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**van=vancomycin

Table 9 gives the applicant's data for the in vitro susceptibility of

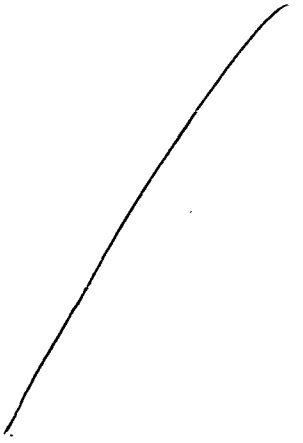


Table 10 gives the applicant's data for the in vitro susceptibility of 1107 isolates of *Streptococcus pyogenes* (β-hemolytic Group A streptococcus). The in vitro data in this table suggests that since telithromycin in plasma and certain fluids and tissues reaches concentrations substantially above the MIC_{90} of the *S. pyogenes* that are susceptible to erythromycin that it may have in vivo activity against this organism. *Streptococcus pyogenes* that are resistant to erythromycin and/or clindamycin have elevated MICs to telithromycin.

Table 10. In vitro activity of telithromycin (μg/mL) against 1107 isolates of *Streptococcus pyogenes* (Vol. 1.242 p104)

Organism	No. of Isolates	MIC Range	MIC_{50} or Range	MIC_{90} or Range
S. pyogenes ery-S	948	≤0.002-0.12	0.008-0.03	0.015-0.06
S. pyogenes ery-R	29	0.03-16	2	8
S. pyogenes ery-R clin-S	103	≤0.06-8	0.5	2
S. pyogenes ery-R clin-R	27	1->16	4	8

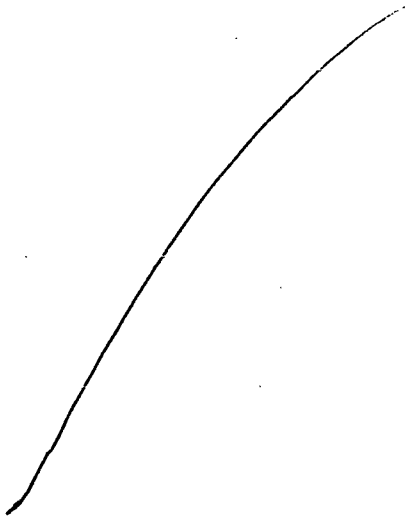
Table 11 gives the applicant's data for the in vitro susceptibility of Group C / G and viridans streptococci. This data is a compilation of US and ex-US isolates. No difference was seen between the MICs of US and ex-US isolates. The in vitro data in this table suggests that since telithromycin in plasma and certain fluids and tissues

reaches concentrations substantially above the MIC_{90} of a variety of β-hemolytic streptococci and viridans streptococci tested that it may have in vivo activity against these organisms.

Table 11. In vitro activity of telithromycin (μg/mL) against Group C, G, and viridans Streptococci (Vol. 1.242 p105)

Organism	No. of Isolates	MIC Range	MIC_{50} or Range	MIC_{90} or Range
Group C	59	≤0.008-0.25	≤0.008-0.015	0.03-0.06
Group G	102	≤0.08-0.06	0.015-0.03	0.15-0.06
Viridans	108	0.001-4	0.005-0.12	0.02-0.5
Viridans peni-S	10	≤0.004-0.25	≤0.004	≤0.004
Viridans peni-R	10	≤0.004-0.12	0.06	0.12
Viridans ery-S	57	0.015-0.5	≤0.003	≤0.003
Viridans ery-R	27		0.06	1

Table 12 is the applicant's data on the in vitro susceptibility of



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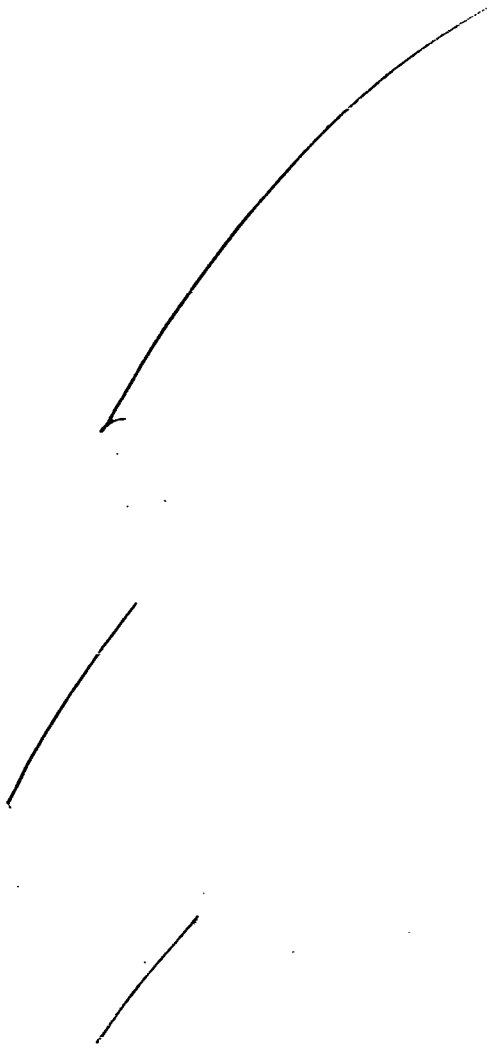


In Vol.1.242 p119 -126 the applicant has provided data for the in vitro activity of telithromycin against a variety of *Streptococcus pneumoniae*. Tables 21 to 25 contain this data. This data is a compilation of isolates from the US and outside the US. No differences were seen between the MICs of isolates from the US and those from outside the US. The in vitro data in these tables suggest that since telithromycin reaches concentrations in plasma and certain fluids and tissues substantially above the MIC_{90} of the *S. pneumoniae* tested, regardless of the organisms susceptibility to penicillin, erythromycin and clindamycin, that it may have in vivo activity against these organisms. *Streptococcus pneumoniae* with a dalfopristin/quinupristin MIC $\geq$ 4 µg/mL have a decreased susceptibility to telithromycin compared to those that are resistant to penicillin, erythromycin, or clindamycin. However the concentrations of telithromycin that are achievable in vivo suggest that telithromycin may be efficacious against these organisms.

Table 21. In vitro activity of telithromycin (ug/mL) against *Streptococcus pneumoniae*

Organism	No. of Isolates	MIC Range	MIC 50 or Range	MIC 90 or Range
S. pneumoniae pen-S	1495	≤0.001-0.5	0.007-0.03	0.007-0.125
S. pneumoniae pen-I	365	0.0015-1	0.0015-0.03	0.007-0.25
S. pneumoniae pen-R	867	0.001-4	0.0015-0.12	0.0015-2

Table 22. In vitro activity of telithromycin against *S. pneumoniae* resistant by either MLS_B or efflux

Organism	No of Isolates	MIC Range	MIC_{90}
S. pneumoniae pen-S, ery-R	23	0.015-0.5	0.25
S. pneumoniae pen-I, ery-S	20	0.004-0.015	0.015
S. pneumoniae pen-I, ery-R	25	0.008-1	0.25
S. pneumoniae ery-R	34	≤0.008-0.12	0.12
S. pneumoniae pen-R, ery-S	20	0.008-0.03	0.008
S. pneumoniae pen-R, ery-R	23	0.008-0.5	0.25

Table 23. The in vitro activity of telithromycin (µg/mL) against *S. pneumoniae* with MLS_B resistance (ery-R) and without MLS_B resistance (ery-S)

Organism	No. of Isolates	MIC Range	MIC_{50} or Range	MIC_{90} or Range
S. pneumoniae ery-R	455	≤0.0075-4	0.015-0.06	0.015-2
S. pneumoniae ery-S	491	0.001-0.25	0.001-0.06	0.001-0.06

Table 24. The in vitro activity of various antimicrobials (µg/mL) against 400 isolates of *Streptococcus pneumoniae*

Antimicrobial	MIC_{50}	MIC_{90}
Telithromycin	0.015	0.12
Linezolid	1	1
Quinupristin/dalfopristin	0.25	0.5
Erythromycin A	0.06	8
Azithromycin	0.12	16
Clarithromycin	0.06	8
Roxithromycin	0.12	1
Clindamycin	0.12	0.12
Lincomycin	0.5	1
Levofloxacin	1	1
Sparfloxacin	0.12	0.25
Trovafloxacin	0.06	0.12
Tetracycline	0.12	32

Table 25. The in vitro activity of telithromycin (µg/mL) against *Streptococcus pneumoniae* categorized as to their susceptibility profile to MLS compounds (Vol. 1.242 p126)

MLS Phenotype	MIC	No. of Isolates	Telithromycin MIC
Erythromycin A	≤0.25	67	≤0.015
Clindamycin	≤0.25	67	≤0.015
Dalfopristin/quinupristin	≤0.25	67	≤0.015
Dalfopristin/quinupristin	≥4	6	1-4
Erythromycin A	2-32		
Clindamycin (efflux)	≤0.25	47	0.12-1
Erythromycin A	≥32		

Clindamycin (MLS_B phenotype)	>1	37	≤0.06

Table 26 is the data the applicant has submitted in the in vitro susceptibility of various strains of *Haemophilus influenzae* to telithromycin. The data is from isolates recovered in the US and ex-US. The difficulty with analyzing the data is that a variety of broth media have been used to generate the MIC values. The NCCLS recommends the use of Haemophilus Test Medium (HTM) broth or agar (4). The applicant notes (Vol. 1.242 p127) that HTM gives higher MIC values than other susceptibility test medium. The applicant has provided data shown in Table 26 to support this claim. Because HTM is the medium recommended by the NCCLS only results using HTM (broth or agar) are given in Table 26.

The data in Table 26 suggests that since telithromycin reaches concentrations in plasma and certain fluids and tissues above the MIC_{90} of the ampicillin-susceptible *H. influenzae* tested, that it may have in vivo activity against these organisms. However because the MIC_{90} of telithromycin is higher against the ampicillin-resistant *H. influenzae* tested and this concentration is closer to the telithromycin achievable in plasma, other body fluid and tissue it may not be as efficacious against these strains of *H. influenzae*.

Table 26. In vitro activity of telithromycin (µg/mL) against *Haemophilus influenzae* using Haemophilus Test Medium agar or broth (Vol. 1.242 p128)

H. influenzae	Medium	No. of Isolates	MIC Range	MIC_{50} or Range	MIC_{90} or Range
Amp-S	broth	699	<0.06-8	1	2
Amp-R BLA +	broth	226	<0.06--16	2	4
Amp-R β-lactamase-negative	broth	27	0.12-4	2	4
Amp-S and -R	broth	249	1-8	2	4
Amp-S	agar	56	0.125-2	1	1
Amp-R BLA +	agar	24	0.5-2	1	2
Amp-R β-lactamase-negative	agar	12	0.125-1	1	1

Table 27 is the data the applicant has provided for the in vitro activity of telithromycin against *Haemophilus parainfluenzae*. The data in the table is from the US and was generated using HTM broth. Because the MIC_{90} of telithromycin is at a concentration of 8 µg/mL the in vivo efficacy of telithromycin may be marginal since the MIC is not substantially higher than the levels of telithromycin achievable in plasma, other body fluids and tissue.

Table 27. The in vitro activity of telithromycin (µg/mL) against *Haemophilus parainfluenza* (Vol. 1.242 p130)

No. of Isolates	MIC Range	MIC_{50}	MIC_{90}
41	0.12-8	2	8

The data in Table 28 is the information the applicant has submitted for the activity of telithromycin against *Moraxella catarrhalis*. The data in this table is a compilation of US and ex-US results. At the time the susceptibility data was generated for these isolates there was no NCCLS recommended method for the susceptibility testing of this organism. A look at the data from the various sources did not show any substantial difference in the MIC range or the MIC_{50} or MIC_{90}. Therefore the data was combined into one table. The data in Table 28 suggests that since telithromycin reaches concentrations in plasma and certain fluids and tissues above the MIC_{90} of the *Moraxella catarrhalis* tested, that it may have in vivo activity against these organisms.

Table 28. The in vitro activity of telithromycin (µg/mL) against *Moraxella catarrhalis (Vol. 1.242 p131)*

No. of Isolates	MIC Range	MIC_{50} or Range	MIC_{90} or Range
1108	0.0008-4	0.02-.25	0.03-0.5

The applicant has provided information on the activity of telithromycin against a variety of intracellular and atypical pathogens. These are *Chlamydia pneumoniae*, *Legionella pneumophilia* and *Mycoplasma pneumoniae*. There are no standardized susceptibility test methods for these organisms. The applicant has provided sufficient documentation of the methods that were used to determine the susceptibility of these organisms to telithromycin.

Table 29 is the applicant's data for the activity of telithromycin against *C. pneumoniae*. The data in the table is a compilation of US and ex-US data. Data on only 20 isolates (5 from the UK and 15 from the US) were submitted in this application. The in vitro data in this table suggests that since telithromycin reaches concentrations in plasma and certain fluids and tissues above the MIC_{90} of the *C. pneumoniae* tested that it may have in vivo activity against these organisms. In addition the applicant has shown that

telithromycin concentrates in polymorphonuclear cells where *C. pneumoniae* resides during infection with the organism (Vol. 1.242 p172).

Table 29. The in vitro activity of telithromycin (μg/mL) against 20 clinical isolates *Chlamydiae pneumoniae* (Vol. 1.242 p132)

MIC Range
0.03-2

Table 30 is the data the applicant has submitted for the in vitro activity of telithromycin against clinical isolates of *Legionella pneumophilia*. As with susceptibility testing of *C. pneumoniae* there is no standardized method for the susceptibility testing of *L. pneumophilia*. The applicant has provided information on the methods used. The methods appear to be appropriate and quality control strains were used. The data in Table 30 is a compilation of results from the US and the UK. There were no significant differences in the results from the US and UK. The in vitro data in this table suggests that since telithromycin reaches concentrations in plasma and certain fluids and tissues above the MIC_{90} of the *L. pneumophilia* tested that it may have in vivo activity against these organisms. In addition the applicant has shown that telithromycin concentrates in alveolar macrophages where *L. pneumophilia* resides during infection with the organism (Vol. 1.242 p172).

