MICROBIOLOGY EXECUTIVE SUMMARY (cont.)

Haemophilus influenzae

β-lactamase negative MIC_{90} = 2 μg/mL

β-lactamase positive strains MIC_{90} = 4 μg/mL

Haemophilus parainfluenzae MIC_{90} = 8 μg/mL

Moraxella catarrhalis (including β-lactamase positive strains)

MIC_{90} = 0.5 μg/mL

Chlamydiae pneumoniae

MIC Range = 0.03 to 2 μg/mL

Legionella pneumophilia

MIC_{90} = 0.12 μg/mL

Mycoplasma pneumoniae

MIC_{90} = 0.005 μg/mL

Miscellaneous organisms:

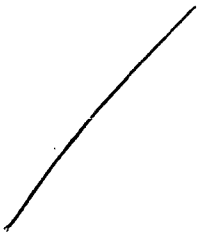
Groups — G streptococci – MIC_{90} = 0.03 μg/mL

Viridans Streptococci – MIC_{90} = 1 μg/mL

Anaerobes

Prevotella bivia – MIC_{90} = 1 μg/mL
Prevotella intermedia – MIC_{90} = 0.06 μg/mL

MICROBIOLOGY EXECUTIVE SUMMARY (cont.)



Postantibiotic Effect (PAE)

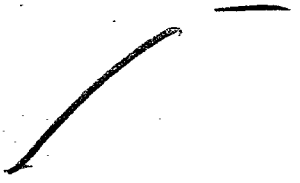
Clinically, the importance of PAE is in the dosing regimens, particularly relevant to short half-life compounds. An infection caused by an organism susceptible to an agent with a significant PAE may require less-frequent dosing than those agents that do not demonstrate a PAE, other factors being equal. Telithromycin has been shown to have a PAE, ranging from approximately 1 hour to 8 hours at 10 x MIC against the pathogens of interest. This PAE is similar to the PAE of macrolides.

Synergism and Antagonism

Little definitive information is available about telithromycin's synergistic or antagonist activity with other antimicrobials or drugs.

Susceptibility Test Interpretive Criteria:

The **Applicant** is proposing that the following interpretive criteria be in the package insert (revised by applicant 3 Apr 2001).



MICROBIOLOGY EXECUTIVE SUMMARY (cont.)

Disc diffusion susceptibility testing

For testing *Streptococcus pneumoniae*:

MIC (µg/mL)	Interpretation
≤1.0	Susceptible
2.0	Intermediate
≥4.0	Resistant

Disc diffusion susceptibility testing

Zone diameter (mm)	Interpretation
≥19	Susceptible
16-18	Intermediate
≤15	Resistant

For testing *Haemophilus influenzae*

Disc diffusion susceptibility testing

The **Agency** after review of the applicant's microbiology data, bacteriological eradication rates, and clinical cure rates is recommending that only the following organisms and the corresponding susceptibility testing interpretive criteria be included in the package label.

STREPTOCOCCUS PNEUMONIAE

MICROBIOLOGY EXECUTIVE SUMMARY (cont.)

MIC

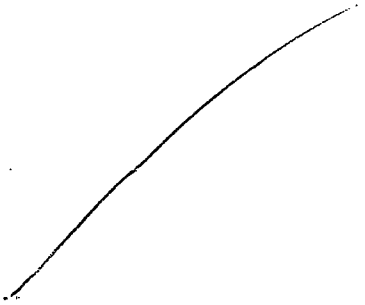
MIC (µg/mL)	Interpretation*

Disk Diffusion Zone Size

Disk Diffusion Zone Size (mm)	Interpretation*

The bacteriological eradication and clinical cure rates using _ _ as indicating susceptibility of *S. pneumoniae* to telithromycin in the indications noted below are (PPb populations):

Indication	Bacteriological eradication	Clinical cure
CAP	143/148 (95%)	142/148 (96%)
AECB	13/14 (93%)	12/14 (86%)
AMS	76/84 (90%)	95/85 (89%)



Due to the lack of resistant isolates "Intermediate and Resistant" interpretive criteria could not be determined.

The bacteriological eradication and clinical cure rates using _ _ as indicating susceptibility of *S. pyogenes* to telithromycin for pharyngitis/tonsillitis (PPb populations) are 213/239 (89%) and 222/239 (93%) respectively.

MICROBIOLOGY EXECUTIVE SUMMARY (cont.)

HAEMOPHILUS INFLUENZAE

MIC

Disk Diffusion Zone Size

The bacteriological eradication and clinical cure rates using ≤ 4 µg/mL as indicating susceptibility of *H. influenzae* and *H. parainfluenzae* to telithromycin in the indications noted below are (PPb populations):

H. influenzae

Indication	Bacteriological eradication	Clinical cure
CAP	82/92 (89%)	84/92 (91%)
AECB	13/22 (59%)	15/22 (68%)
AMS	61/68(90%)	62/68 (91%)

QUALITY CONTROL ORGANISMS AND RANGES FOR SUSCEPTIBILITY TESTING:

Quality control organisms and ranges for , disc diffusion (15 ug disc) susceptibility test methods

Control Strain	MIC (ug/mL)	Zone diameter (mm)
S. pneumoniae ATCC 49619	0.004-0.03	27-33
H. influenzae ATCC 49247	1-4	17-23

SECOND LIST

Based on their relevance to the indications being sought by the applicant and the in vitro susceptibility information provided by the applicant on ≥100 isolates of each organism the following organisms have been placed in the second list of the microbiology portion of the package labeling. Due to the demonstrated lack of in vitro activity of telithromycin against *S. aureus* resistant to methicillin or

MICROBIOLOGY EXECUTIVE SUMMARY (cont.)

erythromycin or clindamycin the labeling reflects that only *S. aureus* that are susceptible to these antimicrobials be considered susceptible to telithromycin.

Gram-positive aerobes

Staphylococcus aureus (metnicillin and/ or erythromycin susceptible strains only)

Streptococcus pneumoniae (penicillin and/or erythromycin resistant isolates)

Viridans streptococci

Gram-negative aerobes
Haemophilus influenzae (β-lactamase positive strains)
Legionella pneumophilia
Moraxella catarrhalis (including β-lactamase positive strains)

ATYPICAL PATHOGENS

Community acquired pneumonia: Clinical outcome at post/therapy/TOC for atypical pathogen isolates in the PPc population using highly specific diagnostic criteria

Pathogen	Telitromycin Results	
	Number treated	Number (%) cured
Chlamydia pneumoniae	34	32 (94)
Mycoplasma pneumoniae	31	30 (97)
Legionella pneumophilia	12	12 (100)

Telithromycin, like macrolides, has been shown to concentrate in both PMNs and macrophages. This ability to concentrate in cells and the fact that the MIC_{90s} for

MICROBIOLOGY EXECUTIVE SUMMARY (cont.)

these organisms are low (≤ 2 µg/mL) may explain why telithromycin was successful in treating pneumonias due to these atypical organisms.

NDA#: 21-144 Addendum (data received after completion of initial review 11/30/00)
Aventis Pharmaceuticals Inc.

INTRODUCTION:

This review is of additional data submitted by the applicant to their initial NDA 21-144 received by the agency 3/1/00. The reader is referred to the initial "Microbiology Review" of the data (submitted 3/1/00) completed 11/30/00 for a more comprehensive discussion of the spectrum of activity of the drug, mechanism of action of the drug, mechanisms of resistance, and data relating to bacteriological eradication and clinical outcome observed during the initial clinical trials.

The additional data to be reviewed are data from three studies. These are a multinational CAP study (3010), and a multinational acute maxillary sinusitis (AMS) study in adults (3011) and a community-acquired pneumonia (CAP) study (2105) done in Japan. The Japanese study will be reviewed as a supportive study and only the data from the 800mg daily dosing in the Japanese data will be reviewed since 600 mg daily dosing was not a part of the original NDA submission. The data from the Japanese CAP study (2105) will not be incorporated into total data since it was a supportive study.

In addition, a review of the literature will be done. The review will ascertain if there have been any reported changes in the activity of the telithromycin against the pathogens associated with the organisms relative to the indications being sought, or other parameters of telithromycin as they relate to clinical microbiology.

The reader is referred to the microbiology review dated 11/30/00 to see the microbiology review of the initial data (3/1/00) submitted to the Agency.

STUDY EVALUATIONS

STUDY 3010 – COMMUNITY ACQUIRED PNEUMONIA (CAP)

STUDY 3010 (CSR No. K20000CLN0026, HMR 3647/3010 dated 24 January 2001 FINAL)

This was an open label, multinational, uncontrolled study of the efficacy and safety of oral HMR 3647 (800 mg once daily) given 7 days for the treatment of community-acquired pneumonia (CAP) in adolescents and adults.

IN VITRO

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The telithromycin MIC_{90s} of the pathogens of interest from the telithromycin bMITT population (single and mixed pathogens) of study 3010 are shown in

Table 1 (Table 64, 3010/b030108a 1st 19 January 2001 and CSR No. K2000CLN0026 HMR 3647A/3010, 42 January 2001 FINAL pg. 127-128). The data in Table 1 suggests that the penicillin or erythromycin resistant isolates of *S. pneumoniae* do not have telithromycin MICs that are different from the overall population of *S. pneumoniae* seen in this study.

Table 1. Telithromycin MIC_{90s} of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Haemophilus parainfluenzae* from the bmITT CAP population single and multiple pathogens.

Organism	No. of isolates	MIC_{90} (µg/ML)	MIC (µg/mL) range
S. pneumoniae	70	0.03	0.004 -2
PR alone	3		0.03
ER alone	1		0.03
PR & ER	5		.06 - 2
PI & ER	3		.03 - 1
H. influenzae	85	4	0.002 - 8
M. catarrhalis	22	0.12	0.06 - 0.12
H. parainfluenzae	79	8	1 - 8
S. aureus	19	0.12	0.6 - 0.25

Of the 70 isolates of *S. pneumoniae* 69 were susceptible to telithromycin (MIC ≤ 1 µg/mL – applicant's proposed interpretive criteria). The one isolate that was not susceptible was classified as intermediate (2 µg/mL) in its susceptibility to telithromycin (applicant's proposed interpretive criteria). This isolate was resistant to both penicillin and erythromycin. Twelve of the 70 isolates of *S. pneumoniae* were resistant to penicillin or erythromycin. Eight were resistant to penicillin, 9 were resistant to erythromycin and 5 were resistant to both penicillin and erythromycin. Genotyping data was available for the nine erythromycin resistant *S. pneumoniae*. Four of the isolates were shown to have the genotype *mef*E (also known as *mef*A) and 4 were shown to have the genotype *erm*B. One of the isolates carried both the *mef*E and *erm*B markers.

The telithromycin MIC_{90s} of the pathogens of interest from the telithromycin PPb population of study 3010 are shown in Table 2. These isolates are from specimens that contained both single and multiple pathogens (Table 65,

3010/b03109a.1st 19 January 2001). The PPb population is a subset of the bmITT population.

