CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 21-144 Review Completed: 29 Mar 04

Date company submitted: 17 Oct 03 Date received by CDER: 18 Oct 03
Reviewer: Fred Marsik, Ph.D. Date assigned: 2 Mar 04

NAME AND ADDRESS OF APPLICANT

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DRUG PRODUCT NAME

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

PROPOSED INDICATIONS

Community-acquired pneumonia due to *Streptococcus pneumoniae* (including penicillin-and/or macrolide-resistant strains, *Haemophilus influenzae* (including ß-lactamase producing strains), *Moraxella catarrhalis* (including ß-lactamase producing strains), *Staphylococcus aureus*, *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*

Acute bacterial exacerbation of chronic bronchitis due to *S. pneumoniae*, *H. influenzae* (including ß-lactamase-producing strains), *M. catarrhalis* (ß-lactamase-producing strains), and/or *S. aureus*

Acute bacterial sinusitis due to *S. pneumoniae*, *H. influenzae* (including ß-lactamase-producing strains, *M. catarrhalis* (including ß-lactamase-producing strains), and/or *S. aureus*

DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT

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

DISPENSED

R_x

RELATED DOCUMENTS

Initial submission:
Applicant submission date: 2/28/00
Received by CDER: 3/1/00
Received by reviewer: 3/3/00
Review completed: 11/30/00

Supplement to initial submission:
Applicant submission date: 12/19/00
Received by CDER: 12/20/00
Received by reviewer: 3/8/01
Review completed: 5/11/01

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

Supplemental submission:
Applicant submission date: 7/24/02
Received by CDER: 7/24/02
Received by reviewer: 7/3/02
Review completed: 12/31/02

IND 55,283 dated 3/27/00

REMARKS

This application was transferred to this reviewer on March 3, 2004 with a due date of March 31, 2004. The reader is referred to the more in-depth microbiology reviews noted under "RELATED DOCUMENTS" above.

CONCLUSION

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

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Telithromycin has been shown to have in vitro activity against *Streptococcus pneumoniae* including strains that are resistant to penicillin and/or erythromycin, *Haemophilus influenzae* (including isolates that are β-lactamase positive), *Moraxella catarrhalis* (including isolates that are β-lactamase positive), *Streptococcus pyogenes* that are susceptible to erythromycin, and *Staphylococcus aureus* that are susceptible to methicillin, erythromycin or clindamycin. These organisms are considered important pathogens associated with one or more of the indications [community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), and acute bacterial sinusitis (ABS)] for which the applicant is seeking approval. The applicant has submitted clinical data to support their claim that telithromycin is efficacious in treating infections caused by these organisms. In addition they have provided in vitro susceptibility information for ≥100 isolates of other organisms, without bacteriological and clinical outcome information, that may be associated with these types of infections. Those organisms, which are associated with the indications sought, and have MIC_{90s} below the concentration of telithromycin that can be achieved on the proposed dosing regimen have been included in the second list of the microbiology section of the product labeling.

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

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

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

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

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

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

Table 1. Pharmacokinetic parameters in young subjects after single and multiple (qd) oral dosing with 800 mg telithromycin

	Mean (CV %)	
	SD	MD
Parameter (plasma)	N=18	N=18
C_{max} (µg/mL)	1.90	2.27
	(42)	(31)
T_{max} (h)	1.0[a]	1.0[a]
	[0.5-4.0][b]	[0.5-3.0][b]
C_{24}(µg/mL)	0.030	0.070
	(45)	(72)
AUC(0-24) (µg.h/mL)	8.25	12.5
	(31)	(43)
$t_{½\lambda 1}$(h)[c]	2.43	2.87
	(41)	(50)
$t_{½\lambda z}$(h)[c]	7.16	9.81
	(19)	(20)

SD = single dose, MD = day 7 of multiple dose (once daily for 7 days)
a = median
b = [min – max]
c = elimination half-lives calculated using a compartmental model

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

Telithromycin is 60 to 70% protein bound.

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

INDICATIONS AND USAGE

The applicant has been given the following "Indications and Usage" for telithromycin.

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*

Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* or *Staphylococcus aureus*

Community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae* (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae* or *Mycoplasma pneumoniae*.

*MDRSP = Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are isolates resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, (e.g. cefuroxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

IN VITRO SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA

Based on the organisms granted to the applicant in the "Indications and Usage Section" of the telithromycin package insert the following in vitro susceptibility test interpretive criteria are included in the package insert. There are no in vitro susceptibility test criteria given for these organisms *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae* because standardized in vitro susceptibility test methods do not exist for these organisms.

Based on the pharmacokinetic/pharmacodynamic characteristics of telithromycin, in vitro susceptibility data from the literature, in vitro susceptibility data of isolates of bacteria obtained during clinical trials and bacteriological and clinical outcome data the following MIC and disk diffusion zone size interpretive criteria are applicable. Disk diffusion testing is done using a disk containing 15 µg telithromycin.

Testing of all bacterial isolates from clinical trials was done using National Committee for Clinical Laboratory Standards (NCCLS) methods (**1,2**).

STREPTOCOCCUS PNEUMONIAE (including multi-drug resistant isolates [MDRSP]*)

The applicant has proposed the following in vitro susceptibility test interpretive criteria for *S. pneumoniae*. Based on an analysis of the data provided by the applicant the Agency concurs with these breakpoints.

Interpretive Category	MIC (µg/mL)	Zone of Inhibition (mm)
Susceptible	≤1.0	≥19
Intermediate	2.0	16 – 18
Resistant	4.0	≤15

*MDRSP = Multi-drug resistant *S. pneumoniae* includes isolates known as PRSP (penicillin-resistant *S. pneumoniae*) and are isolates resistant to two or more of the following antimicrobials: penicillin, 2nd generation cephalosporins (e.g. cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

The bacterial eradication and clinical cure rates using ≤ 1.0 µg/mL as indicating susceptibility of *S. pneumoniae* to telithromycin in the indications noted below were:

Indication	Number of Isolates	Bacterial eradication	Clinical cure
CAP	286	276 (96.5%)	271 (94.6%)
ABS	78	70 (89.7%)	
AECB	26	22 (84.6%)	
Total	390	369 (94.4%)	

The following table (Table 1 as numbered by applicant) provides further information relating to antimicrobial resistant *S. pneumoniae*, telithromycin MIC, bacterial eradication and clinical outcome results for all indications combined (provided by Aventis – e-mail 17 Mar 04). As seen all *S. pneumoniae*, except one isolate, that were resistant to penicillin and or erythromycin had telithromycin MICs of ≤1 µg/mL regardless of the isolates susceptibility to penicillin and/or erythromycin. The bacterial eradication and clinical cure rates for these isolates were ≥78%.

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Table 1 Bacteriological eradication rates and clinical cure rates at Posttherapy/TOC according to MIC values for HMR 3647 by causative pathogen for all indications combined without centers excluded by FDA - PPb population [a] (Continued)

			HMR 3647									
			Bacteriological outcome [c] No. (%)						Clinical outcome [d] No. (%)			
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure	
Streptococcus pneumoniae												
	0.004	5	5	(100.0)	0	(0.0)	0	(0.0)	4	(80.0)	1	(20.0)
	0.008	171	165	(96.5)	6	(3.5)	0	(0.0)	163	(95.3)	8	(4.7)
	0.015	72	66	(91.7)	6	(8.3)	0	(0.0)	64	(88.9)	8	(11.1)
	0.016	99	95	(96.0)	4	(4.0)	0	(0.0)	93	(93.9)	6	(6.1)
	0.03	37	34	(91.9)	3	(8.1)	0	(0.0)	34	(91.9)	3	(8.1)
	0.06	15	14	(93.3)	1	(6.7)	0	(0.0)	14	(93.3)	1	(6.7)
	0.12	9	6	(66.7)	3	(33.3)	0	(0.0)	6	(66.7)	3	(33.3)
	0.25	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1	(33.3)
	0.5	9	8	(88.9)	0	(0.0)	1	(11.1)	8	(88.9)	1	(11.1)
	1	6	6	(100.0)	0	(0.0)	0	(0.0)	6	(100.0)	0	(0.0)
	2	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	N/A	48	44	(91.7)	4	(8.3)	0	(0.0)	44	(91.7)	4	(8.3)
	Total	475	446	(93.9)	28	(5.9)	1	(0.2)	439	(92.4)	36	(7.6)
Streptococcus pneumoniae (Blood culture only)												
	0.008	36	36	(100.0)	0	(0.0)	0	(0.0)	34	(94.4)	2	(5.6)
	0.015	13	11	(84.6)	2	(15.4)	0	(0.0)	11	(84.6)	2	(15.4)
	0.016	16	14	(87.5)	2	(12.5)	0	(0.0)	13	(81.3)	3	(18.8)
	0.03	5	4	(80.0)	1	(20.0)	0	(0.0)	4	(80.0)	1	(20.0)
	0.06	3	3	(100.0)	0	(0.0)	0	(0.0)	3	(100.0)	0	(0.0)
	0.12	2	1	(50.0)	1	(50.0)	0	(0.0)	1	(50.0)	1	(50.0)
	1	3	3	(100.0)	0	(0.0)	0	(0.0)	3	(100.0)	0	(0.0)
	N/A	10	10	(100.0)	0	(0.0)	0	(0.0)	10	(100.0)	0	(0.0)
	Total	88	82	(93.2)	6	(6.8)	0	(0.0)	79	(89.8)	9	(10.2)

a PPb=per protocol bacteriologically evaluable population.
b Causative admission pathogens as assessed by investigators.
c Includes documented and presumed.
d Cure=returned to preinfection state, and improved or postinfection stigmata (no subsequent antibiotic); Failure=failure as assessed by the investigators.

			HMR 3647									
			Bacteriological outcome [c] No. (%)						Clinical outcome [d] No. (%)			
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure	
Streptococcus pneumoniae (PEN-I)												
	0.008	12	12	(100.0)	0	(0.0)	0	(0.0)	12	(100.0)	0	(0.0)
	0.015	4	4	(100.0)	0	(0.0)	0	(0.0)	4	(100.0)	0	(0.0)
	0.016	11	11	(100.0)	0	(0.0)	0	(0.0)	10	(90.9)	1	(9.1)
	0.03	9	9	(100.0)	0	(0.0)	0	(0.0)	9	(100.0)	0	(0.0)
	0.06	3	3	(100.0)	0	(0.0)	0	(0.0)	3	(100.0)	0	(0.0)
	0.12	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.5	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	1	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	Total	44	44	(100.0)	0	(0.0)	0	(0.0)	43	(97.7)	1	(2.3)
Streptococcus pneumoniae (PEN-R)												
	0.008	7	7	(100.0)	0	(0.0)	0	(0.0)	7	(100.0)	0	(0.0)
	0.015	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.016	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.03	8	6	(75.0)	2	(25.0)	0	(0.0)	6	(75.0)	2	(25.0)
	0.06	6	5	(83.3)	1	(16.7)	0	(0.0)	5	(83.3)	1	(16.7)
	0.12	3	1	(33.3)	2	(66.7)	0	(0.0)	1	(33.3)	2	(66.7)
	0.25	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.5	7	6	(85.7)	0	(0.0)	1	(14.3)	6	(85.7)	1	(14.3)
	1	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	2	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	Total	38	32	(84.2)	5	(13.2)	1	(2.6)	32	(84.2)	6	(15.8)

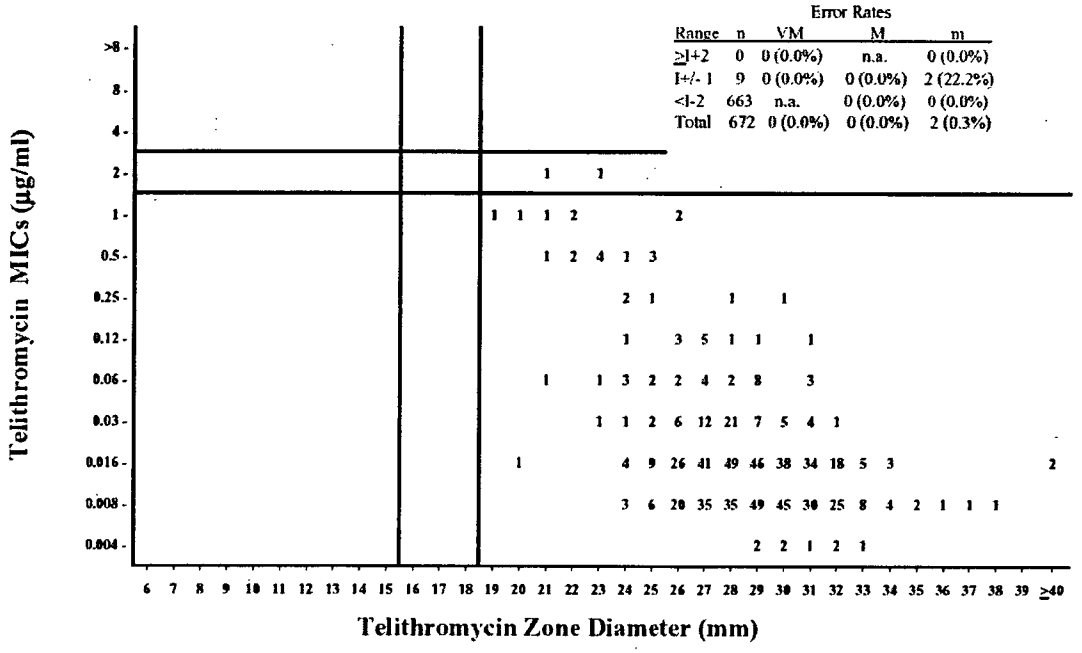
			HMR 3647									
			Bacteriological outcome [c] No. (%)						Clinical outcome [d] No. (%)			
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure	
Streptococcus pneumoniae (ERY-R)												
	0.008	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.015	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.016	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.03	16	14	(87.5)	2	(12.5)	0	(0.0)	14	(87.5)	2	(12.5)
	0.06	13	12	(92.3)	1	(7.7)	0	(0.0)	12	(92.3)	1	(7.7)
	0.12	7	4	(57.1)	3	(42.9)	0	(0.0)	4	(57.1)	3	(42.9)
	0.25	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1	(33.3)
	0.5	9	8	(88.9)	0	(0.0)	1	(11.1)	8	(88.9)	1	(11.1)
	1	6	6	(100.0)	0	(0.0)	0	(0.0)	6	(100.0)	0	(0.0)
	2	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	Total	59	51	(86.4)	7	(11.9)	1	(1.7)	51	(86.4)	8	(13.6)
Streptococcus pneumoniae (PEN-I & ERY-R)												
	0.015	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.03	7	7	(100.0)	0	(0.0)	0	(0.0)	7	(100.0)	0	(0.0)
	0.06	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.12	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.5	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	1	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	Total	15	15	(100.0)	0	(0.0)	0	(0.0)	15	(100.0)	0	(0.0)
Streptococcus pneumoniae (PEN-R & ERY-R)												
	0.008	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.016	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.03	5	3	(60.0)	2	(40.0)	0	(0.0)	3	(60.0)	2	(40.0)
	0.06	6	5	(83.3)	1	(16.7)	0	(0.0)	5	(83.3)	1	(16.7)
	0.12	3	1	(33.3)	2	(66.7)	0	(0.0)	1	(33.3)	2	(66.7)
	0.25	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.5	7	6	(85.7)	0	(0.0)	1	(14.3)	6	(85.7)	1	(14.3)
	1	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	2	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	Total	27	21	(77.8)	5	(18.5)	1	(3.7)	21	(77.8)	6	(22.2)

			HMR 3647									
			Bacteriological outcome [c] No. (%)						Clinical outcome [d] No. (%)			
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure	
Streptococcus pneumoniae (ERY-R/mefE)												
	0.03	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.06	8	7	(87.5)	1	(12.5)	0	(0.0)	7	(87.5)	1	(12.5)
	0.12	6	3	(50.0)	3	(50.0)	0	(0.0)	3	(50.0)	3	(50.0)
	0.25	2	1	(50.0)	1	(50.0)	0	(0.0)	1	(50.0)	1	(50.0)
	0.5	7	6	(85.7)	0	(0.0)	1	(14.3)	6	(85.7)	1	(14.3)
	1	5	5	(100.0)	0	(0.0)	0	(0.0)	5	(100.0)	0	(0.0)
	Total	29	23	(79.3)	5	(17.2)	1	(3.4)	23	(79.3)	6	(20.7)
Streptococcus pneumoniae (ERY-R/ermB)												
	0.008	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.015	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.016	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.03	14	12	(85.7)	2	(14.3)	0	(0.0)	12	(85.7)	2	(14.3)
	0.06	7	7	(100.0)	0	(0.0)	0	(0.0)	7	(100.0)	0	(0.0)
	0.12	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.25	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.5	4	4	(100.0)	0	(0.0)	0	(0.0)	4	(100.0)	0	(0.0)
	1	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	2	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	Total	33	31	(93.9)	2	(6.1)	0	(0.0)	31	(93.9)	2	(6.1)
Streptococcus pneumoniae (ERY-R/mefE & ermB)												
	0.06	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.5	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	Total	4	4	(100.0)	0	(0.0)	0	(0.0)	4	(100.0)	0	(0.0)

The regression analysis used to determine the zone sizes from the MIC data for *S. pneumoniae* is seen in the following graph (provided by Aventis in e-mail of 17 mar 04). This analysis is based on the MIC and zone size determinations for all clinical isolates combined (bmITT population). The "Very Major" (VM), "Major" (M), and "Minor" (m) error rates meet the criteria established by the NCCLS (3).

Figure 1. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, All Strains Combined (n=672)**



The following regression analyzes are done using the resistant populations of *S. pneumoniae* (provided by Aventis in e-mail of 17 mar 04). The populations of resistant *S. pneumoniae* are appropriately categorized using the disc diffusion zones sizes determined from combining all isolates of *S. pneumoniae* together. The "Very Major" (VM), "Major" (M), and "Minor" (m) error rates meet the criteria established by the NCCLS (3).