Table 30. In vitro activity of telithromycin (μg/mL) against 136 isolates of *Legionella pneumophilia* (Vol. 1.242 p133)

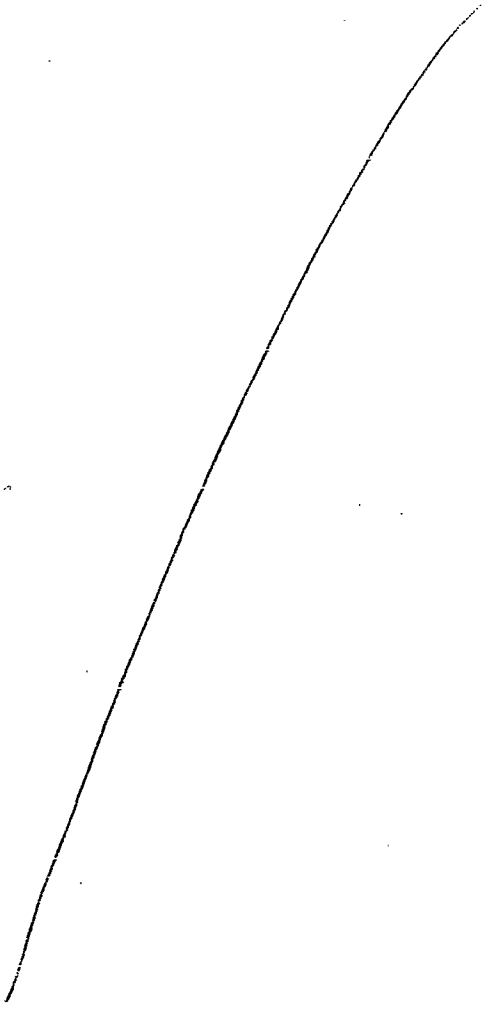
MIC Range	MIC_{50} or Range	MIC_{90} or Range
≤0.004	0.015-0.06	0.03-0.12

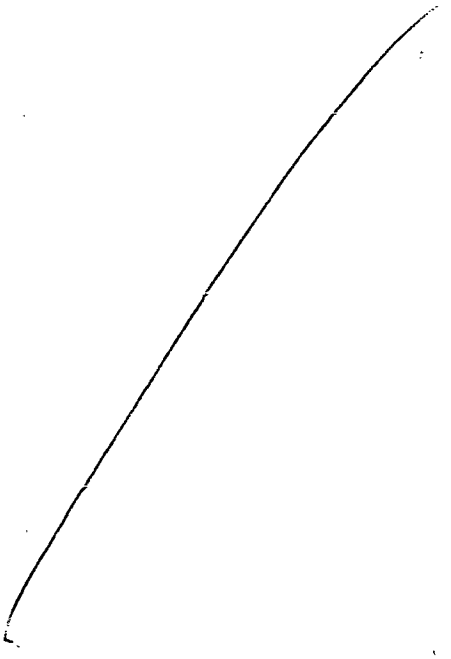
The applicant has also submitted data on the in vitro activity of telithromycin against a variety of species of *Legionella* (Vol. 1.242 p134-135). There are fewer than 100 isolates for each species (1-4 isolates for each species). The MIC range for all the isolates is 0.004-0.25 μg/mL.

The applicant has submitted in vitro susceptibility data for the activity of telithromycin against *Mycoplasma pneumoniae*. As with *C. pneumoniae* and *L. pneumophilia* there is no standardized method for the susceptibility testing of *M. pneumoniae*. The applicant has described the methodologies used by the various investigators to determine the susceptibility of *M. pneumoniae* isolates to telithromycin. All of the methods appear to be appropriate and include controls therefore the data is acceptable. Table 31 is a compilation of the data from US and ex-US sites. The in vitro data in this table suggests that since telithromycin reaches concentrations in plasma and certain fluids and tissues above the MIC_{90} of the *M. pneumoniae* tested that it may have in vivo activity against these organisms.

Table 31. In vitro activity of telithromycin (μg/mL) against 90 isolates of *Mycoplasma pneumoniae* (Vol. 1.242 p138)

MIC Range	MIC_{50} or Range	MIC_{90} or Range
0.00024-0.005	0.00097-0.005	0.00097-0.005





The applicant has provided in vitro susceptibility data for telithromycin against anaerobic bacteria (Vol. 1.242 p147-154). This data is from the US and ex-US. It was generated using a variety of susceptibility test methods. Tables 34 gives the in vitro susceptibility test results for telithromycin against Gram-negative for which there are results of at least 100 isolates and the susceptibility testing was done by NCCLS methodology (9). There were no Gram-positive anaerobes with 100 isolates which met the criteria stated. While the applicant has provided in vitro susceptibility test results for telithromycin by other methodologies they have not provided the data to show the equivalency of that method to the NCCLS method therefore they have not been included in this review. The in vitro data in this table suggests that since telithromycin reaches concentrations in plasma and certain fluids and tissues above the MIC_{90} of *Prevotella bivias*, and *Prevotella intermedia* tested that it may have in vivo activity against these organisms.

Table 34. In vitro activity of telithromycin (µg/mL) against Gram-negative anaerobes

Organism	No. of Isolates	MIC Range	MIC_{50} or Range	MIC_{90} or Range
Prevotella bivia	189	≤0.015->32	0.25-0.5	0.5-1

Prevotella intermedia	175	≤0.008-0.5	≤0.008-0.03	0.06

The applicant in the submission has provided in vitro susceptibility data for a variety of other organisms (Vol. 1.242 p154-158). None of these organisms are germane to the indications which the applicant is seeking (*Mycobacteria* spp) and/or there are fewer than 100 isolates of the organisms therefore they will not be included in the label.

MECHANISM OF ACTION (Vol. 1.3 p105):

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 the formation of the 30S ribosomal subunit.

Telithromycin like other macrolides interacts with the bacterial 23S RNA (rRNA). The interactions are limited to a region of domain II of the rRNA and the peptidyl transferase loop in domain V. The interaction with the 750 loop (position A-752) is due to the C11-C12 side chain. Telithromycin and macrolides protect the same two positions in domain V, A 2058 and A 2059 of 23S rRNA from modification with dimethysulfate. The applicant states that telithromycin also strongly protects A-752 in domain II whereas binding of erythromycin A to the ribosome increased accessibility of A-752 to chemical modifications. Thus it is believed that telithromycin and erythromycin A have different contact sites on the rRNA in the vicinity of A-752 (13).

The applicant indicates (Vol. 1.3 p108) that telithromycin is bactericidal against *S. pneumoniae* that are susceptible to erythromycin A. When a strain of *S. pneumoniae* harbors a gene for resistance to erythromycin A (*mef* E^+ or *erm* B^+) telithromycin is still bactericidal but the effect occurs less rapidly. Telithromycin is apparently bactericidal against *H. influenzae* but the effect takes12 to 24 hours. The evidence suggests that telithromycin is bactericidal against *M. catarrhalis*.

Against *S. pyogenes* telithromycin is believed to be bacteriostatic. Against *S. aureus* and *Enterococcus* species telithromycin is bacteriostatic. It is not clear whether telithromycin is bactericidal against *Bacteriodes fragilis*. Telithromycin is believed to be bactericidal against *Propionibacterium acnes*, *Clostridium perfringens*, *C. diphtheriae* and *H. pylori*.

EPIDEMIOLOGY (Vol. 1.242 p188):

The applicant has provided epidemiological data on the susceptibility of various organisms collected in North America and throughout the world (Vol. 1.242 p188-195). The data for North America is shown in Table 35. Table 35 includes only organisms for which there were 100 or more isolates of the genus. This data was collected during the

winter months of 1996-1997 and 1998-1999 at 11 medical centers in North America (includes a site in Canada). The interpretive criteria for telithromycin were: susceptible = ≤1 µg/mL (≥19mm/23mm); intermediate = 2 µg/mL (16-18mm/20mm); resistant = ≥4 µg/mL (≤15mm/≤19mm).

The data in table 35 indicate that *S. pneumoniae* regardless of its susceptibility to penicillin and *S. pyogenes* are susceptible to achievable levels of telithromycin. Strains of *S. aureus* and . with the phenotype ery-R, clin-R regardless of their susceptibility to methicillin are resistant to telithromycin. Isolates of *S. agalactiae* (Grp B streptococci) are susceptible to telithromycin

Table 35. In vitro activity of telithromycin (µg/mL) against various bacteria from North America

Organism	No. of Isolates	MIC Geometric Mean	Percent Susceptible
S. pneumoniae			
pen-S	373	0.04	100
pen-I	93	0.06	100
pen-R	110	0.21	98.2
S pyogenes	238	≤0.03	99.6
S. aureus			
meth-S, ery-S, clin-S	278	0.08	100
meth-S, ery-R, clin-S	82	0.1	100
meth-S, ery-R, clin-R	16	>64	6.3
meth-R, ery-S&R, clin-S	32	0.1	100
meth-R, ery-R, clin-R	140	>64	0

*Pen-S = ≤0.06 ug/mL, Pen-I = 0.12-1.0 ug/mL, Pen-R = >1 ug/mL

The applicant has also provided surveillance data from the CDC "Emerging Infection Program" (Vol. 1.242 p189) for *S. pneumoniae*. This data encompasses 312 isolates of *S. pneumoniae* recovered during the period of 1994-1998. The MIC determinations for telithromycin resulted in a bimodal distribution. MIC values were centered at ≤0.15 µg/mL and for a smaller group at 0.25-0.5 µg/mL. Isolates with increased telithromycin MICs were those with resistance to quinupristin/dalfopristin or erythromycin A but less often to clindamycin. Telithromycin MICs were 1-4 µg/mL with 6 quinupristin/dalfopristin resistant isolates (1.9%). Forty-seven of 57 isolates with telithromycin MICs of 0.12-1 µg/mL were resistant to erythromycin, but susceptible to clindamycin.

Epidemiological information was not provided by the applicant for any of the other organisms associated with the INDICATIONS they are requesting.

MECHANISM(S) of RESISTANCE and (Vol. 1.3 p110)

The following information relating to mechanisms of resistance in certain groups of organisms indicates that there are certain resistance mechanisms that make an organism resistant to telithromycin (e.g. constitutive MLS_B resistance in *S. aureus*). The same mechanism in another organism (constitutive MLS_B resistance in *S. pneumoniae*) does not make the organism resistant to telithromycin. The various mechanisms of resistance and their influence on the clinical utility of telithromycin will need to be taken into account for labeling. It is recognized that there is a lack of information on mechanisms of resistance in a number of organisms that the applicant is requesting for inclusion in the label for telithromycin. This is due primarily to a general lack of knowledge about these organisms.

The extensive clinical application of macrolide antibiotics over the last several years has resulted in an increase worldwide of macrolide-resistant Gram-positive cocci, especially *S. pneumoniae*. It is estimated that 19 to 34% of *S. pneumoniae* in the United States are resistant to macrolides (14). At the same time, the resistance of *S. pneumoniae* to penicillin, frequently associated with resistance to macrolides has continuously grown (15). The ketolide antibiotics were developed to overcome this problem of macrolide resistance. The ketolide antibiotics, however, are chemical modifications of erythromycin A. While the chemical modification of the erythromycin molecule allows the ketolide to be active against certain macrolide-resistant organisms some of the same macrolide resistance mechanisms may allow an organism to be resistant to ketolides such as telithromycin.

Streptococcus pneumoniae and *Streptococcus pyogenes*

Other than spontaneous mutation causing resistance in *S. pneumoniae* and *S. pyogenes* to macrolides resistance to macrolides among these streptococci can be the result of at least five different mechanisms. These mechanisms are methylation of 23S rRNA (mono- or bi-methylation of a single adenosine residue at position A-2058 or A-2059 residues), efflux, mutation, hydrolysis by esterases and inactivation by 2' OH-phosphorylase or 2'OH-glycoside transferase (16). A sixth possible mechanism mutation in 23S rRNA or ribosomal proteins has recently been described (17). This form of resistance seems not to confer high level resistance to telithromycin (17).

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 (18).] 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 (19).

The resistance conferred by the erm genes prevents macrolides, lincosamides and streptogramins (MLS_B) from binding to the 50S ribosome subunit. There is full cross-resistance among all available macrolides, lincosamides, and group B streptogramins. MLS_B resistance is due to target site modification by a family of enzymes which mono- or di-methylate the N^6 amino group of adenine residue 2058 (*Escherichia coli* numbering system) in 23S rRNA, thus preventing access of the antibiotic to its binding site on the ribosome. The observed cross-resistance to the three structurally unrelated groups of antibiotics is explained by their known overlapping binding site in the 50S ribosomal subunit (20). The ketolide group of antibiotics, as described above, is structurally modified thus allowing them access to the binding sites on the 50S ribosomal subunit.

Resistance mediated by the *erm* genes can be of the inducible or constitutive type. The term "constitutive macrolide resistance" was originally applied to strains of Gram-positive bacteria that were resistant to erythromycin, clindamycin, and streptogramin B (21, 22). These strains had an erythromycin and clindamycin MIC >128 µg/mL. Strains considered "inducibly resistant" to macrolides generally had a lower erythromycin MIC (1-6 µg/mL) and apparent susceptibility to clindamycin. The presence of erythromycin functioned as an inducer, resulting in an increase in methylase production that caused resistance to both erythromycin and clindamycin. In staphylococci, MLS_B resistance can be constitutively expressed. More frequently, it can be induced in the presence of 14- and 15-, but not 16-membered-ring macrolides (21). In contrast, 16-membered-ring macrolides are also able to induce the MLS_B phenotype of resistance in streptococci (23). The inducible phenotype has been observed in *S. pyogenes* (24).

The resistance genes that have been identified to date in bacteria relevant to this application are listed in Table 36 (18).

Table 36. Resistance genes located in bacteria relevant to this application

Gene Activity	Genus or Genera of Organism
Methylases	
Erm A	*Staphylococcus, Streptococcus*
erm B	*Staphylococcus, Streptococcus*
erm C	*Staphylococcus, Streptococcus,*
erm F	*Haemophilus, Prevotella, Streptococcus,*
erm Q	*Streptococcus,*
erm Y	*Staphylococcus*
ATP-binding Transporters	
msr (A)	*Staphylococcus*
vga (A)	*Staphylococcus*
vga (B)	*Staphylococcus*
Hydrolyases	
vgb (A)	*Staphylococcus*
vgb (B)	*Staphylococcus*
Transferases	
Inu (A)	*Staphylococcus*
Inu (B)	

vat (A) *Staphylococcus*

vat (B) *Staphylococcus*

vat (C) *Staphylococcus*

vat (D) —

vat (E) —

Phosphorylases

mph (C) *Staphylococcus*

The applicant has provided data as to the activity of telithromycin against *S. pneumoniae* that are either resistant to erythromycin by an inducible mechanism or are constitutively resistant. This data is shown in Table 37. The data indicate that telithromycin is active against *S. pneumoniae* at levels which are therapeutically achievable whether or not the resistance to erythromycin A is constitutive or inducible.