Table 2. Telithromycin MIC_{90s} of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Haemophilus parainfluenzae* isolated from PPb CAP subjects single and multiple pathogens

Organism	No. of isolates	MIC_{90} (µg/mL)	MIC (µg/mL) range
S. pneumoniae	57	0.03	0.008 - 1
PR	2		0.03
ER	1		0.03
PR & ER	4		0.03 – 0.5
PI & ER	2		1
H. influenzae	49	4	0.002 - 8
M. catarrhalis	13	0.12	0.06 - 0.12
H. parainfluenzae	45	≤8	1 - 8
S. aureus	14	0.12	0.60 - 0.25

Of the 57 *S. pneumoniae* from the PPb population 6 were penicillin-resistant. Four of the *S. pneumoniae* were resistant to penicillin and erythromycin. Two were resistant to only penicillin and one was resistant to only erythromycin. Two of the erythromycin resistant isolates had intermediate resistance to penicillin. Forty-four of the 49 (90%) *H. influenzae* isolates were non beta-lactamase producers.

The telithromycin MIC_{90s} seen in Tables 1 and 2 are similar to the MIC_{90s} for the pathogens of interest reported in the applicant's initial CAP data submitted 3/1/00.

Table 5 shows the telithromycin susceptibility category the organisms in Table 1 would fall into using the Applicant's proposed MIC interpretive criteria (Table 3) and the Agency's proposed MIC interpretive criteria (Table 4).

The applicant's MIC interpretive criteria are shown in Table 3.

Table 3. MIC interpretive criteria as proposed by the Applicant (Vol. 1.3 p115-118).

Organism	MIC interpretive criteria (µg/mL)	Interpretation
Streptococcus pneumoniae	≤ 1	Susceptible (S)
	2	Intermediate (I)
	≥ 4	Resistant (R)
Haemophilus influenzae		Susceptible
		Intermediate
		Resistant

The Agency's proposed MIC interpretive criteria are shown in Table 4.

Table 4. MIC interpretive criteria as proposed by the FDA

Organism	MIC interpretive criteria (µg/mL)	Interpretation
Streptococcus pneumoniae		Susceptible (S)
Haemophilus influenzae	≤ 4	Susceptible
Staphylococcus *aureus**	≤ 0.25	Susceptible

Table 5. Susceptibility interpretation for telithromycin of isolates in the telithromycin CAP bmITT population as determined by using the Applicant's or the Agency's MIC

susceptibility interpretive criteria.

Organism	Number of isolates	Susceptibility of isolates using	
		Applicants interpretive criteria [number(%)]	FDA's interpretive Criteria [number(%)]
S. pneumoniae	71	70(99)=S, 1(1)=I	
H. influenzae	85		77(91)=S
S. aureus	22	22/22(100)=S	22(100)=S

* The interpretive criteria are the same as for *H. influenzae*
** The applicant has not proposed interpretive criteria.
S=Susceptible, I=Intermediate, R=Resistant

IN VIVO

The review of the bacteriological and clinical outcomes for this study will concentrate on the PPb population. This population is defined in the protocol as: "All PPc subjects with bacteriologically proven infection (isolation of a causative pathogen in an "adequate" pretreatment culture collected at pretherapy/entry within 48 hours before the first dose of study drug), and who had one of the following: (1) a bacteriological sample collected in the posttherapy/TOC window (days 17 to 24) that were classifiable (i.e., not indeterminate), (2) an unsatisfactory outcome that occurred up through and including day 24 (as unsatisfactory response was carried forward), or (3) no sample collected at posttherapy/TOC because of clinical resolution". The applicant defines adequate sample on pg. 78 – 79. This reviewer considers the definitions standard and appropriate. (CSR No K20000CLN0026, 24 January 2001 - Final pg. 78 - 79). There were 149 subjects in the PPb population. This represents 35.6% of the total 418 subjects in the bmITT population.

Table 6 summarizes the bacteriological eradication rates and clinical cure rate for subjects in the PPb population with single and multiple pathogen infections (CSR No K20000CLN0026, 24 January 2001 - Final pg. 315).

Table 6. Bacteriological eradication, persistence and clinical cure rates at

post/therapy/TOC for the telithromycin treated CAP PPb population with single and multiple pathogens

Pathogen	Bacteriological eradication rate (%)	Documented bacteriological persistence (%)	Clinical cure rate (%)
S. pneumoniae	57/57 (100)	0	57/57 (100)
H. influenzae	47/49 (95.9%)	2/49 (4.1)	49/49 (100)
M. catarrhalis	13/13 (100)	0	13/13 (100)
*H. parainfluenzae**	42/46 (91.3)	1/46 (6.5)	42/46 (91.3)
S. aureus	12/14 (86)	1/14 (7)	12/14 (86)

* There was 1 (2.2%) recurrence

There were a total of 6 persistent pathogens isolated at the post therapy/TOC visit. Two *H. influenzae*, 1 *H. parainfluenzae*, 1 *S. aureus*, and [redacted]. The susceptibility of the pathogens for the remaining four subjects were as follows (CSR No. K2000CLN0026, 24 January 2001, pg. 110).

Subject 447/002 (*H. influenzae*): for telithromycin, this pathogen was intermediate (MIC 4 µg/mL) at visit 1, it increased its MIC at visit 2 (MIC 8 µg/mL) and became intermediate at visit 4 (MIC 4 µg/mL).

Subject 453/009 (*H. influenzae*): for telithromycin, this pathogen was susceptible (MIC 1 µg/mL) at visit 1 and increased its MIC to 2 µg/mL at visit 4, although still susceptible.

Subject 446/002 (*H. parainfluenzae*): for telithromycin, this pathogen was resistant (MIC 8 µg/mL) at visits 1, 2, and 3.

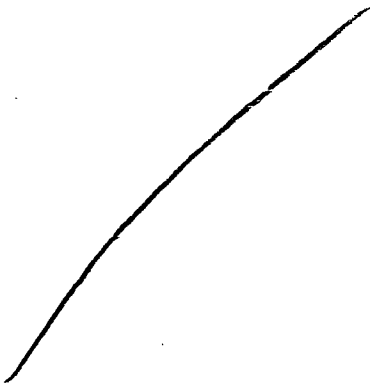
Subject 472/013 (*S. aureus*): for telithromycin, this pathogen was susceptible at both visits 1 and 2 (MIC 0.06 µg/mL and 0.12 µg/mL, respectively); for erythromycin A, this pathogen was also susceptible at both visits (MIC 0.25 µg/mL and 0.5 µg/mL respectively).

Of the 57 *S. pneumoniae* from the PPb population 48 were isolated from the respiratory tract and 9 from blood culture. Of the 9 from blood cultures 6 were

isolated only from the blood and 3 were isolated from both the respiratory tract and blood.

Of the 57 *S. pneumoniae* 6 were penicillin resistant. Four of the *S. pneumoniae* were resistant to penicillin and erythromycin. Two of the erythromycin resistant isolates had intermediate resistance to penicillin. As can be seen in Table 6 there was 100% bacteriological eradication and clinical cure of *S. pneumoniae* regardless of its susceptibility to penicillin or erythromycin. Since the PPb single pathogen is a subset of the single and multiple pathogen population the same bacteriological and clinical cure rates were seen when *S. pneumoniae* was a single pathogen.

In the case of *H. influenzae* 44 of the 49 isolates did not produce β-lactamase. There was 100% clinical cure for these strains of *H. influenzae* and 95.1% (42/44) bacteriological eradication.



The CAP bacteriological and clinical cure rates from the first data submitted (3/1/00) and the current data (1/24/01) are seen in Table 7. It can be seen that there were similar bacteriological eradication rates and clinical cure rates for the initial data and the new data for *S. pneumoniae*, *M. catarrhalis*, and *S. aureus*. For *H. influenzae* the bacteriological and clinical cure rates are different by 10% or greater between the two sets of data. For *H. parainfluenzae* there is a greater than 10% difference between the bacteriological eradication rates for the two sets of data.

Table 7. Comparison between the CAP PPb population (single and mixed infection) bacteriological eradication rates and clinical cure rates seen in original data (3/1/00) and the current data (1/24/01) and combined cure rate.

Pathogen	Bacteriological eradication rate (%)			Clinical cure rate (%)		
	3/1/00	1/24/01	Combined	3/1/00	1/24/01	Combined
S. pneumoniae	93/98 (95)	57/57 (100)	150/155 (97)	93/98 (95)	57/57 (100)	150/155 (97)
H. influenzae	41/49 (84)	47/49 (96)	88/98 (90)	41/49 (84)	49/49 (100)	90/98* (92)
M. catarrhalis	11/12 (92)	13/13 (100)	24/25 (96)	10/12 (83)	13/13 (100)	23/25 (92)
H. parainfluenzae	10/13 (77)	42/46 (91)	52/59 (88)	11/13 (85)	42/46 (91)	53/59 (90)
S. aureus	3/4 (75)	12/15 (80)	15/19 (79)	3/4 (75)	12/15 (80)	15/19 (79)

* 14 β-lactamase positive

Atypical Organism Results

The methods described below were used to detect the presence of atypical pathogens (CSR No. K2000CLN0026, 24 January 2001 Final, pg. 56-57.

Chlamydia pneumoniae infection:

Serology on acute and convalescent serum samples using a microimmunoflourescent (MIF) technique to determine antibody titers. The testing was done in Dr. — laboratory at the — The kits used were manufactured by —.

PCR was done on samples collected from the oropharynx by swabbing the site in an attempt to identify *C. pneumoniae* as the etiologic agent. This testing was done in the laboratory of Dr. —.

Mycoplasma pneumoniae infection:

Serology was done on acute and convalescent serum samples using an ELISA technique manufactured by — The testing was done in the laboratory of Dr. — at the —.

PCR was done on samples from the oropharynx collected by swab and on sputum samples. No kit manufacturer's name was provided. The testing was done in the laboratory of Dr [redacted] at the [redacted]

Legionella pneumophilia infection

Serology was done on cute and convalescent serum using an enzyme immunoassay (EIA) technique to determine the titer to *L. pneumophilia*. Convalescent serum was screened using a diagnostic kit manufactured by [redacted] When the results were positive or equivocal both the acute and convalescent serum was tested by an immunoflourescence antibody test (IFAT). No name was provided for the manufacturer of the IFAT test. Testing was done in the laboratory of Dr. [redacted] at the [redacted]

Soluble antigen testing was done on urine samples for the presence of *L. pneumophilia* serogroup 1 urinary antigen using an ELISA technique with the [redacted] EIA kit. The tests were done in the laboratory of [redacted] at the [redacted]

The diagnostic criteria used to classify a subject as having an infection with an atypical organism are noted below.

Chlamydia pneumoniae – To establish a definitive diagnosis of *C. pneumoniae* pneumonia, there were to have been clinical signs and symptoms of pneumoniae with a negative aerobic culture for any "typical" pathogen from a respiratory specimen in association with any of the following criteria.

A nasopharyngeal culture positive for *C. pneumoniae*.

A positive serology of a 4-fold increase in microimmunofluorescence IgG or IgM (polyclonal) titers of paired sera.

A positive serology of a single IgM titer $\geq$1:32 by microimmunofluorescence in combination with a positive PCR for *C. pneumoniae*.

Mycoplasma pneumoniae – To establish a definitive diagnosis of *M. pneumoniae*, there were to have been clinical signs and symptoms of

pneumonia with a negative aerobic culture for any "typical" pathogen from a respiratory specimen in association with any one of the following criteria.