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Figure 2. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Penicillin-Susceptible (n=543)**

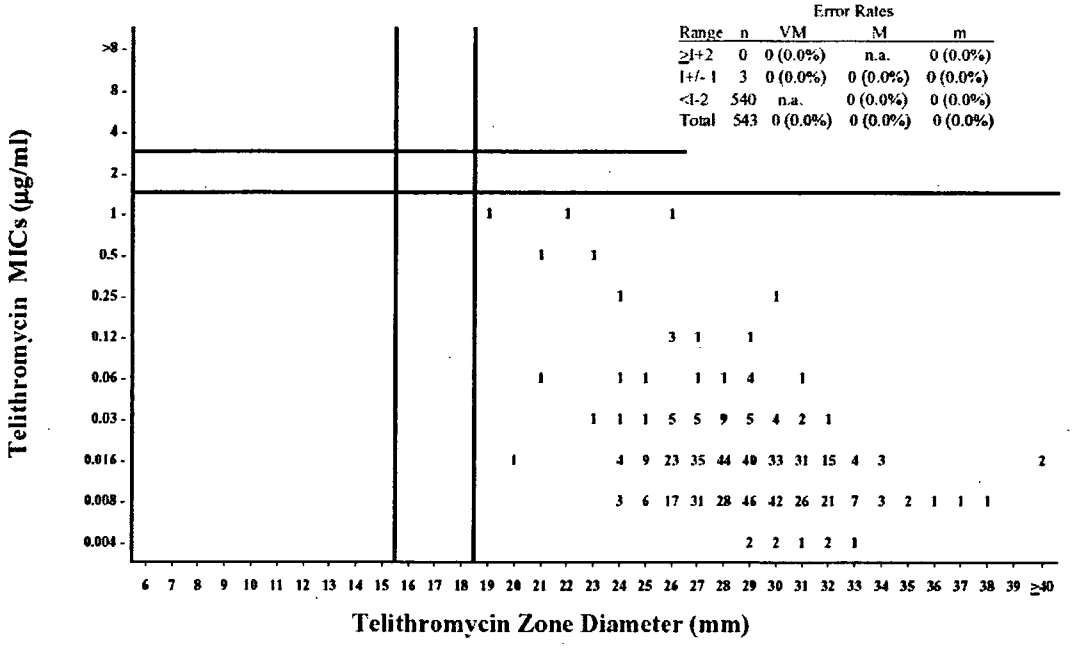


Figure 3. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Penicillin-Intermediate (n=70)**

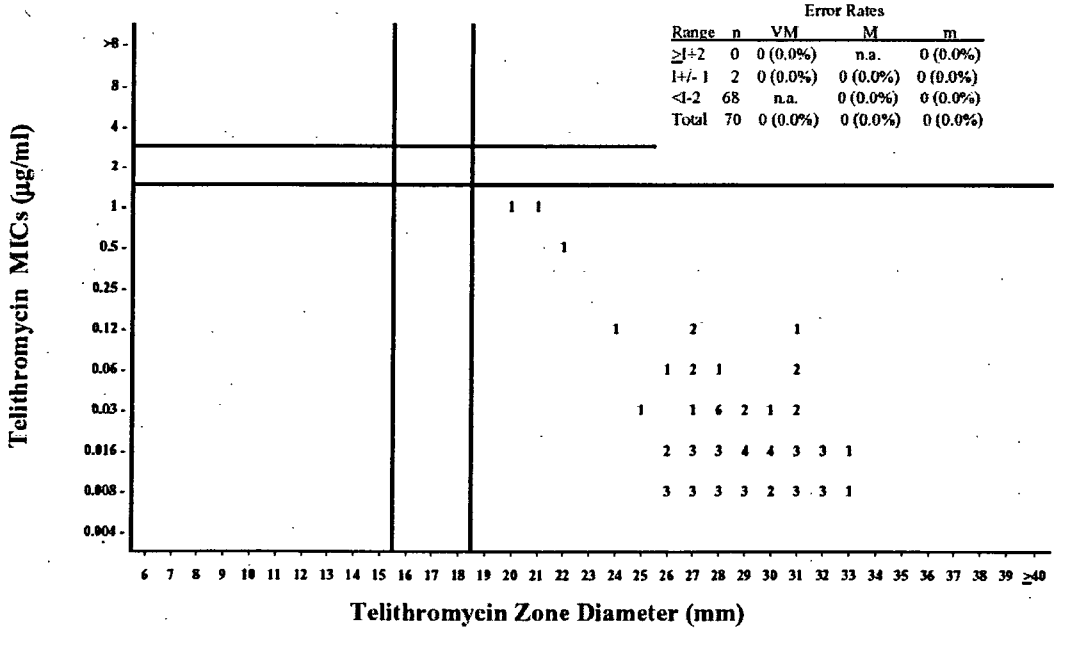


Figure 4. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Penicillin-Resistant (n=59)**

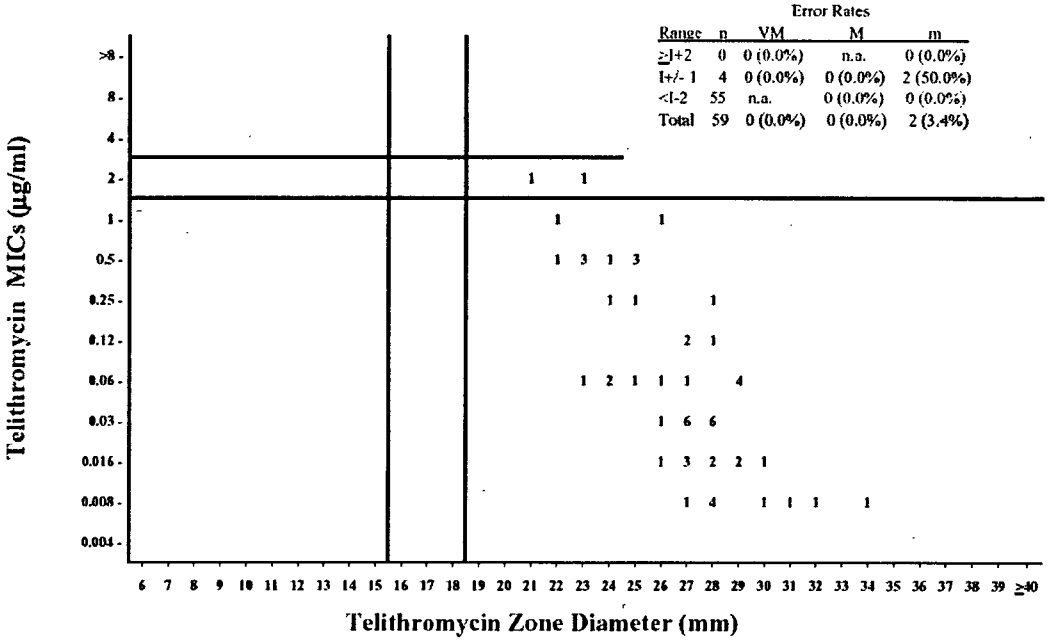


Figure 5. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Erythromycin-Susceptible (n=584)**

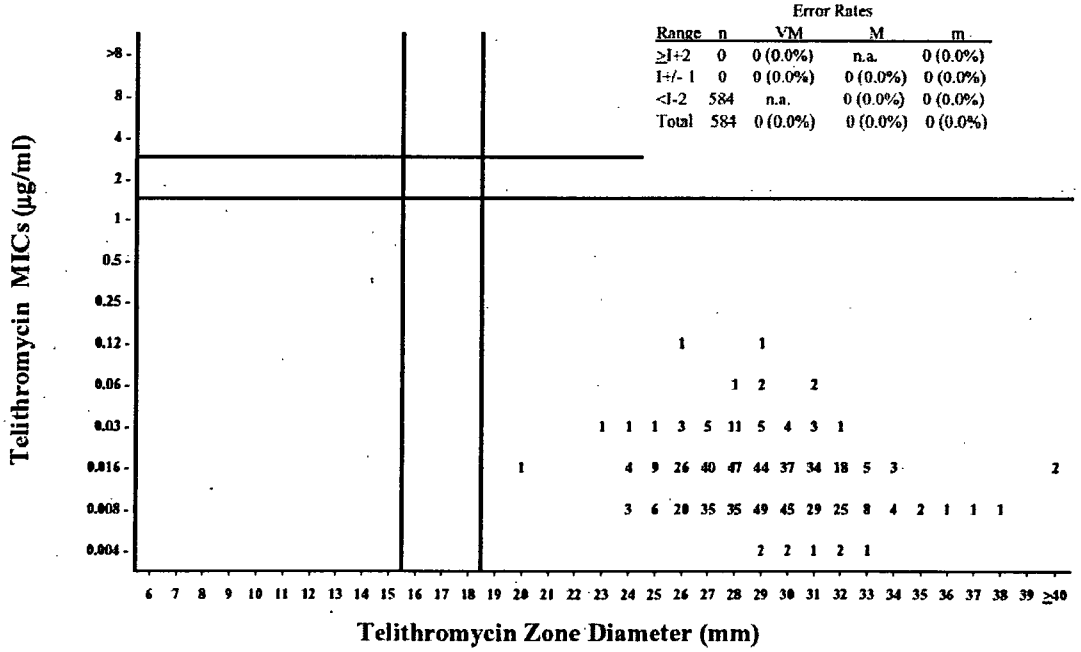
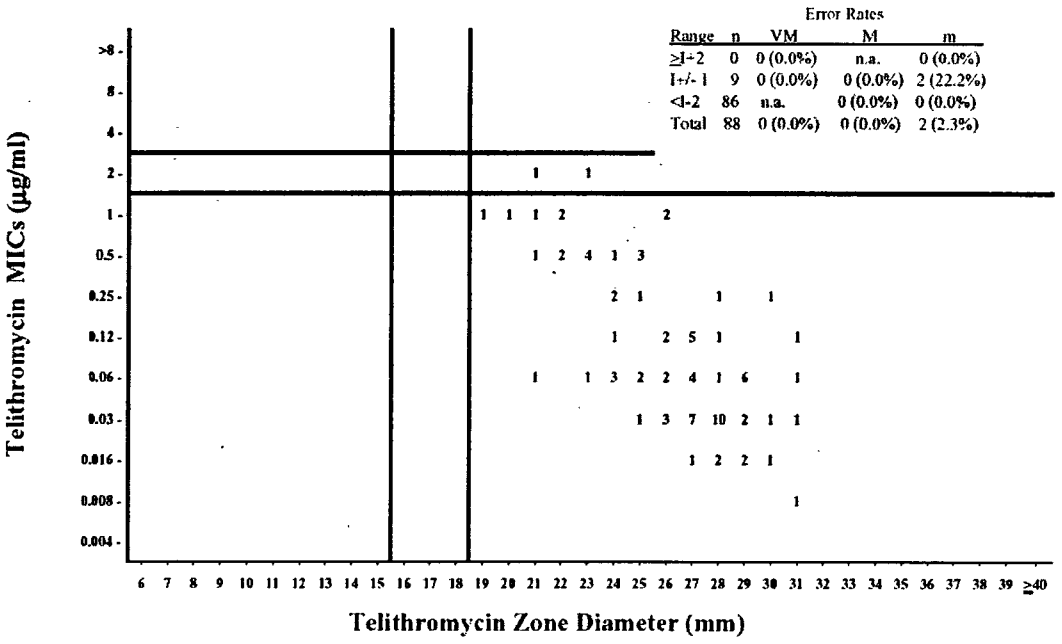


Figure 6. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Erythromycin-Resistant (n=88)**

(There were no erythromycin-intermediate strains recovered)



HAEMOPHILUS INFLUENZAE

The applicant has proposed the following in vitro susceptibility tests for *H. influenzae*. After review of the data provided by the applicant the Agency concurs with these breakpoints.

Interpretive Category	MIC (µg/mL)	Zone of Inhibition (mm)
Susceptible	≤4.0	≥15
Intermediate	8.0	12 – 14
Resistant	≥16.0	≤11

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

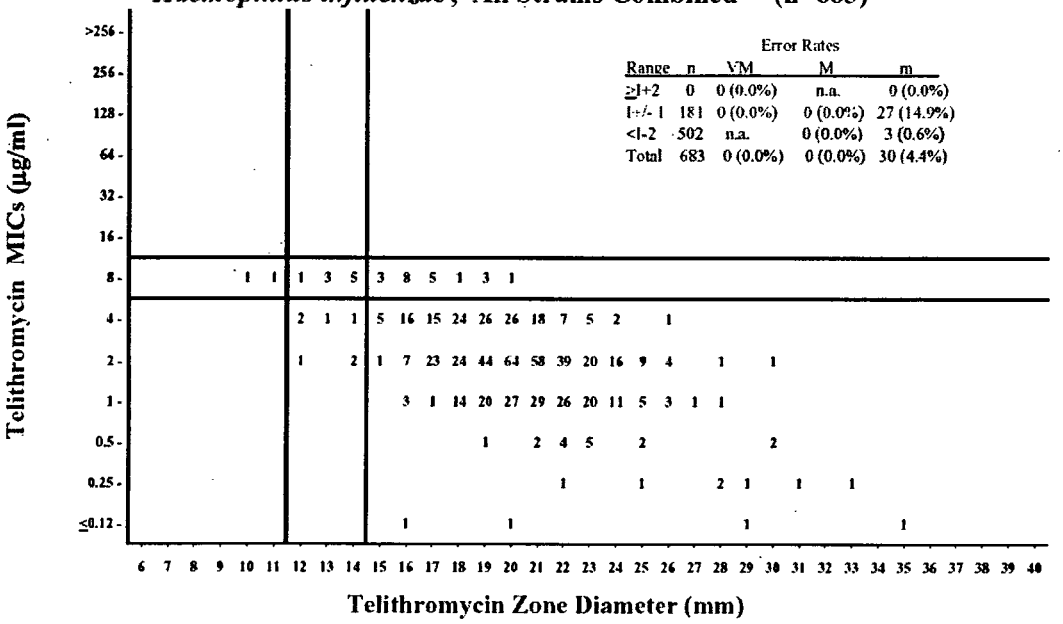
H. influenzae

Indication	Number of Isolates	Bacterial eradication (%)
CAP	193	170 (88.0)
AECB	52	37 (71.1)
ABS	55	48 (87.2)
Total	300	255 (85.0)

The regression analysis data for determining the zone sizes based on the MICs for *H. influenzae* is seen in the following graph (provided by Aventis in e-mail of 17 mar 04). This analysis is based on the MIC and zone size determinations for all isolates (bmITT population). The "Very Major" (VM), "Major" (M), and "Minor" (m) error rates meet the criteria established by the NCCLS (3).

Figure 7. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Haemophilus influenzae*, All Strains Combined (n=683)**



STAPHYLOCOCCUS AUREUS

The applicant has proposed the following in vitro susceptibility test interpretive criteria.

[redacted]

After review of the data the Agency does not agree that there is enough bacterial eradication and clinical cure data from studies to support these breakpoints. The Agency feels that there is only data to provide a breakpoint that characterizes *S. aureus* isolates as susceptible to telithromycin and therefore the following interpretive criteria are appropriate.

Interpretive Category	MIC (µg/mL)	Zone of Inhibition (mm)
Susceptible	0.25	≥22

The bacterial eradication and clinical outcome rates for all indications with infections caused by *S. aureus* with telithromycin MICs of ≤ 0.25 µg/mL were 84% (57/68) and 81% (55/68) respectively.

The regression analysis data for determining the zone sizes based on MICs for *S. aureus* is seen in the following graph (provided by Aventis in e-mail of 17 mar 04). This analysis is based on the MIC and zone size determinations for all isolates (bmITT population). The applicant calculated the error rates based on their proposed interpretive criteria of [redacted]

The "Very Major" (VM), "Major" (M), and "Minor" (m) error rates provided by the applicant meet the criteria established by the NCCLS (3). The Agency feels the more appropriate breakpoint is ≤0.25 µg/mL = susceptible with no intermediate or resistant breakpoints determined because of the lack of data to

determine these breakpoints. Because of the lack of data it is not possible to calculate accurate error rates for the breakpoint of ≤0.25 µg/mL = susceptible.

Figure 10. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***S. aureus*, All Strains Combined (n=139)**

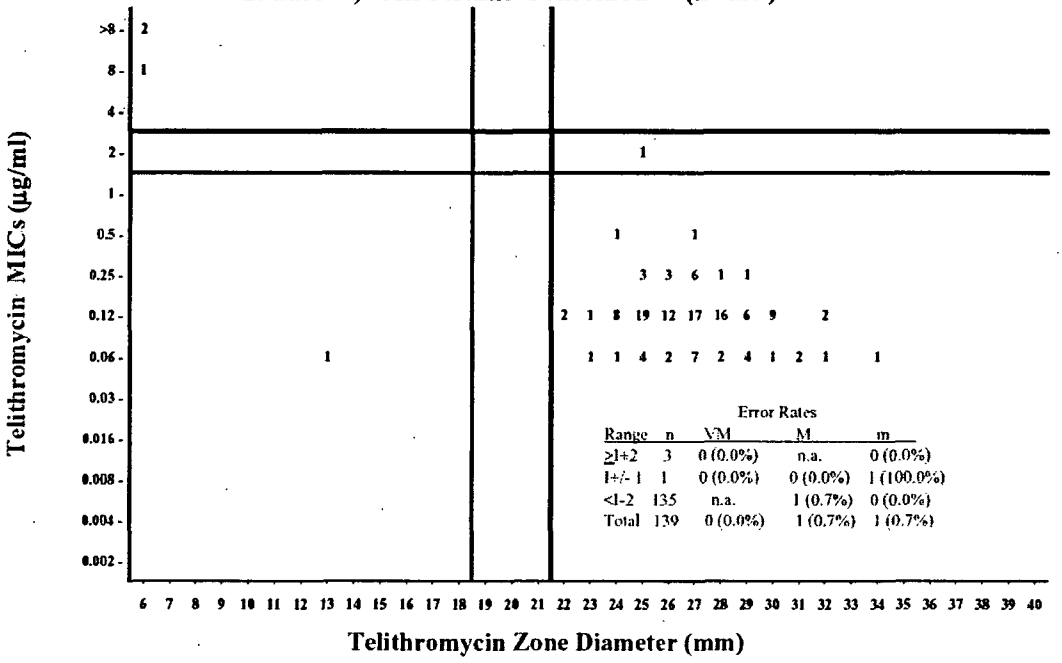


Figure 11. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Staphylococcus aureus*, Oxacillin-Susceptible (n=130)**

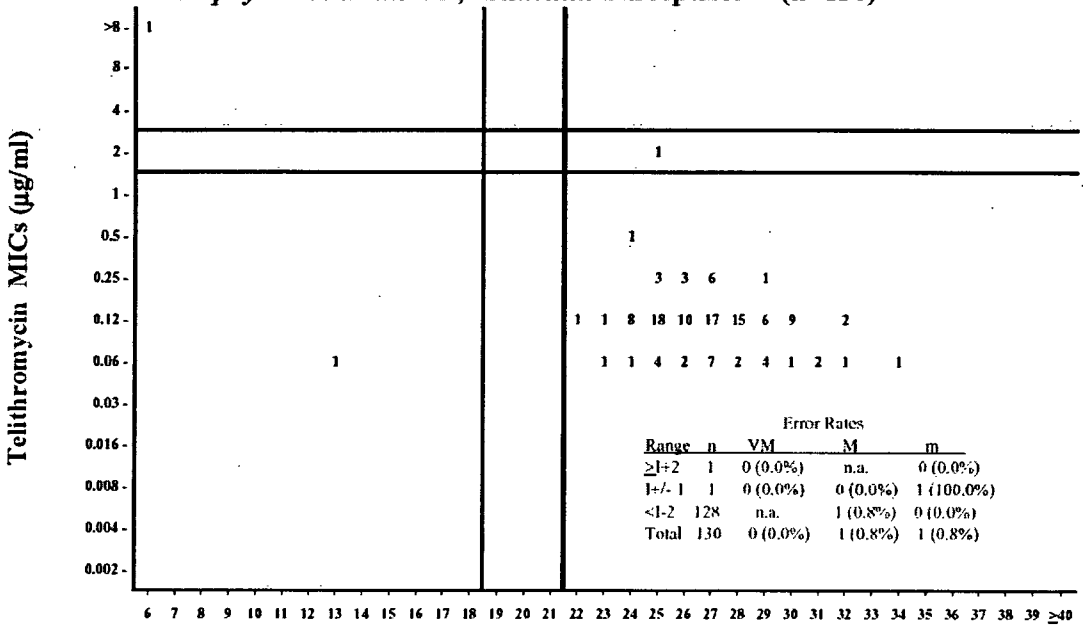
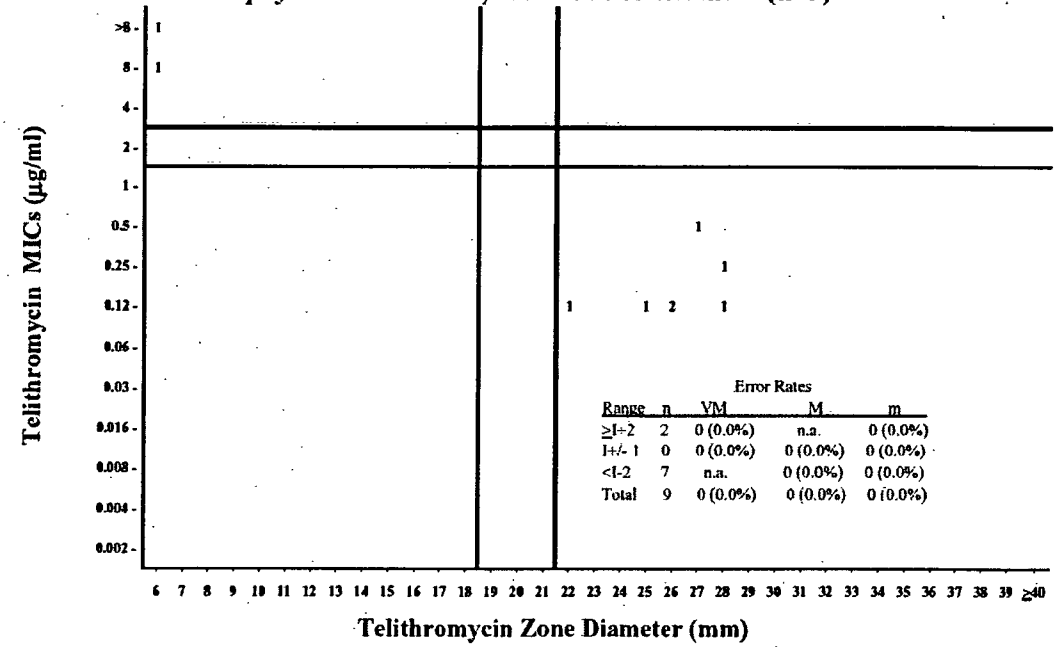


Figure 12. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Staphylococcus aureus*, Oxacillin-Resistant (n=9)**



QUALITY CONTROL ORGANISMS AND RANGES FOR SUSCEPTIBILITY TESTING:

The Agency concurs with the following MIC and disc diffusion quality control criteria.