Table 37. In vitro activity of telithromycin (µg/mL) against *Streptococcus pneumoniae* that are constitutively or inducibly resistant to erythromycin A (Vol. 1.242 p123)

Mechanism	No. of isolates	MIC Range	MIC_{50}	MIC_{90}
Inducible	32	0.001-0.08	0.005	0.02
Constitutive	40	0.005-0.6	0.04	0.3

The applicant has provided data to show that spontaneous mutation to telithromycin can occur by serial passage of two strains of erythromycin A resistant *S. pneumoniae* in telithromycin (Vol. 1.242 p181). With *S. pneumoniae* strain SJ5 after 7 passages the MIC increased from 0.01 µg/mL to 10 µg/ mL telithromycin. In the case of *S. pneumoniae* strain CR96 after 8 passages the MIC went from 0.01 to 20 µg/mL telithromycin. The clinical significance of this is uncertain but may suggest that after constant exposure to telithromycin *S. pneumoniae* can become resistant to telithromycin.

Against *S. pyogenes* that are resistant to both erythromycin and clindamycin, suggesting a constitutive resistance to erythromycin the MIC is elevated appreciably compared to *S. pyogenes* isolates that are resistant to erythromycin and susceptible to clindamycin (Vol.1.242 p104). This data is shown in Table 38. The applicant indicates that telithromycin is bacteriostatic against *S. pyogenes* that are constitutively resistant to erythromycin A (Vol. 1.242 p103).

Table 38. In vitro activity of telithromycin (µg/mL) against *Streptococcus pyogenes* resistant to erythromycin and/or clindamycin

Resistance	No. of Isolates	MIC Range	MIC_{50}	MIC_{90}
ery-R, clin-S	103	≤0.06-8	0.5	2
ery-R, clin-R	27	1->16	4	8

The applicant has provided data on *S. pyogenes* isolates (Vol. 1.242 p177) with the *erm* B gene. This data is shown in Table 39. As it can be seen *S. pyogenes* that carry the *erm* B gene have both an MIC_{50} and MIC_{90}, >32 µg/mL, which exceeds the therapeutic levels achievable with telithromycin dosing.

Table 39. In vitro activity of telithromycin (µg/mL) against strains of *Streptococcus pyogenes* that contain the *erm* B gene.

No. of Isolates	MIC Range	MIC_{50}	MIC_{90}
11	2->32	>32	>32

The applicant has provided data to show the activity of telithromycin against strains of *S. pyogenes* and *S. pneumoniae* that have the genes which mediate the efflux mechanism of resistance (*mef* A and *mef* E respectively) (Table 40). This data shows that strains of *S. pyogenes* carrying the *mef* A gene an elevated telithromycin MIC compared to those strains that do not carry the *mef* A gene (MIC_{90} range 0.015 – 0.06 µg/mL - Table 10). The data for the *S pneumoniae* isolates with the mef E gene show that these isolates have an elevated telithromycin MIC when compared to those strains that are susceptible to erythromycin (MIC_{90} 0.008 µg/mL – Table 22).

Table 40. In vitro activity of telithromycin (µg/mL) against strains of *Streptococcus pyogenes* and *Streptococcus pneumoniae* carrying the genes mediating resistance by the efflux mechanism

Organism	No. of Isolates	Gene Type	MIC Range	MIC_{50}	MIC_{90}
S. pyogenes	20	*mef* A	0.25-4	0.5	1
S. pneumoniae	30	*mef* E	0.03-0.1	0.12	0.5

Telithromycin has not been found to induce resistance to itself or other macrolides by activation of the erm genes (25, Vol. 1.242 p179-180).

Staphylococcus aureus

The applicant has indicated (Vol. 1.242 P177) that 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). Comparable results have been found with coagulase-negative staphylococci having *erm* A, *erm* B or *erm* C genes alone or in combination. Telithromycin has good activity against MLS_B inducible *S. aureus* (see Table 35).

In staphylococci active efflux is mainly encoded by *msr* A (26) and *msr* B (27) genes. The products of these two pumps, which belong to the ATP-binding transporter superfamily. These genes confer an inducible resistance to 14- and 15-membered macrolides, and B-type streptogramins :MS phenotype. The applicant cites a study that showed *S. aureus* and coagulase-negative staphylococci harboring the *mrs* B gene had decreased susceptibility to erythromycin and streptogramin B, but remained susceptible to telithromycin (MICs ranged from 0.05 to 2 µg/mL) (Vol. 1.242 p181).

Other Organisms

The applicant did not provide any information on mechanisms of resistance in other organisms that may influence the organism's susceptibility to telithromycin.

INTRACELLULAR CONCENTRATION (Vol. 1.242 p172)

Understanding the intracellular concentration that telithromycin can achieve is important because of the fact that the applicant is requesting that telithromycin be approved for the treatment of infections caused by intracellular pathogens (*C. pneumoniae*, and *L. pneumophilia*).

Uptake of telithromycin by polymorphonuclear neutrophils (PMN) was studied using labeled [^{3}H] telithromycin and a — technique. Telithromycin (extracellular concentration of 2.5 µg/mL) was gradually accumulated by PMNs with an intracellular/extracellular concentration ratio ranging from 27.0 +/- 8.1 (5 min) to 348 +/- 27.1 (160 min). In the PMN telithromycin was located primarily in the granule fraction (56+/- 10.9%). The uptake of telithromycin was temperature dependent and energy activation at 5 minutes was about 128+/- 9.4 kj/mol. Telithromycin was gradually released from the PMN from 17% at 5 min to 45% at 60 min. This data suggests that telithromycin may achieve concentrations in PMNs high enough to kill intracellular pathogens such as *C. pneumoniae,* — *and L. pneumophilia*

Macrophage

The uptake of telithromycin was studied in peritoneal macrophages. The uptake as rapid and the intracellular/extracellular ratio was 65 (extracellular concentration of 2 µg/mL) after 60 min.

TIME-KILL KINETICS (Vol. 1.242 p161-166)

Strain variation within groups of organisms seems to play a role in whether telithromycin is bactericidal or bacteriostatic. The general conclusions below were drawn from the data supplied by the applicant. Various experimental protocols were used in an attempt to determine if telithromycin was bacteriostatic or bactericidal.

Streptococcus pneumoniae

Using an initial inoculum size of 6 $\log_{10}$ CFU/mL and the criteria of a reduction in the initial inoculum size of $\geq$3 $\log_{10}$ CFU/mL) telithromycin at a concentration of 0.25 µg/mL was considered bactericidal against both erythromycin-resistant and –susceptible strains of *S. pneumoniae* after 24 hours. Using the same criteria it was considered bactericidal also against both penicillin-susceptible and –resistant *S. pneumoniae* after 4 hours. The bactericidal activity of telithromycin appears to be substantially slower if the *S. pneumoniae* carries the erm gene.

Staphylococcus aureus

Telithromycin is predominantly bacteriostatic against *S. aureus*.

Haemophilus influenzae

The applicant has indicated that they feel that telithromycin is slowly bactericidal against *H influenzae* that the bactericidal activity is strain-dependent and inoculum concentration dependent.

Moraxella catarrhalis
The applicant was not able to conclude that the activity of telithromycin against this organism is bactericidal.

Streptococcus pyogenes

The applicant has concluded that telithromycin is bacteriostatic against *S. pyogenes*.

POST-ANTIBIOTIC EFFECT (PAE) (Vol. 1.242 p166-172)

The applicant has submitted post-antibiotic effect data generated by a variety of experimental procedures. Because PAE results are influenced by the methodology used this Reviewer has chosen to look at the data from a method that is familiar. This method (Craig, WA, Antibiotics in Laboratory Medicine, Williams and Wilkins, 1996, p296-329) uses Mueller-Hinton broth an inoculum concentration of 10^6 to 10^7 CFU/mL with test organisms exposed to 4 to 5X the telithromycin MIC for the respective organism for 1-2 hours. The results of the study using this methodology (CDN/98/647/572, 7.E.1.111, 7:v017:p004) are shown in Table 41. The data in Table 41 shows that the PAE of telithromycin is organism dependent. This is generally representative of the other data that the applicant has submitted for PAE.

Table 41. Post-antibiotic effect (PAE) of telithromycin at 4X the MIC of various organisms

Organism	PAE (hours)
H. influenzae	5.2
M. catarrhalis	1.2 to 1.55
S. aureus meth-R	>2
S. aureus pen-S/pen-R	0.53 to 1.38
S. pyogenes ery-S	9.51
S. pyogenes ery-R	6.11
S. pneumoniae	4.31 to 9.10

The applicant has also provided data for the PAE of telithromycin in vivo (Vol. 1.242 p171-172). This data was generated using a neutropenic mouse thigh model. The extent of killing (bactericidal activity) at 2 and 4 hours was compared with the doses administered. Post antibiotic effect in vivo: the time for control organisms to grow one $\log_{10}$ from zero hour (C) was compared with the time for the treated organism to grow one $\log_{10}$ from the number of organisms present in the thigh when serum concentrations of free telithromycin fell below the MIC (T). The difference in time (T-C) is the duration of the PAE in vivo. The results of these experiments are seen in Table 42.
For low doses the PAE in vivo for *S. pneumoniae* is about one hour, but at higher doses the PAE increases. While the correlation of these results with results in humans cannot be made the data shows that increasing the dose increases the PAE.

Table 42. The in vivo post-antibiotic effect (PAE) of telithromycin against *S. pneumoniae.*

Dose (mg/kg)	Change in $\log_{10}$ CFU/thigh at		Time to grow one $\log_{10}$ CFU/thigh (h)		PAE (hours)
	2 h	4 h	2 h	4 h	
0.29	+0.18	+0.79	2.81	3.69	0.88
1.17	-0.10	+0.10	2.81	3.44	0.63
4.69	-1.64	-1.53	2.81	6.05	3.24
18.8	-2.56	-5.32	3.30	8.82	5.79

The applicant's conclusion from the in vivo PAE studies is that telithromycin produced in vivo concentration dependent killing and prolonged PAEs (V0l. 1.242 p171). This conclusion is consistent with the data provided.

POST-ANTIBIOTIC LEUKOCYTE EFFECT (PALE):

The applicant did not provide any data on the PALE of telithromycin.

SUB-MIC EFFECTS:

The applicant did not provide any information on the effects of sub-inhibitory effects of telithromycin on bacteria.

INTERACTION WITH OTHER DRUGS:

The applicant has not provided any data on the interaction (synergism, antagonism, etc.) of telithromycin with other antibacterial drugs. They have provided data on the interaction of telithromycin with the antifungals itraconazole (Vol. 6.1 p 261) and ketoconazole (Vol. 6.1 p260). In both cases the maximum plasma concentration and AUC of telithromycin were increased. However, the applicant noted that this did not necessitate a dosage adjustment.

SUSCEPTIBILITY TEST METHODS AND METHODS FOR THE DETECTION OF RESISTANCE:

Susceptibility Testing Methods:

Stability of telithromycin in various susceptibility test media at different storage temperatures (Vol. 1.242 p 82-83).

The data provided by the applicant shows that telithromycin remained active in all the media recommended for susceptibility testing of bacteria by the NCCLS for [redacted] hours when stored at [redacted]

Stability of telithromycin in solubilizing buffer (pH 8) (vol. 1/242 p83-84).

The data provided by the applicant showed that telithromycin remained stable for [redacted]

Influence of CO_2 on susceptibility test results (Vol. 1.242 p84-86).

The data provided by the applicant showed that incubation in an environment of 5-7% CO_2 increased the MIC values almost two fold for *H. influenzae*, *S. pneumoniae* and *S. pyogenes* whether the testing was done with broth or agar as recommended by the NCCLS. There was no CO_2 effect on *S. aureus* or *E. faecalis*.

Effect of inoculum size on MIC results (Vol. 1.242 p86-87).

The applicant provided data to show that as long as the inoculum concentration of 10^4 to 10^6 CFU/mL is used there was no shift in the MIC values for telithromycin. MIC value shifts were noticeable when the inoculum concentration was $\geq 10^7$ CFU/mL.

Effect of age of colonies used to prepare inoculum (vol. 1.242 p91).

The applicant has indicated that as long as the inoculum is made from colonies that are 16 hours old there is no major variation in the MIC values obtained. The use of an inoculum made from colonies that are 16 hours old is consistent with the recommendations of the NCCLS (4).

Effect of medium composition on MIC values (Vol. 1.242 p87- 89).

The applicant has provided susceptibility test results for selected organisms on a variety of media. These data have shown that media composition can have an effect on the MIC value obtained for telithromycin. For instance Isosensitest medium can give MIC values for *Enterococcus* sp. and *S. pyogenes* that are up to 3 $\log_2$ higher than Mueller-Hinton agar.

The applicant has indicated that susceptibility testing of *H. influenzae* on HTM agar as recommended by the NCCLS can be influenced by the manufacturer of the medium. They have indicated that HTM produced by [redacted] produced poor growth in comparison to HTM manufactured by [redacted] and [redacted]. They concluded that their own preparation of HTM gave them the most satisfactory growth.

Comparison of MIC determinations: agar medium versus broth medium (Vol. 1.242 p 98).

The applicant has only provided information (no actual data) on the results of the MIC values obtained for *S. aureus and Enterococcus* sp. when test in Mueller Hinton broth and agar as recommended by the NCCLS. They indicate that the correlation coefficient was 0.97 and the R-squared 94%. No information for other organisms was given.

Disc diffusion susceptibility test method.

The applicant notes that the concentration of the telithromycin in the disc used for disc diffusion testing is 15 µg/disc (Vol. 1.242 p235). No data is provided as to how this concentration was determined.

Quality control of susceptibility test methods.