A positive serology of a 4-fold increase in paired serum IgG titers for *M. pneumoniae*.

A positive serology of a single IgM titer ≥1:16 in combination with a positive PCR for *M. pneumoniae*.

Legionella pneumophilia – To establish a definitive diagnosis of *L. pneumophilia* there were to have been clinical signs and symptoms of pneumonia with a negative aerobic culture for any "typical" pathogen from a respiratory specimen in association with at least one of the following criteria.

A positive serology of a 4-fold increase in paired serum IgG/IgM titers with a single titer >1:128.

A positive urinary antigen for *L. pneumophilia* serogroup 1.

The above criteria for a definitive diagnosis of infection with the organisms noted is in agreement with what the Agency had recommended to the applicant on 20 September 1999.

Using the above definitive criteria the applicant has submitted the data shown in Table 8 (CSR No. K20000CLN0026- 1:v022:p128, 24 January 2001 Final). This is the data from the PPc population. The PPc population is defined as the "Per protocol population for analysis of clinical outcome: all mITT subjects excluding those with major protocol violations".

Table 8. Clinical outcome of posttherapy/TOC in subjects with infection due to atypical pathogens (excluding subjects with common pathogens) - PPc

Pathogen/diagnosis criteria	Number	Clinical outcome number of subjects (%) Clinical Cure	Failure
Chlamydia pneumoniae		3 (100)	0
Total	3		
Fourfold increase in IgG	1	1 (100)	0
Fourfold increase in IgM	3	3 (100)	0
Mycoplasma pneumoniae		2 (100)	0
Total	2		
Fourfold increase in IgG	2	1 (100)	0

Legionella pneumophilia		4 (100)	0
Total	4		
Fourfold increase in IgG or IgM			
single titer >1:128	2	2 (100)	0
Positive urinary antigen for *L. pneumophilia* serogroup 1	2	2 (100)	0

In their previous submission the applicant had provided definitive diagnosis for 33 cases of *C. pneumoniae*, 29 cases of *M. pneumoniae*, and 10 cases of *L. pneumophilia*.

STUDY 3011- ACUTE MAXILLARY SINUSITIS

Study 3011 (CSR No. K2000CLN0027, HMR 3647A/3011, 15 February 2001 FINAL)

This was a multinational randomized double-blinded active-controlled study for the evaluation of the efficacy and safety of oral HMR 3647 800 mg once a day for 5 days versus cefuroxime axetil 250 mg twice a day for 10 days in the treatment of acute maxillary sinusitis (AMS).

IN VITRO

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The telithromycin MIC_{90s} of the pathogens of interest from the telithromycin treatment bmITT population from study 3011 are shown in Table 9 (HMR3647A/3011/b200051at.ist 18 December 2000 Table 96). The bmITT population was the mITT subjects with a bacteriological sample at pretherapy/entry containing at least one pathogen considered by the investigator to be responsible for infection.

Table 9. Telithromycin MIC_{90s} of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Haemophilus parainfluenzae* from the AMS bmITT population of the telithromycin treatment group

Organism	No. of isolates	MIC_{90} (µg/ML)	MIC (µg/mL) range
S. pneumoniae	35*	0.12	0.008 - 2
PR alone	2		0.008
PR & ER	9		0.06 - 2

PI & ER	6		0.016-0.06
ER alone	1		0.5
*H. influenzae**	38	4	0.12 - 8
M. catarrhalis	9	0.12	0.06 - 1.0
H. parainfluenzae	6	8	2 - 8
S. aureus	14	0.12	0.12 - 0.25

*Eight of the 38 (21%) *H. influenzae* were β-lactamase producers HMR3647A/3001/lef0136t.1st, 26 Jan 2001, Table 126).

The telithromycin MIC_{90s} of the pathogens of interest from the telithromycin PPb populations from study 3011 are shown in Table 10 (HMR3647A/3011/b20005at.ist, 18 Dec.2000, Table 102). The PPb population is made up of PPc subjects who are mITT subjects without major protocol violations. These subjects had isolation of a causative pathogen from adequate culture at pretherapy/entry and with a bacteriological sample at posttherapy/TOC that was classifiable, except an unsatisfactory outcome during the study or no bacteriological sample collected at posttherapy/TOC due to clinical resolution. (HMR3647A/3011/b030109a.1st, 2 February 2001, Table 78 and CSR No. K2000CLN0027 15 Feb 2001 p.8).

The telithromycin MIC_{90s} for the AMS isolates are similar to the MIC_{90s} for the isolates from the AMS subjects seen in the initial (3/1/00) data submitted by the applicant.

Table 10. Telithromycin MIC_{90s} of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis, Staphylococcus aureus* and *Haemophilus parainfluenzae* isolated from the AMS PPb populations of the telithromycin treatment group (single and mixed infection)

Organism	No. of isolates	MIC_{90} (μg/mL)	MIC (μg/mL) range
S. pneumoniae	27	0.25	0.008 – 2
PR alone	2		0.008-2
PI & ER	4		0.03-0.06
ER alone	1		0.5
PR&ER	7		0.06-2
*H. influenzae**	30	4	0.12 - 8

M. catarrhalis	7	0.12	0.06 - 1
H. parainfluenzae	5	8	4 - 8
S. aureus	10	0.12	0.12 - 0.25

*Seven of the 30 (23%) *H. influenzae* were β-lactamase producers (HMR36476A/3011/lef188t.1st, 26 Jan 2001, Table 113).

Genotyping results were available for 10 of the erythromycin resistant *S. pneumoniae*. Six were of the mefE genotype and 4 were of the ermB genotype (CSR No. K20000CLN0027, 15 Feb2001, p. 154).

Table 11 shows the number of isolates categorized as susceptible, intermediate, and resistant to telithromycin in the bmITT populations seen in Table 10 using the Applicant's proposed MIC susceptibility test interpretive breakpoints (Table 4) and the FDA's proposed MIC susceptibility test interpretive criteria (Table 5) (HMR3647A/3011/3b03018b.1st, 2Feb01 Table 75).

Table 11. Susceptibility interpretation for telithromycin of isolates in the AMS bmITT population as determined by using the Applicant's or the FDA's MIC susceptibility test interpretive criteria

Organism	Number of isolates	Susceptibility of isolates using	
		Applicants interpretive criteria from Table 3 [number(%)]	FDA's interpretive criteria from Table 4 [number(%)]
S. pneumoniae	35	34(97)=S, 1(3)=I	
H. influenzae	38		36(95)=S

*** The interpretive criteria are the same as for *H. influenzae***
**** The applicant has not proposed interpretive criteria.**

S=Susceptible, I=Intermediate, R=Resistant

IN VIVO

The review of the bacteriological and clinical outcome for this study will be done on the PPb population of the telithromycin treatment group. This population is made up of PPc subjects who are mITT subjects without major protocol violations. These subjects had isolation of a causative pathogen from adequate culture at pretherapy/entry and with a bacteriological sample at posttherapy/TOC that was classifiable, except an unsatisfactory outcome during the study or no bacteriological sample collected at posttherapy/TOC due to clinical resolution. There were 100 subjects that were evaluable in the PPb telithromycin treatment group (CSR No. K2000CLN, 15 February 2001 FINAL, pg. 119). The telithromycin treatment group was treated for 5 days with 400 mg of telithromycin twice daily.

The bacteriological eradication, persistence, and clinical cure rates for the telithromycin treated AMS PPb population is shown in Table 12.

Table 12. Bacteriological eradication, persistence and clinical cure rates at post/therapy/TOC for the telithromycin treated AMS PPb population with single and multiple pathogens.

Pathogen	Bacteriological eradication rate (%)	Bacteriological persistence* (%)	Clinical cure rate (%)
S. pneumoniae	26/29 (89)	3/29 (15)	25/29 (86)
H. influenzae	26/32 (81)	6/32 (19)	26/32 (81)
M. catarrhalis	7/7 (100)	0	7/7 (100)
H. parainfluenzae	3/6 (50)	3/6 (50)	3/6 (50)
S. aureus	12/12 (100)	0	11/12 (92)

* Persistence includes both presumed persistence and persistence

The telithromycin MIC range for the 3 persistent *S. pneumoniae* was 0.008 – 0.120 µg/ mL making them all susceptible by both the Applicant's and the FDA's proposed interpretive criteria. For the 6 persistent *H. influenzae* the MIC range was 2 – 8 µg/mL. By the Applicant's provisional susceptibility test interpretive criteria four of the *H. influenzae* were considered susceptible to telithromycin,

one had intermediate resistance to telithromycin and one was resistant to telithromycin. By the Agency's proposed susceptibility test interpretive criteria five of the six *H. influenzae* associated with bacteriological persistence would be considered susceptible to telithromycin. For the 3 persistent *H. parainfluenzae* by the Applicant's provisional susceptibility test interpretive criteria two *H. parainfluenzae* had intermediate resistance to telithromycin and one was resistant to telithromycin. By the Agency's proposed susceptibility test interpretive criteria 2 of the *H. parainfluenzae* would be considered susceptible.

A comparison of the bacteriological and clinical cure rates for telithromycin treated AMS from the initial data (3/1/00) and current data (2/15/01) are shown in Table 13. The largest differences between the 3/1/00 and 2/15/01 data are with *H. influenzae* and *M. catarrhalis*. While one could speculate that the difference seen for *M. catarrhalis* could be due to sample size no clear explanation can be suggested for the difference in the *H. influenzae* rates.

Table 13. Comparison between the AMS telithromycin treated PPb populations bacteriological eradication rates and clinical cure rates in the initial data (3/1/00) and the current data (2/15/01)

Pathogen	Bacteriological eradication rate (%)			Clinical cure rate (%)		
	3/1/00	2/15/01	Combined	3/1/00	2/15/01	Combined
S. pneumoniae	47/51 (92)	26/29 (89)	73/80 (91)	47/51 (92)	25/29 (86)	72/80 (90)
H. influenzae	26/27 (96)	26/32 (81)	52/62 (84)	26/27 (96)	26/32 (81)	52/62* (84)
M. catarrhalis	8/10 (80)	7/7 (100)	15/17 (88)	8/10 (80)	7/7 (100)	15/17 (88)
H. parainfluenzae	No data	3/6 (50)	3/6 (50)	No data	3/6 (50)	3/6 (50)
S. aureus	10/10 (100)	12/12 (100)	22/22 (100)	10/10 (100)	11/12 (92)	21/22 (95)

* Four isolates from the initial data were β-lactamase positive and 7 (11/62 = 17%) from study 3011 were β-lactamase positive.

CONCLUSIONS for STUDIES 3010 and 3011

As noted in Table 7 above the bacteriological eradication rates and clinical cure rates from the original data (3/1/01) and the data in this review for CAP due to *S. pneumoniae*, *M catarrhalis* or *S. aureus* are very similar. The recent data shows

higher bacteriological eradication rates and clinical cure rates than the original data. For CAP due to *H. influenzae* there is a greater than 10% difference in the bacteriological eradication rates and the clinical cure rates between the original data and the data in this review. The clinical cure rates for *H. parainfluenzae* are similar between the original data and the data in this review, however there is a greater than 10% difference between the bacteriological eradication rates. The reason(s) for this greater than 10% difference is not known. Further clinical studies would be needed to better define the bacteriological eradication and clinical cure rates for these organisms in CAP. It is curious that the bacteriological eradication rates and the clinical cure rates are higher in the recent data than in the initial data for all organisms of interest. The reason for this is not known. Overall the clinical bacteriological eradication rates and the clinical cure rates are better than 79% for all organisms of interest.