QC Strain	Minimum Inhibitory (µg/mL)	Disk Diffusion (Zone diameter in mm)
Staphylococcus aureus ATCC® 29213	0.06 – 0.25	Not applicable
Staphylococcus aureus ATCC 25923	Not Applicable	24 - 30
Streptococcus pneumoniae ATCC 49619	0.004 - 0.03	27 - 33
Haemophilus influenzae ATCC 49247	1.0 - 4.0	17 - 23

ATCC = American Type Culture Collection

Moraxella catarrhalis

Community-acquired Pneumonia

There were 34 isolates of *M. catarrhalis* from patients in the PPb population. Table 2 shows telithromycin MICS for these isolates and the bacterial eradication (presumed) for this organism. As can be seen *M. catarrhalis* is extremely susceptible to telithromycin and there was better than 90% eradication of the organism from patients with CAP.

Table 2. Telithromycin MICs for *Moraxella catarrhalis*
CAP isolates and bacterial eradication (presumed) rates

Telithromycin MIC (µg/mL)	Number of Isolates	Eradication (presumed) %
0.008	1	1 (100)
0.06	15	13 (86.7)
0.12	18	18 (100)
Total	34	32 (94.1)

Acute exacerbation of chronic bronchitis

Twenty-nine isolates of *M. catarrhalis* were obtained during AECB clinical trials. Of these 27 (93.1%) were eradicated (presumed).

Acute bacterial sinusitis (ABS)

There were 17 patients with acute bacterial sinusitis from whom *M. catarrhalis* was isolated. Of the 17 patients 15 (88.2%) had the organism eradicated (presumed).

The following table shows bacterial eradication and clinical cure rates for all indications where *M. catarrhalis* was the etiological pathogen.

Table 3

Bacteriological eradication rates and clinical cure rates at Posttherapy/TOC according to MIC values for HMR 3647 by causative pathogen for all indications combined without centers excluded by FDA - PPb population [a]□ (Continued)

Moraxella (Branhamella) catarrhalis											
0.004	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
0.008	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
0.06	28	23	(82.1)	4	(14.3)	1	(3.6)	23	(82.1)	5	(17.9)
0.12	44	42	(95.5)	1	(2.3)	1	(2.3)	42	(95.5)	2	(4.5)
0.25	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1	(33.3)
1	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
N/A	24	20	(83.3)	4	(16.7)	0	(0.0)	20	(83.3)	4	(16.7)
Total	103	91	(88.3)	10	(9.7)	2	(1.9)	91	(88.3)	12	(11.7)

INTRACELLULAR BACTERIA

The applicant provided clinical and diagnostic evidence in their previous submissions for the occurrence of 34 cases of *Chlamydia* (*Chlamydophilia*) *pneumoniae*, 31 cases of *Mycoplasma pneumoniae* and 13 cases of *Legionella pneumophilia* CAP. In vitro studies have shown that telithromycin concentrates in macrophages and PMNs to levels that exceed the MICs of these intracellular pathogens. The clinical cure rates for the CAP infections caused by these organisms were demonstrated in clinical trials to be better than 94%. Based on the in vitro susceptibility of these organisms to telithromycin, the fact that telithromycin concentrates in macrophages and the clinical cure rates for these infections demonstrated during clinical trials it would be appropriate to include *C. pneumoniae* and *M. pneumoniae* in the CAP indication. It is not recommended to include *L. pneumophilia* in the CAP indication because of the small number of clinical cases and some discrepancies in the diagnostic test results used to confirm the presence of this organism. It is recommended that *L. pneumophilia* be placed in the "second list" because telithromycin in vitro susceptibility information on better than 100 isolates of the organism shows that the MIC_{90} for the organism is well below the therapeutically achievable concentration of telithromycin that can be achieved using the proposed telithromycin dosing regimen, telithromycin concentrates in macrophages, and the organism is relevant to the CAP indication.

SECOND LIST OF BACTERIA

The following bacteria are proposed for the second list based on the criteria that they are relevant to the indications, they have MIC_{90s} that indicate they would be susceptible to achievable concentrations of telithromycin based on the dosing regimen and the applicant provided in vitro susceptibility data on ≥100 clinical isolates.

Aerobic gram-positive microorganisms

[redacted]

Streptococcus pyogenes (erythromycin susceptible isolates only)

Streptococci (Lancefield groups C and G)

Viridans group streptococci

Anaerobic bacteria

Prevotella bivia.

Prevotella intermedia

Peptostreptococcus spp.

Other microorganisms

Legionella pneumophila

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Sixth Edition; Approved Standard, NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Eighth Edition; Approved Standard, NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.
3. NCCLS. Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters: Approved Guideline -2nd ed. NCCLS document M23-A2. NCCLS, 940 West Valley Rd., Suite 1400, Wayne, PA 19087-1898.

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Microbiology

Telithromycin belongs to the ketolide class of antibacterials and is structurally related to the macrolide family of antibiotics. Telithromycin concentrates in phagocytes where it exhibits activity against intracellular respiratory pathogens. *In vitro*, telithromycin has been shown to demonstrate concentration-dependent bactericidal activity against isolates of Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP*]).

*MDRSP=Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP) penicillin-resistant *Streptococcus pneumoniae*), and isolates resistant to two or more of the following antimicrobials: penicillin, 2nd generation cephalosporins (e.g. cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole

Mechanism of action

Telithromycin blocks protein synthesis by binding to domains II and V of 23S rRNA of the 50S ribosomal subunit. By binding at domain II, telithromycin retains activity against gram-positive cocci (e.g., *Streptococcus pneumoniae*) in the presence of resistance mediated by methylases (*erm* genes) that alter the domain V binding site of telithromycin. Telithromycin may also inhibit the assembly of nascent ribosomal units.

Mechanism of resistance

Staphylococcus aureus and *Streptococcus pyogenes* with the constitutive macrolide-lincosamide-streptogramin B ($cMLS_B$) phenotype are resistant to telithromycin.

Mutants of *Streptococcus pneumoniae* derived in the laboratory by serial passage in subinhibitory concentrations of telithromycin have demonstrated resistance based on L22 riboprotein mutations (telithromycin MICs are elevated but still within the susceptible range), one of two reported mutations affecting the L4 riboprotein, and production of K-peptide. The clinical significance of these laboratory mutants is not known.

Cross resistance

Telithromycin does not induce resistance through methylase gene expression in erythromycin-inducibly resistant bacteria, a function of its 3-keto moiety. Telithromycin has not been shown to induce resistance to itself.

List of Microorganisms

Telithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical settings as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin and erythromycin susceptible isolates only)

Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP*])

*MDRSP=Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *S. pneumoniae*), and are isolates resistant to two or more of the following antimicrobials: penicillin, 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Aerobic gram-negative microorganisms

Haemophilus influenzae

Moraxella catarrhalis

Other microorganisms

Chlamydophila (Chlamydia) pneumoniae

Mycoplasma pneumoniae

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

At least 90% of the following microorganisms exhibit *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for telithromycin. However, the safety and efficacy of telithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Streptococcus pyogenes (erythromycin susceptible isolates only)

Streptococci (Lancefield groups C and G)

Viridans group streptococci

Anaerobic bacteria

Prevotella bivia

Prevotella intermedia

Peptostreptococcus spp.

Other microorganisms

Legionella pneumophila

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods (broth or agar dilution)[1,3] or equivalent with standardized inoculum and concentrations of telithromycin powder. The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antibiotics. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg telithromycin to test the susceptibility of microorganisms to telithromycin. Disc diffusion zone sizes should be interpreted according to criteria in Table —

Table — Susceptibility Test Result Interpretive Criteria for Telithromycin

	Minimal Inhibitory Concentrations (µg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R[a]	S	I	R[a]
Staphylococcus aureus	≤ 0.25			≥ 22		
Streptococcus pneumoniae	≤ 1	2	≥ 4	≥ 19	16-18	≤ 15
Haemophilus influenzae	≤ 4	8	≥ 16	≥ 15	12-14	≤ 11

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antibacterial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations

where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality control:

Standardized susceptibility test procedures require the use of quality control microorganisms to determine the performance of the test procedures[1,2,3]. Standard telithromycin powder should provide the MIC ranges for the quality control organisms in Table – For the disk diffusion technique, the 15-µg telithromycin disk should provide the zone diameter ranges for the quality control organisms in Table —

Table — Acceptable Quality Control Ranges for Telithromycin

QC Strain	Minimum Inhibitory Concentration (µg/mL)	Disk Diffusion (Zone diameter in mm)
Staphylococcus aureus ATCC® 29213	0.06-0.25	Not Applicable
Staphylococcus aureus ATCC 25923	Not Applicable	24-30
Streptococcus pneumoniae ATCC 49619	0.004-0.03	27-33
Haemophilus influenzae ATCC 49247	1.0-4.0	17-23

ATCC = American Type Culture Collection

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Sixth Edition; Approved Standard, NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Eighth Edition; Approved Standard, NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.
3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing: Fourteenth Informational Supplement; Approved Standard, NCCLS Document M2-A8 and M7-A6, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2004.

INTRODUCTION

IN VITRO

Spectrum of Activity

The applicant is proposing that telithromycin can be used to treat upper-respiratory infections caused by the following organisms.

Streptococcus pneumoniae including strains that are resistant to penicillin, erythromycin A, tetracycline, cefotaxime, fluroquinolones and tetracycline

Haemophilus influenzae (including isolates that are β-lactamase positive)

Moraxella catarrhalis (including isolates that are β-lactamase positive)

Staphylococcus aureus

These organisms are considered important pathogens associated with one or more of the indications [community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), and acute bacterial sinusitis (ABS) the applicant is seeking. The applicant has submitted clinical data to support their claim that telithromycin is efficacious in treating the indicated infections caused by the organisms indicated.

STREPTOCOCCUS PNEUMONIAE

Table 1 shows in vitro activity of telithromycin against penicillin- susceptible – and resistant *S. pneumoniae.*

Table 1. In vitro activity of telithromycin against penicillin-susceptible and -resistant *S. pneumoniae* (summary of studies from U.S., Canada, Europe and Asia)

Organism	Total Number of Isolates	MIC_{90} Range µg/mL
S. pneumoniae penicillin susceptible	2455	≤0.008-0.25
S. pneumoniae penicillin resistant	1317	0.007-2.0

Table 2 shows in vitro activity of telithromycin against *S. pneumoniae* resistant to erythromycin by possession of the *erm*B or *mef*A, and *erm*B+*mef*A genes. Of the 300 erythromycin resistant *S. pneumoniae* containing the *erm*B and *mef*A genes 201 are resistant to penicillin and 13 are resistant to levofloxacin. This data shows that *S. pneumoniae* that are resistant to penicillin, erythromycin, and levofloxacin are inhibited by low concentrations of telithromycin.

Table 2. In vitro activity of telithromycin and other antimicrobials against *S. pneumoniae* resistant to erythromycin by possession if the *erm*B or *mef*A and *erm*B+*mef*A genes

	S. pneumoniae resistant to erythromycin by possession of the following genes		
	*erm*B	*mef*A	*erm*B+*mef*A
Antimicrobial	MIC_{90} (µg/mL)	MIC_{90} (µg/mL)	MIC_{90} (µg/mL)

Telithromycin	0.5	1	1
Erythromycin A	>256	16	>256
Penicillin G	4	4	4
Levofloxacin	1	1	1

Number of isolates: *erm*B = 527, *mefA* =2,155, *erm*B+*mef*A = 300

Table 3 shows in vitro activity of telithromycin against *S. pneumoniae* that are resistant to a variety of antimicrobials. Here as seen these organisms are susceptible to low concentrations of telithromycin.

Table 3. In vitro activity of telithromycin against *S. pneumoniae* resistant to a variety of antimicrobials

Antimicrobial	No. of isolates	Telithromycin MIC_{90} (µg/mL)
Cefotaxime		
susceptible	102	0.25
intermediate	168	0.5
resistant	148	1
Tetracycline resistant	15	0.01
Co-trimoxazole resistant	20	0.007
Ofloxacin resistant	15	0.03
Levofloxacin resistant	81	1

CONCLUSION – *S. pneumoniae*

The in vitro data shown in Tables 1 to 3 show that regardless of the susceptibility of *S. pneumoniae* to other antimicrobials *S. pneumoniae* is inhibited by low concentrations of telithromycin. The concentrations of telithromycin that inhibit these organisms are achievable using the proposed dosing regimen for telithromycin (see "Pharmacokinetic" section).

STAPHYLOCOCUS AUREUS

Table 4 shows in vitro susceptibility test results for a variety of *S. aureus*. As seen, those *S. aureus* that are constitutively resistant to erythromycin have higher telithromycin MICs compared to those *S. aureus* that are inducibly resistant to erythromycin. The telithromycin MICs for the isolates of *S. aureus* that are constitutively resistant to erythromycin exceed the therapeutically achievable concentrations of telithromycin that can be achieved with the proposed dosing regimen (see "Pharmacokinetic" section).

Table 4. Telithromycin MICs for *Staphylococcus aureus*

Phenotypic characteristic	No. of isolates	MIC range (μg/mL)	MIC_{50} range (μg/mL)	MIC_{90} range (μg/mL)
Methicillin susceptible (MSSA)	614	0.015->128	0.04-0.13	0.12-0.3
MSSA erythromycin susceptible	547	≤0.03-0.25	0.12	0.12
MSSA erythromycin resistant	24	0.06->128	0.12	>128
MSSA inducible resistant to erythromycin	86	0.02-128	0.5	1
MSSA constitutively resistant to erythromycin	15	>128	>128	>128
Methicillin resistant (MRSA)	503	0.005->128	0.04->128	0.03->128
MRSA erythromycin susceptible	45	0.03-0.25	0.13	0.12-0.25
MRSA erythromycin resistant	120	0.03->128	0.25->32	>128
MRSA inducible resistance to erythromycin	20	0.06-0.25	0.13	0.13
MRSA constitutively resistant to erythromycin	20	>128	>128	>128

CONCLUSION - *S. aureus*

Staphylococcus aureus that are constitutively resistant to erythromycin are resistant to telithromycin. Therefore it is appropriate to indicate in the package insert that telithromycin should be used to treat only those infections that are caused by erythromycin susceptible *S. aureus*. *S. aureus* that are not constitutively resistant to erythromycin are inhibited in vitro by concentrations of telithromycin that are achievable using the proposed dosing regimen (see "Pharmacokinetic" section).

HAEMOPHILUS INFLUENZAE

Table 5 shows in vitro activity of telithromycin against *H. influenzae*. A higher concentration of telithromycin is required to inhibit these organisms than is needed to inhibit the growth of *S. pneumoniae* or *S. aureus*. The isolates of *H. influenzae* that are resistant to ampicillin have a higher telithromycin MIC than those that are susceptible to ampicillin.

Table 5. In vitro activity of telithromycin (μg/mL) against ampicillin susceptible and resistant *Haemophilus influenzae*

H. influenzae	No. of Isolates	MIC Range	MIC_{50} or Range	MIC_{90} or Range
Ampicillin susceptible	699	<0.06-8	1	2
Ampicillin resistant by β-lactamase production	226	<0.06 -16	2	4
Ampicillin resistant β lactamase negative	27	0.12 - 4	2	4

Investigations into the susceptibility of *H. influenzae* to various antimicrobials shows that *H. influenzae* resistant to cefuroxime (≥16 μg/mL) have elevated telithromycin MICs (1). This data is shown in Table 6.

Table 6. Telithromycin MIC_{90s} for cefuroxime-susceptible and resistant *Haemophilus influenzae*

Organism	Number of isolates	Telithromycin MIC_{90} (µg/mL)
H. influenzae cefuroxime susceptible	101	4
H. influenzae cefuroxime resistant	42	16

CONCLUSION *H. influenzae*

The 4 µg/mL concentration needed to inhibit the growth of ampicillin-resistant *H. influenzae* puts them at the upper concentration of telithromycin that is achievable using the proposed dosing regimen (see "Pharmacokinetic" section). *Haemophilus influenzae* that are resistant to cefuroxime have elevated telithromycin MICS, some as high as 16 µg/mL. The telithromycin MIC of 16 µg/mL is outside the telithromycin therapeutic level that can be achieved with the proposed dosing regimen (see "Pharmacokinetic" section). These organisms may not respond to treatment with telithromycin. It is estimated that there are < 2% of *H. influenzae* in the United States that are resistant to cefuroxime. It is felt, by this reviewer, that it is not necessary at this time to put a note in the package insert concerning cefuroxime-resistant *H. influenzae* and their susceptibility to telithromycin. This situation does, however, warrant post marketing surveillance and should be evaluated if clinical failures are reported to the Agency when telithromycin is used to treat *H. influenzae* infections.

MORAXELLA CATARRHALIS

Table 7 shows in vitro susceptibility of *M. catarrhalis* to telithromycin. The literature (1) reports that the in vitro activity of telithromycin is equivalent against both β-lactamase negative and β-lactamase positive isolates of *M. catarrhalis*. Better than 90% of *M. catarrhalis* in the U.S. produce β-lactamase.

Table 7. Telithromycin MICs for *Moraxella catarrhalis*

Organism	No. of studies	No. of isolates	MIC_{90} (µg/mL)
Moraxella catarrhalis	4	728	0.12

CONCLUSION – *M. catarrhalis*

Moraxella catarrhalis are susceptible in vitro to concentrations of telithromycin that are achievable using the proposed telithromycin dosing regimen (see "Pharmacokinetic" section).

INTRACELLULAR BACTERIA

Table 8 shows in vitro activity of telithromycin against bacteria that live within cells. Because standardized in vitro susceptibility test methods do not exist for these organisms the results in Table 8 have been determined by a variety of methods. Telithromycin concentrates in cells (e.g. macrophages- see "Pharmacokinetic" section) to concentrations that are greater than the in vitro concentrations of telithromycin, shown in this table, needed to inhibit the growth of these organisms. This data suggests that telithromycin may have efficacy against these organisms in vivo.

Table 8. In vitro activity of telithromycin against intracellular bacteria

Organism	No. of studies	No. of isolates	MIC_{90} Range (µg/mL)
Legionella pneumophila	3	136	0.03-0.12
Chlamydia pneumoniae	2	20	0.03-2.0*
Mycoplasma pneumoniae	3	87	0.0009-0.005

*Not a MIC_{90} range because of the small number of isolates

CONCLUSION - Intracellular bacteria

The concentrations of telithromycin that have been shown to accumulate in the macrophages using the proposed telithromycin dosing regimen (see "Pharmacokinetic" section) are higher than the telithromycin concentrations that have been shown in vitro to inhibit the growth of *L. pneumophila*, *C. pneumoniae*, and *M. pneumoniae*. This suggests that telithromycin may be effective for treating infections due to these organisms.

OTHER BACTERIA

The applicant has also provided in vitro susceptibility test information for other bacteria. Information provided for these bacteria did not include bacteriological and clinical outcome information or the information was not sufficient. The organisms for which in vitro susceptibility data for 100 isolates or more was provided, those that are associated with the indications sought and for which 90% or greater of the tested population are susceptible by in vitro test criteria to therapeutically achievable concentrations of telithromycin using the dosage regimen proposed by the applicant are shown in Table 9. Note: The *Peptostreptococcus* spp. data was received from Aventis by e-mail on 24 Mar 04.