The applicant has provided data from a ten-laboratory study for the establishment of susceptibility quality control values for broth dilution testing and discs diffusion testing (Vol. 1.242 p 242 and section 9.1). All laboratories according to the applicant used NCCLS methods. The quality control values are shown in Table 43. During clinical trials it was found that the QC values in Table 43 gave good correlation ($\geq$ 98%) except for *H. influenzae* ATCC 49247 were there was only 85% correlation. When analyzed this lower correlation was believed due to a particular lot of test medium. A lower correlation was also observed with the comparator drugs clarithromycin and azithromycin so it is not felt that the QC range needs to be modified at this time for telithromycin (7:v001:p 244).

Table 43. Quality control ranges for broth microdilution and disc diffusion (15 ug disc) susceptibility methods

Control Strain	MIC (ug/mL)	Zone diameter (mm)

S. aureus ATCC* 29213	0.06-0.25	NA
S. aureus ATCC 25923	NA**	24-30
S. pneumoniae ATCC 49619	0.008-0.03	27-33
H. influenzae ATCC 49247	1-4	17-23

*ATCC is a registered trademark of the American Type Culture Collection
**NA=not applicable

The applicant also provided data from a thirty-laboratory study that evaluated the reproducibility of the chosen quality control ranges (Vol. 1.242 p 244). The information provided by the applicant indicated that with the exception of the *H. influenzae* data with *H. influenzae* (ATCC 49247) that there was >95% agreement between the laboratories. The agreement for the *H. influenzae* was 84.8%.

A review of the data submitted by the applicant for *S. aureus* ATCC 29213, *S. aureus* ATCC 25923, ——— ., *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247 indicates that the quality control ranges proposed by the applicant are appropriate.

The applicant has not provided information on the quality control strains or ranges used to assure that the susceptibility values obtained from the testing of *C. pneumoniae*, *L. pneumophilia* and *M. pneumoniae* are reproducible.

Influence of serum on the MIC of telithromycin (Vol. 1.242 p93-94).

The applicant has provided data to show that the addition of up to 40% human serum does not have an effect on telithromycin MICs.

Conclusion

Because it is recognized in the literature and the applicant has demonstrated that medium composition, inoculum size, etc can influence the results of susceptibility testing only results obtained by methods recommended by the NCCLS will be used in analyzing susceptibility data for the purposes of this review. When there is no NCCLS method only the results of method(s) that have been verified and validated and have appropriate quality control methods will be considered for analysis.

IN VIVO

ANIMAL AND HUMAN STUDIES

PHARMACOKINETICS

Absorption (Vol. 1.2 p14): In fasting adults, peak plasma telithromycin concentrations of approximately 2 µg/mL are attained within a median of 1 hour after a

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 mean pharmacokinetics of telithromycin after a single once-daily 800-mg dose and multiple 800-mg doses for 7 days is shown in Table 44.

Table 44. Pharmacokinetics of telithromycin after one dose 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.

Distribution (Vol. 1.2 p15): Telithromycin is 60 to 70% protein bound. The majority of telithromycin is bound by human serum albumin. Plasma, bronchial mucosa, epithelial lining fluid, and tonsil telithromycin concentration after 800 mg once daily dosing for 5 days are shown in Table 45.

Table 45. Telithromycin concentrations in various tissues after 800 mg dosing for five days

Site	Hours Post Dose	Concentration (µg/mL) Tissue or Fluid	Plasma	Ratio
Bronchial mucosa	2			2.11
Epithelial lining fluid	2			4.8
	8			6.5
	24			14.3
Tonsils	3			3.38
	12			7.1
	24			13.1

* Units in µg/mg

The applicant provided data to show that telithromycin is concentrated by white blood cells and is eliminated more slowly from white blood cells than from plasma (Vol. 6.2 p2). The mean white blood cell concentrations of telithromycin peaked at 72.1 µg/mL and remained at 14.1 µg/mL 24 hours after 5 days of repeated dosing of 600 mg once daily. After 10 days of 600 mg once daily dosing, white blood cell concentrations remained at 9.9 µg/mL 48 hours after the last dose. The concentration of telithromycin in alveolar macrophages was shown to be 41 µg/mL after 24 hours following 5 days of dosing at 600 mg daily. The data is presented in Table 46.

Table 46. The mean concentrations of telithromycin in white blood and alveolar macrophage cells after 5 days of daily 600 or 800 mg dosing

Cell Type	Hours Post-Dose	Dose (mg)	Number of Patients	Concentration (ug/mL) Intracellular	Plasma	Ratio
White blood cells	2	600	5	64.6	0.775	87
	6	600	5	72.1	0.201	380
	12	600	5	39.4	0.049	1046
	24	600	5	14.1	0.014	1085
Alveolar macrophages	2	800	5	65	1.07	55
	8	800	6	100	0.605	180
	24	800	6	41	0.0703	536

Patient with hepatic insufficiency showed a 40% increase in the terminal elimination half-life of telithromycin (Vol. 6.1 p235). Patients with renal insufficiency showed an increase in the C_{max} and AUC (Vol. 6.1 p236). In both situations the applicant did not feel a dosage adjustment was necessary.

Metabolism (Vol. 1.2 p17-18): Telithromycin is primarily metabolized in the liver by cytochrome P450 3A4 (CYP3A4). Following oral administration, two thirds of the dose is eliminated as metabolites and one third remains unchanged. Approximately 76% are excreted in the feces and 17% in urine. Approximately one-third of telithromycin is excreted unchanged, 20% in feces and 12% in urine.
Four metabolites (Vol. 1.3 p 113) have been identified. None of the metabolites have more activity than the parent compound against *S. pneumoniae*, S. *aureus*, or —

Applicant's rationale for dose selection (Vol. 1.2 p41):

The applicant has stated that their rationale for the telithromycin dosage of 800 mg once daily is based on: the terminal half-life in man of about 10 hours, by its ability to concentrate in white blood cells and by data obtained from the thigh infection model in

neutropenic and non-neutropenic mice showing that the major pharmacokinetic parameter for telithromycin is the AUC/MIC ratio.

The applicant has provided data on the distribution on telithromycin in tonsilar tissue (Vol. 1.242 p318). Twenty-two patients were divided into 2 groups of 8 and one group of six. The patients received four doses of telithromycin before tonsillectomy and tissue distribution was recorded 3, 12 and 24 hours after the fourth dose. The concentration in the tissue was measured using a *Bacillus subtilis* (ATCC 6633) assay method. Samples of blood were also collected in order to measure plasma concentrations. The results are shown in Table 47.

Table 47. Tonsillar concentrations of telithromycin

No. of Patients	Sampling Time (h)	Plasma Levels (ug/mL)	Tonsil Levels (ug/mL)
8	3	1.22	3.95
8	12	0.23	0.88
6	24	0.58	0.72

The concentrations of telithromycin after 3, 12, and 24 hours are above the geometric mean (Table 35) of 0.03 µg/mL for *S. pyogenes* that are not erythromycin resistant. In the case of erythromycin-resistant *S. pyogenes* only the concentration after 3 hours is above the MIC_{90} of 2 µg/mL (Table 38). This suggests that telithromycin would not be efficacious in the treatment of erythromycin-resistant *S. pyogenes*.

PHARMACODYNAMICS:

The applicant has provided pharmacodynamic information on telithromycin using animal models (Vol. 1.3 p112). 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. The following is a description of the mouse model used to determine the parameter (28). Neutropenic mice were infected with a strain of *S. pneumoniae* (ATCC 10813) and two hours after infection the neutropenic mice had $10^{6.6}$ CFU/thigh. The mice were treated for 24 hours with 2.34-150mg/kg of HMR 3647 divided into doses administered every 3, 6, 12 and 24 hours. An E_{max} dose-response model was used to calculate the dose producing a net bacteriostatic effect over 24 hours of therapy. The static dose (mg/kg/24hr) was not altered by the dosing interval (15.7+/- 2.4, 13.8 +/- 2.1, 15.6 +/- 1.5, and 20.7 +/- 3.4 for 3, 6, 12 and 24hr dosing respectively). The murine PK of HMR 3647 was determined by HPLC at doses of 4.69 to 75 mg/kg. Over this range the murine half-life was increased from 90 to 205 minutes. The peak/dose and AUC/dose decreased from 1 to 0.2 and 2.3 to 1.1 respectively. Protein binding was 89% at serum level less than 1 mg/L, but decreased to 79 and 66% at 5 and 10 mg/L respectively. Various PK/PD parameters were calculated using both total and free drug. The 24hr AUC/MIC for free drug was the parameter that best correlated with efficacy (R^2 = 90% versus 70% for peak/MIC

and 46% for time above MIC. 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.

The 24-hour AUC/MIC is the sum of the AUCs for all doses administered every 24 hours divided by the MIC. The applicant has provided data (Vol. 1.263 p235) from animal experiments that a 24-hour AUC/MIC ratio for telithromycin of >1000 was necessary for the elimination of the infecting *S. pneumoniae* in the neutropenic mouse thigh model. The literature indicates that a 24-hr AUC/MIC ratio of $\geq$100 is associated with the least mortality in animals (29).

Recently it has been suggested that a ratio of $\geq$ 25-30 for the 24-h AUC/MIC and a time above MIC >40-50% of the dosing interval is a good therapeutic goal for the treatment of acute bacterial rhinosinusitis using macrolides (3). Based on this recommendation it appears that telithromycin in the dosage being proposed by the applicant would be appropriate for the treatment of acute maxillary sinusitis, an infectious disease process similar to rhinosinusitis.

ANIMAL DISEASE MODELS (Vol. 1.3 p110-112)

Infections of the lungs were induced in mice and rabbits with *S. pneumoniae* with different phenotypes of resistance to penicillin and erythromycin A and *H. influenzae* and in a guinea pig for *L. pneumophilia*.

In murine -pneumococcal pneumonia, two studies have been carried out. In a comparative study of telithromycin versus erythromycin, mice were challenged either with an erythromycin A susceptible or resistant stain (MIC for erythromycin A >128 µg/mL). At 100mg/kg of telithromycin, the survival rate was 75% after challenge with erythromycin A-resistant isolates, with a decrease of bacterial lung burden (>3 $\log_{10}$ CFU/lung) after one dose of telithromycin. After bacterial challenge with erythromycin A- susceptible (MIC 0.06 µg/mL) strain and 50 mg/kg of telithromycin 100% survival was recorded.

In a second study, well-defined *S. pneumoniae* isolates (*mef* E^+ and *erm* B^+ gene) were used for lung infections. In the case of the mef E^+ strain there was a reduction of 3 $\log_{10}$ CFU/g of lung burden after 50 mg/kg every 12 hours and > 6 $\log_{10}$ CFU/g for 100 mg/kg every 12 hours. When mice were challenged with *S. pneumoniae* stains carrying the erm B^+ gene, a drop in the bacterial lung burden of 6 $\log_{10}$ CFU/g after 100 mg/kg every 12 hours of telithromycin was recorded. In a rabbit model of pneumococcal pneumoniae telithromycin was shown to be active regardless of the mechanism of resistance of the *S. pneumoniae*

Dunkin-Hartley guinea pigs infected with *L. pneumophilia* by the intra-tracheal route and treated with 10 mg/lg of telithromycin once or twice daily survived their infections. When infected by the intraperitoneal route and treated with 30-mg/kg telithromycin there was an 89% survival rate. By the end of 192 hours *L. pneumophilia* could not be recovered from the lungs of the remaining guinea pigs.

PROVISIONAL SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA

Based on the in vitro susceptibility profiles of *S. pneumoniae*, *S. pyogenes*, *S. aureus*, *H. influenzae*, and *H. parainfluenzae*, the pharmacokinetics and pharmacodynamics of telithromycin provisional interpretive criteria were established by the applicant. These interpretive criteria were used to categorize isolates of these organisms from clinical studies as to their susceptibility to telithromycin after in-vitro susceptibility testing. The susceptibility category was then correlated with the clinical and microbiologic outcomes to determine if the provisional criteria were clinically useful. There are no standardized susceptibility test methods and thus no recognized in vitro susceptibility interpretive criteria for *C. pneumoniae*, *L. pneumophilia*, and *M. pneumoniae*.

The applicant (Vol. 1.3 p115-118) has provided scattergrams for the interpretive criteria chosen for *S. aureus*, [redacted], *S. pneumoniae*, streptococci other than *S. pneumoniae* and *H. influenzae*. The scattergram provided by the applicant for the [redacted]

The applicant has not in the *H. influenzae* scattergram included the susceptibility profiles for *H. parainfluenzae*. The applicant did not provide provisional interpretive criteria for *M. catarrhalis*.

The provisional interpretive criteria using a 15 µg disk are shown in Table 48.

Table 48. Provisional susceptibility interpretive criteria as proposed by the applicant (Vol. 1.3 p115-118).

Organism	MIC Interpretive Criteria (ug/mL)	15 µg Disk Disc Diffusion Interpretive Criteria (mm)	Interpretation
Streptococcus pneumoniae &	≤ 1	≥19	Susceptible
[redacted]	2	16 -18	Intermediate
[redacted]	≥ 4	≤ 15	Resistant
		[redacted]	
Haemophilus influenzae		[redacted]	Susceptible Intermediate Resistant

CORRELATION OF PROVISIONAL SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA WITH CLINICAL OUTCOME

CONTROLLED STUDIES

COMMUNITY ACQUIRED PNEUMONIA (CAP)

Data for the CAP indication come from three double-blind active-controlled studies (Studies 3006, 3009, and 3001) and one uncontrolled, open label study (3000).

Study 3006 – This targeted outpatients with CAP due to either common or atypical pathogens, with clarithromycin at 500 mg two times daily (bid) as the comparator.

Study 3001 – This study targeted subjects whose CAP was presumably due to common pathogens, with high dose amoxicillin (1000 mg three times daily [tid]) as the comparator.

Study 3009 – This study targeted outpatients with CAP due either to common or atypical pathogens, with trovafloxacin at 200 mg once daily as the comparator. Study 3009 was stopped prematurely after the FDA restricted the use of trovafloxacin to inpatient use for severe infections as a result of safety concerns. Recruitment of telithromycin subjects was continued as an open label study (performed in South Africa) in an attempt to have additional cases of penicillin G-resistant *S. pneumoniae* in the program.

Study 3009OL- This study was a continuation of study 3009. Study 3009OL was conducted in South Africa and included a higher percentage of black subjects (46.2%) and male subjects (64.2%) than had been in studies presented in the NDA (13.4% and 53.5% respectively).