Table 13 shows that the bacteriological eradication and clinical cure rates for AMS associated with *S. pneumoniae* and *S. aureus* are similar for the original data (3/1/00) and the data in this review. Except for *H. parainfluenzae* the overall bacteriological eradication rates and the clinical cure rates for all organisms are over 80% for all organisms of interest. Further clinical studies would be needed to better define the bacteriological eradication and clinical cure rates for *M. catarrhalis*, *S. aureus*, and *H. parainfluenzae* organisms in AMS. Based on the scarcity of AMS experience associated with *H. parainfluenzae* it is recommended that *H. parainfluenzae* not be listed in the package labeling with AMS.

SUMMARY OF PENICILLIN AND/OR ERYTHROMYCIN-RESISTANT *S. PNEUMONIAE* FOR ALL STUDIES

Table 14 is a summary of the penicillin and/or erythromycin resistant *S. pneumoniae* from all of the studies (telithromycin treatment PPb populations) submitted by the applicant.

Table 14. NDA 21-144 *Streptococcus pneumoniae* resistance data from all studies (telithromycin treatment PPb populations)

***Streptococcus pneumoniae* resistance data before 12/20/00**

		Resistance Type		
		PRSP	PISP	ERYRSP
Infection Classification		Community Acquired Pneumonia (CAP)*		
Single		7	6	7
Mixed		3	1	2
	Total	10	7	9
		Acute Maxillary Sinusitis		

	(AMS)		
Mixed	4	7	9
	Acute Exacerbation of Chronic Bronchitis (AECB)		
Mixed	0	2	0
Total – Single (all indications)	7	6	7
Total – Mixed (all indications)	7	10	11
TOTAL- Single + Mixed (all indications)	14	16	18

***Streptococcus pneumoniae* data after 12/20/00 (studies, 3010, and 3011)**

		PRSP	PISP	ERYRSP
		Community Acquired Pneumoniae (CAP)**		
Single		4	4	8
Mixed		4	2	6
	Total	8	6	14
		Acute Maxillary Sinusitis (AMS)		
Single		8	3	10
Mixed		1	1	2
	Total	9	4	12
TOTAL- Single (all indications)		12	7	18
TOTAL – Mixed (all indications)		5	3	8
TOTAL – Single + Mixed (all indications)		17	10	26

TOTALS FROM ALL STUDIES AND INDICATIONS (BEFORE AND AFTER 12/20/00)

	PRSP	PISP	ERYRSP
Single	19	13	25
Mixed	12	13	19
TOTALS	**31**	**26**	**44**

* 6/10 PRSP from blood, 4/10 PRSP from sputum
** Two isolates were from blood - both were PISP
PRSP = Penicillin resistant (≥2 ug/ mL) *S. pneumoniae* , PISP = Penicillin intermediate *(0.12 - 1 ug/mL) S. pneumoniae* , ERYRSP = Erythromycin resistant (>1 ug/mL) *S. pneumoniae*

There were a total of 31 penicillin resistant *S. pneumoniae*, 26 penicillin intermediate *S. pneumoniae*, and 44 erythromycin resistant *S. pneumoniae* from all of the studies.

SUMMARY OF β-LACTAMASE POSITIVE *H. INFLUENZAE*

Forty-one of the 184 (22%) *H. influenzae* from all studies were β-lactamase positive [23/98 (23%) from CAP studies, 7/24 (29%) from AECB studies,11/62 (17%) from AMS studies]. There were 20 from the initial data (3/1/00) and 21 from studies 3010 and 3011. Strains that were β-lactamase positive had a dilution higher telithromycin MIC_{90} than did the strains that did not produce β-lactamase (4 vs. 2 μg/mL respectively).

ATYPICAL ORGANISMS (Section 8 Vol. 113, 26 Feb 01)

In the case of atypical organisms associated with pneumonia the applicant has shown the following success rates when the subject had been treated with telithromycin. All of the pneumonia cases diagnosed as being caused by atypical organisms were diagnosed based on the strict diagnostic criteria agreed upon by the Applicant and the Agency in the September 1999 meeting. All of the cases in Table 15 also had no other pathogens isolated from sputum specimens.

Table 15. Community acquired pneumonia: Clinical outcome at post/therapy/TOC for atypical pathogen isolates in the PPc population using highly specific diagnostic criteria (all CAP studies except Japanese study 2105)

Pathogen	Telitromycin Results	
	Number treated	Number (%) cured
Chlamydia pneumoniae	34	32 (94)
Mycoplasma pneumoniae	31	30 (97)

Legionella pneumophilia	12	12 (100)

The success rate of telithromycin in treating pneumonia that is due to the intracellular atypical organisms *Mycoplasma pneumoniae, Legionella pneumophilia*, and *Chlamydiae pneumoniae* can be explained by the low MIC_{90s} of these organisms and the fact that telithromycin concentrates in PMNs and macrophages. The MIC_{90s} for the *M. pneumoniae* and *L. pneumophilia* are $\leq$ 0.125 µg/mL and for *C. pneumoniae* $\leq$ 2 µg/mL (Vol. 1.242 p130-132). Telithromycin has been shown to concentrate in PMNs at an intracellular/extracellular ratio (extracellular concentration of 2.5 µg/mL) ranging from 27 to 348 in 160 minutes. In macrophages an intracellular/extracellular ratio (extracellular concentration of 2 µg/mL) of 65 has been shown (Vol. 1.242 p172).

STUDY 2105 – COMMUNITY ACQUIRED PNEUMONIA (JAPANESE STUDY)

STUDY 2105 (CSR No. J2001CLN0001, HMR 3647/A/2105 dated 21 February 2001 FINAL)

Study 2105 was a double blind, multicenter, randomized study for the evaluation of difference in efficacy and safety between oral telithromycin 600mg and 800mg once daily dose for 7 days in the treatment of community-acquired pneumonia in adolescents and adults.

The Applicant has submitted clinical microbiology information for both the 600mg and 800mg. Because the 600mg dosing regimen was not a part of the Applicant's initial submission (3/2000) information relating to this data will not be included in this review.

IN VITRO

In vitro susceptibility testing of isolates was originally done in a laboratory located in Japan. At the request of the Agency these isolates were send to the reference laboratory (CMI, Wilsonville, OR) used by the Applicant for testing of isolates from other studies. In analyzing the data only susceptibility test results generated by the CMI laboratory will be used. For the *S. pneumoniae* there were 4 penicillin discrepant results. All of these discrepancies were in the classification of the isolates as either intermediate to penicillin or susceptible to penicillin. All 4 isolates were called intermediate in their susceptibility to penicillin by the Japanese laboratory and were found to be susceptible to penicillin by CMI. Two the discrepancies were by more than one two-fold dilution and the other 2 were by only one two-fold dilution. Because it was possible for this reviewer to visit the CMI laboratory during the review of this application and assure himself that susceptibility testing was being done according to the NCCLS method the CMI

results will be the final results. Due to the small number of discrepancies and dilution range of the discrepancies it is not felt that the isolates need to be re-tested.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The telithromycin MIC range of the organisms isolated from patients enrolled in the 800 mg dosing population are seen in Table16 (Aventis NDA 21-144 Amendment to pending application dated 21 March 01 Attachment 1). The MIC values for the *S. aureus* and *M. catarrhalis* were determined in Japan. Because there are so few of these isolates retest in the CMI laboratory will not be requested.

Table 16. Telithromycin MIC range for organisms isolated from single and multiple infections for the community acquired pneumoniae study done in Japan (2105)

Organism	Number of isolates	Telithromycin MIC µg/mL (#) range
Streptococcus pneumoniae		
Penicillin susceptible (1)	5	0.06 (1), 0.12 (2), 0.25 (2)
Penicillin resistant (1)	2	0.060 (2)
Penicillin intermediate (2)	4	0.008 (1), 0.016 (2), 0.12 (1)
Penicillin intermediate erythromycin susceptible	1	0.008
Erythromycin resistant	9	0.016 (2), 0.06 (3), 0.12 (2), 0.25 (2)
Haemophilus influenzae	9	1 (1), 2 (6), 4 (2)
Staphylococcus aureus (3)	4	0.06 (2), 0.12 (2)
Moraxella catarrhalis (3)	2	0.06 (2)

1. All resistant to

erythromycin
2. Four of the 5 were erythromycin resistant
3. MICs determined in Japanese laboratory

Table 17 shows the bacteriological eradication and clinical cure outcomes for the two penicillin-resistant *S. pneumoniae* subjects and for those subjects with erythromycin-resistant *S. pneumoniae* (Aventis NDA 21-144 Amendment to pending application dated 21 March 01 Attachment 1). Both subjects with penicillin resistant or intermediate *S. pneumoniae* were clinical cures. All subjects with erythromycin-resistant *S. pneumoniae* were also clinical cures.

Table 17. Bacteriological and clinical outcome for Japanese CAP subjects (800 mg) with *Streptococcus pneumoniae* (single and mixed infection) (PPb) correlated with telithromycin MIC

Penicillin or erythromycin category	Telithromycin MIC (ug/mL)	Genotype	Bacteriological outcome	Clinical outcome
Penicillin resistant (1)	0.06	*mef*E	Presumed eradication	Cure
	0.06	*erm*B	Eradication	Cure
Erythromycin resistant (2)	0.25	*erm*B	Presumed eradication	Cure
	0.15	*erm*B	Eradication	Cure
	0.12	*erm*B	Eradication	Cure
	0.06	*erm*B	Presumed eradication	Cure
Penicillin intermediate (3)	0.008	None	Eradication	Cure
	0.015	*erm*B	Eradication	Cure

1. All erythromycin resistant
2. 3 penicillin susceptible, 1 penicillin intermediate
3. 1 erythromycin susceptible, 1 erythromycin resistant

There were 9 subjects in the PPb population with pneumoniae caused by *H. influenzae* (5 single infection and 4 mixed infection). The telithromycin MIC range for *H. influenzae* was 1 to 4 µg/mL. Six of these had the *H. influenzae* eradicated and three were presumed eradicated. Eight were classified as clinical cures with one classified as indeterminate (telithromycin MIC = 2µg/mL) (Aventis

NDA 21-144 Amendment to pending application dated 21 March 01 Attachment 2).

There were two subjects with pneumoniae in the PPb population caused by *M. catarrhalis* (one with single infection and one with mixed infection). The telithromycin MICs for the two *M. catarrhalis* isolates were 0.12 µg/mL. Both of the subjects were classified as have the organisms eradicated and were considered clinical cures (CSR No. J2001CLN0001, HMR 3647A/2105, 21 Feb 01, 1:v065:p093).

ATYPICAL ORGANISMS

Infection with atypical organisms was considered when the following criteria were met (Aventis correspondence dated 4/20/01 – Amendment to pending application received in response to question from reviewer).