Table 9. Activity of telithromycin against bacteria associated with indications for which their are no clinical-study data

Organism	No. of Isolates	Telithromycin MIC_{90} (µg/mL) Range
Legionella pneumophila	136	0.03- 0.12
Staphylococcus aureus erythromycin susceptible	592	0.12-0.25
Streptococci Lancefield Groups C and G	161	0.015-0.06
Streptococcus pyogenes	499	0.015-0.06
Viridans streptococci	212	≤0.003-0.05
Anaerobes		
Peptostreptococcus spp.	232	0.008-4.0
Prevotella bivia	189	0.5-1
Prevotella intermedia	175	0.06 (not a range)

Conclusion – Other bacteria

The bacteria in Table 9 meet the criteria for inclusion in the second list of the microbiology section of the package insert.

Mechanism(s) of Action

The mode of action of telithromycin is inhibition of protein synthesis. Telithromycin blocks protein synthesis by binding to domains II and V of 23S rRNA of the 50S ribosomal subunit. By binding at domain II, telithromycin retains activity against gram-positive cocci (e.g. *Streptococcus pneumoniae*) that

by expression of methylase (*erm* gene) alter the domain V binding site. Telithromycin also inhibits the assembly of the nascent 50S ribosomal subunit.

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

Mechanism(s) of resistance

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

Laboratory mutants of *S. pneumoniae* have demonstrated resistance to telithromycin based on

- Type II mutations affecting the L4 proteins
- L22 protein mutations (telithromycin MICs are elevated but still with proposed susceptible range)
- Production of K-peptide, a specific pentapeptide acting as a "bottle brush" that cleans the ribosome of the bound antibiotic

The clinical significance of these laboratory mutants of *S. pneumoniae* is not known. The fact that such mutants could be induced in the laboratory suggests that it may be prudent to monitor for the development of telithromycin in *S. pneumoniae* once the drug is approved.

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*.

Haemophilus influenzae resistant to cefuroxime (≥8 µg/mL) have been shown to have elevated telithromycin MICs (MIC_{90} = 16 µg/mL) compared to cefuroxime susceptible *H. influenzae* (MIC_{90} = 4 µg/mL). The reason for this decreased susceptibility of cefuroxime resistant *H. influenzae* to telithromycin is not understood. The incident of cefuroxime-resistant *H. influenzae* in the Untied States is believed to be <2%.

Erythromycin-resistant *Streptococcus pyogenes* that possess the *erm*B gene, have both an MIC_{50} and MIC_{90} = >32µg/mL. *Streptococcus pyogenes* that do not possess the *erm*B gene have a telithromycin MIC_{90} = 2 µg/mL) Thus telithromycin can be used to treat only those infections that are due to S. pyogenes that do not possess the *erm*B gene.

IN VIVO

Pharmacokinetics

Telithromycin is 60 to 70% protein bound. Albumin is the major serum factor responsible for binding (25%) with lower concentrations from acid α l-glycoprotein (11%) and lipoproteins LDL and VLDL and HDL (10%) each.

The dosing regimen for telithromycin is:

Infection	Daily dose and route of administration	Frequency of administration	Duration of treatment
Acute bacterial exacerbation of chronic bronchitis	800 mg oral (2 tablets of 400 mg)	once daily	5 days
Acute bacterial sinusitis	800 mg oral (2 tablets of 400 mg)	once daily	5 days
Community-acquired pneumonia	800 mg oral (2 tablets of 400 mg)	once daily	7-10 days

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

Table 10. Pharmacokinetic parameters in young subjects after single and multiple (qd) oral dosing with 800 mg telithromycin

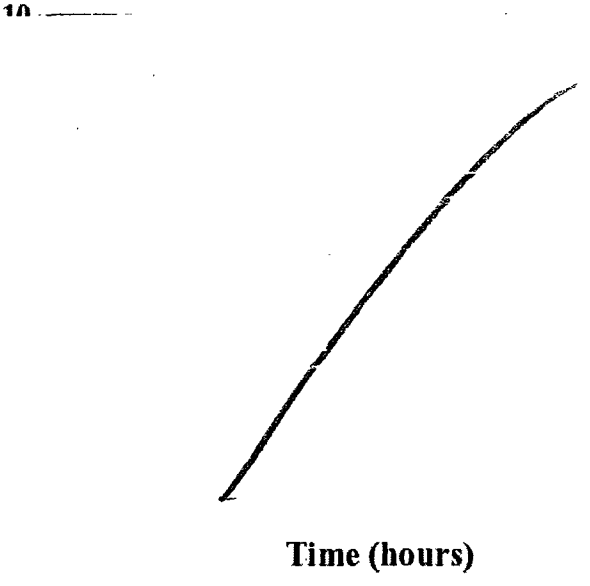
	Mean (CV %)	
	SD	MD
Parameter (plasma)	N=18	N=18
C_{max} (µg/mL)	1.90 (42)	2.27 (31)
T_{max} (h)	1.0[a]	1.0[a]
C_{24}(µg/mL)	0.030 (45)	0.070 (72)
AUC(0-24) (µg.h/mL)	8.25 (31)	12.5 (43)
$t_{½\lambda 1}$(h)[c]	2.43 (41)	2.87 (50)
$t_{½\lambda z}$(h)[c]	7.16 (19)	9.81 (20)

SD = single dose, MD = day 7 of multiple dose (once daily for 7 days)
a = Median
b - [min-max]
c = elimination half-lives calculated using a compartmental model

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. No pharmacokinetic differences were seen between men and women.

Plasma concentrations in young and elderly (≥ 60 years old) subjects receiving an 800-mg dose of telithromycin are shown below. The graph shows that elderly people eliminate telithromycin at a slower rate than young people. However, the difference in elimination rate does not justify different dosing regimens for these populations.

Telithromycin plasma concentrations in young and elderly subjects



The volume of distribution of telithromycin in various biological tissues after multiple dosing is shown in Table 11. As seen in Table 11 the epithelial lining fluid had concentrations of telithromycin for up to 24 hours that were greater then the MIC_{90s} for the target pathogens. In the case of the alveolar macrophages the concentration of telithromycin at 48 hours was above the MIC_{90s} of the target pathogens.

Table 11. Concentrations of telithromycin after dosing with 800 mg in respiratory tissue and macrophages

		Mean concentration (µg/mL) at				
Tissue	Subject	2h	8h	12h	24h	48h
Epithelial lining fluid	Healthy	5.4	4.2	-	1.17	0.3
	RTI patients	14.9	-	3.27	0.84	-
Alveolar macrophages	Healthy	65	100	-	41	2.15
	RTI patients	69	-	318	162	-

RTI = Respiratory tract infection

The pharmacokinetics in elderly patients (≥65 years) with CAP compared to young subjects (≤65 years) indicates that there is a 1.3 fold increase in C_{max} and a 1.4 fold increase in AUC in elderly patients at the therapeutic dose of telithromycin (800 mg qd). A similar magnitude of change was observed in healthy elderly subjects.

The pharmacokinetics of telithromycin in 200 patients with CAP (mean age 42.6 years) was evaluated. At the on-therapy visit (day 3 to 5), blood samples were collected before dosing and a 1, 2, 4, 6 and 8 hours after dosing. The telithromycin C_{max} and AUC values were 2.89 µg/mL and 13.0 µg.h/mL respectively.

This compares to 2.27 µg/mL and 12.5 µg.h/mL in healthy subjects. It appears that respiratory infections do not alter the pharmacokinetics of telithromycin.

Compared with control subjects, plasma concentrations of telithromycin in subjects with mild to severe renal impairment were 1.4 fold higher for C_{max} to 1.5 fold higher for AUC.

For patients with hepatic impairment the C_{max} and AUC values were similar to those in healthy patients. Metabolic clearance of telithromycin was lower in patients with hepatic impairment but there was also a 1.4 fold increase in renal clearance in these patients that resulted in no change in exposure. There was a slight increase in the terminal half-life in subjects with hepatic impairment (1.2 to 1.4 fold increase). The applicant does not feel that that this will result in further accumulation after multiple dosing given the minor contribution of the terminal half-life to the overall AUC of telithromycin.

Pharmacodynamics

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

Clinical efficacy

Telithromycin has been evaluated clinically in 3 therapeutic areas:

- Community acquired pneumoniae (CAP)
- Acute exacerbation of chronic bronchitis (AECB)
- Acute bacterial sinusitis

All the clinical studies were designed according to the FDA "Points to Consider" and the Infectious Disease Society of America guidelines. All studies were international in scope and the FDA-approved protocol was common to all study centers. Microbiology was performed at central laboratories in the United States (CMI, Portland, OR) and in Europe (GR Micro, London). All susceptibility testing was done according to National Committee for Clinical Laboratory (NCCLS) standards (**2,3**). Each study site isolated the organisms and screened for antimicrobial susceptibility with a disk diffusion assay. Isolates were then sent to the central laboratories for re-identification, zone size of inhibition and MIC determination. Because 2 central laboratories were involved in producing the microbiological data there was a validation study conducted by exchange of isolates between the 2 laboratories. The validation study of the susceptibility test method results for the two central laboratories showed that 97.7% of the results were within ± 1 two fold dilution. The laboratories tested isolates of *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, *Haemophilus parainfluenzae*, and *M. catarrhalis* for their susceptibility to telithromycin and other antimicrobials. Being within ± 1 two-fold dilution is within the technical variability of the test method. This allows the results from the two laboratories to be combined.

The main analysis populations for determining telithromycin efficacy in the clinical studies were as follows:

Population	Definition
mITT	All randomized subjects, as treated, with a confirmed diagnosis of infection who received at least 1 dose of study medication. A confirmed diagnosis was defined by clinical signs and symptoms and X-ray findings, as specified in the protocols. This definition was intended to exclude subjects with a clear misdiagnosis, for whom study medication could have no therapeutic effect.

PPc	All mITT subjects except those with major protocol violations and/or indeterminate responses
bmITT	All mITT subjects with a pathogen at pretherapy/entry considered by the investigator to be responsible for infection
PPb	All PPc subjects with isolation of a causative pathogen from an adequate culture at pretherapy/entry.

All of the bacteriological analysis of clinical trial data that follows is based on the PPb population unless otherwise indicated.

Streptococcus pneumoniae

In the following disease entities caused by *S. pneumoniae* the patient populations were analyzed to determine if the following (Table 12) proposed in vitro susceptibility test interpretive criteria were appropriate for classifying an isolate of *S. pneumoniae* as susceptible, intermediate or resistant to telithromycin.

Table 12. Telithromycin proposed interpretive criteria MIC breakpoints for *Streptococcus pneumoniae*

	MIC (µg/mL)
Interpretive category	*S. pneumoniae*
Susceptible	≤1.0
Intermediate	2
Resistant	≤4.0

Community acquired pneumoniae (CAP)

A total of 2,991 patients were enrolled in CAP studies (excluding patients in Japanese studies). There were 2,289 patients scheduled to receive telithromycin and 702 for comparator drugs. These represented the mITT population. The clinical cure rate was 83.1% for telithromycin and 80.9% for the combined comparators (amoxicillin, clarithromycin and trovafloxacin).

For the PPb population (evaluable patients with bacteriologic outcome) there were 799 patients, 653 of whom received telithromycin and 144 of whom received comparator dugs (clarithromycin, trovafloxacin, or amoxicillin). The overall bacterial eradication rate (or presumed eradication rate) was 90.4% for telithromycin and 91.6% for comparator drugs. Since the applicant is proposing that telithromycin can be used for the treatment of CAP due to resistant strains of *S. pneumoniae* data for such isolates [Pen-R, Ery-R, Ery-R(*mef*A) and Ery-R (*erm*B)] have been analyzed separately.

Table 13 shows bacteriological and clinical outcomes for CAP studies. No clinical isolates with telithromycin MICs > 1 µg/mL were recovered during these studies. There were 5 isolates at 1.0 µg/mL (proposed susceptible breakpoint) and 3 at 0.5 µg/mL. As noted all of these patients were clinical cures and had eradication (or presumed eradication) of *S. pneumoniae.*

Table 13. Community acquired pneumonia studies: *S. pneumoniae*- telithromycin MICs, bacterial eradication, and clinical cure rates

Telithromycin MIC (µg/mL)	Number	Bacterial Eradication/Presumed (%)	Clinical Outcome Cure (%)

		Eradicated	
0.004	4	4 (100)	4 (100)
0.008	125	123 (98.4)	121 (96.8)
0.015	32	30 (93.8)	29 (90.6)
0.016	81	79 (97.5)	77 (95.1)
0.03	23	21 (91.3)	21 (91.3)
0.06	6	6 (100)	6 (100)
0.12	6	4 (66.7)	4 (66.7)
0.25	1	1 (100	1 (100
0.5	3	3 (100)	3 (100)
1	5	5 (100)	5 (100)
Total	286	276 (96.5)	271 (94.8)

Table 14 shows telithromycin MICs for the *S. pneumoniae* isolated from blood of patients with CAP and the percent with bacterial eradication. As with the CAP isolates there were 3 isolates at the proposed susceptible breakpoint (1 µg/mL) and all 3 patients had bacterial eradication. There were 6 penicillin-resistant *S. pneumoniae* isolates from the blood of which 4 were eradicated. There were also 6 erythromycin-resistant *S. pneumoniae* of which 4 were eradicated.

Table 14. Telithromycin MICs for *S. pneumoniae* blood isolates and eradication (presumed)

Telithromycin MIC (µg/ml)	Number	Eradication (%)
0.008	32	32 (100)
0.015	13	11 (84.6)
0.016	14	13 (92.9)
0.03	5	4 (80)
0.06	3	3 (100)
0.12	2	1 (50)
1	3	3 (100)
Total	72	67 (93.1)

Table 15 shows telithromycin MICs for the penicillin-resistant isolates from CAP patients and the percent eradication (presumed eradication). As can be seen when comparing Table 15 and 13 there is one of the 5 *S. pneumoniae* that was penicillin resistant that had a telithromycin MIC of 1 µg/mL. Two of the three *S pneumoniae* that have a telithromycin MIC of 0.5 µg/mL were penicillin resistant and the one *S. pneumoniae* with a telithromycin MIC of 0.25 µg/mL is penicillin resistant. All of the patients' penicillin-resistant *S. pneumoniae* had 100% bacterial eradication (presumed) and clinical cure.

Table 15. Telithromycin MICs and bacterial eradication (presumed) for penicillin resistant *Streptococcus pneumoniae*

Telithromycin MIC (µg/mL)	Numbers	Bacterial eradication (%)
0.008	3	3 (100)
0.15	2	2 (100)
0.03	6	4 (66.7)
0.06	2	2 (100)
0.12	2	1 (50)
0.25	1	1 (100)

0.5	2	2 (100)
1	1	1 (100)
Total	19	16 (84.2)

Table 16 shows telithromycin MIC for those isolates from CAP patients that were resistant to erythromycin and the bacterial eradication (presumed) rates. As seen when these results are compared to Table 13 all of the isolates with MICs ranging from 0.25 to 1 µg/mL were resistant to erythromycin. All of the patients with these isolates had 100% eradication and clinical cure.

Table 16. Telithromycin MICs and bacterial eradication for erythromycin-resistant S. pneumoniae from CAP patients

Telithromycin MIC (µg/mL)	Numbers	Bacterial eradication/presumed (%)
0.016	1	1 (100)
0.03	9	7 (77.8)
0.06	5	5 (100)
0.12	5	3 (60.0)
0.25	1	1 (100)
0.5	3	3 (100)
1	5	5 (100)
Total	29	25 (86.2)

Because *S. pneumoniae* can be resistant to erythromycin by at least two individual mechanisms and by a combination of these mechanisms (*mef*A, *erm*B, and *mef*A+*erm*B) the applicant analyzed the telithromycin data by the mechanisms of resistant. Table 17 shows this analysis. The analysis shows that telithromycin has activity at therapeutic levels (see "pharmacokinetic" section) against *S. pneumoniae* resistant to erythromycin by the *mef*(A), *erm*(B) or a combination of the *mef*(A) + *erm*(B) genes.

Table 17. Telithromycin MICs of *S. pneumoniae CAP* isolates with different mechanisms of erythromycin resistance

Genotype	Telithromycin MIC (µg/mL)	Number of Isolates	Eradicated (presumed) (%)
Erythromycin Resistant			
mef(A) only	0.03	1	1 (100)
	0.06	5	5 (100)
	0.12	8	6 (75)
	1	4	4 (100)
Total		18	16 (88.9)
Erythromycin Resistant			
erm(B) only	0.016	2	2 (100)
	0.03	11	8 (72.7)
	0.06	5	4 (80)
	0.12	4	4 (100)
	0.25	3	3 (100)
	0.5	2	2 (100)
	1	1	1 (100)
Total		28	24 (85.7)
Erythromycin Resistant	0.12	1	1 (100)
mef(A) + *erm*(B)	0.5	2	2 (100)

Total	3	3 (100)

Multi-Drug Resistant *S. pneumoniae*

The following information pertains to data in tables 2-5 (as numbered by the applicant in their submission) that analyzed the clinical outcome of patients with CAP caused by multi-drug resistant *S. pneumoniae* (MDRSP).

2.1 DEFINITION OF MULTI-DRUG RESISTANT *STREPTOCOCCUS PNEUMONIAE*

For the purposes of these analyses, multi-drug resistant *S. pneumoniae* (MDRSP) was defined as resistance to at least 2 of the following 5 classes of antimicrobials tested:

- Penicillin
- Macrolide (erythromycin)*
- Cephalosporin (cefuroxime axetil)
- Trimethoprim-sulfamethoxazole (cotrimoxazole)
- Tetracyclines (tetracycline and doxycycline).

* Susceptibility and resistance to azithromycin, clarithromycin, and dirithromycin can be predicted by testing erythromycin [2].

The definition of resistance to each antimicrobial is given in Table 1 below.

Table 1 – Definition of *Streptococcus pneumoniae* antimicrobial resistance according to Minimum Inhibitory Concentration (MIC)* value

Antimicrobial	Abbreviation	MIC (µg/mL)
Penicillin	PEN	≥2
Erythromycin†	ERY	≥1
Cefuroxime axetil	CEF	≥4‡
Cotrimoxazole	COT	≥4/76
Doxycycline+	DOX	≥8‡
Tetracycline+	TET	≥8

*MIC: minimum inhibitory concentration
† Also predicts resistance to azithromycin, clarithromycin, and dirithromycin
‡ Value differs from that provided in *Proposed Approach to Efficacy Analyses: Telithromycin Activity Against Multi-Drug Resistant Streptococcus pneumoniae* (submitted December 22, 2003) to conform to NCCLS criteria [2]
+ resistance to either doxycycline or tetracycline is considered predictive of resistance to other members of the tetracycline class of antimicrobials

2.2 POPULATIONS FOR ANALYSIS

The following definitions were used to select populations for analysis:

- mITT: all randomized subjects, as treated, with a confirmed diagnosis of infection who received at least 1 dose of study medication. A confirmed diagnosis was defined by clinical signs and symptoms, and X-ray findings, as defined in the protocols.

- PPc: all mITT subjects except those with major protocol violations and/or indeterminate responses.
- PPb: All PPc subjects with isolation of a causative pathogen from an adequate culture at pretherapy/entry.
- bmITT: All mITT subjects with a pathogen at pretherapy/entry considered by the investigator to be responsible for infection. In the bmITT analyses, subjects with indeterminate or missing outcomes are treated as failures ($bmITT_{(f)}$). A sensitivity analysis performed in the bmITT population which indeterminate outcomes are treated as missing is also provided ($bmITT_{(m)}$).