Study 3000 – This was an uncontrolled open study for a more precise evaluation of the pharmacokinetic profile in subjects (a population pharmacokinetic approach), and to investigate the relationships between pharmacokinetic parameters and efficacy and safety outcomes.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS (AECB)

The data for the AECB indication come from two double blind, active-controlled studies (studies 3007 and 3003).

Study 3007 – This is the main study used to support the claim for AECB. Cefuroxime axetil at 500mg bid is the comparator.

Study 3003 – This study focused on the efficacy of telithromycin in subjects with chronic obstructive pulmonary disease (COPD). Amoxicillin/clavulanic acid at 500/125mg tid is the comparator.

ACUTE SINUSITIS (AS)

The data for AS comes from one double-blind active-controlled study (study 3005) and one double blind, uncontrolled study (3002).

Study 3005 – This is the main study to support the claim for AS. Amoxicillin/clavulanic acid at 500/125-mg tid is the comparator. The study involved a comparison of two doses of telithromycin: 800 mg once daily for 5 days, compared to 800 mg once daily for 10 days.

Study 3002 – Because of constraints in obtaining sinus puncture samples, no comparator control group was included in this study. The aim of the study was to obtain bacteriological documentation of AS infection. The study involved a comparison of two doses of telithromycin: 800 mg once daily for 5 days, compared to 800 mg once daily for 10 days.

TONSILLITIS/PHARYNGITIS (T/P)

The data for the T/P indication comes from two double blind, active-controlled studies (studies 3008 and 3004).

Study 3008 – This study used clarithromycin at 250 mg bid for 10 days as the comparator.

Study 3004 – This study used penicillin VK 500 mg for 10 days as the comparator. The dose used is in agreement with the American Heart Association recommendation for the treatment of T/P. The data from this study is supportive only, as agreed with the FDA.

Categorization of clinical outcome for all studies:

The investigator based on the evolution of clinical signs; symptoms and x-ray findings assessed the clinical outcome. A severity scale was established to allow for more consistent follow-up throughout the study (mild, moderate, and severe). In addition the following approach was taken as is recommended the FDA draft guidance For industry "Evaluating Clinical Studies of Antimicrobials, February 1997.

The test of cure (TOC) was established at 7-15 days after the end of the longest treatment.

All symptoms were recorded at all visits using a scale for non-continuous variables.

The definition of success, which is classically "cure + improved" when the endpoint is close to the end of treatment, was modified. The investigator was asked to distinguish between whether the subject had returned to their pre-infection state or had residual symptoms that represented a normal course of clearance. Residual symptoms requiring subsequent treatment with other antibiotics was considered a failure.

Discontinuation of subjects with a resistant causative pathogen isolated at pre-therapy/entry was not mandatory but left up to the discretion of the investigator.

Susceptibility of causative pathogens was based on inhibition zone values obtained by the disk diffusion method at the local laboratories during the study. In controlled studies, discontinuation could result from isolation of a pathogen either resistant to telithromycin or the comparator drug.

Treatment was also considered as a failure if subjects discontinued study medication due to an adverse event, and the investigator decided that the anti-infective treatment should be continued with a subsequent antibiotic.

Isolation of causative pathogens:

A sample for bacteriological diagnosis was to be taken before the treatment where possible in all studies.

Susceptibility testing:

Susceptibility to telithromycin was tested by disk diffusion (15 µg disk) at the investigator's laboratory for the primary cultures (for the tonsillitis study 3004, all the primary cultures were sent to a single laboratory). Subcultures of primary isolates were then sent to a central laboratory (US studies: Clinical Microbiology Institute, Inc., Wilsonville, OR; EU studies: GR Micro Ltd., London, UK) for identification and simultaneous testing of the disk zone inhibition and MIC broth dilution method. The applicant notes that in both laboratories the NCCLS methods were used for susceptibility testing. The applicant has provided data on the comparison of susceptibility test results between the two laboratories (Vol. 1.3 p119). The data presented by the applicant shows good agreement between the two laboratories.

If the subculture of an isolate was not viable or a different organism was grown at the central laboratory, the local laboratory was asked to send another subculture. If the difference persisted, or the isolate was again not viable, the attempt to recover the particular isolate was terminated.

Local microbiology data was used for the identification of the bacteria per protocol population (PPb) and the analysis of bacteriological outcome. These data are those used in Section 8.G, Integrated Summary of Efficacy and in Section 3.H.3.3, Clinical Studies of Application claim of the Application Summary.

Central laboratory data on concordant isolates were used to assess the correlation between clinical outcome and MIC, bacteriological outcome and MIC, disk zone inhibition and MIC, and to define penicillin-resistant and erythromycin-resistant pathogens and the bacteriological outcome in these subjects. These data are presented in Section 7.C1.5.1.1, 7:V001:p249 "Correlation between MIC values and clinical and bacteriological outcome in all studies".

Population analysis:

Analyses of efficacy are based on clinical and bacteriological outcome data assessed at post therapy/TOC (days 17 to 21) and late post therapy (days 31 to 36) in the individual

studies. Late post therapy was for follow up to determine if there was recurrence of the illness. These analyses were performed for four populations:

The modified intent-to-treat (mITT) population was defined as all randomized subjects, as treated, with a confirmed diagnosis of infection who received at least one dose of study medication. Clinical signs and symptoms and x-ray findings as defined in the protocols defined a confirmed diagnosis. This definition was intended to exclude subjects with a clear misdiagnosis, in whom study medication could have not therapeutic effect.

The per-protocol clinical population (PPc) was defined as all the mITT subjects except those with major protocol violations.

The per-protocol bacteriological population (PPb) was defined as all PPc subjects with isolation of a causative pathogen from an adequate culture (Gram stain criteria in CAP and AECB) at pre-therapy/entry.

The bacteriological MITT population (bmITT) was defined as all mITT subjects with a pathogen as pre-therapy/entry considered by the investigator to be responsible for infection. In AECB, an adequate Gram stain of the sputum sample was required, given the high level of colonization in this indication.

The data for all of the clinical indications that follow are from the analysis of the PPb groups.

COMMUNITY ACQUIRED PNEUMONIA (Vol. 1.242 p276-293, 9:v001 p360-368 & Aventis CD correspondence dated 10/18/00)

NOTE: The following data is after certain sites and investigators were disqualified by the FDA due to questionable study data. The data is from the "causative pathogens" tables. (Aventis CD correspondence 10/18/00).

Table 49 shows the bacteriological and clinical outcomes for CAP subjects who had *S. pneumoniae, H. influenzae, H.parainfluenzae, S. aureus, or M. catarrhalis* as the etiological agent and were treated with telithromycin (800 mg/daily for 7 days). There was no difference between the outcomes for the US and European studies. Therefore the results of the two studies were combined. The data in this table for *H. parainfluenzae, S. aureus*, and *M. catarrhalis* did not appear in the original NDA submission (1.242). It appeared in the "Safety Data Summary" information submitted in 9:v001p360-368). The data in Table 49 and the PK/PD characteristics of telithromycin when give as recommended in this application suggests that telithromycin would be efficacious in the treatment of CAP caused by *S. pneumoniae* (penicillin or erythromycin susceptible strains only) and *H. influenzae* (β-lactamase negative strains only). Because of the small numbers of *S. aureus, M. catarrhalis*, and *H. parainfluenzae* no conclusions can be made on the drugs efficacy in the treatment of CAP due to these organisms.

Table 49. Bacteriological and clinical outcome at test of cure for community acquired pneumoniae treated with telithromycin (all CAP studies combined) correlated

with MIC (Aventis CD correspondence of 10/18/00).

Base Line Pathogen	Telithromycin Base Line MIC (ug/mL)	Total No.	Bacteriological Outcome Number (%) Eradication	Persistence	Clinical Outcome Number (%) Cure	Failure
*Streptococcus pneumoniae**	0.004	1	1 (100)	0	1 (100)	0
	0.008	16	16(100)	0	16 (100)	0
	0.015	65	63 (97)	2(3)	63 (95)	2 (5)
	0.03	11	9 (82)	2 (18)	9 (82)	2 (18)
	0.06	2	2 (100)	0	2 (100)	0
	0.12	2	1 (100)	1 (50)	1 (100)	1 (50)
	1	1	1 (100)	0	1 (100)	0
TOTAL		98	93 (95)	5 (5)	93 (95)	5 (5)
*Haemophilus influenzae***	0.12	1	1 (100)	0	1 (100)	0
	0.25	1	1(100)	0	1 (100)	0
	1	15	12 (80)	3 (20)	11 (73)	4 (27)
	2	22***	18 (82)	3 (14)	19 (87)	3 (13)
	4	9	8 (89)	1 (11)	8 (89)	1 (11)
	8	1	1 (100)	0	1 (100)	0
TOTAL		49	41 (84)	7 (14)	41 (84)	8 (16)
Haemophilus parainfluenzae	1	1	1 (100)	0	1 (100)	0
	2	4	3 (75)	1 (25)	4 (100)	0
	4	6	5 (83)	1 (17)	5 (83)	1 (17)
	8	2	1 (50)	1 (50)	1 (50)	1 (50)
TOTAL		13	10 (77)	3 (23)	11 (85)	2 (15)
*Staphylococcus aureus****	0.06	1	1 (100)	0	1 (100)	0
	0.12	3	2 (67)	1 (33)	2 (67)	1 (33)
TOTAL		4	3 (75)	1 (25)	3 (75)	1 (25)
Moraxella catarrhalis	0.06	6	5 (83)	1 (17)	4 (67)	2 (33)
	0.12	6	6 (100)	0	6 (100)	0
TOTAL		12	11 (92)	1 (8)	10 (83)	2 (17)

* Three of the *S. pneumoniae* isolates carried the *erm* B gene one carried the mef E gene. All isolates had a telithromycin MIC of ≤0.12 µg/mL. See Table 50 for outcomes. Ten isolates were resistant to penicillin. All of the penicillin-resistant *S. pneumoniae* had telithromycin MICs of ≤1 µg/mL. There were 3 cases of bacteriological persistence and clinical failure for the penicillin-resistant *S. pneumoniae*. Seven isolates had

intermediate susceptibility to penicillin. All of these isolates had telithromycin MICs of ≤0.0.03 µg/mL. There were no incidences of bacteriological persistence or clinical failure for the penicillin-intermediate strains. Nine isolates were resistant to erythromycin. These isolates had telithromycin MICs of ≤1 µg/mL (Vol. 1.242 p281 & 283 and correspondence of 9/20/00 p8). There were three incidences of bacteriological persistence and clinical failure for the erythromycin-resistant strains.
**Nine isolates were β-lactamase producers. These isolates had telithromycin MICs of ≤4 µg/mL.
*** One recurrence with an isolate that had a telithromycin MIC of 2 µg/mL.
**** One isolate was methicillin resistant. It had a telithromycin MIC of 0.12 µg/ mL. It was associated with bacteriological persistence and clinical failure.

The outcomes of CAP associated with *S. pneumoniae* isolates found to contain either the erm B or mef E genes is shown in Table 50 (Vol. 1.242 p293). There is not enough data to make any conclusions in relation to either gene influencing the outcome of therapy with telithromycin.

Table 50. Clinical outcome of CAP associated with *Streptococcus pneumoniae* carrying either the *erm* B or *mef* E gene

Study #	Gene	Clinical Outcome	
		Cure	Failure
3000	erm B	0	1
3001	erm B	1	1
3006	mef E	1	0
3009	NONE		

Table 51 shows the bacteriological and clinical outcome data correlated with the zone sizes for *S. pneumoniae, H. influenzae, H. parainfluenzae, S. aureus* and *M. catarrhalis*. There was no difference in the zone size distribution between the North America and European data so the results were combined into one table.

Table 51. Bacteriological and clinical outcome at test of cure for community acquired pneumoniae treated with telithromycin (all CAP studies combined) correlated with disc diffusion zone size (Aventis CD correspondence 10/18/00).

Base Line Pathogen	Telithromycin Base Line Zone Diameter	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
Streptococcus pneumoniae	20	1	1 (100)	0	1 (100)	0
	24	1	0	1 (100)	0	1 (100)
	25	4	3 (75)	1 (25)	3 (75)	1 (25)
	26	4	4 (100)	0	4 (100)	0

	27	17	15 (88)	2 (12)	14 (82)	3 (18)
	28	17	16 (94)	1 (6)	16 (94)	1 (6)
	29	19	19 (100)	0	19 (100)	0
	30	14	14 (100)	0	14 (100)	0
	31	11	11 (100)	0	11 (100)	0
	32	8	8 (100)	0	8 (100)	0
	33	2	2 (100)	0	2 (100)	0
TOTAL		98	93 (95)	5 (5)	92 (94)	6 (6)
Haemophilus influenzae	13	1	1 (100)	0	1 (100)	0
	16	1	1(100)	0	1 (100)	0
	17	6	5 (83)	1 (17)	5 (83)	1 (17)
	18	7	4 (57)	3 (43)	5 (71)	2 (29)
	19	7	5 (71)	2 (29)	5 (71)	2 (29)
	20*	6	5 (83)	0	5 (83)	1 (17)
	21	6	6 (100)	0	6 (100)	0
	22	8	8 (100)	0	7 (88)	1 (12)
	23	2	1 (50)	1 (50)	1 (50)	1 (50)
	24	3	3 (100)	0	3 (100)	0
	26	2	2 (100)	0	2 (100)	0
TOTAL		49	41 (84)	7 (14)	41 (84)	8 (16)
Haemophilus parainfluenzae	12	1	1 (100)	0	1 (100)	0
	13	1	1 (100)	0	1 (100)	0
	14	3	2 (67)	1 (33)	2 (67)	1 (33)
	15	1	0	1 (100)	0	1 (100)
	16	2	2 (100)	0	2 (100)	0
	17	2	1 (50)	1 (50)	2 (100)	0
	19	1	1 (100)	0	1 (100)	0
	20	1	1 (100)	0	1 (100)	0
	22	1	1 (100)	0	1 (100)	0
TOTAL		13	10 (77)	3 (23)	11 (85)	2 (15)
S. aureus	22	1	0	1 (100)	0	1 (100)
	23	1	1 (100)	0	1 (100)	0
	25	2	2 (100)	0	2 (100)	0
TOTAL		4	3 (75)	1 (25)	3 (75)	1 (25)
Moraxella catarrhalis	26	1	1 (100)	0	1 (100)	0
	27	2	2 (100)	0	2 (100)	0
	29	2	2 (100)	0	2 (100)	0
	30	2	2 (100)	0	2 (100)	0
	31	1	1 (100)	0	1 (100)	0
	32	2	2 (100)	0	2 (100)	0
	33	2	1 (50)	1 (50)	1 (50)	1 (50)

TOTAL	12	11 (92)	1 (8)	11 (92)	1 (8)

* One recurrence

Streptococcus pneumoniae blood isolates associated with cases of community acquired pneumonia caused by *S. pneumoniae* (Aventis 7 Sep 2000 Table n08/b200054t). The applicant did not provide an update of this data in the Aventis CD ROM correspondence dated 10/18/00.