Chlamydia pneumoniae

1. *C. pneumoniae* was isolated
2. There was a positive result with a PCR test
3. Serology tests were positive
   A fourfold or higher increase in *Chlamydia* antibody titers in paired samples or a single CF antibody titer ≥1:16.

Several different test kits methods were used. These were a [redacted] method, a [redacted] method, a [redacted] test kit ([redacted] and [redacted], Kit [redacted]). Some testing for *C. pneumoniae* and *M. pneumoniae* was down in local laboratories and some was done in a central laboratory. All *Legionella* testing was done in a central laboratory.

Mycoplasma pneumoniae

1. *M. pneumoniae* was isolated
2. There was a positive result with a PCR test
3. Serology tests were positive

   A fourfold or higher increase in *M. pneumoniae* antibody titers in paired serum samples, or a single CF antibody titer ≥1:64, or a single HA antibody titer ≥1:320.

Legionella pneumoniae

1. Legionella strains were cultured

2. Thee was a positive result with a PCR test
3. Serology tests were positive
   Antibody titer against *L. pneumophilia* serogroup I increased fourfold in paired samples (≥1:128 in post therapy), or a single antibody titer ≥1:256
4. Positive result by urine antigen

Table 18 shows the number and types of atypical pneumonia diagnosed using the above criteria.

Table18. Atypical pneumoniae cases diagnosed in the telithromycin 800mg daily dose study

Organism	Number of cases	Clinical outcome
Chlamydia pneumoniae	2	2/2 cured
C. pneumoniae + *H. influenzae*	3	3/3 cured
C. pneumoniae + *S. pneumoniae*	1	1/1 cured
Mycoplasma pneumoniae	1	1/1 cured
Legionella pneumophilia	1	1/1 cured

CONCLUSIONS FOR JAPANESE CAP STUDY 2105

The in vitro susceptibility results for clinical isolates are similar to results from previous studies submitted by the applicant. The clinical efficacy seen in the treatment of pneumonia due to penicillin and/or erythromycin resistant *S. pneumoniae* is similar to what has been seen in previous studies. The in vitro susceptibility results of telithromycin against the *H. influenzae* and *M. catarrhalis* clinical isolates from study 2105 are similar to results seen in previous studies. There were six cases of pneumonia due to *C. pneumoniae*, one case of due to *M. pneumoniae* and one case due to *L. pneumophilia* in the telithromycin 800mg study. All of these were successfully treated with telithromycin.

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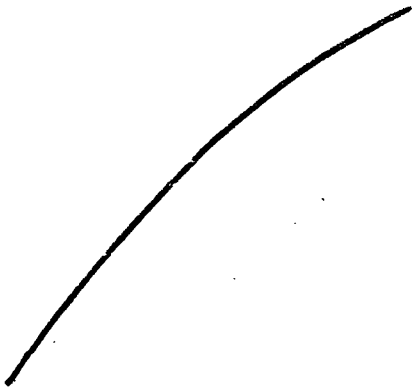

CONCLUSIONS

Streptococcus pneumoniae

The microbiology data in this submission and the microbiology data from the initial submission (3/1/00) indicates that telithromycin has in vitro activity against penicillin and/or erythromycin resistant *S. pneumoniae*. The bacteriological eradication rates and clinical cure rates suggest that telithromycin is active against penicillin/and/or erythromycin susceptible strains of *S. pneumoniae* associated with CAP, AECB and AMS. However, there were only 17 of 174 total cases of CAP (all studies) in the telithromycin treated PPb populations caused by PRSP with a 82% (14/17) clinical cure rate and 6 cases of bacteremia with PRSP with a clinical cure rate of 67% (4/6). For ERSP there were also only 17 of 174 cases of CAP in the telithromycin treated PPb populations caused by these organisms. In these cases there was a clinical success rate of 82% (14/17) and there were only 6 cases of bacteremia associated with ERSP with a clinical success rate of 67% (4/6).

In the case of AMS there were total of 91 *S. pneumoniae* isolated from the 5 and ten-day telithromycin treatment PPb populations (HMR3647A/v08/0000049t.1st/4Jan01 Table SE 59). For infections associated with *S. pneumoniae* overall there was a clinical cure rate of 90% (82/91). Of the *S. pneumoniae* isolates 13 were PRSP. In these cases there was a clinical cure rate of 85% (11/13). The higher cure rate for PRSP was in the 10-day treatment group (3/3) versus the 5-day treatment group (8/10). There were a total of 21 ERSP isolated from all cases of AMS treated with telithromycin. Of the 21 infections associated with ERSP there was a clinical cure rate of 86% (18/21). The clinical cure rate was equivalent in both the 5 and 10 day treatment groups.

In the case of AECB no PRSP were isolated. The clinical cure rate was 86% (12/14) (Aventis CD correspondence 10/18/00).

Because of the lack of adequate clinical experience with telithromycin to treat CAP, AMS or AECB due to PRSP the labeling needs to reflect that telithromycin only be used for the treatment of penicillin and erythromycin-susceptible *S. pneumoniae*.

Nineteen *S. pneumoniae* were identified in the bmITT populations from all studies that carried the *mef*E gene. Twenty-two *S. pneumoniae* were identified in the bmITT populations from all studies that carried the *erm*B gene. Two isolates of *S. pneumoniae* were found to have both the *erm*B and *mef*E genes. These isolates had erythromycin MICs of 8 µg/mL and telithromycin MICs of 0.5 µg/ mL.

Tables 20 and 21 show the telithromycin MIC and the erythromycin MICs for those *S. pneumoniae* having the *erm*B and *mef*E genes. As can be seen in Table 20 strains of *S. pneumoniae* that were erythromycin resistant (≥ 1 µg/mL) and carried the *mef*E gene tended to have higher telithromycin MICs than those isolates that carried the *erm*B gene shown in Table 21. Those *S. pneumoniae* that carry the *erm*B gene overall have the higher erythromycin MICs but the telithromycin MICs are lower than for those *S. pneumoniae* with the *mef*E gene. This is consistent with the fact that telithromycin binds to two sites on the ribosome while erythromycin binds to one site. The fact that the *mef*E containing strains have high telithromycin MICs suggests the efflux pump mechanism for elimination of the two drugs is similar. However, it also suggests that perhaps the side-chain of cladinose on the telithromycin molecule hinders the elimination of telithromycin from the cell by the efflux pump mechanism. Telithromycin cure rates are not that much different for the *erm*B and *mef*E gene containing strains. What effect the presence of the *erm*B and *mef*E genes will have on the development of resistance to telithromycin can only speculative at this time. However, it is a distinct possibility that because there already exist mechanisms that allow organisms to tolerate the presence of telithromycin that development of resistance to telithromycin will occur more rapidly than if the mechanisms were not already present. It is recommended that if the drug is approved that the company is required to carefully monitor for the development of increases in the concentration of telithromycin as indicated by a shift in the telithromycin MIC_{90} from the current 0.25 µg/mL to anything higher. This data needs to also be accompanied by specific cure rates for any indications granted.

Table 20. *Streptococcus pneumoniae mef*E containing strains (bmITT populations) correlated with telithromycin and erythromycin MICs

Telithromycin MIC MIC (µg/mL)	Erythromycin MIC MIC (µg/mL)	Number of strains with *mef*E gene	Source	Clinical outcome
0.03	4	1	3006-sputum	cure

0.06	2	1	3011-sinus5d	failure
0.06	4	1	30090L-blood	cure
0.06	8	1	3011-sinus5d	cure
0.06	4	1	3010-sputum	cure
0.12	4	1	3009OL-blood	failure
0.12	4	1	3011-sinus5d	failure
0.25	4	1	3011-sinus5d	cure
0.25	8	1	3011-sinus5d	cure
0.25	16	1	3002sinus10d	failure
0.5	8	3	3011-sinus5d	cure
0.5	8	1	3011-sinus5d	indeter
1	32	1	3009OL-sputum	cure
1	8	2	3010-blood	cure
1	16	1	3002-sinus5d	cure
2	8	1	3010-sputum	indeter

Table 21. *Streptococcus pneumoniae ermB* containing strains (bmITT populations) correlated with telithromycin and erythromycin MICs.

Telithromycin MIC MIC (µg/mL)	Erythromycin MIC MIC (µg/mL)	Number of strains with *ermB* gene	Source	Clinical outcome
0.008	8	1	3005-sinus10d	cure
0.015	8	1	3002sinus10d	cure
0.016	8	2	3011sinus5d	indeter
0.03	8	1	3010-sputum	cure
0.03	32	1	3009-sputum	cure
0.03	8	3	3011sinus5d	cure
0.03	32	1	3002-sinus10d	cure
0.03	32	1	3000-sputum	cure
0.03	32	1	3002-sinus5d	cure
0.03	32	1	3001-blood	cure
0.03	32	1	3001-sputum	failure
0.03	32	1	3000-blood	failure
0.03	8	1	3010-sputum	cure
0.06	8	1	3011-sinus5d	cure
0.06	32	3	3002-sinus10d	cure
0.25	8	1	3010-sputum	cure

2	8	1	3011-sinus5d	cure

Haemophilus influenzae

From all of the CAP studies (PPb populations) there were a total of 105 cases of pneumonia associated with *H. influenzae* with an overall cure rate of 91% (95/105) (HMR3647A/v08/0000045t.1st, 4 Jan 01. Of these 14 (9 from initial submission data and 5 from study 3010) were associated with β-lactamase positive *H. influenzae* for which there was a clinical cure rate of 86% (12/14). All of the β-lactamase positive *H. influenzae* had telithromycin MICs of ≤4 µg/mL.

For AMS there were a total of 71 isolates of *H. influenzae* from all telithromycin treated PPb populations with an overall clinical cure rate of (89%). Of these 71 isolates 13 were β-lactamase positive with an overall cure rate of 85% (11/134). Twelve of the 13 isolates had telithromycin MICs of ≤4 µg/mL and one isolate having a telithromycin MIC of 8 µg/mL.

For the AECB population four of the 24 *H. influenzae* isolates were β-lactamase positive. Two (2/4) of these were considered clinical failures (Aventis CD correspondence 10/18/00).

Because of insufficient experience with telithromycin to treat CAP, AMS or AECB caused by β-lactamase positive *H. influenzae* the labeling reads "

Haemophilus parainfluenzae

The Reviewer is proposing that the labeling reflect that the susceptibility interpretive criteria be specific for *H. influenzae* rather than *Haemophilus* spp. This is because as indicated by the Applicant (revised labeling submitted by Applicant 4/6/01 and correspondence dated 4/19/01) and concurred with by this Reviewer there is not enough clinical experience with telithromycin for the treatment of clinically significant infections caused by *H. parainfluenzae*. Therefore *H. parainfluenzae* should not be included in any given indications. In addition *H. parainfluenzae* would not be eligible for the second list because the telithromycin MIC_{90} for *H. parainfluenzae* is 8 µg/mL which is at the upper limit of

the therapeutically achievable level of telithromycin in tissue. Organisms in order to make the second list among other criteria must have MIC_{90s} that are within therapeutically achievable levels using standard dosing regimens.