2.3 INCLUDED STUDIES

Data from the following studies were included in the analyses:

- **CAP**: controlled CAP studies 3001, 3006, 3009 (without centers excluded by the agency per *Amendment 1*), and 4003 (as requested in the January 24, 2003, Approvable letter, the 5-day telithromycin treatment group from Study 4003 was excluded from the aggregate analysis); uncontrolled CAP studies 3000, 3009OL, 3010 and 3012. Tables are provided for the following: All Studies, Controlled Studies, Uncontrolled Studies, Individual Studies. For CAP subjects with pneumococcal bacteremia, tables are provided for All Studies only.
- **AECB**: controlled studies 3003, 3007 (without centers excluded by the Agency per *Amendment 1*), and 3013. Tables are provided for the following: All Studies and Individual Studies.
- **AS**: controlled studies 3005 (without centers excluded by the Agency per *Amendment 1*), and 3011. For purposes of comparison, only the 5-day treatment group from Study 3005 is pooled with Study 3011 in the aggregate rows. Tables are provided for the following: Controlled Studies and Individual Studies.

2.4 DESCRIPTION OF TABLES

Tables display the clinical outcome (cure, failure, indeterminate) of patients with *S. pneumoniae* in the PPb and bmITT populations, according to treatment regimen (columns), and are presented according to the resistance profile of the isolated organism (rows), as follows:

- **PEN-R**: isolate resistant to penicillin*
- **ERY-R**: isolate resistant to erythromycin*
- **PEN-R & ERY-R**: isolate resistant to penicillin and erythromycin*
- **PEN-R and/or ERY-R**: isolate resistant to penicillin and/or erythromycin*

* these resistance profiles could include resistance to additional antibiotics that were tested

- **PEN-R only**: isolate showed resistance to penicillin and no other antibiotic tested
- **ERY-R only**: isolate showed resistance to erythromycin and no other antibiotic tested

- **PEN-R and at least 1 other antibiotic**: isolate showed resistance to penicillin and at least 1 other antibiotic tested
- **ERY-R and at least 1 other antibiotic**: isolate showed resistance to erythromycin and at least 1 other antibiotic tested
- **CEF-R and at least 1 other antibiotic**: isolate showed resistance to cefuroxime axetil and at least 1 other antibiotic tested
- **COT-R and at least 1 other antibiotic**: isolate showed resistance to cotrimoxazole (trimethoprim-sulfamethoxazole) and at least 1 other antibiotic tested
- **TET-R and at least 1 other antibiotic**: isolate showed resistance to doxycycline or tetracycline, together with at least 1 other antibiotic tested
- **MDRSP**: isolate showed resistance to any 2 of the antibiotics tested

Table 2 – Clinical cure at posttherapy/test of cure in community acquired pneumonia[a] subjects with antibiotic-resistant *Streptococcus pneumoniae* (all studies)

	PPb				bmITT$_{(m)}$				bmITT$_{(f)}$			
	Telithromycin		Comp [b]		Telithromycin		Comp [b]		Telithromycin		Comp [b]	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
All *S. pneumoniae*	312/333	(93.7)	63/70	(90.0)	366/396	(92.4)	79/91	(86.8)	366/425	(86.1)	79/104	(76.0)
PRSP +/or ERSP	37/41	(90.2)	5/6		42/48	(87.5)	6/7		42/53	(79.2)	6/7	
PRSP	20/23	(87.0)	1/1		22/27	(81.5)	2/2		22/31	(71.0)	2/2	
ERSP	29/33	(87.9)	4/5		33/38	(86.8)	5/6		33/41	(80.5)	5/6	
PRSP + ERSP	12/15	(80.0)	0/0		13/17	(76.5)	1/1		13/19	(68.4)	1/1	
PRSP only	0/0		0/0		0/0		0/0		0/0		0/0	
ERSP only	5/6		0/0		5/6		0/0		5/6		0/0	
MDRSP	34/37	(91.9)	5/6		40/45	(88.9)	8/9		40/50	(80.0)	8/9	
MDRSP incl. PEN	20/23	(87.0)	1/1		22/27	(81.5)	2/2		22/31	(71.0)	2/2	
MDRSP incl. ERY	24/27	(88.9)	4/5		28/32	(87.5)	5/6		28/35	(80.0)	5/6	
MDRSP incl. CEF	22/24	(91.7)	2/2		25/29	(86.2)	5/5		25/33	(75.8)	5/5	
MDRSP incl. COT	26/29	(89.7)	3/3		30/34	(88.2)	6/6		30/39	(76.9)	6/6	
MDRSP incl. TET	10/12	(83.3)	3/4		15/18	(83.3)	3/4		20/15	(75.0)	3/4	

[a] all CAP studies: 3000, 3001, 3006, 3009, 3009OL, 3010, 3012 (complete), and 4003 (not including 5-day treatment group, per Agency request).
[b] Comp: comparators in controlled studies: amoxicillin (Study 3001); clarithromycin (Studies 3006 and 4003); trovafloxacin (Study 3009).
bmITT$_{(f)}$: bmITT population with indeterminate treated as failure; bmITT$_{(m)}$: bmITT population with indeterminate treated as missing.
PRSP: penicillin-resistant *S. pneumoniae*; **ERSP**: erythromycin-resistant *S. pneumoniae*; **PRSP+ERSP**: *S. pneumoniae* resistant to penicillin and erythromycin; **PRSP+/or ERSP**: *S. pneumoniae* resistant to penicillin and/or erythromycin; **PRSP only**: *S. pneumoniae* resistant to penicillin and no other antibiotic; **ERSP only**: *S. pneumoniae* resistant to erythromycin and no other antibiotic; **MDRSP**: multi-drug resistant *S. pneumoniae* including resistance to any 2 or more of the tested classes; **MDRSP incl.**: MDRSP including resistance to one of the following antibiotics as indicated: **PEN**: penicillin; **ERY**: erythromycin; **CEF**: cefuroxime axetil; **COT**: trimethoprim-sulfamethoxazole; **TET**: tetracyclines

Table 3 - Clinical cure at posttherapy/test of cure in community acquired pneumonia[a] subjects with antibiotic-resistant *Streptococcus pneumoniae* (all controlled studies)

	PPb				$bmITT_{(m)}$				$bmITT_{m}$			
	Telithromycin		Comp [b]		Telithromycin		Comp [b]		Telithromycin		Comp [b]	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
All *S. pneumoniae*	73/78	(93.6)	63/70	(90.0)	90/98	(91.8)	79/91	(86.8)	90/109	(82.6)	79/104	(76.0)
PRSP+/or ERSP	7/8		5/6		7/9		6/7		7/10		6/7	
PRSP	3/4		1/1		3/5		2/2		3/6		2/2	
ERSP	5/6		4/5		5/6		5/6		5/6		5/6	
PRSP + ERSP	1/2		0/0		1/2		1/1		1/2		1/1	
PRSP only	0/0		0/0		0/0		0/0		0/0		0/0	
ERSP only	2/2		0/0		2/2		0/0		2/2		0/0	
MDRSP	6/7		5/6		7/9		8/9		7/10	(70.0)	8/9	
MDRSP incl. PEN	3/4		1/1		3/5		2/2		3/6		2/2	
MDRSP incl. ERY	3/4		4/5		3/4		5/6		3/4		5/6	
MDRSP incl. CEF	4/4		2/2		4/5		5/5		4/6		5/5	
MDRSP incl. COT	5/6		3/3		6/7		6/6		6/8		6/6	
MDRSP incl. TET	1/2		3/4		2/4		3/4		2/4		3/4	

[a] all controlled CAP studies: 3001, 3006, 3009, and 4003 (not including 5-day treatment group, per Agency request).
[b] Comp: comparators in controlled studies: amoxicillin (Study 3001); clarithromycin (Studies 3006 and 4003); trovafloxacin (Study 3009).
$bmITT_{m}$: bmITT population with indeterminate treated as failure; **$bmITT_{m}$**: bmITT population with indeterminate treated as missing.
PRSP: penicillin-resistant *S. pneumoniae*; **ERSP**: erythromycin-resistant *S. pneumoniae*; **PRSP+ERSP**: *S. pneumoniae* resistant to penicillin and erythromycin; **PRSP+/or ERSP**: *S. pneumoniae* resistant to penicillin and/or erythromycin; **PRSP only**: *S. pneumoniae* resistant to penicillin and no other antibiotic; **ERSP only**: *S. pneumoniae* resistant to erythromycin and no other antibiotic; **MDRSP**: multi-drug resistant *S. pneumoniae* including resistance to any 2 or more of the tested classes; **MDRSP incl.**: MDRSP including resistance to one of the following antibiotics as indicated: **PEN**: penicillin; **ERY**: erythromycin; **CEF**: cefuroxime axetil; **COT**: trimethoprim-sulfamethoxazole; **TET**: tetracyclines

Table 4 - Clinical cure at posttherapy/test of cure in community acquired pneumonia[a] subjects with antibiotic-resistant *Streptococcus pneumoniae* (all uncontrolled studies)

	PPb		$bmITT_{(m)}$		$bmITT_{(f)}$	
	n/N	(%)	n/N	(%)	n/N	(%)
All *S. pneumoniae*	239/255	(93.7)	276/298	(92.6)	276/316	(87.3)
PRSP+/or ERSP	30/33	(90.0)	35/39	(89.7)	35/43	(81.4)
PRSP	17/19	(89.5)	19/22	(86.4)	19/25	(76.0)
ERSP	24/27	(88.9)	28/32	(87.5)	28/35	(80.0)
PRSP + ERSP	11/13	(84.6)	12/15	(80.0)	12/17	(70.6)
PRSP only	0/0		0/0		0/0	
ERSP only	3/4		3/4		3/4	
MDRSP	28/30	(93.3)	33/36	(91.7)	33/40	(82.5)
MDRSP incl. PEN	17/19	(89.5)	19/22	(86.4)	19/25	(76.0)
MDRSP incl. ERY	21/23	(91.3)	25/28	(89.3)	25/31	(80.6)
MDRSP incl. CEF	18/20	(90.0)	21/24	(87.5)	21/27	(77.8)
MDRSP incl. COT	21/23	(91.3)	24/27	(88.9)	24/31	(77.4)
MDRSP incl. TET	9/10	(90.0)	13/14	(92.9)	13/16	(81.3)

[a] all uncontrolled CAP studies: 3000, 3009OL, 3010, and 3012.
$bmITT_{(f)}$: bmITT population with indeterminate treated as failure; **$bmITT_{(m)}$**: bmITT population with indeterminate treated as missing.
PRSP: penicillin-resistant *S. pneumoniae*; **ERSP**: erythromycin-resistant *S. pneumoniae*; **PRSP+ERSP**: *S. pneumoniae* resistant to penicillin and erythromycin: **PRSP+/or ERSP**: *S. pneumoniae* resistant to penicillin and/or erythromycin; **PRSP only**: *S. pneumoniae* resistant to penicillin and no other antibiotic; **ERSP only**: *S. pneumoniae* resistant to erythromycin and no other antibiotic; **MDRSP**: multi-drug resistant *S. pneumoniae* including resistance to any 2 or more of the tested classes; **MDRSP incl.**: MDRSP including resistance to one of the following antibiotics as indicated: **PEN**: penicillin; **ERY**: erythromycin; **CEF**: cefuroxime axetil; **COT**: trimethoprim-sulfamethoxazole; **TET**: tetracyclines

Table 5 - Clinical cure at posttherapy/test of cure in community acquired pneumonia[a] subjects with antibiotic-resistant *Streptococcus pneumoniae* bacteremia (all studies)

	PPb				$bmITT_{(m)}$				$bmITT_{(f)}$			
	Telithromycin		Comp [b]		Telithromycin		Comp [b]		Telithromycin		Comp [b]	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Total bacteremia	67/76	(88.2)	15/19	(78.9)	71/83	(85.5)	15/21	(71.4)	71/92	(77.2)	15/24	(62.5)
PRSP+/or ERSP	11/13	(84.6)	0/1		11/13	(84.6)	0/1		11/16	(68.8)	0/1	
PRSP	5/7		0/0		5/7		0/0		5/10	(50.0)	0/0	
ERSP	8/10	(80.0)	0/1		8/10	(80.0)	0/1		8/11	(72.7)	0/1	
PRSP + ERSP	2/4		0/0		2/4		0/0		2/5		0/0	
PRSP only	0/0		0/0		0/0		0/0		0/0		0/0	
ERSP only	0/0		0/0		0/0		0/0		0/0		0/0	
MDRSP	11/13	(84.6)	0/1		11/13	(84.6)	0/1		11/16	(68.8)	0/1	
MDRSP incl. PEN	5/7		0/0		5/7		0/0		5/10		0/0	
MDRSP incl. ERY	8/10	(80.0)	0/1		8/10	(80.0)	0/1		8/11	(72.7)	0/1	
MDRSP incl. CEF	5/7		0/0		5/7		0/0		5/10	(50.0)	0/0	
MDRSP incl. COT	7/9		0/0		7/9		0/0		7/12	(58.3)	0/0	
MDRSP incl. TET	4/5		0/1		4/5		0/1		4/6		0/1	

[a] all CAP studies: 3000, 3001, 3006, 3009, 3009OL, 3010, 3012 (complete), and 4003 (not including 5-day treatment group, per Agency request).
[b] Comp: comparators in controlled studies: amoxicillin (Study 3001); clarithromycin (Studies 3006 and 4003); trovafloxacin (Study 3009).
$bmITT_{(f)}$: bmITT population with indeterminate treated as failure; $bmITT_{(m)}$: bmITT population with indeterminate treated as missing.
PRSP: penicillin-resistant *S. pneumoniae*; **ERSP**: erythromycin-resistant *S. pneumoniae*; **PRSP+ERSP**: *S. pneumoniae* resistant to penicillin and erythromycin; **PRSP+/or ERSP**: *S. pneumoniae* resistant to penicillin and/or erythromycin; **PRSP only**: *S. pneumoniae* resistant to penicillin and no other antibiotic; **ERSP only**: *S. pneumoniae* resistant to erythromycin and no other antibiotic; **MDRSP**: multi-drug resistant *S. pneumoniae* including resistance to any 2 or more of the tested classes; **MDRSP Incl.**: MDRSP including resistance to one of the following antibiotics as indicated: **PEN**: penicillin; **ERY**: erythromycin; **CEF**: cefuroxime axetil; **COT**: trimethoprim-sulfamethoxazole; **TET**: tetracyclines

CONCLUSION – CAP - *S. pneumoniae*

The data from the CAP clinical study shows that telithromycin was active at therapeutically achievable levels against penicillin and/or erythromycin-resistant *S. pneumoniae*. Cap infections due to penicillin and/or erythromycin-resistant *S. pneumoniae* had a bacterial eradication rate of 50 to 100%. The overall bacterial eradication rate for CAP due to *S. pneumoniae* was 97% with a clinical cure rate of 95%. No *S. pneumoniae* isolates from CAP had a telithromycin MIC greater than 1 µg/mL.

From the summary of clinical outcome for patients who had CAP due to multi-drug resistant *S. pneumoniae* it is evident that clinical cure rates in telithromycin-treated patients are similar irrespective of the classes of antibiotic to which the *S. pneumoniae* were resistant. The lowest cure rates were seen in the PRSP+ERSP category.

In the case of patients with CAP due to multi-drug resistant *S. pneumoniae* with bacteremia the cure rate in the PPb group was 80% and higher.

The proposed in vitro susceptibility test interpretive criteria for *S. pneumoniae* of ≤1 µg/mL = susceptible, 2 µg/mL = intermediate and ≥4 µg/mL = resistant to telithromycin are appropriate for *S. pneumoniae* associated with CAP.

Acute exacerbations of chronic bronchitis (AECB)

Table 18 shows the telithromycin MICs for isolates of *S. pneumoniae* from cases of AECB and the bacterial eradication rates. Two of the *S. pneumoniae* isolates were resistant to penicillin. One was eradicated (presumed) by telithromycin. Additionally two isolates were erythromycin resistant. One was eradicated (presumed) by telithromycin.

Table 18. Telithromycin MICs for *Streptococcus pneumoniae* isolates from acute exacerbation of chronic bronchitis and bacterial eradication (presumed) rates

Telithromycin MIC (µg/mL)	Number of Isolates	Eradication (presumed) %
0.008	8	7 (87.5)
0.015	7	6 (85.7)
0.016	8	7 (87.5)
0.03	1	1 (100)
0.12	1	1 (100)
0.5	1	0 (0)
Total	26	22 (84.6)

CONCLUSION – AECB – *S. pneumoniae*

The proposed in vitro susceptibility test interpretive criteria for *S. pneumoniae* of ≤1 µg/mL = susceptible, 2 µg/mL = intermediate and ≥4 µg/mL = resistant to telithromycin are appropriate for *S. pneumoniae* associated with AECB.

Acute bacterial sinusitis

There were 78 *S. pneumoniae* isolates from patients in the PPb population of the acute sinusitis clinical trials. Table 19 shows the telithromycin MICs for the isolates and the bacterial eradication rates. Overall 70 (89.7%) of the 78 S. pneumoniae were eradicated with telithromycin therapy. Thirteen (17%) of the 78 *S. pneumoniae* isolates were penicillin resistant. Eleven (85%) of the 13 penicillin-resistant isolates were eradicated. One of the penicillin-resistant *S. pneumoniae* that was eradicated had a telithromycin MIC of 2 µg/mL. Twenty-one of the *S. pneumoniae* were resistant to erythromycin and 18 (86%) were eradicated with telithromycin treatment. Eleven of the *S. pneumoniae* isolates were resistant to both penicillin and erythromycin. Nine (82%) of the 11 were eradicated with telithromycin treatment.

Table 19. Telithromycin MICs for *Streptococcus pneumoniae* isolates from acute sinusitis and bacterial eradication (presumed) rates

Telithromycin MIC (µg/mL)	Number of Isolates	Eradication (presumed) %
0.004	1	1 (100)

0.008	16	15 (93.8)
0.015	33	30 (90.9)
0.016	1	1 (100)
0.03	12	11 (91.7)
0.06	7	6 (85.7)
0.12	1	0 (0)
0.25	2	1 (50)
0.5	3	3 (100)
1	1	1 (100)
2	1	1 (100)
Total	78	70 (89.7)

The table below (Table 6 as numbered by the applicant) shows the clinical cure rates post therapy for telithromycin in acute bacterial sinusitis patients with multi-drug resistant *S. pneumoniae* (see CAP analysis above for definitions). The clinical cure rate was 75% or better in all of the analyzed populations.

The clinical cure rates posttherapy for telithromycin and comparator-treated ABS subjects with antibiotic-resistant *S. pneumoniae* using data from controlled studies only, are presented in Table 6.

Table 6 - Clinical cure at posttherapy/test of cure in acute bacterial sinusitis[a] subjects with antibiotic-resistant *Streptococcus pneumoniae* (all controlled studies)

	PPb				bmITT$_{(m)}$				bmITT$_{(f)}$			
	Telithromycin		Comp [b]		Telithromycin		Comp [b]		Telithromycin		Comp [b]	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
All *S. pneumoniae*	27/31	(87.1)	14/16	(87.5)	33/37	(89.2)	17/20	(85.0)	33/40	(82.5)	17/21	(81.0)
PRSP +/or ERSP	12/14	(85.7)	6/6		15/17	(88.2)	6/7		15/18	(83.3)	6/8	
PRSP	7/9		4/4		9/11	(81.8)	4/5		9/11	(81.8)	4/6	
ERSP	10/12	(83.3)	5/5		13/15	(86.7)	5/5		13/16	(81.3)	5/6	
PRSP+ ERSP	5/7		3/3		7/9		3/3		7/9		3/4	
PRSP only	0/0		0/0		0/0		0/0		0/0		0/0	
ERSP only	4/4		2/2		4/4		2/2		4/4		2/2	
MDRSP	9/11	(81.8)	4/4		12/14	(80.0)	4/5		12/15	(80.0)	4/6	
MDRSP incl. PEN	7/9		4/4		9/11	(81.8)	4/5		9/11	(81.8)	4/6	
MDRSP incl. ERY	6/8		3/3		9/11	(81.8)	3/3		9/12	(75.0)	3/4	
MDRSP incl. CEF	7/9		4/4		10/12	(83.3)	4/5		10/12	(83.3)	4/6	
MDRSP incl. COT	9/11	(81.8)	3/3		12/14	(85.7)	3/4		12/15	(80.0)	3/4	
MDRSP incl. TET	3/3		0/0		4/4		0/0		4/5		0/0	

[a] all controlled ABS studies: 3005 (5-day arm only) and 3011.
[b] Comp: comparators in controlled studies: amoxicillin-clavulanic acid (Study 3005); cefuroxime axetil (Study 3011).
bmITT$_{(f)}$: bmITT population with indeterminate treated as failure; bmITT$_{(m)}$: bmITT population with indeterminate treated as missing.
PRSP: penicillin-resistant *S. pneumoniae*; **ERSP**: erythromycin-resistant *S. pneumoniae*; **PRSP+ERSP**: *S. pneumoniae* resistant to penicillin and erythromycin; **PRSP+/or ERSP**: *S. pneumoniae* resistant to penicillin and/or erythromycin; **PRSP only**: *S. pneumoniae* resistant to penicillin and no other antibiotic; **ERSP only**: *S. pneumoniae* resistant to erythromycin and no other antibiotic; **MDRSP**: multi-drug resistant *S. pneumoniae* including resistance to any 2 or more of the tested classes; **MDRSP Incl.**: MDRSP including resistance to one of the following antibiotics as indicated: **PEN**: penicillin; **ERY**: erythromycin; **CEF**: cefuroxime axetil; **COT**: trimethoprim-sulfamethoxazole; **TET**: tetracyclines

CONCLUSION – ABS – *S. pneumoniae*

The proposed in vitro susceptibility test interpretive criteria for *S. pneumoniae* of ≤ 1 µg/mL = susceptible, 2 µg/mL = intermediate and ≥ 4 µg/mL = resistant to telithromycin are appropriate for *S. pneumoniae* associated with ABS.