Table 52 gives the bacteriological and clinical outcome of patients who had *S. pneumoniae* isolated from their blood during an episode of community acquired pneumonia. Two of the isolates were resistant to erythromycin with one of these isolates being resistant to penicillin also. One patient was cured and one patient failed. The applicant was not clear as to which patient failed (7:v001p282).

Table 52. Bacteriological and clinical outcome for patients having community acquired pneumonia and *Streptococcus pneumoniae* isolated from blood cultures correlated with telithromycin MIC (Aventis 7 Sep 2000 Table n08/b200054t).

Telithromycin MIC (ug/mL)	Number of Isolates	Bacteriological Outcome Eradication (%)	Bacteriological Outcome Persistence (%)	Clinical Outcome Cure (%)	Clinical Outcome Failure (%)
0.008	4	4 (100)	0	4 (100)	0
0.015	21	19 (90)	2 (10)	19 (90)	2 (10)
0.03*	3	2 (67)	1 (33)	2 (67)	1(33)
0.06	2	2 (100)	0	2 (100)	0
0.12	1	0	1 (100)	0	1 (100)
TOTAL	31	27 (87)	4 13)	27 (87)	4(13)

* Two isolates harboring *erm* B genes

ACUTE EXACERBATION OF CHRONIC BRONCHITIS (AECB) (Vol. 1.242 p319-331 and Aventis CD correspondence 10/18/00)

NOTE: The following data is after certain sites and investigators were disqualified by the FDA due to questionable study data. The data is from the "causative pathogens" tables. (Aventis CD correspondence 10/18/00).

Table 53 shows the bacteriological and clinical outcome of patients treated with telithromycin for treatment of various organisms implicated in acute exacerbation of chronic bronchitis. The data shown is the combined data from studies 3003 and 3007.

It appears from this data that telithromycin can be used successfully to treat AECB caused by *S. pneumoniae* (penicillin or erythromycin susceptible strains only) and *H. influenzae* (β-lactamase negative strains only). However, in the case of *H. parainfluenzae* the efficacy of telithromycin is questionable based on the fact the MIC_{90} of 8 µg/mL (Table 27) approaches the plasma, other body fluid and tissue

concentrations of telithromycin. Too little data is available for *S. aureus* and *M. catarrhalis* to make any judgements on the efficacy of telithromycin in treating AECB associated with these organisms. It is felt that more clinical study data needs to be collected on these organism in cases of AECB before it can be included under the AECB indication. The applicant did not provide any bacteriological or clinical outcome data for AECB caused by *C. pneumoniae* or *M. pneumoniae*. Therefore these organisms from the microbiological perspective cannot be included under the AECB indication.

Table 53. Bacteriological and clinical outcome at test of cure for acute exacerbation of chronic bronchitis treated with telithromycin (studies 3003 and 3007 combined) correlated with MIC (Aventis CD correspondence 10/18/00)

Base Line Pathogen	Telithromycin Base Line MIC (ug/mL)	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
*Streptococcus pneumoniae**	0.008	4	4 (100)	0	4 (100)	0
	0.015	9	8 (89)	1 (11)	7 (78)	2 (22)
	0.12	1	1 (100)	0	1 (100)	0
TOTAL		14	13 (93)	1 (7)	12 (86)	2 (14)
*Haemophilus influenzae***	1	11	6 (55)	5 (45)	7 (63)	4 (37)
	2	11	7 (64)	4 (36)	8 (72)	3 (27)
	4	1	1 (100)	0	1 (100)	0
	8	1	0	1 (100)	0	1 (100)
TOTAL		24	14 (58)	10 (42)	16 (67)	8 (33)
Haemophilus parainfluenzae	1	1	1 (100)	0	1 (100)	0
	2***	4	4 (100)	0	4 (100)	0
TOTAL		5	4 (100)	0	5 (100)	0
Moraxella catarrhalis	0.06	3	3 (100)	0	3 (100)	0
	0.12	5	5 (100)	0	5 (100)	0
	0.25	1	1 (100)	0	1 (100)	0
TOTAL		9	9 (100)	0	9 (100)	0
Staphylococcus aureus	0.12	1	1 (100)	0	1 (100)	0
TOTAL		1	1 (100)	0	1 (100)	0

*Two isolates had intermediate resistance to penicillin. These isolates had telithromycin MICs of ≤0.16 µg/mL (Aventis correspondence 10/18/00). There were no incidences of bacteriological persistence or clinical failure for these strains.

** Seven isolates produced β-lactamase (Aventis correspondence 10/18/00). Six of these isolates had telithromycin MICs of ≤2 µg/ mL and one had a telithromycin MIC of 8 µg/mL. Four (57%) of the β-lactamase positive strains had bacteriological persistence and were considered clinical failures.
***One isolate was β-lactamase positive.

Table 54 gives the susceptibility test zone sizes as they correlate to bacteriological and clinical outcomes for AECB.

Table 54. Bacteriological and clinical outcome at test of cure for acute exacerbation of chronic bronchitis treated with telithromycin (studies 3003 and 3007 combined) correlated with disc diffusion zone size (Aventis CD correspondence 10/18/00)

Base Line Pathogen	Telithromycin Base Line Zone Diameter	Total No.	Bacteriological Outcome Number (%) Eradication	Persistence	Clinical Outcome Number (%) Cure	Failure
Streptococcus pneumoniae	26	2	2 (100)	0	2 (100)	0
	27	3	2 (67)	1 (33)	1 (33)	2 (67)
	28	2	2 (100)	0	2 (100)	0
	29	1	1 (100)	0	1 (100)	0
	30	4	4 (100)	0	4 (100)	0
	31	2	2 (100)	0	2 (100)	0
TOTAL		14	13 (93)	1 (7)	12 (86)	2 (14)
Haemophilus influenzae	15	1	1 (100)	0	1 (100)	0
	16	2	1 (50)	1 (50)	1 (50)	1 (50)
	17	1	1 (100)	0	1 (100)	0
	18	6	3 (50)	3 (50)	4 (67)	2 (33)
	19	4	2 (50)	2 (50)	3 (75)	1 (25)
	20	3	2 (67)	1 (33)	2 (67)	1 (33)
	21	5	2 (40)	3 (60)	2 (40)	3 (60)
	22	1	1 (100)	0	1 (100)	0
	23	1	1 (100)	0	1 (100)	0
TOTAL		24	14 (58)	10 (42)	16 (67)	8 (33)
Haemophilus parainfluenzae	14	1	1 (100)	0	1 (100)	0
	17	2	2 (100)	0	2 (100)	0
	21	1	1 (100)	0	1 (100)	0
	23	1	1 (100)	0	1 (100)	0
TOTAL		5	5 (100)	0	5 (100)	0
Moraxella						

catarrhalis	26	2	2 (100)	0	2 (100)	0
	27	3	3 (100)	0	3 (100)	0
	29	1	1 (100)	0	1 (100)	0
	30	2	2 (100)	0	2 (100)	0
	34	1	1 (100)	0	1 (100)	0
TOTAL		9	9 (100)	0	9 (100)	0
Staphylococcus aureus	24	1	1 (100)	0	1 (100)	0
TOTAL		1	1 (100)	0	1 (100)	0

ACUTE SINUSITIS (AS) (Vol. 1.242 p293-306)

Table 55 gives the results of the 5 and 10-day courses of telithromycin for the treatment of maxillary sinusitis. This data show a bacteriological eradication and clinical cure rate equivalency for the 5 and 10 day courses of treatment.

Table 55. The bacteriological and clinical outcomes of the 5 and 10 day courses of telithromycin treatment of acute maxillary sinusitis

Study #	5 day Treatment		10 Day Treatment	
	Bacteriological Outcome %	Clinical Outcome %	Bacteriological Outcome %	Clinical Outcome %
3002	92.9	91.1	89.9	91
3005	85.7	75.8	85.7	74.1

Table 56 and 57 give the results of studies 3002 and 3005 for AMS. For the *S. pneumoniae* and *H. influenzae* the data was combined from studies 3002 and 3005. The data from both studies were combined because there were no major differences in the MIC distribution of the organisms in both studies. *Moraxella catarrhalis* and *S. aureus* data come only from study 3002. Based on this data it appears that telithromycin would be efficacious in the treatment of AS due to *S. pneumoniae* (penicillin and erythromycin susceptible and resistant strains), *H. influenzae, M catarrhalis,* and *S. aureus*. This outcome is consistent with the hypothesis made from the in vitro spectrum of susceptibility to telithromycin and its phamacokinetics and pharmacodynamics.

The applicant provided no data on *H. parainfluenzae*. This is consistent with the fact that this organism is not a common isolate from cases AS (3). It cannot be included as an organism under the acute sinusitis indication.

Table 56. Bacteriological and clinical outcome at test of cure for acute maxillary sinusitis treated with telithromycin correlated with organism MIC

Base Line Pathogen	Telithromycin Base Line MIC (ug/mL)	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure

*Streptococcus pneumoniae**	0.008	4	4 (100)	0	4 (100)	0
	0.015	34	31 (91)	3 (9)	31 (91)	3 (9)
	0.03	8	7 (88)	1 (12)	7 (88)	1 (12)
	0.06	3	3 (100)	0	3 (100)	0
	0.25	1	1 (100)	0	1 (100)	0
	1	1	1 (100)	0	1 (100)	0
TOTAL		51	47 (92)	4 (8)	47 (92)	4 (8)
*Haemophilus influenzae***	1	15	15 (100)	0	15 (100)	0
	2	11	10 (91)	1 (9)	10 (91)	1 (9)
	8	1	1 (100)	0	1 (100)	0
TOTAL		27	26 (96)	1 (4)	26 (96)	1 (4)
Moraxella catarrhalis	0.06	3	2 (67)	1 (33)	2 (67)	1 (33)
	0.12	7	6 (86)	1 (14)	6 (86)	1 (14)
TOTAL		10	8 (80)	2 (20)	8 (80)	2 (20)
Staphylococcus aureus	0.06	5	5 (100)	0	5 (100)	0
	0.12	5	5 (100)	0	5 (100)	0
TOTAL		10	10 (100)	0	10 (100)	0

*Four of the isolates were resistant to penicillin and seven had intermediate resistance to penicillin. All of these isolates had telithromycin MICs of ≤0.06 µg/mL. Nine of the isolates were resistant to erythromycin. These isolates had telithromycin MICs of ≤1 µg/mL.

** Four isolates were β-lactamase producers. These isolates had telithromycin MICs of ≤2 µg/mL.

Table 57 gives the in vitro susceptibility of the *S. pneumoniae* to penicillin and erythromycin as it relates to bacteriological and clinical cure. The data provided by the applicant suggests that the susceptibility of *S. pneumoniae* to either penicillin or erythromycin does not influence the ability of telithromycin to treat AMS infections caused by these organisms.

Table 57. Bacteriological and clinical outcome at test of cure for acute maxillary sinusitis treated with telithromycin correlated with penicillin or erythromycin susceptibility *of S. pneumoniae*

Base Line Pathogen	Telithromycin Base Line MIC (ug/mL)	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
Streptococcus						

pneumoniae						
pen -I	0.008	1	1 (100)	0	1 (100)	0
	0.015	4	4 (100)	0	4 (100)	0
	0.03	1	1 (100)	0	1 (100)	0
	0.06	1	1 (100)	0	1 (100)	0
TOTAL		7	7 (100)	0	7 (100)	0
pen-R	0.008	1	1 (100)	0	1 (100)	0
	0.03	2	2 (100)	0	2 (100)	0
	0.06	1	1 (100)	0	1 (100)	0
TOTAL		4	4 (100)	0	4 (100)	0
ery-R						
	0.008	1	1 (100)	0	1 (100)	0
	0.015	1	1 (100)	0	1 (100)	0
	0.03	2	2 (100)	0	2 (100)	0
	0.06	3	3 (100)	0	3 (100)	0
	0.25	1	0	1 (100)	0	1 (100)
	1	1	1 (100)	0	1 (100)	0
TOTAL		9	8	1	8	1
GRAND TOTAL		21	20 (95)	1 (5)	20 (90)	1 (5)

Table 58 gives the susceptibility test zone size data for the organisms correlated with acute maxillary sinusitis. The data *from studies 3002 and 3005 were combined for S. pneumoniae and H. influenzae* because there was no major difference in the zone size distribution. The *M. catarrhalis* and *S. aureus* data came only from study 3002.

Table 58.Bacteriological and clinical outcome at test of cure for acute maxillary sinusitis treated with telithromycin correlated with disc diffusion zone size.