Streptococcus pyogenes

In vitro studies have shown that telithromycin is bacteriostatic against *S. pyogenes* and that isolates of *S. pyogenes*, which are erythromycin-resistant have elevated MICs to telithromycin. The telithromycin MICs against these strains have been shown to be as high as 8 µg/mL. In addition clinical cure rates for pharyngitis associated with ERSP treated with telithromycin were shown to be 40% (Vol. 1.242 p. 309). For these reasons this Reviewer recommends that *S. pyogenes* not be included in the package label for telithromycin or if it is included that it be included only for *S. pyogenes* that are susceptible to erythromycin.

From the literature and information provided by the Applicant it is evident that the presence of the *erm*B gene in strains of *S. pyogenes* confers tolerance in this organism to high levels of telithromycin. Genotyping to characterize the resistance mechanism was done on 17 of 18 *S. pyogenes* that were erythromycin resistant. Five of the isolates were found to have the *erm*B gene, nine were found to have the *mef*A gene, and three were found to possess both the *erm*B and *mef*E genes. Four of the five *S. pyogenes* carrying the *ermB* gene had telithromycin MICs of 8 µg/mL and the fifth isolate had a telithromycin MIC of 0.5 µg/mL. Three of the nine *S. pyogenes* carrying the *mefA* gene had telithromycin MICs of 1 µg/mL while the remaining 6 had telithromycin MICs of 0.5 µg/mL. Two of the *S. pyogenes* carrying both the *erm*B and *mef*E gene had telithromycin MICS of 0.5 while the third *S. pyogenes* had a telithromycin MIC of 1 µg/mL. It is of interest to note that the *erm*B gene when present in the *S. pyogenes* confers a higher level of resistance to telithromycin then when it is present in *S. pneumoniae* even though the erythromycin MIC is not as high as in *S. pneumoniae*. The *mef*E gene also appears to confer a higher level of resistance to telithromycin in *S. pyogenes* then it does in *S. pneumoniae*.

Staphylococcus aureus

Telithromycin has been shown to have minimal to no activity against methicillin-resistant *S. aureus* or strains that are constitutively resistant to erythromycin.

There were 18 Isolates of *S. aureus* associated with CAP in telithromycin treated PPb populations HMR3647A/v08/b2000054t.1st, 21 Feb. 001 Table SE33). Of these 14 (78%) were considered clinical cures. One *S. aureus* was methicillin resistant and this was classified as a clinical failure.

Staphylococcus aureus was associated with 19 cases of AMS in the telithromycin treated PPb population (HMR3647A/v08/0000049t.1st, 4Jan 01, Table SE 59). In this population there was a 95% cure rate.

There was on case of AECB associated with *S. aureus* in the telithromycin treated PPb populations. This one case was considered a clinical cure.

Moraxella catarrhalis

Fourteen isolates of *M. catarrhalis* (HMR3647A/v08/0000173t.ist, 12Jan01 Table SE13) were isolated from the patients with CAP from all of the telithromycin PPb populations. Fourteen of the sixteen (88%) were considered to be clinical cures after treatment with telithromycin.

Eighteen isolates of *M. catarrhalis* were isolated from patients with AECB (HMR3647A/vb/000045t, 21Feb01 Table SE59) in the telithromycin PPb populations for both the 5 and 10 courses of therapy. Seventeen of the 18 (94%) were considered to have been treated successfully with telithromycin.

Nine isolates of *M. catarrhalis* were isolated from cases of AECB in the telithromycin PPb treated populations. All 9 of these were considered successfully treated with telithromycin.

The role that *M. catarrhalis* plays in causing CAP, AMS, or AECB in adults is not well documented.

Atypicals

The applicant provided clinical and diagnostic evidence for the occurrence of 34 cases of *C. pneumoniae*, 31 cases of *M. pneumoniae* and 12 cases of *L. pneumophilia* CAP. In vitro studies have shown the telithromycin concentrates in PMNs and macrophages to levels that exceed the MIC of these intracellular pathogens. The clinical cure rates with telithromycin for infections due to these organisms were better than 94%. Based on the telithromycin MIC_{90s} for *M. pneumoniae*, and *L. pneumophilia* (based on 100 isolates of each), the fact that telithromycin concentrates well above the MIC_{90s} in PMNs and macrophages and the clinical cure rates it is recommended that these organisms be placed in the in vitro list of the package insert. The Applicant submitted in vitro susceptibility test results for only 20 clinical isolates of *C. pneumoniae*.

NDA#: 21-144 Addendum (data received after completion of initial review 11/30/00)
Aventis Pharmaceuticals Inc.

REVIEW AND ANALYSIS OF SCATTERGRAMS

Initial scattergrams (3/1/00) from PPb data.

Acrobat Document

APPEARS THIS WAY ON ORIGINAL

Scattergrams (submitted 3/28/01) from all PPb populations including data from studies 3010 and 3011. The scattergrams were accompanied by line listings of the data used to create each scattergram.

APPEARS THIS WAY ON ORIGINAL

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Scattergrams (submitted 4/20/01) from all bmITT populations including studies 3010 and 3011. The scattergrams were accompanied by line listings of the data used to create the each scattergram.

APPEARS THIS WAY ON ORIGINAL

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Table 22 updates the false susceptible and false resistance data using the FDA proposed susceptibility test interpretive criteria when the organisms from the PPb populations of studies 3010 and 3011 are included. Data from Japanese study 2105 have not been included due to lack of disk susceptibility test results.

Table 22 Resulting discrepancies between MIC and disk diffusion interpretive criteria using FDA proposed susceptibility interpretive criteria on PPb populations

Organism	Number of isolates	Interpretive criteria MIC (µg/mL)	Zone size (mm)	Interpretation	Discrepancies number (%)
S. pneumoniae	244				
H. influenzae	174	≤4	≥16	Susceptible	FS=1(0.6) FR=3(1.7)
S. aureus	39	≤0.25	≥22	Susceptible	FS=0 FR=0

*FS=false susceptible **FR=false resistant

Table 23 shows discrepancies between the FDA proposed telithromycin MIC and disk diffusion interpretive criteria using the larger bmITT telitheromycin treated populations. The discrepancies seen in Tables 20 and 21 are quite similar.

Table 23. Resulting discrepancies between MIC and disk diffusion interpretive criteria using for telithromycin treated bmITT populations using FDA proposed susceptibility test interpretive criteria

Organism	Number of isolates	Interpretive criteria MIC ug/mL	Zone size (mm)	Interepretation	Discrepancies false susceptible No. (%)	false resistant No. (%)
S. pneumoniae	363					

H. influenzae	338	≤ 4	≥ 16	S	5(1.5)	7(2.1)
S. aureus	88	≤ 0.25	≥ 22	S	1(1.1)	0

S = Susceptible, I = Intermediate, R = Resistant

Table 24 shows the bacteriological and clinical cure rates for the various MIC susceptibility interpretive criteria when all isolates from the telithromycin PPb populations are used.

Table 24. Cumulative bacteriological eradication and clinical cure rates for the telithromycin PPb populations for all indications associated with FDA MIC susceptible interpretive criteria

Organism	MIC (ug/mL) interpretive criteria	Bacteriological eradication rate (%)	Clinical cure rate (%)
S. pneumoniae			
H. influenzae			
	≤4	134/160 (84)	139/160 (87)
S. aureus	≤0.25	35/39 (89.7)	34/39 (87.2)

To help in setting the breakpoint for *H. influenzae* Table 25 shows the bacteriological eradication and clinical cure rates break for *H. influenzae* by individual indications at the different telithromycin susceptible interpretive

breakpoints. This breakdown shows that the AECB indication had the lowest bacteriological and clinical cure rates of the all indications studied.

Table 25. Bacteriological eradication and clinical cure rates for *Haemophilus influenzae* from telithromycin treated PPb population by indication correlated with various telithromycin MIC interpretive criteria.

Indication	Telithromycin MIC ug/mL	Bacteriological eradication rate (%)	Clinical cure rate (%)
CAP	≤ 1	21/25 (84)	21/25 (84)
	≤ 2	34/38 (89)	34/38 (89)
	≤ 4	27/29 (93)	28/29 (97)
	≤ 8	5/14 (36)	6/14 (43)
AMS	≤ 1	12/13 (92)	13/13 (100)
	≤ 2	19/21 (90)	20/21 (95)
	≤ 4	10/11 (91)	10/11 (91)
	≤ 8	0/1 (0)	0/1 (0)
AECB	≤ 1	6/11 (55)	7/11 (64)
	≤ 2	7/11 ((64)	8/11 ((73)
	≤ 4	1/1 (100)	1/1 (100)
	≤ 8	0/1 (0)	0/1 (0)
All indications	≤ 1	39/49 (80)	41/49 (84)
	≤ 2	60/70 (86)	62/70 (89)
	≤ 4	38/41 (93)	39/41 (95)
	≤ 8	5/16 (31)	6/16 (38)

IN VITRO SUSCEPTIBILITY TESTING INTERPRETIVE CRITERIA

Based on the microbiology and clinical information reviewed in the initial submission and the amendments (study 3010 CAP 1/15/01 & study 3011 AMS 1/26/01) and analysis of the scattergram plots of MIC versus disk diffusion zone size the following interpretive criteria are recommended.

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5 Draft Labeling Page(s) Withheld

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/s/

Frederic Marsik
10/31/02 06:43:21 AM
MICROBIOLOGIST
Review finalized 11May01 initialized by Al Sheldon 10May01

Albert Sheldon
10/31/02 07:29:04 AM
MICROBIOLOGIST

Lillian Gavrilovich
11/1/02 10:35:45 AM
MEDICAL OFFICER

NDA#: 21-144
Aventis Pharmaceuticals Inc.

Division of Anti-Infective Drug Products
Clinical Microbiology Review # 1

NDA#: 21-144
Date Completed: 11/30/00

Applicant:

Aventis Pharmaceuticals Inc.
10236 Manon Park Drive
PO Box 9627
Kansas City, MO 64134-0627

Contact Person:

J. Michael Nicholas, Ph.D.
Vice President, U.S. Regulatory Affairs, Marketed Products
816-966-5000

Therapeutic Type: Antibacterial

Providing for:

Treatment of:

Community Acquired Pneumonia due to:
- *Streptococcus pneumoniae* (including penicillin and erythromycin-resistant strains)
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*
- *Chlamydia pneumoniae*
- *Legionella pneumophilia*
- *Mycoplasma pneumoniae*

Acute Bacterial Exacerbations of Chronic Bronchitis due to:
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus* (methicillin and erythromycin susceptible strains only)

Acute Sinusitis due to:
- *Streptococcus pneumoniae* (including penicillin and erythromycin-resistant strains)

Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Staphylococcus aureus (methicillin and erythromycin susceptible strains only)

Tonsillitis/pharyngitis due to:
Streptococcus pyogenes (in patients 13 years old and above)

Product Name:
Proprietary: KETEK™
Established Name: Telithromycin
Code Name/Number: HMR 3647 (RU66647)
Chemical Name: 11,12-dideoxy-3-de [(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-hexopyranosyl) oxy] 6-O-methyl-3-oxy-12, 11-[oxycarbonyl[[4-[4-(3-pyrindyl)-1H-imidazol-1-yl]butyl]imino]]erythromycin
Chemical formula (empirical): $C_{43}H_{65}N_5O_{10}$
Molecular weight: 812.03

Dosage form: Tablet
Strength: 400 mg
Route of administration: Oral
Dosage/Duration: Two 400 mg tablets daily (800 mg) for 7-10 days for Community Acquired Pneumonia (CAP) and 5 days for Acute Bacterial Exacerbation's of Chronic Bronchitis (ABECB), Acute Sinusitis, and Tonsillitis/Pharyngitis

Dispensed: R_x

Initial Submission Date(s):
Applicant submission date: 2/28/2000
Received by CDER: 3/1/2000
Received by reviewer: 3/3/2000
Review completed: 11/30/00

Supplements/Amendments: Safety Update dated 10-July-2000, Aventis responses to Microbiology questions on CD ROM dated 28-Aug-200, and 10-Oct-2000.