Haemophilus influenzae

In the following disease entities caused by *H. influenzae* the patient populations were analyzed to determine if the following (Table 20) proposed in vitro susceptibility test interpretive criteria were appropriate for classifying an isolate of *H. influenzae* as susceptible, intermediate or resistant to telithromycin.

Table 20. Telithromycin proposed MIC interpretive criteria (breakpoints) for *Haemophilus influenzae*

	MIC (µg/mL)
Interpretive category	*H. influenzae*
Susceptible	≤4.0
Intermediate	8
Resistant	≥16.0

Community-acquired pneumonia

H. influenzae was diagnosed as the cause of CAP in 204 patients during clinical trials. Of the 204 *H. influenzae* isolates 26 were found to be β-lactamase inhibitors. Three *H. influenzae* isolates were resistant to azithromycin but were susceptible to telithromycin. Table 21 shows the telithromycin MICs and the eradication (presumed) rates for the 204 *H. influenzae* isolates.

Table 21. Telithromycin MICs for *Haemophilus influenzae* and bacterial eradication (presumed) rates for CAP

Telithromycin MIC (µg/mL)	Number of Isolates	Eradication (presumed) %
0.002	1	1 (100)
0.12	1	1 (100)
0.25	3	3 (100)
0.5	5	3 (60)
1	47	41 (87.2)
2	96	86 (89.6)
4	40	35 (87.5)
8	11	11 (100)
Total	204	181 (88.7)

Table 22 shows the activity of telithromycin against just the ß-lactamase producing isolates of *H. influenzae* and the bacterial eradication rates.

Table 22. Telithromycin MICs for beta-lactamase producing *Haemophilus influenzae* and bacterial eradication (presumed) rates for CAP

Telithromycin MIC (µg/mL)	Number of Isolates	Eradication (presumed) %
0.12	1	1 (100)
0.5	1	1 (100)
1	6	5 (83.3)
2	12	11 (91.7)

4	5	4 (80)
8	1	1 (100)
Total	26	23 (88.5)

CONCLUSION – CAP – *H. influenzae*

The in vitro susceptibility test criteria for telithromycin tested against *H. influenzae* of ≤4 µg/mL = susceptible, 8 µg/mL = intermediate, and ≥16 µg/mL = resistant are appropriate based on bacteriological eradication and clinical cure rates for CAP due to *H. influenzae*.

Acute exacerbation of chronic bronchitis

There were 56 isolates of *H. influenzae* from patients with AECB in the clinical trials. There were 10 cases were the *H. influenzae* isolate produced β-lactamase. In 5 of these cases the *H. influenzae* was eradicated. Table 23 shows the telithromycin MICs for the *H. influenzae* isolates and the bacterial eradication rates.

Table 23. Telithromycin MICs for *Haemophilus influenzae* isolates from acute exacerbation of chronic bronchitis and bacterial eradication (presumed) rates

Telithromycin MIC (µg/mL)	Number of Isolates	Eradication (presumed) %
0.5	1	1 (100)
1	16	9 (56.3)
2	28	21 (75)
4	7	6 (85.7)
8	4	1 (25)
Total	56	38 (67.9)

CONCLUSION – AECB – *H. influenzae*

The in vitro susceptibility test criteria for telithromycin tested against *H. influenzae* of ≤4 µg/mL = susceptible, 8 µg/mL = intermediate, and ≥16 µg/mL = resistant are appropriate based on bacteriological eradication and clinical cure rates for AECB due to *H. influenzae*.

Acute bacterial sinusitis (ABS)

Fifty-seven patients with maxillary sinusitis had *H. influenzae* as the etiological agent. Table 24 shows the telithromycin MICs for the isolates and the eradication (presumed) rates.

Table 24. Telithromycin MICs for *Haemophilus influenzae* isolates from acute bacterial sinusitis and bacterial eradication rates

Telithromycin MIC (µg/mL)	Number of Isolates	Eradication (presumed) %
0.12	1	1 (100)
0.5	1	1 (100)

1	16	15 (93.8)
2	26	21 (80.8)
4	11	10 (90.9)
8	2	1 (50.0)
Total	57	49 (86.0)

CONCLUSION – ABS – *H. influenzae*

The in vitro susceptibility test criteria for telithromycin tested against *H. influenzae* of ≤4 µg/mL = susceptible, 8 µg/mL = intermediate, and ≥16 µg/mL = resistant are appropriate based on bacteriological eradication and clinical cure rates for ABS due to *H. influenzae*.

The following table (Table 1 provided by Aventis – e-mail 17 Mar 04) shows the bacterial eradication rates clinical cure rates for all indications in various populations diagnosed with infection caused by *H. influenzae* correlated with the telithromycin MIC.

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Table 1 Bacteriological eradication rates and clinical cure rates at Posttherapy/TOC according to MIC values for HMR 3647 by causative pathogen for all indications combined without centers excluded by FDA - PPb population [a]□ (Continued)

		HMR 3647									
			Bacteriological outcome [c] No. (%)					Clinical outcome [d] No. (%)			
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure	
Haemophilus influenzae												
	0.002	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.12	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.25	3	3	(100.0)	0	(0.0)	0	(0.0)	3	(100.0)	0	(0.0)
	0.5	8	5	(62.5)	2	(25.0)	1	(12.5)	6	(75.0)	2	(25.0)
	1	82	68	(82.9)	14	(17.1)	0	(0.0)	69	(84.1)	13	(15.9)
	2	177	152	(85.9)	22	(12.4)	3	(1.7)	155	(87.6)	22	(12.4)
	4	69	59	(85.5)	9	(13.0)	1	(1.4)	60	(87.0)	9	(13.0)
	8	17	12	(70.6)	4	(23.5)	1	(5.9)	13	(76.5)	4	(23.5)
	Not done	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	N/A	41	39	(95.1)	2	(4.9)	0	(0.0)	38	(92.7)	3	(7.3)
	Total	402	343	(85.3)	53	(13.2)	6	(1.5)	349	(86.8)	53	(13.2)
Haemophilus influenzae (beta-lactamase producer)												
	0.12	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.5	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	1	12	9	(75.0)	3	(25.0)	0	(0.0)	9	(75.0)	3	(25.0)
	2	28	22	(78.6)	5	(17.9)	1	(3.6)	22	(78.6)	6	(21.4)
	4	8	5	(62.5)	3	(37.5)	0	(0.0)	5	(62.5)	3	(37.5)
	8	4	2	(50.0)	2	(50.0)	0	(0.0)	3	(75.0)	1	(25.0)
	Total	54	40	(74.1)	13	(24.1)	1	(1.9)	41	(75.9)	13	(24.1)
Haemophilus influenzae (AZI-R)												
	8	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1	(33.3)
	Total	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1	(33.3)

a PPb=per protocol bacteriologically evaluable population.
b Causative admission pathogens as assessed by investigators. AMP-R=resistant to ampicillin, AZI-R=resistant to azithromycin.
c Includes documented and presumed.
d Cure=returned to preinfection state, and improved or postinfection stigmata (no subsequent antibiotic); Failure=failure as assessed by the investigators.

Clinical and bacteriological outcomes at TOC in telithromycin-treated subjects with cefuroxime-resistant *H. influenza* isolates by telithromycin MIC values.

bmITT Population

Indication	Study	Telithromycin MIC (mcg/mL)	Subjects	Outcome	
				Bacteriological Eradication	Clinical Cure
CAP	3009	8	1	IND	IND
	3010	2	1	1	1
AMS	3011	4	1	1	1
	3011	2	1	1	1

PPb Population

Indication	Study	Telithromycin MIC (mcg/mL)	Subjects	Outcome	
				Bacteriological Eradication	Clinical Cure
CAP	3009	-	0	-	-
	3010	-	0	-	-
AMS	3011	-	0	-	-
	3011	2	1*	1	1

TOC = Test-of-cure visit

bmITT = bacteriologically evaluable modified intent-to-treat population

PPb = bacteriologically evaluable per protocol population

CAP = community-acquired pneumonia

AMS = acute sinusitis

IND = indeterminate outcome

*One subject was in both bmITT and PPb populations

CONCLUSION – *H. influenzae*

There was presumed eradication of *H. influenzae* in CAP patients regardless of β-lactamase production in better than 85% of that population. For all indications with *H. influenzae* (non- β-lactamase + β-lactamase producing) isolates as the etiologic agent with telithromycin MICs ≤ 8 μg/mL the bacterial eradication and clinical cure rates were 84% (302/359) and 86% (309/359) respectively. For all indications with *H. influenzae* β-lactamase producing isolates as the etiologic agent the bacterial and clinical cure rates were 74% (40/54) and 76% (41/54) respectively. This data suggests that telithromycin may not be as effective in eradicating non- CAP infections as it is for treating CAP infections caused by β-lactamase producing *H. influenzae.*

As noted under "Mechanism(s) of Resistance" there are reports of cefuroxime-resistant *H. influenzae* (≥16 μg/mL) and these organisms may be resistant to telithromycin (MIC = ≥ 16 μg/mL). The following table (Aventis e-mail 21 Mar 04) shows the bacterial eradication and clinical cure rates for patients who were infected with cefuroxime-resistant *H. influenzae* correlated with the telithromycin MIC for these isolates. Because the cefuroxime-resistant *H. influenzae* experience is very small it is not possible to know what the efficacy of telithromycin is for treating infections caused by cefuroxime-resistant H. influenzae. However, it is advisable to monitor for the presence of cefuroxime resistance in *H. influenzae* and the therapeutic efficacy of telithromycin in treating infections caused by these cefuroxime-resistant *H. influenzae.*

The in vitro susceptibility test criteria for telithromycin tested against *H. influenzae* of ≤4 μg/mL = susceptible, 8 μg/mL = intermediate, and ≥16 μg/mL = resistant are appropriate based on bacteriological eradication and clinical cure rates for CAP, AECB, and ABS due to *H. influenzae.*

Moraxella catarrhalis

Community-acquired Pneumonia

There were 34 isolates of *M. catarrhalis* from patients in the PPb population. Table 25 shows telithromycin MICS for these isolates and the bacterial eradication (presumed) for this organism. As can be seen *M. catarrhalis* is extremely susceptible to telithromycin and there was better than 90% eradication of the organism from patients with CAP.

Table 25. Telithromycin MICs for *Moraxella catarrhalis*
CAP isolates and bacterial eradication (presumed) rates

Telithromycin MIC (µg/mL)	Number of Isolates	Eradication (presumed) %
0.008	1	1 (100)
0.06	15	13 (86.7)
0.12	18	18 (100)
Total	34	32 (94.1)

Acute exacerbation of chronic bronchitis

Twenty-nine isolates of *M. catarrhalis* were obtained during AECB clinical trials. Of these 27 (93.1%) were eradicated (presumed).

Acute bacterial sinusitis (ABS)

There were 17 patients with acute maxillary sinusitis from whom *M. catarrhalis* was isolated. Of the 17 patients 15 (88.2%) had the organism eradicated (presumed).

Table 26 shows bacterial eradication and clinical cure rates for all indications where *M. catarrhalis* was the etiologic agent.

Table 26 - *Moraxella catarrhalis*

Bacteriological eradication rates and clinical cure rates at Posttherapy/TOC according to MIC values for HMR 3647 by causative pathogen for all indications combined without centers excluded by FDA - PPb population [a]□ (Continued)

Moraxella (Branhamella) catarrhalis												
	0.004	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.008	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.06	28	23	(82.1)	4	(14.3)	1	(3.6)	23	(82.1)	5	(17.9)
	0.12	44	42	(95.5)	1	(2.3)	1	(2.3)	42	(95.5)	2	(4.5)
	0.25	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1	(33.3)
	1	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	N/A	24	20	(83.3)	4	(16.7)	0	(0.0)	20	(83.3)	4	(16.7)
	Total	103	91	(88.3)	10	(9.7)	2	(1.9)	91	(88.3)	12	(11.7)

CONCLUSION – CAP, AECB, and ABS – *M. catarrhalis*

From the bacterial eradication and clinical cure rate data from patients with CAP, AECB and ABS associated with *M. catarrhalis* it appears that these infections can be treated efficaciously with telithromycin using the dosing regimen proposed.

Staphylococcus aureus

In the following disease entities caused by *S. aureus* the patient populations were analyzed to determine if the following (Table 27) proposed in vitro susceptibility test interpretive criteria were appropriate for classifying an isolate of *S. aureus* as susceptible, intermediate or resistant to telithromycin.

Table 27. Telithromycin proposed MIC interpretive criteria breakpoints for *Staphylococcus aureus*

Community-acquired Pneumonia

There were 32 bacteriologically evaluable patients in the CAP studies who were identified as having *S. aureus* infection. Of the 32 *S. aureus* isolates 2 were oxacillin-resistant. One oxacillin-resistant isolate had a telithromycin MIC of 0.12 µg/mL while the other isolate had a telithromycin MIC of 8 µg/mL. The patient with the oxacillin-resistant isolate with a telithromycin MIC of 0.12 µg/mL failed to respond to therapy. The other patient with oxacillin-resistant *S. aureus* responded to therapy. Table 28 shows telithromycin MICs for the *S. aureus* isolates and the bacterial eradication (presumed) rates.

Table 28. Telithromycin MICs for *Staphylococcus aureus*
CAP isolates and bacterial eradication (presumed) rates

Telithromycin MIC (µg/mL)	Number of Isolates	Eradication (presumed) %
0.06	4	2 (50)
0.12	22	19 (86.4)
0.25	5	4 (80)
8	1	1 (100)
Total	32	26 (81.3)

CONCLUSION – CAP – *S. aureus*

The data from the patients that had CAP due to *S. aureus* did not provide data to support the proposed breakpoints of . The in vitro susceptibility breakpoint that could be supported from the CAP data is only ≤0.25 µg/mL = susceptible.

Acute exacerbation of chronic bronchitis

In the AECB trials there were only 5 patients from whom *S. aureus* was isolated. All five isolates had a telithromycin MIC of 0.12 µg/mL. Three (60%) of the 5 isolates were eradicated after treatment with telithromycin. None of the *S. aureus* were oxacillin resistant.

CONCLUSION – AECB – *S. aureus*

There was not enough clinical data from the AECB population to make any determination for *S. aureus* in vitro susceptibility test MIC interpretive criteria.

Acute bacterial sinusitis

Table 29 gives the bacterial eradication, and clinical cure rates for sinusitis where *S. aureus* was isolated along with the telithromycin MICs for the *S. aureus* isolates. Nineteen patients in the ABS PPb population treated with telithromycin had only *S. aureus* isolated. There was 100% bacteriological eradication (presumed) and clinical cure. The telithromycin MICs for the *S. aureus* isolates ranged from 0.06 to 0.25µg/mL.

Table 29. *Staphylococcus aureus* isolates from acute bacterial sinusitis correlated with bacterial eradication, clinical cure rates and telithromycin MICs.

REGIMEN=HMR 3647 5 days Study number=3002

SUBNO	AGE	SEX	PPB	BASACD	BASASOCD	CFU	MIC	D_CLRSG4	D_DTOCS
0406004	45	female	X	Staphylococcus aureus	SINUS PUNCTURE	-	0.060	Cure	Presumed eradication
0504009	52	female		Staphylococcus aureus	SINUS PUNCTURE	<10XX3	0.060	Failure	Eradication
0602003	33	female		Staphylococcus aureus	SINUS PUNCTURE	-	0.060	Cure	Presumed eradication
0603015	26	male		Staphylococcus aureus	SINUS PUNCTURE	-	0.060	Cure	Presumed eradication
0603021	49	female		Staphylococcus aureus	SINUS PUNCTURE	-	0.120	Cure	Presumed eradication
0609002	21	male		Staphylococcus aureus	SINUS PUNCTURE	-	0.120	Cure	Presumed eradication
0701010	43	female		Staphylococcus aureus	SINUS PUNCTURE	>=10XX4	0.060	Indeterminate	Indeterminate
	-	female		Streptococcus pneumoniae	SINUS PUNCTURE	>=10XX4	-	Indeterminate	Indeterminate
0701013	34	female	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.060	Cure	Presumed eradication
0708030	37	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX4	0.120	Cure	Presumed eradication
0709004	58	female	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Cure	Presumed eradication
0709010	56	female		Staphylococcus aureus	SINUS PUNCTURE	>=10XX4	0.060	Indeterminate	Indeterminate
1502007	47	female		Staphylococcus aureus	SINUS PUNCTURE	-	0.120	Indeterminate	Indeterminate
1901015	50	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX4	0.120	Cure	Presumed eradication
1902004	65	male		Staphylococcus aureus	SINUS PUNCTURE	-	16.000	Cure	Presumed eradication
1902009	43	male	X	Staphylococcus aureus		>=10XX4	-	Cure	Presumed eradication
2101002	40	female	X	Staphylococcus aureus	SINUS PUNCTURE		0.120	Cure	Presumed eradication
	-	female		Streptococcus pyogenes	SINUS PUNCTURE		-	Cure	Presumed eradication

REGIMEN=HMR 3647 5 days Study number=3011

SUBNO	AGE	SEX	PPB	BASACD	BASASOCD	CFU	MIC	D_CLRSG4	D_DTOCS
0603001	32	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.250	Cure	Presumed eradication
0616005	56	male		Staphylococcus aureus	SINUS PUNCTURE	>=10XX7	0.120	Cure	Presumed eradication
0619001	47	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Cure	Presumed eradication
0629005	61	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX7	0.250	Cure	Presumed eradication
0629006	56	female	X	Haemophilus parainfluenzae	SINUS PUNCTURE	>=10XX5	4.000	Failure	Persistence
	-	female		Peptostreptococcus micros	SINUS PUNCTURE	>=10XX7	0.060	Failure	Persistence
	-	female		Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Failure	Persistence
0629010	53	female		Haemophilus influenzae	SINUS PUNCTURE	>=10XX4	4.000	Cure	Presumed eradication
	-	female		Staphylococcus aureus	SINUS PUNCTURE	>=10XX4	0.250	Cure	Presumed eradication
	-	female		Streptococcus pneumoniae	SINUS PUNCTURE	>=10XX7	0.030	Cure	Presumed eradication
0654002	41	female		Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Indeterminate	Indeterminate
0659011	46	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX7	-	Cure	Presumed eradication
0659014	43	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX7	-	Cure	Presumed eradication
0682019	29	male	X	Staphylococcus aureus	SINUS ENDOSCOPY	>=10XX5	0.120	Cure	Presumed eradication
0707012	32	female	X	Staphylococcus aureus	SINUS ENDOSCOPY	-	0.120	Cure	Presumed eradication
0731034	24	female	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Cure	Presumed eradication
0733007	42	female	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX7	0.120	Cure	Presumed eradication
0743004	53	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Cure	Presumed eradication
0755008	23	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Cure	Presumed eradication
	-	male		Streptococcus oralis	SINUS PUNCTURE	>=10XX7	0.008	Cure	Presumed eradication
	-	male		Trichosporon, NOS	SINUS PUNCTURE	>=10XX5	-	Cure	Presumed eradication
0756004	24	female		Staphylococcus aureus	SINUS PUNCTURE	>=10XX4	0.120	Indeterminate	Indeterminate
	-	female		Staphylococcus epidermidis	SINUS PUNCTURE	>=10XX5	0.060	Indeterminate	Indeterminate
	-	female		Streptococcus oralis	SINUS PUNCTURE	>=10XX5	0.008	Indeterminate	Indeterminate