Base Line Pathogen	Telithromycin Base Line Zone Diameter	Total No.	Bacteriological Outcome Number (%) Eradication	Persistence	Clinical Outcome Number (%) Cure	Failure
Streptococcus pneumoniae	19	1	1 (100)	0	1 (100)	0
	23	2	1 (50)	1	1 (50)	1
	24	2	1 (100)	1	1 (100)	1
	25	3	3 (100)	0	3 (100)	0
	26	10	9 (90)	1	9 (90)	1
	27	4	4 (100)	0	4 (100)	0
	28	10	10 (100)	0	10 (100)	0
	29	4	3 (75)	1	3 (75)	1
	30	3	3 (100)	0	3 (100)	0
	31	9	8 (89)	1	8 (89)	1
	32	1	1 (100)	0	1 (100)	0

	34	1	1 (100)	0	1 (100)	0
	44	1	1 (100)	0	1 (100)	0
TOTAL		51	46 (90)	5 (10)	46 (90)	5 (10)
Haemophilus influenzae	16	3	3 (100)	0	3 (100)	0
	17	1	1 (100)	0	1 (100)	0
	19	4	3 (75)	1 (25)	3 (75)	1 (25)
	20	4	3 (75)	1 (25)	3 (75)	1 (25)
	21	5	5 (100)	0	5 (100)	0
	22	6	6 (100)	0	6 (100)	0
	23	1	1 (100)	0	1 (100)	0
	24	1	1 (100)	0	1 (100)	0
	25	1	1 (100)	0	1 (100)	0
	26	1	1 (100)	0	1 (100)	0
TOTAL		27	25 (93)	2 (7)	25 (93)	2 (7)
Moraxella catarrhalis	25	1	0	1 (100)	0	1 (100)
	29	4	4 (100)	0	4 (100)	0
	30	4	3 (75)	1 (25)	3 (75)	1
	31	1	1 (100)	0	1 (100)	0
TOTAL		10	8 (80)	2 (20)	8 (80)	2 (20)
Staphylococcus aureus	22	1	1 (100)	0	1 (100)	0
	25	3	3 (100)	0	3 (100)	0
	26	2	2 (100)	0	2 (100)	0
	27	3	3 (100)	0	3 (100)	0
	31	1	1 (100)	0	1 (100)	0
TOTAL		10	10 (100)	0	10 (100)	0

The applicant has provided (Vol. 1.242 p30 Table 215) information on the organisms that were correlated with the acute maxillary sinusitis for which treatment with telithromycin was not successful. Six of the sixteen organisms for which the applicant is not seeking inclusion with the indication were associated with treatment failure. The other organisms are organisms that the applicant is asking for under the indication. All of these but one *H. influenzae* had in vitro MICs to telithromycin of $\leq$ 1 µg/mL. Four of these eight organisms were, however, resistant to erythromycin and/or clindamycin. While the clinical significance of these is not clear it could suggest that even though in vitro susceptibility testing indicates susceptibility to telithromycin erythromycin or clindamycin may provide in vivo resistance to telithromycin.

PHARYNGITIS/TONSILLITIS

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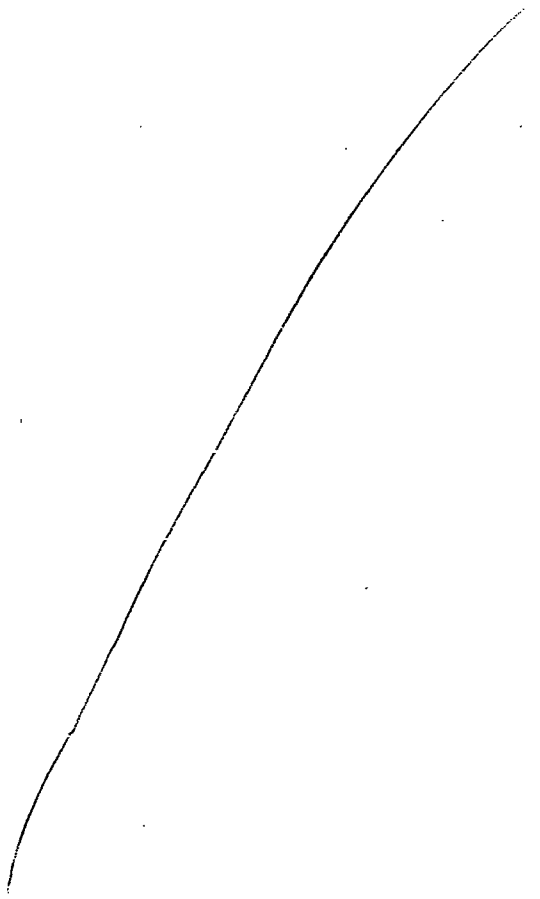

SUSCEPTIBILITY TEST RESULTS FOR ALL INDICATIONS CORRELATED WITH BACTERIOLOGICAL AND CLINICAL OUTCOME (Data is for all isolates not single causative isolates The data set analyzed was the PPb data set).

The following tables combine all of the bacteriological and clinical outcome results from all of the studies for each organism correlated with either the MIC or disc diffusion zone size. This data when compared to the susceptible profiles of the same organisms seen in each of the clinical studies does not reveal any major difference in the susceptibility profiles of the organisms. The data in the following tables will be used along with the pharmacokinetic and pharmacodynamic profiles of telithromycin and the in vitro susceptibility profiles of the individual organisms to set the MIC and disk diffusion zone size interpretive criteria for the organisms.

Streptococcus pneumoniae (vol. 1.242 p249-250 & 253, 9:vol 001 p428 & Aventis CD correspondence data from "causative pathogens" tables 10/18/00).

Table 63 shows the bacteriological and clinical outcome results for *S. pneumoniae* from all studies correlated with the susceptibility test MIC results. The applicant provided a

break out of the bacteriological and clinical outcome results for erythromycin-resistant *S. pneumoniae*. There were a total of 3 bacteriological and clinical failures for this group of organisms (Table not shown).

Table 63. Bacteriological and clinical outcome for *Streptococcus pneumoniae* from all studies correlated with MIC (Aventis CD correspondence 10/18/00)

Base Line Pathogen	Telithromycin Base Line MIC	Total No.	Bacteriological Outcome Number (%) Eradication	Persistence	Clinical Outcome Number (%) Cure	Failure
*S. pneumoniae**	0.004	1	1 (100)	0	1 (100)	0
	0.008	24	24 (100)	0	24 (100)	0
	0.015	108	102 (94)	6 (5)	100 (93)	8 (7)
	0.03	19	16 (84)	3 (16)	16 (84)	3 (16)
	0.06	5	5 (100)	0	5 (100)	0
	0.12	3	2 (67)	1 (33)	2 (67)	1 (33)
	0.25	1	0	1 (100)	0	1 (100)
	1	2	2 (100)	0	2 (100)	0
TOTAL		163	152 (93)	11 (7)	150 (92)	13 (8)

*Fourteen isolates were resistant to penicillin, 16 had intermediate susceptibility to penicillin. All of these strains had telithromycin MICs of ≤1 µg/mL. For the penicillin resistant strains there were 3 incidences of bacteriological persistence and clinical failure. For the penicillin-intermediate strains there were no incidences of bacteriological persistence or clinical failure. Eighteen were resistant to erythromycin. All of these strains had telithromycin MICs of ≤1 µg/mL. There were four incidences of bacteriological persistence and clinical failure for these strains.

Table 64 shows the bacteriological and clinical outcome results for *S. pneumoniae* from all studies correlated with the susceptibility test zone size results (7:v001 p249 plus data from 9/7/00 correspondence Tab 2 and Aventis CD correspondence 10/18/00).

Table 64. Bacteriological and clinical outcome for *Streptococcus pneumoniae* from all studies correlated with disc diffusion zone size (Aventis CD correspondence).

Base Line Pathogen	Telithromycin Base Line Zone Diameter	Total No.	Bacteriological Outcome Number (%) Eradication	Persistence	Clinical Outcome Number (%) Cure	Failure
S. pneumoniae	19	1	1 (100)	0	1 (100)	0
	20	1	1 (100)	0	1 (100)	0
	23	2	1 (50)	1 (50)	1 (50)	1 (50)
	24	3	1 (33)	2 (67)	1 (33)	2 (67)
	25	7	6 (86)	1 (14)	6 (86)	1 (14)
	26	16	15 (94)	1 (6)	15 (94)	1 (6)

	27	24	21 (88)	3 (12)	19 (79)	5 (21)
	28	29	28 (97)	1 (3)	28 (97)	1 (3)
	29	24	23 (96)	1 (4)	23 (96)	1 (4)
	30	21	21 (100)	0	21 (100)	0
	31	22	21 (95)	1 (5)	21 (95)	1 (5)
	32	9	9 (100)	0	9 (100)	0
	33	2	2 (100)	0	2 (100)	0
	34	1	1 (100)	0	1 (100)	0
	44	1	1 (100)	0	1 (100)	0
TOTAL		163	152 (93)	11 (7)	150 (92)	13 (8)

Haemophilus influenzae

Table 65 gives the correlation of the MIC for *H. influenzae* from all studies with the bacteriological and clinical outcomes (9/7/00 correspondence from Aventis & Aventis CD correspondence "causative pathogen" tables 10/18/00).

Table 65. Bacteriological and clinical outcome for *Haemophilus influenzae* from all studies correlated with MIC (Aventis CD correspondence 10/18/00)

Base Line	Telithromycin	Total	Bacteriological Outcome		Clinical Outcome	
Pathogen	Base Line MIC	No.	Number (%) Eradication	Persistence	Number (%) Cure	Failure
*H. Influenzae**	0.012	1	1 (100)	0	1 (100)	0
	0.25	1	1 (100)	0	1 (100)	0
	1	41	32 (78)	9 (22)	32 (78)	9 (22)
	2**	44	35 (80)	8 (19)	37 (84)	7 (16)
	4	10	9 (90)	1 (10)	9 (90)	1 (10)
	8	3	2 (67)	1 (33)	2 (67)	1 (33)
TOTAL		100	80 (80)	19 (19)	82 (82)	18 (18)

Twenty isolates were β-lactamase positive. Seventeen of these isolates had telithromycin MICs of ≤2 µg/mL, one isolate had a an MIC of 1 µg/mL and two isolates had telithromycin MICs of 8 µg/mL. One of the isolates with a telithromycin MIC of 2 µg/mL had bacteriological persistence and was considered a clinical failure. Another isolate with a MIC of 2 µg/mL associated with recurrence was considered a clinical failure, and one isolate with a MIC of 8 had bacteriological persistence and was considered a clinical failure.
** One recurrence.

Table 66 correlates the disc diffusion zone size with bacteriological and clinical outcome (7:v001 p251, 9/7/00 correspondence Tab 2 & Aventis CD correspondence 10/18/00).

Table 66. Bacteriological and clinical outcome for *Haemophilus influenzae* from all studies correlated with disc diffusion zone size (Aventis CD correspondence 10/18/00).

Base Line Pathogen	Telithromycin Base Line Zone Diameter	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
H. influenzae	13	1	1 (100)	0	1 (100)	0
	15	1	1 (100)	0	1 (100)	0
	16	6	5 (83)	1 (17)	5 (83)	1 (17)
	17	8	7 (88)	1 (12)	7 (88)	1 (12)
	18	13	7 (54)	6 (46)	9 (69)	4 (21)
	19	15	10 (67)	5 (33)	1 (67)	4 (33)
	20*	13	10 (77)	2 (23)	11 (85)	2 (15)
	21	16	13 (81)	3 (19)	13 (81)	3 (19)
	22	15	15 (100)	0	15 (100)	0
	23	4	3 (75)	1 (25)	3 (75)	1 (25)
	24	4	4 (100)	0	4 (100)	0
	25	1	1 (100)	0	1 (100)	0
	26	3	3 (100)	0	3 (100)	0
TOTAL		100	80 (80)	20 (20)	83 (83)	17 (17)

*One recurrence.

Moraxella catarrhalis (vol. 1.242 p252 & 258 & 9 vol. 001p433 & Aventis CD correspondence "causative pathogens" tables 10/18/00)

Table 67 shows the bacteriological and clinical outcomes for *M. catarrhalis* from all studies correlated with the MIC for the *M. catarrhalis* isolates.

Table 67. Bacteriological and clinical outcome for *Moraxella catarrhalis* from all studies correlated with MIC (Aventis CD correspondence 10/18/00).

Base Line Pathogen	Telithromycin Base Line MIC (ug/mL)	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
M. catarrhalis	0.006	12	10 (83)	2 (17)	10 (83)	2 (17)
	0.12	18	17 (94)	1 (6)	17 (94)	1 (6)
	0.25	1	1 (100)	0	1 (100)	0
TOTAL		31	28 (90)	3 (10)	27 (87)	4 (13)

Table 68 shows the correlation of disc diffusion zone size with bacteriological and clinical outcome (7:v001 p. 258 plus 9/7/00 Aventis correspondence Tab 2).

Table 68. Bacteriological and clinical outcome for *Moraxella catarrhalis* from all studies correlated with disc diffusion zone size (Aventis CD correspondence 10/18/00).

Base Line Pathogen	Telithromycin Base Line Zone Diameter (mm)	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
M. catarrhalis	25	1	0	1 (100)	0	1 (100)
	26	3	3 (100)	0	3 (100)	0
	27	5	5 (100)	0	5 (100)	0
	29	7	7 (100)	0	7 (100)	0
	30	8	7 (88)	1 (14)	6 (75)	2 (25)
	31	2	2 (100)	0	2 (100)	0
	32	2	2 (100)	0	2 (100)	0
	33	2	1 (50)	1 (50)	1 (50)	1 (50)
	34	1	1 (100)	0	1 (100)	0
TOTAL		31	28 (90)	3 (10)	27 (87)	4 (13)

Haemophilus parainfluenzae (vol. 1.242 p251 & 256 & 9 vol.001 p431 and Aventis CD correspondence "causative pathogens" table 10/18/00)

Table 69 shows the bacteriological and clinical outcome for *H. parainfluenzae* from all studies correlated with MIC for the *H. parainfluenzae* isolates.

Table 69. Bacteriological and clinical outcome for *Haemophilus parainfluenzae* from all studies correlated with MIC (Aventis CD correspondence 10/18/00)

Base Line Pathogen	Telithromycin Base Line MIC (ug/mL)	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
*H. parainfluenzae**	1	2	2 (100)	0	2 (100)	0
	2	8	7 (88)	1 (12)	8 (100)	0
	4	6	5 (83)	1 (17)	5 (83)	1 (17)
	8	2	1 (50)	1 (50)	1 (50)	1 (50)
TOTAL		18	15 (83)	3 (17)	16 (83)	2 (17)

*One isolate was a β-lactamase producer with a telithromycin MIC of 2 μg/mL.

Table 70 shows the bacteriological and clinical outcome for *H. parainfluenzae* from all studies correlated with the disc diffusion zone size for tall *H. parainfluenzae* isolates (7: v001 p258 plus 9/7/00 Aventis correspondence Tab 2 and Aventis CD correspondence 10/18/00).

Table 70. Bacteriological and clinical outcome for *Haemophilus parainfluenzae* from all studies correlated with disc diffusion zone size (Aventis CD correspondence 10/18/00).