Related Documents: IND 55,283 dated 3/27/00

Remarks: The microbiology portion of this application is approvable when the indicated changes to the microbiology portion of the package labeling have been made.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Telithromycin has been shown to have in vitro activity against *Streptococcus pneumoniae* including strains that are resistant to penicillin or erythromycin, *Haemophilus influenzae* including strains that are β-lactamase positive, *Moraxella catarrhalis*, *Streptococcus pyogenes* that are susceptible to erythromycin, and *Staphylococcus aureus* that are susceptible to methicillin, erythromycin or clindamycin. These organisms are considered important pathogens associated with one or more of the indications [community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), acute maxillary sinusitis (AMS) and pharyngitis/tonsillitis] for which the applicant is seeking approval. The applicant has submitted clinical data to support their claim that telithromycin is efficacious in treating infections caused by these organisms. In addition they have provided in vitro susceptibility information for ≥100 isolates of other organisms, without bacteriological and clinical outcome information, that may be associated with these types of infections. Those organisms, which are associated with the indications sought, have been included in the second list of the microbiology section of the product labeling.

The mode of action of telithromycin (HMR 3647) is inhibition of protein synthesis. This inhibition of protein synthesis occurs by interaction with the bacterial 50S subunit of the ribosome. This inhibits the process of messenger RNA (mRNA) translation. The applicant states that telithromycin also inhibits the assembly of the nascent 50S ribosomal subunit and also the formation of the 30S ribosomal subunit.

Strain variation within groups of organisms determines whether telithromycin is bactericidal or bacteriostatic. The following is generally true. Telithromycin is bactericidal against penicillin or erythromycin susceptible and resistant *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. It is bacteriostatic against *S. pyogenes* and *S. aureus*.

The predominant forms of macrolide resistance in *Streptococcus pneumoniae* are mediated by mef A, a gene encoding an efflux pump in the major facilitator superfamily, or by erm B, a rRNA methylase. [Note that the *mef* A and *mef* E genes originally named for the macrolide efflux determinants in *S. pyogenes* and *S. pneumoniae* respectively, have been classified into one group *mef* A]. Virtually all clinical isolates of macrolide-resistant *S. pneumoniae* that have been examined for macrolide resistance have contained either mef A or erm B, and occasional strains have contained both genes. Telithromycin has in vitro activity against strains of *S. pneumoniae* that carry the *mef* A and *erm* B genes.

Telithromycin is inactive against *S. aureus* isolates resistant to erythromycin A by a constitutive MLS_B mechanism coded by one of *erm* A, *erm* B, *erm* C or combination of two or three of these genes (MIC>128 µg/mL).

Telithromycin has good activity against MLS_B inducible *S. aureus*. Telithromycin has no activity against methicillin-resistant *S. aureus*

Telithromycin has in vitro activity against erythromycin-susceptible strains of *S. pyogenes* at concentrations that are achievable therapeutically. Erythromycin-resistant *Streptococcus pyogenes*, such as those that carry the *erm* B gene, have both an MIC_{50} and MIC_{90}, >32µg/mL, which exceeds the therapeutic level achievable with telithromycin dosing. Thus telithromycin can be used to treat only those infections that are due to erythromycin-susceptible *S. pyogenes*.

In fasting adults, peak plasma telithromycin concentrations of approximately 2 µg/mL are attained within a median of 1 hour after an 800-mg oral dose. Steady state plasma concentrations are reached after 2 to 3 days of once daily dosing with 800 mg and are approximately 1.5 times the single-dose concentration after 7 days of dosing. The mean terminal elimination half-life after the last dose is 10 hours. The pharmacokinetics of telithromycin after a single once-daily 800-mg dose and multiple 800-mg doses for 7 days is shown in the following table.

Pharmacokinetics of telithromycin after one dose of 800 mg and 7 days of 800 mg doses in 18 healthy adults

Parameter	Single dose	Seven days
C_{max} (µg/mL)	1.9	2.27
Tmax*	1	1
AUC $_{(0\text{-}24)}$ (µg.h/mL)	8.25	12.5
Terminal $t_{1/2}$ (h)	7.16	9.81
C_{24h} (µg/mL)	0.03	0.07

*Median values

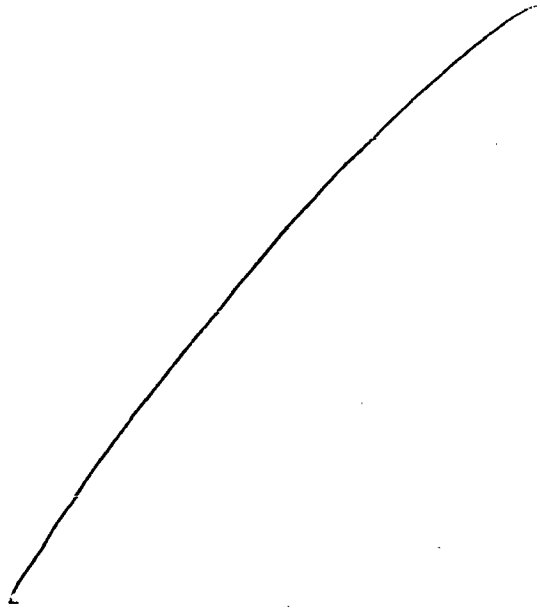
In a patient population of 219 subjects, mean peak and trough plasma concentrations were 2.9 and 0.2 µg/mL after 3 to 5 days of 800-mg doses daily.

Telithromycin is 60 to 70% protein bound.

The murine thigh-infection model was used to determine the pharmacokinetic/pharmacodynamic (PK/PD) parameter that is most meaningful in understanding the in vivo efficacy of telithromycin. It was concluded that the 24-hour AUC/MIC ratio is the major determinant of in-vivo activity for HMR 3647. From this data it was concluded that once-daily dosing would be appropriate for HMR 3647.

Based on the pharmacokinetic/pharmacodynamic characteristics of telithromycin, in vitro susceptibility data from the literature and as provided by the applicant against the target pathogens, and sufficient bacteriological and clinical outcome data the following MIC and disk diffusion zone size interpretive criteria are applicable. The error rate bounded method was not used to correlate the MIC with the disc diffusion zone size because there were too few or no isolates of *S. pneumoniae*, *S. aureus*, *M. catarrhalis* or *S. pyogenes* that were found to be resistant to telithromycin. The error rate bounded

method was used to set disc diffusion interpretive breakpoints for *H. influenzae*. Disk diffusion testing is done using a disk containing 15 µg telithromycin.



STREPTOCOCCUS PNEUMONIAE (penicillin and erythromycin susceptible strains only):

MIC

MIC (µg/mL)	Interpretation*

Disk Diffusion Zone Size

Disk Diffusion Zone Size (mm)	Interpretation*

The bacteriological eradication and clinical cure rates using as indicating susceptibility of *S. pneumoniae* to telithromycin in the indications noted below were:

Indication	Bacteriological eradication	Clinical cure
CAP	92/97 (95 %)	92/97 (95%)
AECB	13/14 (93%)	12/14 (86%)

AMS	46/50 (92%)	46/50 (92%)

[redacted]

The bacteriological eradication and clinical cure rates using [redacted] as indicating susceptibility of *S. pyogenes* to telithromycin for pharyngitis/tonsillitis were 218/241 (90%) and 232/239 (96%) respectively.

[redacted]

The bacteriological eradication and clinical cure rates using [redacted] as indicating susceptibility of *H. influenzae* and *H. parainfluenzae* to telithromycin in the indications noted below were:

H. influenzae

Indication	Bacteriological eradication	Clinical cure
CAP	32/39 (82%)	32/39 (82%)

AECB	13/22 (59%)	15/22 (68%)
AMS	25/26 (96%)	25/26 (96%)

QUALITY CONTROL ORGANISMS AND RANGES FOR SUSCEPTIBILITY TESTING:

Quality control ranges for broth microdilution and disc diffusion (15 ug disc) susceptibility methods

Control Strain	MIC (ug/mL)	Zone diameter (mm)
S. pneumoniae ATCC 49619	0.004-0.03	27-33
H. influenzae ATCC 49247	1-4	17-23

ATYPICAL PATHOGENS

Pneumonia, without the presence of any common pathogens, that were treated with telithromycin resulted in a clinical cure in 1 subject (100%) with *C. pneumoniae* infection, in 1 subject (100%) with a positive diagnosis of *M. pneumoniae* infection, and 4 subjects (100%) with a positive diagnosis of infection due to *L. pneumophilia.*

SECOND LIST

Based on their relevance to the indications being sought by the applicant and the in vitro susceptibility information provided by the applicant on ≥100 isolates of each organism the following organisms have been placed in the second list of the microbiology portion of the package labeling.

Gram-positive aerobes

Group G streptococci

Viridans streptococci

Gram-negative aerobes

Legionella pneumophilia

INTRODUCTION:

Telithromycin is a semisynthetic ketolide antibacterial that has a primarily gram-positive spectrum of activity with activity against a select number of fastidious gram-negative bacteria. Telithromycin differs chemically from the macrolide-azalide group of antibacterials by the substitution of a keto function at position 3 on the macrolactone ring in place of a cladinose moiety. Telithromycin is given orally.

The applicant has provided the microbiology data that they feel will help support their request for the antibacterial to be used for the following indications.

Community Acquired Pneumonia due to
- *Streptococcus pneumoniae* (including penicillin and erythromycin-resistant strains)
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*
- *Chlamydia pneumoniae*
- *Legionella pneumophilia*
- *Mycoplasma pneumoniae*

Acute Bacterial Exacerbations of Chronic Bronchitis due to:
- *Streptococcus* pneumoniae
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus* (methicillin and erythromycin susceptible strains only)

Acute sinusitis due to:
- *Streptococcus pneumoniae* (including penicillin and erythromycin-resistant strains)
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus* (methicillin and erythromycin susceptible strains only)

Tonsillitis/pharyngitis due to:
- *Streptococcus pyogenes* (in patients 13 years old and above)

The above organisms are clinically associated with the stated indications with the exception of *Haemophilus parainfluenzae*. *Haemophilus parainfluenzae* is not very commonly associated with "Community Acquired Pneumonia" (CAP) (1, 2) or Acute Sinusitis (AMS) (3).