Patients in 3002,3005,3011 with S. aureus

REGIMEN=Cefuroxim Axetil Study number=3011

SUBNO	AGE	SEX	PPB	BASACD	BASASOCD	CFU	MIC	D_CLRSG4	D_DTOCS
0601029	38	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX7	0.120	Cure	Presumed eradication
0612005	50	female		Haemophilus parainfluenzae	SINUS PUNCTURE	>=10XX5	8.000	Indeterminate	Indeterminate
	-	female		Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.060	Indeterminate	Indeterminate
0707007	49	female	X	Staphylococcus aureus	SINUS ENDOSCOPY	-	0.060	Cure	Presumed eradication
0743006	47	male	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX7	-	Failure	Presumed persistence
0746004	50	female	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Cure	Presumed eradication

REGIMEN=HMR 3647 10 days Study number=3002

SUBNO	AGE	SEX	PPB	BASACD	BASASOCD	CFU	MIC	D_CLRSG4	D_DTOCS
0404002	38	male	X	Prevotella oralis	SINUS PUNCTURE	>=10XX5	0.008	Cure	Presumed eradication
	-	male		Peptostreptococcus, NOS	SINUS PUNCTURE	>=10XX4	-	Cure	Presumed eradication
	-	male		Staphylococcus aureus	SINUS PUNCTURE	>=10XX4	0.060	Cure	Presumed eradication
	-	male		Streptococcus, group G	SINUS PUNCTURE	>=10XX5	-	Cure	Presumed eradication
0405003	56	female	X	Eubacterium, NOS	SINUS PUNCTURE	-	-	Cure	Presumed eradication
	-	female		Staphylococcus aureus	SINUS PUNCTURE	-	0.060	Cure	Presumed eradication
0405012	58	male	X	Haemophilus influenzae	SINUS PUNCTURE	-	2.000	Cure	Presumed eradication
	-	male		Staphylococcus aureus	SINUS PUNCTURE	-	0.120	Cure	Presumed eradication
	-	male		Streptococcus pneumoniae	SINUS PUNCTURE	-	-	Cure	Presumed eradication
0406006	57	male		Staphylococcus coagulase negative	SINUS PUNCTURE	-	-	Cure	Presumed eradication
0603013	36	female		Staphylococcus aureus	SINUS PUNCTURE	-	0.120	Cure	Presumed eradication
0603047	25	male		Haemophilus influenzae	SINUS PUNCTURE	<10XX3	2.000	Cure	Presumed eradication
	-	male		Staphylococcus aureus	SINUS PUNCTURE	-	0.120	Cure	Presumed eradication
0701003	22	female	X	Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.060	Cure	Presumed eradication
0705004	55	female		Escherichia coli	SINUS PUNCTURE	>=10XX5	16.000	Cure	Presumed eradication
	-	female		Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.060	Cure	Presumed eradication
0708006	30	female		Staphylococcus aureus	SINUS PUNCTURE	<10XX3	0.120	Cure	Presumed eradication
0708036	30	male		Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Failure	Presumed persistence
1901007	55	male		Staphylococcus aureus	SINUS PUNCTURE	>=10XX5	0.120	Cure	Presumed eradication
1901014	22	male		Staphylococcus aureus	SINUS PUNCTURE	>=10XX3	0.120	Cure	Presumed eradication

CONCLUSION – ABS - *S. aureus*

The data from the patients that had ABS due to *S. aureus* did not provide data to support the proposed breakpoints of [redacted] The in vitro susceptibility breakpoint that could be supported from the ABS data is only ≤0.25 µg/mL = susceptible.

Table 30 provides the bacterial eradication and clinical cure rates for all indications by telithromycin MIC. The bacterial eradication and clinical outcome rates for all indications with infection caused by *S. aureus* with telithromycin MICs of ≤ 0.25 µg/mL were 84% (57/68) and 81% (55/68) respectively.

Table 30. Bacterial eradication, clinical cure rates and associated telithromycin MIC for *Staphylococcus aureus* for all indications

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Table 1 Bacteriological eradication rates and clinical cure rates at Posttherapy/TOC according to MIC values for HMR 3647 by causative pathogen for all indications combined without centers excluded by FDA - PPb population [a]□ (Continued)

			HMR 3647								
			Bacteriological outcome [c] No. (%)						Clinical outcome [d] No. (%)		
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure
Staphylococcus aureus											
	0.06	9	7	(77.8)	2	(22.2)	0	(0.0)	7	(77.8)	2 (22.2)
	0.12	50	42	(84.0)	7	(14.0)	1	(2.0)	40	(80.0)	10 (20.0)
	0.25	9	8	(88.9)	1	(11.1)	0	(0.0)	8	(88.9)	1 (11.1)
	8	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0 (0.0)
	N/A	15	14	(93.3)	1	(6.7)	0	(0.0)	14	(93.3)	1 (6.7)
	Total	84	72	(85.7)	11	(13.1)	1	(1.2)	70	(83.3)	14 (16.7)
Staphylococcus aureus (OXA-R)											
	0.12	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1 (33.3)
	8	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0 (0.0)
	Total	4	3	(75.0)	1	(25.0)	0	(0.0)	3	(75.0)	1 (25.0)

CONCLUSION – *S. aureus*

Telithromycin eradicated *S. aureus* from the majority of patients with CAP. Only 2 isolates of *S. aureus* were resistant to oxacillin and only one of these infections responded to treatment with telithromycin. Because of the lack of clinical experience in treating CAP due to oxacillin-resistant *S. aureus* it would not be appropriate to include oxacillin (methicillin)-resistant *S. aureus* in the indication for CAP.

In the case of *S. aureus* associated with AECB there were only 5 cases. Three of the five *S. aureus* were presumed eradicated. This number is too small to determine if telithromycin is effective in treating this disease entity due to *S. aureus*. For ABS there were 19 patients in the PPb population. In all cases there was bacterial eradication and clinical cure.

The lack of clinical experience with *S. aureus* having MICs greater than 0.25 µg/mL precludes defining an intermediate and resistant MIC breakpoint. The appropriate in vitro susceptibility test telithromycin MIC interpretive breakpoint for *S. aureus* is ≤0.25 µg/mL.

Intracellular bacteria

The applicant provided clinical and diagnostic evidence in their previous submissions (NDA 21-144 submitted 28 Feb 00 and NDA 21-144 submitted 26 Feb 01) for the occurrence of 34 cases of *Chlamydia (Chlamydophila) pneumoniae*, 31 cases of *Mycoplasma pneumoniae* and 13 cases of *Legionella pneumophila* CAP. In vitro studies have shown that telithromycin concentrates in macrophages and PMNs to concentrations that exceed the MICs of these intracellular pathogens (see "In Vivo" section above). The clinical cure rates for the CAP infections caused by these organisms were demonstrated in clinical trials to be better than 94%. Based on the in vitro susceptibility of these organisms to telithromycin, the fact that telithromycin concentrates in macrophages and the clinical cure rates for these infections demonstrated during clinical trials it would be appropriate to include *C. pneumoniae* and *M. pneumoniae* in the CAP

indication. It is not recommended to include *L. pneumophila* in the CAP indication because of the small number of clinical cases and some discrepancies in the diagnostic test results used to confirm the presence of this organism. It is recommended that *L. pneumophila* be placed in the "second list" because telithromycin in vitro susceptibility information on better than 100 isolates of the organism shows that the MIC_{90} (see "Spectrum of Activity" above) for the organism is well below the therapeutically achievable concentration of telithromycin that can be achieved in the plasma using the proposed telithromycin dosing regimen, telithromycin concentrates in macrophages, and the organism is relevant to the CAP indication.

MIC AND DISC DIFFUSION INTERPRETIVE CRITERIA

Based on the pharmacokinetic/pharmacodynamic characteristics of telithromycin, in vitro susceptibility data from the literature, in vitro susceptibility data of bacterial isolates obtained during clinical trials and bacteriological and clinical outcome data the following MIC and disk diffusion zone size interpretive criteria are applicable. Disk diffusion testing is done using a disk containing 15 µg telithromycin.

STREPTOCOCCUS PNEUMONIAE (including multi-drug resistant isolates [MDRSP*])

Interpretive Category	MIC (µg/mL)	Zone of Inhibition (mm)
Susceptible	≤1.0	≥19
Intermediate	2.0	16 – 18
Resistant	≥4.0	≤15

*MDRSP = Multi-drug resistant *S. pneumoniae* includes isolates known as PRSP (penicillin-resistant S. pneumoniae) and are isolates resistant to two or more of the following antimicrobials: penicillin, 2nd generation cephalosporins (e.g. cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

The bacterial eradication and clinical cure rates using ≤ 1.0 µg/mL as indicating susceptibility of *S. pneumoniae* to telithromycin in the indications noted below were:

Indication	Number of Isolates	Bacterial eradication	Clinical cure
CAP	286	276 (96.5%)	271 (94.6%)
ABS	78	70 (89.7%)	
AECB	26	22 (84.6%)	
Total	390	369 (94.4%)	

The following tables provide further information relating to antimicrobial resistant *S. pneumoniae*, telithromycin MIC, bacterial eradication and clinical outcome results for all indications combined (provided by Aventis – e-mail 17 Mar 04). As is seen those *S. pneumoniae* that are resistant to penicillin, or erythromycin and had telithromycin MIC of ≤1 µg/mL had bacteriological eradication rates clinic outcome results ranging from 33 to 100%. The bacteriological eradication and clinical cure outcomes were dependent on the organism's susceptibility to penicillin and erythromycin.

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Table 1 Bacteriological eradication rates and clinical cure rates at Posttherapy/TOC according to MIC values for HMR 3647 by causative pathogen for all indications combined without centers excluded by FDA - PPb population [a] (Continued)

			HMR 3647									
			Bacteriological outcome [c] No. (%)						Clinical outcome [d] No. (%)			
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure	
Streptococcus pneumoniae												
	0.004	5	5	(100.0)	0	(0.0)	0	(0.0)	4	(80.0)	1	(20.0)
	0.008	171	165	(96.5)	6	(3.5)	0	(0.0)	163	(95.3)	8	(4.7)
	0.015	72	66	(91.7)	6	(8.3)	0	(0.0)	64	(88.9)	8	(11.1)
	0.016	99	95	(96.0)	4	(4.0)	0	(0.0)	93	(93.9)	6	(6.1)
	0.03	37	34	(91.9)	3	(8.1)	0	(0.0)	34	(91.9)	3	(8.1)
	0.06	15	14	(93.3)	1	(6.7)	0	(0.0)	14	(93.3)	1	(6.7)
	0.12	9	6	(66.7)	3	(33.3)	0	(0.0)	6	(66.7)	3	(33.3)
	0.25	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1	(33.3)
	0.5	9	8	(88.9)	0	(0.0)	1	(11.1)	8	(88.9)	1	(11.1)
	1	6	6	(100.0)	0	(0.0)	0	(0.0)	6	(100.0)	0	(0.0)
	2	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	N/A	48	44	(91.7)	4	(8.3)	0	(0.0)	44	(91.7)	4	(8.3)
	Total	475	446	(93.9)	28	(5.9)	1	(0.2)	439	(92.4)	36	(7.6)
Streptococcus pneumoniae (Blood culture only)												
	0.008	36	36	(100.0)	0	(0.0)	0	(0.0)	34	(94.4)	2	(5.6)
	0.015	13	11	(84.6)	2	(15.4)	0	(0.0)	11	(84.6)	2	(15.4)
	0.016	16	14	(87.5)	2	(12.5)	0	(0.0)	13	(81.3)	3	(18.8)
	0.03	5	4	(80.0)	1	(20.0)	0	(0.0)	4	(80.0)	1	(20.0)
	0.06	3	3	(100.0)	0	(0.0)	0	(0.0)	3	(100.0)	0	(0.0)
	0.12	2	1	(50.0)	1	(50.0)	0	(0.0)	1	(50.0)	1	(50.0)
	1	3	3	(100.0)	0	(0.0)	0	(0.0)	3	(100.0)	0	(0.0)
	N/A	10	10	(100.0)	0	(0.0)	0	(0.0)	10	(100.0)	0	(0.0)
	Total	88	82	(93.2)	6	(6.8)	0	(0.0)	79	(89.8)	9	(10.2)

a PPb=per protocol bacteriologically evaluable population.
b Causative admission pathogens as assessed by investigators.
c Includes documented and presumed.
d Cure=returned to preinfection state, and improved or postinfection stigmata (no subsequent antibiotic); Failure=failure as assessed by the investigators.

			HMR 3647									
			Bacteriological outcome [c] No. (%)						Clinical outcome [d] No. (%)			
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure	
Streptococcus pneumoniae (PEN-I)												
	0.008	12	12	(100.0)	0	(0.0)	0	(0.0)	12	(100.0)	0	(0.0)
	0.015	4	4	(100.0)	0	(0.0)	0	(0.0)	4	(100.0)	0	(0.0)
	0.016	11	11	(100.0)	0	(0.0)	0	(0.0)	10	(90.9)	1	(9.1)
	0.03	9	9	(100.0)	0	(0.0)	0	(0.0)	9	(100.0)	0	(0.0)
	0.06	3	3	(100.0)	0	(0.0)	0	(0.0)	3	(100.0)	0	(0.0)
	0.12	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.5	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	1	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	Total	44	44	(100.0)	0	(0.0)	0	(0.0)	43	(97.7)	1	(2.3)
Streptococcus pneumoniae (PEN-R)												
	0.008	7	7	(100.0)	0	(0.0)	0	(0.0)	7	(100.0)	0	(0.0)
	0.015	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.016	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.03	8	6	(75.0)	2	(25.0)	0	(0.0)	6	(75.0)	2	(25.0)
	0.06	6	5	(83.3)	1	(16.7)	0	(0.0)	5	(83.3)	1	(16.7)
	0.12	3	1	(33.3)	2	(66.7)	0	(0.0)	1	(33.3)	2	(66.7)
	0.25	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.5	7	6	(85.7)	0	(0.0)	1	(14.3)	6	(85.7)	1	(14.3)
	1	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	2	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	Total	38	32	(84.2)	5	(13.2)	1	(2.6)	32	(84.2)	6	(15.8)

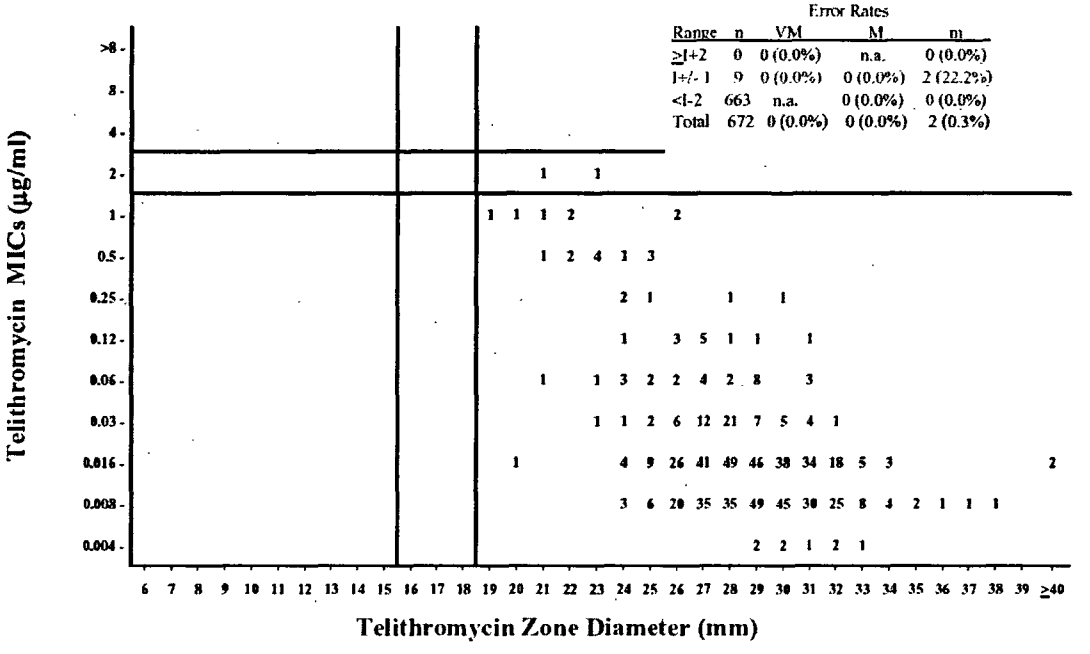
			HMR 3647							
			Bacteriological outcome [c] No. (%)					Clinical outcome [d] No. (%)		
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence	Cure		Failure
Streptococcus pneumoniae (ERY-R)										
	0.008	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.015	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.016	2	2	(100.0)	0	(0.0)	0 (0.0)	2	(100.0)	0 (0.0)
	0.03	16	14	(87.5)	2	(12.5)	0 (0.0)	14	(87.5)	2 (12.5)
	0.06	13	12	(92.3)	1	(7.7)	0 (0.0)	12	(92.3)	1 (7.7)
	0.12	7	4	(57.1)	3	(42.9)	0 (0.0)	4	(57.1)	3 (42.9)
	0.25	3	2	(66.7)	1	(33.3)	0 (0.0)	2	(66.7)	1 (33.3)
	0.5	9	8	(88.9)	0	(0.0)	1 (11.1)	8	(88.9)	1 (11.1)
	1	6	6	(100.0)	0	(0.0)	0 (0.0)	6	(100.0)	0 (0.0)
	2	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	Total	59	51	(86.4)	7	(11.9)	1 (1.7)	51	(86.4)	8 (13.6)
Streptococcus pneumoniae (PEN-I & ERY-R)										
	0.015	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.03	7	7	(100.0)	0	(0.0)	0 (0.0)	7	(100.0)	0 (0.0)
	0.06	2	2	(100.0)	0	(0.0)	0 (0.0)	2	(100.0)	0 (0.0)
	0.12	2	2	(100.0)	0	(0.0)	0 (0.0)	2	(100.0)	0 (0.0)
	0.5	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	1	2	2	(100.0)	0	(0.0)	0 (0.0)	2	(100.0)	0 (0.0)
	Total	15	15	(100.0)	0	(0.0)	0 (0.0)	15	(100.0)	0 (0.0)
Streptococcus pneumoniae (PEN-R & ERY-R)										
	0.008	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.015	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.03	5	3	(60.0)	2	(40.0)	0 (0.0)	3	(60.0)	2 (40.0)
	0.06	6	5	(83.3)	1	(16.7)	0 (0.0)	5	(83.3)	1 (16.7)
	0.12	3	1	(33.3)	2	(66.7)	0 (0.0)	1	(33.3)	2 (66.7)
	0.25	2	2	(100.0)	0	(0.0)	0 (0.0)	2	(100.0)	0 (0.0)
	0.5	7	6	(85.7)	0	(0.0)	1 (14.3)	6	(85.7)	1 (14.3)
	1	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	2	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	Total	27	21	(77.8)	5	(18.5)	1 (3.7)	21	(77.8)	6 (22.2)

			HMR 3647							
			Bacteriological outcome [c] No. (%)					Clinical outcome [d] No. (%)		
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence	Cure		Failure
Streptococcus pneumoniae (ERY-R/mefE)										
	0.03	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.06	8	7	(87.5)	1	(12.5)	0 (0.0)	7	(87.5)	1 (12.5)
	0.12	6	3	(50.0)	3	(50.0)	0 (0.0)	3	(50.0)	3 (50.0)
	0.25	2	1	(50.0)	1	(50.0)	0 (0.0)	1	(50.0)	1 (50.0)
	0.5	7	6	(85.7)	0	(0.0)	1 (14.3)	6	(85.7)	1 (14.3)
	1	5	5	(100.0)	0	(0.0)	0 (0.0)	5	(100.0)	0 (0.0)
	Total	29	23	(79.3)	5	(17.2)	1 (3.4)	23	(79.3)	6 (20.7)
Streptococcus pneumoniae (ERY-R/ermB)										
	0.008	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.015	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.016	2	2	(100.0)	0	(0.0)	0 (0.0)	2	(100.0)	0 (0.0)
	0.03	14	12	(85.7)	2	(14.3)	0 (0.0)	12	(85.7)	2 (14.3)
	0.06	7	7	(100.0)	0	(0.0)	0 (0.0)	7	(100.0)	0 (0.0)
	0.12	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.25	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	0.5	4	4	(100.0)	0	(0.0)	0 (0.0)	4	(100.0)	0 (0.0)
	1	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	2	1	1	(100.0)	0	(0.0)	0 (0.0)	1	(100.0)	0 (0.0)
	Total	33	31	(93.9)	2	(6.1)	0 (0.0)	31	(93.9)	2 (6.1)
Streptococcus pneumoniae (ERY-R/mefE & ermB)										
	0.06	2	2	(100.0)	0	(0.0)	0 (0.0)	2	(100.0)	0 (0.0)
	0.5	2	2	(100.0)	0	(0.0)	0 (0.0)	2	(100.0)	0 (0.0)
	Total	4	4	(100.0)	0	(0.0)	0 (0.0)	4	(100.0)	0 (0.0)

The regression analysis for determining the zone sizes can be seen in the following graph (provided by Aventis in e-mail of 17 mar 04). This analysis is based on the MIC and zone size determinations for all clinical isolates combined (bmITT population). The "Very Major" (VM), "Major" (M), and "Minor" (m) error rates meet the criteria established by the NCCLS (4).

