susceptibly (MIC) to Amoxicillin/clavulanate-Patients Treated with Augmentin 45/6.4 mg/kg/day for 10 days (Per Protocol Population)

Amoxicillin/clavulanate MICs (mcg/mL)	Bacteriological response (days 4-6)			
	Eradication		Persistence	
	n/N	(%)	n/N	(%)
Total	18/20	90	2/20	10
0.015	1/1	100	0/1	0
0.03	8/9	89	1/9	10
0.06	1/1	100	0/1	0
0.25	1/2	50	1/2	50
0.5	2/2	100	0/2	0
1.0	2/2	100	0/2	0
2.0	1/1	100	0/1	0
4.0	1/1	100	0/1	0
8.0	1/1	100	0/1	0

Table 5. Clinical and Bacteriological Efficacy at Test of Cure (TOC) for *Streptococcus pneumoniae* Susceptibly (MIC) to Amoxicillin/clavulanate-Patients Treated with Augmentin 875/125 mg q12h (Per Protocol Population)

Amoxicillin/clavulanate MICs (mcg/mL)	Clinical response TOC (days 28-35)				Bacteriological Response TOC (days 28-35)			
	Success		Failure		Success		Failure	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Total	5/6	83.3	1/6	16.7	5/6	83.3	1/6	16.7
0.03	3/4	75	0/4	0	3/4	75	0/4	0
0.12	1/1	100	0/1	0	1/1	100	0/1	0
2.0	1/1	100	0/1	0	1/1	100	0/1	0

Table 6. Clinical and Bacteriological Efficacy of *Streptococcus pneumoniae* Susceptibly (MIC) to Amoxicillin/clavulanate-Patients Treated with Augmentin 500/125mg tid for 7 days (per protocol)

Amoxicillin/clavulanate MICs (mcg/mL)	Clinical response F/U (days 14-21)				Bacteriological Response F/U (days 14-21)			
	Success		Failure		Success		Failure	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Total	9/9	100	0/9	0	7/9	77.8	2/9	22.2
≤0.03	4/4	100	0/4	0	4/4	100	0/4	0
0.06	1/1	100	0/1	0	1/1	100	0/1	0
0.125	1/1	100	0/1	0	1/1	100	0/1	0
0.5	1/1	100	0/1	0	1/1	100	0/1	0
2.0	2/2	100	0/2	0	0/2	0	2/2	100

Table 7. Augmentin (amoxicillin/clavulanate potassium)

Formulation - Bioavailability Relationships.

NDA	Approval Date	Product	Strength		Ratio	Comparative Bioavailability			
			Amoxicillin	Clavulanate	(A/C)				
50-575	######	Oral Suspension	125	31.25	4:1				
			250	62.50		[redacted]			
50-725	######	Oral Suspension	200	28.50	7:1		Scale Equiv. (Study #318)**		
			400	57.00					
50-597	######	Chewable Tablet	125	31.25	4:1	[redacted]			
			250	62.50		[redacted]			
50-726	######	Chewable Tablet	200	28.50	7:1		Scale Equiv. (Study #318)**		
			400	57.00					
50-564	######	Tablet	250	125.00	2:1			Study #360	q8h
			500	125.00	4:1			Study #360	q8h, q12h
50-720	######	Tablet	875	125.00	7:1			Study #360	q12h
50-755		Oral Suspension	600	42.90	14:1				

[redacted]

[redacted]

**Only study that was designed to demonstrate equivalence.