IN VITRO

ANTIMICROBIAL SPECTRUM OF ACTIVITY:

The ketolide HMR3647 (telithromycin) belongs to a new class of the 14-membered ring macrolide antibiotics, which are characterized by a 3-keto group (imidazo-pyridyl) on the erythronolide A ring instead of the sugar α-L-cladinose moiety. Telithromycin basically has the same antibacterial spectrum as erythromycin A. In vitro it has activity against multiresistant pneumococci, and *Haemophilus influenzae*.

The following tables (Tables 1-6) summarize the published in vitro susceptibility data for telithromycin. The data were obtained by an independent literature search done by the Reviewer. This information will serve as a basis for comparison to the in vitro susceptibility data submitted by the applicant.

Table 1 is published results of the in vitro activity of telithromycin against a variety of bacteria. The results in this table were generated using the National Committee for Clinical Laboratory Standards (NCCLS) (4) microbroth dilution susceptibility test method.

Table1. Susceptibility of Gram-positive clinical isolates and *Haemophilus influenzae* stock cultures to HMR 3647 (5, 6)

Microorganism	No. isolates	Range	MIC µg/ mL MIC_{50}	MIC_{90}
Enterococcus faecalis	359	≤0.12->16	≤0.12	2
E. faecalis vancomycin susceptible (6)	10	0.03-0.5	0.03	0.25
E. faecalis vancomycin resistant (6)	10	0.03-8	1	8
Enterococcus faecium vancomycin susceptible	55	≤0.12-8	2	8
E. faecium vancomycin Resistant	39	≤0.12->16	4	8
Enterococcus spp.(a)	38	≤0.12->16	≤0.12	8

Staphylococcus aureus Oxacillin susceptible	316	≤0.12->16	≤0.12	≤0.12
S. aureus oxacillin Resistant	259	≤0.12->16	0.25	>16
Streptococcus pyogenes	175	≤0.12-≤0.12	≤0.12	≤0.12
Streptococcus agalactiae	90	≤0.12-1	≤0.12	≤0.12
Streptococcus pneumoniae Penicillin susceptible	358	≤0.12-0.25	≤0.12	≤0.12
Penicillin intermediate	82	≤0.12-0.5	≤0.12	0.25
Penicillin resistant	105	≤0.12-0.5	≤0.12	≤0.12
Streptococcus viridans Group	125	≤0.12-0.5	≤0.12	≤0.12
Streptococcus spp. (b)	62	≤0.12-4	≤0.12	≤0.12
Corynebacterium spp.(c)	29	≤0.12->16	≤0.12	>16
Other Gram-Positive spp.	54	≤0.12->16	≤0.12	≤0.12
Haemophilus influenzae ampicillin susceptible. β-lactamase negative	84	0.25-8	2	4
ampicillin resistant, β-lactamase negative	27	0.12-4	2	4
ampicillin				

resistant, β-lactamase positive	89	0.25-8	2	4

a. Organisms include: 17 *E. avium*, 3 *E. casseliflavus*, 1 *E. cecorum*, 10 *E. durans*, 2 *E. raffinosus*, and 5 *E. gallinarum*
b. Organisms include: 1 *S. anginosus*, 8 *S. bovis*, 3 *S. constellatus*, 1 *S. intermedius*, 19 *S. mitis*, 2 *S. milleri*, 2 *S. mutans*, 7 *S. sanguis*, 3 serogroup C, 1 Serogroup F, and 8 serogroup g and 7 *Streptococcus* isolates with no species identified.
c. Organisms include: 15 *C. jeikeium*, 2 *C. minuitissium*, 1 *C. striatum*, 2 group 2, 1 group ANF-1, 1 group ANF-3, 1 *C. aquaticum*, and 1 *C. urealyticum*

Torres (7) noted that of 202 *Enterococcus* strains of different species those strains that were susceptible to erythromycin had a lower telithromycin MIC_{90} (0.03 μg/mL) than the enterococci that were either erythromycin or penicillin resistant or carried the VanA gene or were penicillin resistant (telithromycin MIC_{90} = 4 μg/mL).

Table 2 gives the activity of HMR3647 against macrolide (erythromycin) and lincosamide (clindamycin) – resistant strains of various bacteria. The results in this table were generated using the NCCLS microbroth dilution susceptibility test method (4).

Table 2. In vitro activity of HMR 3647 against macrolide- and lincosamide-resistant bacterial isolates (5)

Microorganisms (number tested)	Resistance phenotype	Number of isolates	MIC μg/mL MIC_{50}	MIC μg/mL MIC_{90}	% of isolates for which MIC was <1 ug/mL
Staphylococcus aureus (515)	Ery S	265	≤0.12	≤0.12	100
	Ery R	249	2	8	23
	Clin S	330	≤0.12	≤0.12	100
	Clin R	185	>16	>16	26
Streptococcus pneumoniae (545)	Ery S	445	≤0.12	≤0.12	100
	Ery I	37	≤0.12	≤0.12	100
	Ery R	63	≤0.12	≤0.12	100
	Clin S	514	≤0.12	≤0.12	100
	Clin R	30	≤0.12	≤0.12	100

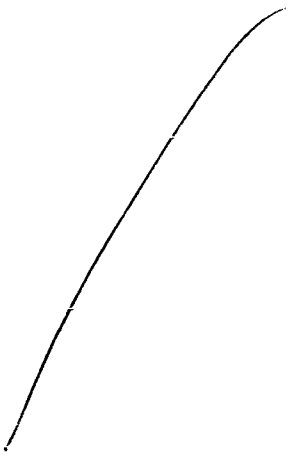


Table 3 gives published results for the in vitro activity of HMR347 against isolates of *Moraxella catarrhalis*. The results in this table were generated using the NCCLS microbroth dilution susceptibility test method (4).

Table 3. In vitro activity of HMR347 against *Moraxella catarrhalis*

		MIC µg/mL		
	No. of Isolates	Range	MIC_{50}	MIC_{90}
Reference 6	30	0.03-0.25	0.06	0.12
Reference 8	150	0.06-0.25	0.12	0.12

Table 4 is the results of in vitro testing of telithromycin against *Chlamydia pneumoniae*. The results were generated using the methodology as described in reference 9. Currently there is no recognized standard susceptibility test method for *Chlamydia*. The method utilized a cell culture method using Hep-2 cells. Only two strains (CWL 029 and G 954) of *C. pneumoniae* were tested. No conclusions can be made about the activity of telithromycin from the results of tests on two strains. A search of the literature at the time this review was done did not find a substantial amount of information on the in vitro activity of telithromycin against *C. pneumoniae*.

Table 4. In vitro activity of telithromycin (HMR 3647) against two strains *Chlamydia pneumoniae* (9).

Chlamydia pneumoniae strain	MIC (µg/mL)

CWL 029	0.0156
G954	0.0156

Table 5 indicates the in vitro activity of telithromycin against 41 clinical isolates of *Mycolplasma pneumoniae* (10). As noted for *Chlamydia* susceptibility testing there is no standardized method of susceptibility testing for *Mycoplasma*. The susceptibility testing used in reference 10 was by a broth mirodilution method using a modification of Chanock broth and an inoculum of 10^6 CFU/mL. The plates were sealed and incubated at 37^C for 3 to 6 days. A search of the literature at the time this review was done for in vitro activity of telithromycin against *M. pneumoniae* revealed a paucity of papers.

Table 5. In vitro activity of telithromycin (HMR3647) against 41 clinical isolates of *Mycoplasma pneumoniae* (10)

Telithromycin MIC (µg/mL)		
Range	MIC_{50}	MIC_{90}
0.00024-0.0019	0.00097	0.00097

Table 6 indicates the in vitro susceptibility test results of telithromycin against 46 clinical isolates of *Legionella pneumophilia* (11). There is no standardized method for performing susceptibility testing antimicrobials against *L. pneumophilia*. The method used in the paper from which this data was taken was a microbroth dilution method using a special broth and a final inoculum of 5×10^5 CFU/mL. The temperature at which the test was incubated and the length of incubation before reading the test were not given in the paper. A search of the literature for in vitro susceptibility test results of telithromycin activity against *L. pneumophilia* revealed a paucity of papers.

Table 6.The published in vitro activity of telithromycin against 46 clinical isolates of *Legionella pneumophilia* (11)

Telithromycin MIC (µg/mL)				
Mean	MIC_{50}	MIC_{90}	Minimum	Maximum
0.054	0.032	0.125	0.016	0.344

IN VITRO SUSCEPTIBILITY TEST DATA SUBMITTED BY APPLICANT

The applicant in their submission package has provided summary tables of the in vitro activity of telithromycin against the various bacteria they wish to have in their label (Section 7:v001.242). Tables 7-34 of this review represent summaries of the in vitro susceptibility data the applicant has submitted for telithromycin. The data agrees with the information (Tables 1-6) found by this Reviewer in an independent search of the literature for the in vitro activity of telithromycin relative to the pathogens requested to be included in the label.

Table 7 gives the applicant's data on the in vitro activity of telithromycin against *S. aureus*. This is a compilation of data from the US, UK, Canada and other foreign countries. A review of the data from these various sources did not reveal any major differences in the susceptibility profiles. Thus it is the feeling of this reviewer that a table combining all of the data gives a true in vitro picture of the susceptibility of *S. aureus* to telithromycin. The data in Table 8 shows that *S. aureus* susceptible to methicillin may have a consistently lower telithromycin MIC_{90} than *S. aureus* that are resistant to methicillin. Methicillin susceptible and resistant *S. aureus* that are constitutively resistant to erythromycin are resistant to telithromycin. Also those *S. aureus* that are either susceptible to or resistant to methicillin that are resistant to both erythromycin and clindamycin are resistant to telithromycin. Therefore it is important that susceptibility testing being done on all *S. aureus* to determine if the isolate is susceptible to telithromycin before using the drug.

Table 7. In vitro activity of telithromycin (μg/mL) against *Staphylococcus aureus* (Vol. 1.242 p 100)

S. aureus	Total No. of Isolates	MIC Range	MIC_{50} or MIC_{50} Range	MIC_{90} or MIC_{90} Range
MSSA*	614	0.015->128	0.04-0.13	0.12-0.3
MSSA-ery**-R (IR)***	86	0.02-128	0.5	1
MSSA-ery R (CR)****	15	>128	>128	>128
MSSA-ery-S	547	≤0.03-0.25	0.12	0.12
MSSA-ery-R	24	0.06->128	0.12	>128
MSSA-ery-R clin***** S	82	0.06-1.0	0.12	0.12
MSSA-ery-R clin R	16	0.25->64	>64	>64
MRSA******	503	0.005->128	0.04->128	0.3->128
MRSA-ery-S	45	0.03-0.25	0.13	0.12-0.25
MRSA-ery-R	120	0.03->128	0.25->32	>128

MRSA-ery-R (IR)	20	0.06-0.25	0.13	0.13
MRSA-ery-R (CR)	20	>128	>128	>128
MRSA-ery R clin S	32	0.06-1	0.12	0.12
MRSA ery R clin R	140	>64	>64	>64

*MSSA=Methicillin-susceptible
**ery=erythromycin A
***IR=inducible-resistance
****CR=constitutive-resistance
*****clin=clindamycin
******MRSA=Methicillin-resistant

Table 8 gives the applicant's data for the activity of telithromycin against