Base Line Pathogen	Telithromycin Base Line Zone Size (mm)	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
H. parainfluenzae	12	1	1 (100)	0	1 (100)	0
	13	1	1 (100)	0	1 (100)	0
	14	4	27(75)	1 (25)	3 (75)	1 (25)
	15	1	0	1(100)	0	1(100)
	16	2	2 (100)	0	2 (100)	0
	17	3	2 (67)	1 (33)	2 (67)	1 (33)
	18	1	1 (100)	0	1 (100)	0
	19	1	1 (100)	0	1 (100)	0
	20	1	1 (100)	0	1 (100)	0
	21	1	1 (100)	0	1 (100)	0
	22	1	1 (100)	0	1 (100)	0
	23	1	1 (100)	0	1 (100)	0
TOTAL		18	15 (83)	3 (17)	16 (88)	2 (12)

Staphylococcus aureus (vol.1.242 p252 & 257 and Aventis CD correspondence "causative pathogens" table10/18/00)

Table 71 shows the bacteriological and clinical outcome for *S. aureus* from all studies correlated with the MIC of the *S. aureus* isolates.

Table 71. Bacteriological and clinical outcome for *Staphylococcus aureus* from all studies correlated with MIC (Aventis CD correspondence 10/18/00)

Base Line Pathogen	Telithromycin Base Line MIC (ug/mL)	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
*S. aureus**	0.06	6	6 (100)	0	6 (100)	0
	0.12	9	8 (89)	1 (11)	8 (89)	1 (11)
TOTAL		15	14 (93)	1(7)	14 (93)	1 (7)

* Two strains were methicillin resistant. Both strains had a telithromycin MICs of 0.12 µg/mL. There was one incident of bacteriological persistence and clinical failure with these strains.

Table 72 shows the bacteriological and clinical outcome for *S. aureus* from all studies correlated with the disc diffusion zone size for the *S. aureus* isolates (7:vol.001 p257 plus 9/7/00 Aventis CD correspondence 10/18/00).

Table 72. Bacteriological and clinical outcome for *Staphylococcus aureus* from all studies correlated with zone size (Aventis CD correspondence 10/18/00).

Base Line Pathogen	Telithromycin Base Line zone size (mm)	Total No.	Bacteriological Outcome Number (%)		Clinical Outcome Number (%)	
			Eradication	Persistence	Cure	Failure
*S. aureus**	22	2	1 (50)	1 (50)	1 (50)	1 (50)
	23	1	1 (100)	0	1 (100)	0
	24	1	1 (100)	0	1 (100)	0
	25	4	4 (100)	0	4 (100)	0
	26	3	3 (100)	0	3 (100)	0
	27	3	3 (100)	0	3 (100)	0
	31	1	1 (100)	0	1 (100)	0
TOTAL		15	14 (93)	1(7)	14 (93)	1(7)

*Two strains were methicillin resistance. One strain had a telithromycin zone size of 22mm and the other a zone size of 26mm. There was one incident of bacteriological persistence and clinical failure with these strains.

Streptococcus pyogenes (Vol. 1.242 p250 & 254)
Table 73 shows the bacteriological and clinical outcome for *S. pyogenes* from all studies correlated with the MIC of the *S. pyogenes* isolates.

Table 73. Bacteriological and clinical outcome for *Streptococcus pyogenes* from all studies correlated with MIC (9:Vol001p432).

Base Line Pathogen	Telithromycin Base Line MIC (ug/mL)	Total No.	Bacteriological Outcome Number (%)			Clinical Outcome Number (%)	
			Eradication	Persistence	Recurrence	Cure	Failure
S. pyogenes	0.008	1	1	0	0	1	0
	0.015	107	94 (89)	4 (4)	9 (7)	100 (93)	7 (7)
	0.03	118	110 (94)	3 (2)	5 (4)	110 (94)	7 (6)
	0.06	15	13 (87)	2 (13)	0	13 (87)	2 (13)
	0.5	5	0	5 (100)	0	5 (100)	0
	1	1	0	1 (100)	0	1 (100)	0
	Not Done	2	2 (100)	0	0	2 (100)	0
TOTAL		249	220 (88)	15 (6)	14 (6)	232 (93)	17 (7)

Table 74 shows the bacteriological and clinical outcomes for *S. pyogenes* from all studies correlated with the disc diffusion zone size for the *S. pyogenes* isolates.

Table 74. Bacteriological and clinical outcome for *Streptococcus pyogenes* pharyngitis from all studies correlated with zone size

Base Line Pathogen	Telithromycin Base Line Zone Diameter (mm)	Total No.	Bacteriological Outcome Number (%)			Clinical Outcome Number (%)	
			Eradication	Persistence	Recurrence	Cure	Failure
S. pyogenes	19	4	2 (50)	2 (50)	0	4 (100)	0
	20	7	4 (57)	3 (43)	0	7 (100)	0
	21	11	9 (82)	1 (9)	1 (9)	11 (100)	0
	22	21	17 (81)	0	4 (19)	20 (95)	1 (5)
	23	32	24 (75)	5 (16)	3 (9)	26 (81)	6 (19)
	24	40	37 (93)	1 (3)	2 (4)	37 (93)	3 (7)
	25	43	42 (98)	0	1 (2)	41 (95)	2 (5)
	26	29	27 (93)	0	2 (7)	28 (96)	1 (4)
	27	27	25 (93)	2 (7)	0	25 (93)	2 (7)
	28	18	18 (100)	0	0	18 (100)	0
	29	7	7 (100)	0	0	7 (100)	0
	30	6	4 (66)	1 (17)	1 (17)	4 (66)	2 (34)
	31	1	1 (100)	0	0	1 (100)	0
	32	1	1 (100)	0	0	1 (100)	0
TOTAL		247	218 (88)	15 (6)	14 (6)	230 (93)	17 (7)

SUMMARY OF NUMBER OF RESISTANT ORGANISMS FROM CLINICAL STUDIES TREATED WITH TELITHROMYCIN.

The following data is a summarization of the information in the Aventis correspondence dated 10/18/00 (data is from "causative pathogens" tables).

Table 75 summarizes the number of resistant organisms treated with telithromycin in each of the studies.

Table 75. Summary of numbers of resistant organisms from all clinical studies (Aventis CD correspondence of 10/18/00)

Study	Organism	Resistance (number)
Community Acquired Pneumonia (CAP)	*S. pneumoniae*	Penicillin resistant (10)
		Penicillin intermediate (7)
		Erythromycin resistant (9)
Acute Maxillary Sinusitis		Penicillin resistant (4)
		Penicillin intermediate (7)

		Erythromycin resistant (9)
Acute Exacerbation of Chronic Bronchitis		Penicillin intermediate (2)
		Erythromycin resistant (none)
TOTAL		Penicillin resistant (14) Penicillin intermediate (16) Erythromycin resistant (18)
CAP	*H. influenzae*	Beta-lactamase positive (9)
Acute Maxillary Sinusitis		Beta-lactamase positive (4)
Acute Exacerbation of Chronic Bronchitis		Beta-lactamase positive (7)
TOTAL		Beta-lactamase positive (20)
CAP	*S.aureus*	MRSA (1)
Acute Maxillary Sinusitis	*S. aureus*	MRSA (not indicated)
Acute Exacerbation of Chronic Bronchitis	*S. aureus*	MRSA (1)
TOTAL		
Pharyngitis/Tonsillitis	*S. pyogenes*	Erythromycin resistant (28)

IN VITRO SUSCEPTIBILITY OF TARGET PATHOGENS PRETHERAPY

Susceptibility testing of pre-therapy derived organisms showed that none of the *S. pneumoniae*, *M. catarrhalis*, or *S. aureus* was initially resistant to telithromycin. Of the *H. influenzae* isolates 2.9 % were resistant, while in the PPb population 4.3% of the *H. influenzae* and 40% of the *H. parainfluenzae* were resistant to telithromycin.

IN VITRO SUSCEPTIBILITY OF SUPERINFECTION, REINFECTION AND RECURRENCE PATHOGENS

There were no superinfection pathogens isolated during the study in the bmITT or PPb populations. At the post-therapy/TOC visit, there was 1 reinfection pathogen of *S. pneumoniae*. In vitro susceptibility testing showed this isolate to be susceptible to telithromycin and resistant to penicillin and erythromycin.

At the late posttherapy visit, there was 1 recurrence pathogen of *S. pneumoniae* isolated from the subject. This *S. pneumoniae* was classified as colonization and was not associated with clinical signs or symptoms of infection.

ATYPICAL ORGANISM (*Chlamydia pneumoniae, Mycoplasma pneumoniae,* and *Legionella pneumophilia*) DATA SUMMARY

None of the following data was incorporated in the original NDA submission. All of this information and data was included in the safety data summary (9/7/00 Aventis CD 9:v026: p118).

The diagnosis of infection due to the organisms *C. pneumoniae*, *M. pneumonia* and *L. pneumophilia* was done by indirect methods (serology) because of the difficulty of routinely culturing these organisms.

The following methods were used to detect the presence of:

- *C. pneumoniae* – Culture of nasopharyngeal swabs (in selected centers of studies 3006 and 3009); acute (pre-therapy/entry visit) and convalescent (post-therapy/TOC or late post-therapy visit) serology by microimmunofluorescence method; sputum samples tested by PCR (Studies 3006 and 3009).

- *M. pneumoniae* – Acute and convalescent serology by enzyme-linked immunosorbent assay (ELISA) method; sputum samples tested by PCR (Studies 3006 and 3009).

- *L. pneumophilia* – Serology using indirect antibody testing after a screening ELISA (US studies) or microagglutination (EU studies); urine samples tested for the presence of serogroup I urinary antigen using an ELISA technique.

The positive diagnostic criteria that were agreed on (20 September 1999) were as follows. If there was a negative aerobic culture for any "typical" pathogen and the following criteria were met.

- *C. pneumoniae* – Positive culture when available, fourfold increase in microimmunofluorescence IgG (polyclonal) titers of paired samples, or a single IgM titer $\geq$1:32 by microimmunofluorescence in combination with a positive PCR for *C. pneumoniae*.

- *M. pneumoniae* – Positive culture when available, fourfold increase in serum IgG in paired samples, or a single IgM titer $\geq$1:16 by microimmunofluorescence in combination with a positive PCR for *M. pneumoniae*.

- *L. pneumophilia* – Positive culture when available, fourfold increase in paired serum of IgG or IgM, or a positive urine antigen for *L. pneumophilia* serogroup I.

The clinical outcome of patients presumed to have infection with one of the atypical pathogens is seen in Table 76 (9:v026:p118).

Table 76. Clinical outcome at posttherapy/TOC in subjects with presumed infection due to atypical pathogens – PPc population treated for 7 – 10 days with telithromycin

Pathogen	Number of Subjects	Clinical Outcome Cure (%)	Failure (%)
Positive Diagnosis			
Chlamydia pneumoniae	4	4 (100)	0
Mycoplasma pneumoniae	43	40 (93)	3 (7)
Legionella pneumophilia	4	4 (100)	0
Presumptive Diagnosis			
Chlamydia pneumoniae	24	21 (88)	3 (12)

In the PPb population, the atypical infection was associated with common pathogens for 1 of the 4 subjects with *C. pneumoniae*, for 15 of the 43 subjects with *M. pneumoniae*, and none of the 4 subjects with *L. pneumophilia*.

Following a meeting with the FDA on 20 September 1999, the criteria for the diagnosis of atypical infections were redefined to be highly specific. The clinical outcome at the posttherapy/TOC visit in subjects with infection due to atypical pathogens using the highly specific diagnosis criteria (excluding subjects with common pathogens) in the PPc population is shown in Table 77 (9:v026:p119). Clinical outcome in subjects with pneumonia due to atypical infection without common pathogens was a clinical cure in 1 subject (100%) with a positive diagnosis of infection due to *C. pneumoniae*, 1 subject (100%) with a positive diagnosis of infection due to *M. pneumoniae*, and 4 subjects (100%) with a positive diagnosis of infection due to *L. pneumophilia* (9:v026:p119). Because of this very small population of patients diagnosed as having infection with an atypical pathogen these organisms can not be included in the indications being requested by the applicant.

Table 77. Clinical outcome at posttherapy/TOC in subjects with infection due to atypical pathogens using highly specific criteria treated with Telithromycin for 7 – 10 days – PPc population (9:v026p119)

Pathogen	Number of	Clinical Outcome

	Subjects	Cure (%)	Failure (%)
Chlamydia pneumoniae total	1		
Fourfold increase in IgG	1	1 (100)	0
Fourfold increase in IgM	0		
Single IgM titer>=1:32, positive PCR	0		
Mycoplasma pneumoniae total	1		
Fourfold increase in IgG	1	1 (100)	0
Single IgM titer >=1:16, positive PCR	0		
Legionella pneumophilia total	4*		
Fourfold increase in antibody titer	3	3 (100)	0
Positive urinary antigen	2	2 (100)	0

*One subject had a fourfold increase in antibody titer and a positive urine antigen test.

ESTABLISHMENT OF SUSCEPTIBILITY TESTING INTERPRETIVE CRITERIA FOR LABELING:

The pharmacokinetic profile for the telithromycin dose of 800 mg once daily shows that the C_{max} (µg/mL) is 1.9 after a single dose and after seven days is 2.3. The $AUC_{(0-24)}$ (µg•h/mL) after a single dose is 8.25 and after seven days 12.5. After 3 to 5 days of 800 mg dosing the mean peak and trough plasma concentrations were found to be 2.9 and 0.2 µg/mL respectively. From the mouse thigh infection model the 24hr AUC/MIC for free drug was the parameter that best correlated with efficacy (R^2 = 90% versus 70% for peak/MIC and 46% for time above MIC) (28). This pharmacokinetic/pharmacodynamic information combined with the in vitro susceptibility profile of the target pathogens *S. pneumoniae (including penicillin and erythromycin resistant strains)*, *H. influenzae* (including β-lactamase positive strains), *M. catarrhalis, S. aureus* (methicillin, erythromycin and or clindamycin susceptible strains only), *and S. pyogenes* (erythromycin-susceptible strains only) suggests the following in vitro susceptibility interpretive criteria would be appropriate.

The following scattergrams show the MICs and disc diffusion zone sizes for all of the isolates of each organism. These scattergrams have been constructed using numbers that reflect the disqualified centers (Aventis Disc correspondence 03 Nov 2000). They are in adobe format.

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