Figure 1. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, All Strains Combined (n=672)**



The following regression analyzes are done using the various resistant populations of *S. pneumoniae* (provided by Aventis in e-mail of 17 mar 04). The populations of resistant *S. pneumoniae* are appropriately categorized using the disc diffusion zones sizes determined from combining all isolates of *S. pneumoniae* together. The "Very Major" (VM), "Major" (M), and "Minor" (m) error rates meet the criteria established by the NCCLS (**4**).

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Figure 2. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Penicillin-Susceptible (n=543)**

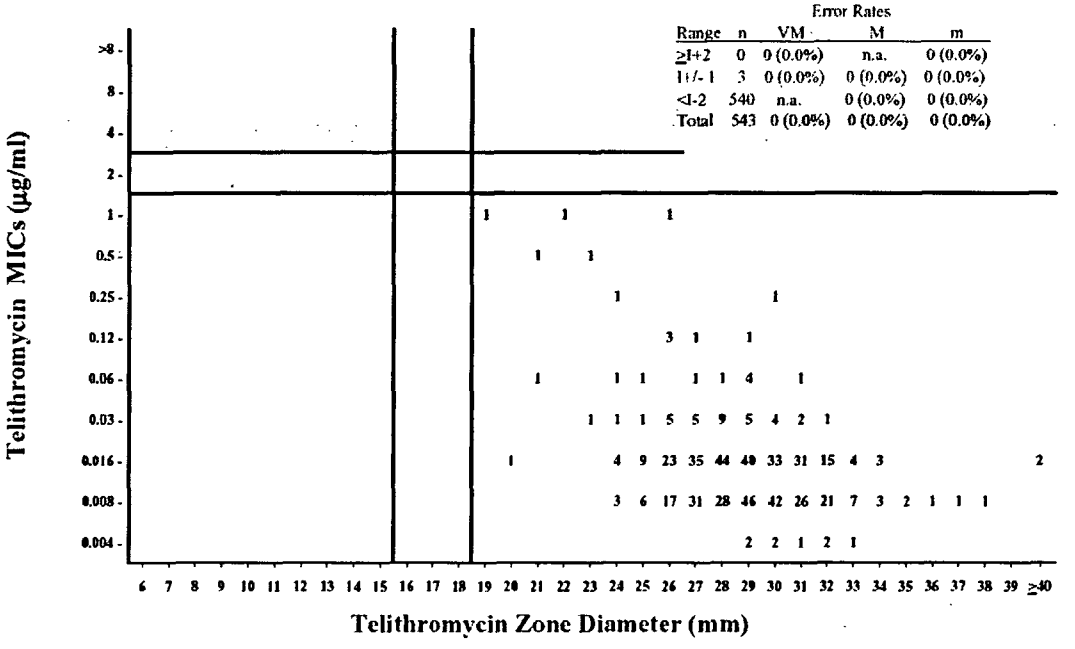


Figure 3. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Penicillin-Intermediate (n=70)**

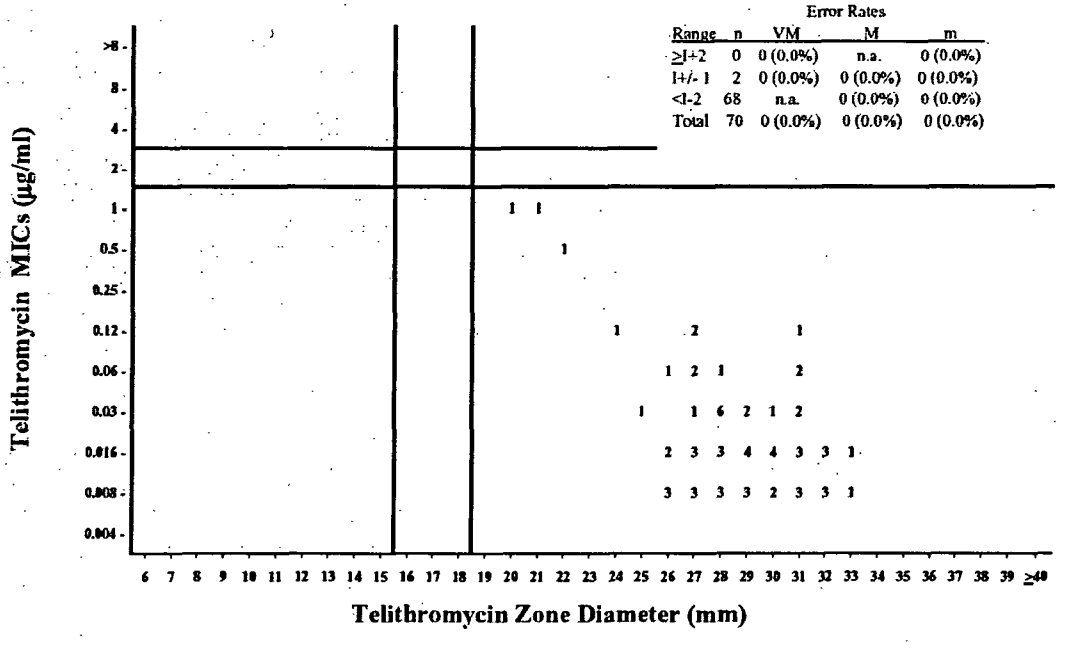


Figure 4. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Penicillin-Resistant (n=59)**

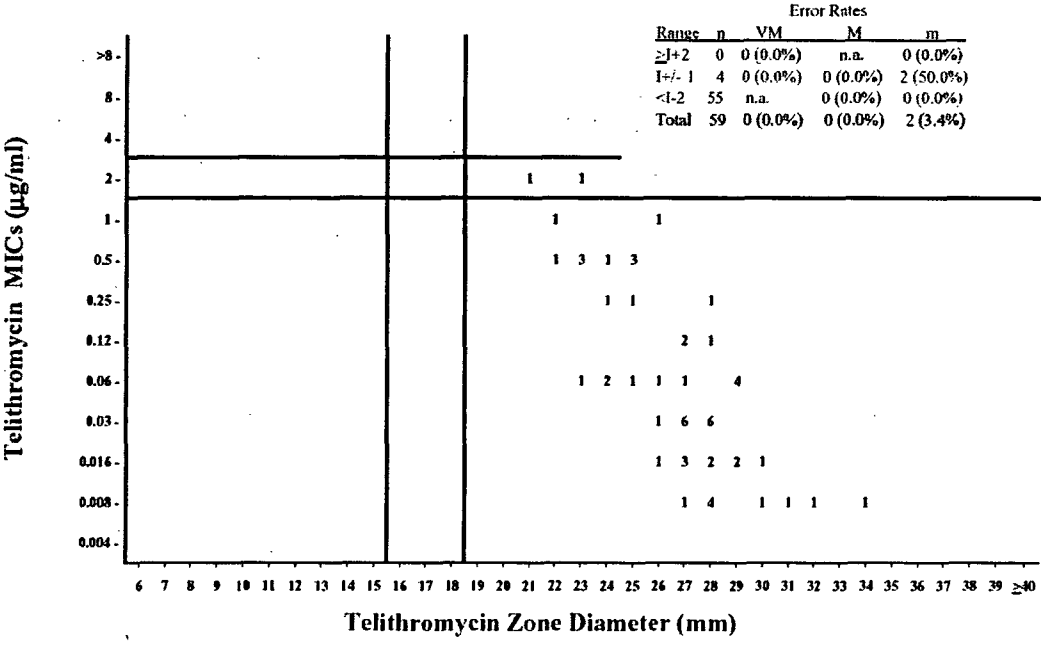


Figure 5. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Erythromycin-Susceptible (n=584)**

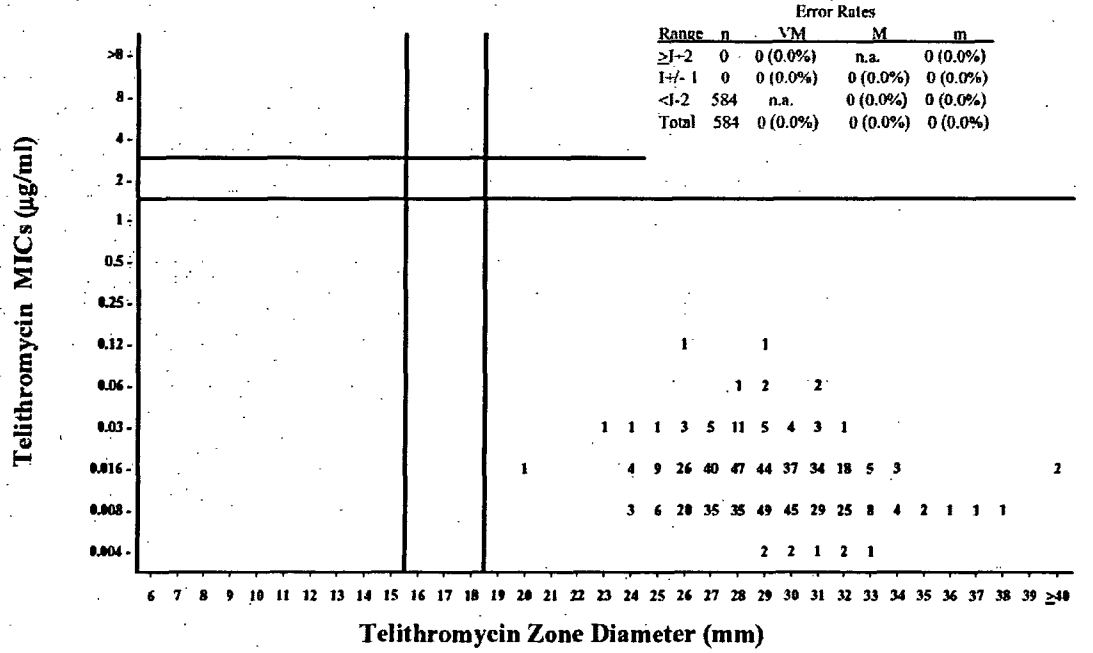
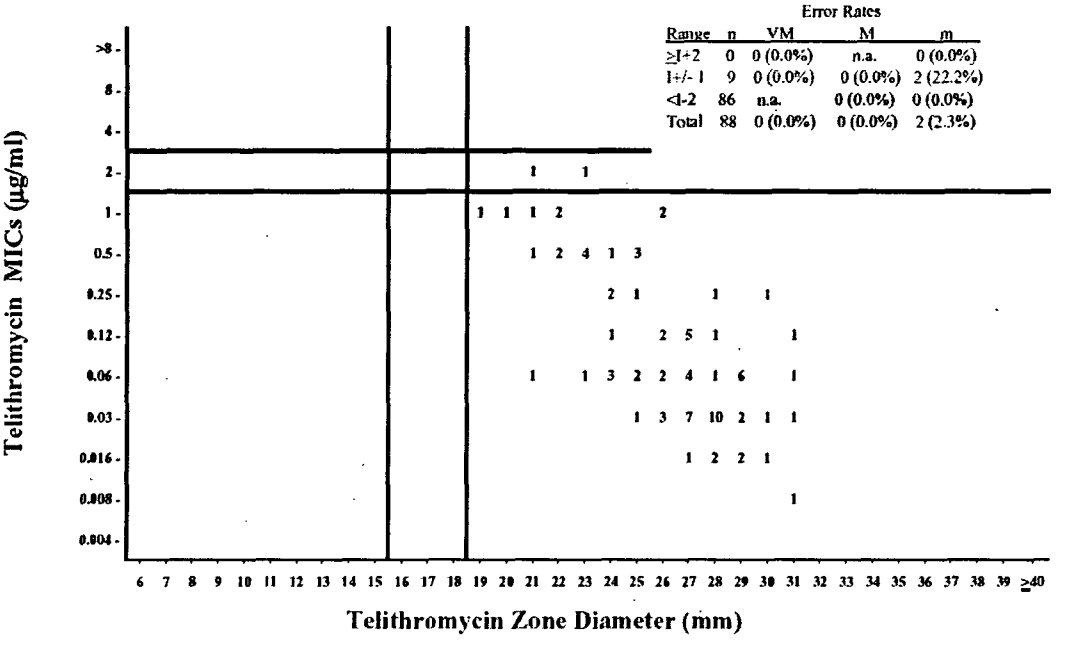


Figure 6. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Streptococcus pneumoniae*, Erythromycin-Resistant (n=88)**

(There were no erythromycin-intermediate strains recovered)



HAEMOPHILUS INFLUENZAE

The applicable MIC and zone size interpretive criteria are shown below.

Interpretive Category	MIC (µg/mL)	Zone of Inhibition (mm)
Susceptible	≤4.0	≥15
Intermediate	8.0	12 – 14
Resistant	≥16.0	≤11

The bacterial eradication rates using ≤ 4 µg/mL as indicating susceptibility of *H. influenzae* to telithromycin in the indications noted below are:

H. influenzae

Indication	Number of Isolates	Bacterial eradication (%)
CAP	193	170 (88.0)
AECB	52	37 (71.1)
ABS	55	48 (87.2)
Total	300	255 (85.0)

The regression analysis data for determining the zone sizes can be seen in the following graph (provided by Aventis in e-mail of 17 mar 04). This analysis is based on the MIC and zone size determinations for all isolates (bmITT population). The "Very Major" (VM), "Major" (M), and "Minor" (m) error rates meet the criteria established by the NCCLS (4).

Figure 7. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Haemophilus influenzae*, All Strains Combined (n=683)**

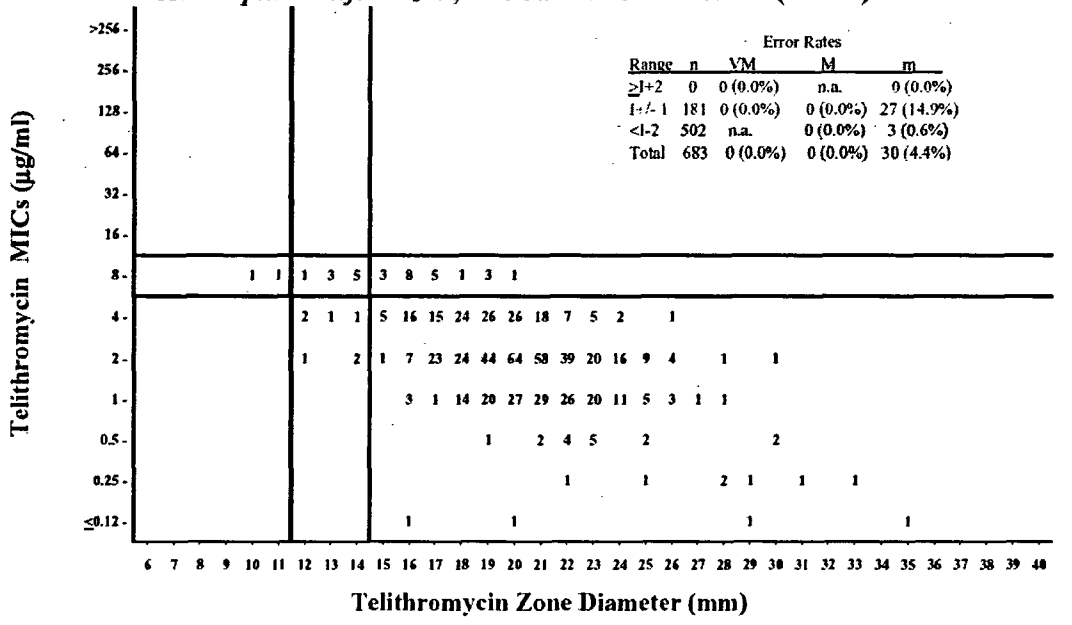


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Table 1 Bacteriological eradication rates and clinical cure rates at Posttherapy/TOC according to MIC values for HMR 3647 by causative pathogen for all indications combined without centers excluded by FDA - PPb population [a]□ (Continued)

			HMR 3647									
			Bacteriological outcome [c] No. (%)						Clinical outcome [d] No. (%)			
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure	
Haemophilus influenzae												
	0.002	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.12	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	0.25	3	3	(100.0)	0	(0.0)	0	(0.0)	3	(100.0)	0	(0.0)
	0.5	8	5	(62.5)	2	(25.0)	1	(12.5)	6	(75.0)	2	(25.0)
	1	82	68	(82.9)	14	(17.1)	0	(0.0)	69	(84.1)	13	(15.9)
	2	177	152	(85.9)	22	(12.4)	3	(1.7)	155	(87.6)	22	(12.4)
	4	69	59	(85.5)	9	(13.0)	1	(1.4)	60	(87.0)	9	(13.0)
	8	17	12	(70.6)	4	(23.5)	1	(5.9)	13	(76.5)	4	(23.5)
	Not done	2	2	(100.0)	0	(0.0)	0	(0.0)	2	(100.0)	0	(0.0)
	N/A	41	39	(95.1)	2	(4.9)	0	(0.0)	38	(92.7)	3	(7.3)
	Total	402	343	(85.3)	53	(13.2)	6	(1.5)	349	(86.8)	53	(13.2)
Haemophilus influenzae (beta-lactamase producer)												
	0.12	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	0.5	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)
	1	12	9	(75.0)	3	(25.0)	0	(0.0)	9	(75.0)	3	(25.0)
	2	28	22	(78.6)	5	(17.9)	1	(3.6)	22	(78.6)	6	(21.4)
	4	8	5	(62.5)	3	(37.5)	0	(0.0)	5	(62.5)	3	(37.5)
	8	4	2	(50.0)	2	(50.0)	0	(0.0)	3	(75.0)	1	(25.0)
	Total	54	40	(74.1)	13	(24.1)	1	(1.9)	41	(75.9)	13	(24.1)
Haemophilus influenzae (AZI-R)												
	8	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1	(33.3)
	Total	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1	(33.3)

a PPb=per protocol bacteriologically evaluable population.
b Causative admission pathogens as assessed by investigators. AMP-R=resistant to ampicillin, AZI-R=resistant to azithromycin.
c Includes documented and presumed.
d Cure=returned to preinfection state, and improved or postinfection stigmata (no subsequent antibiotic); Failure=failure as assessed by the investigators.

STAPHYLOCOCCUS AUREUS

The applicant has proposed the following in vitro susceptibility test interpretive criteria.

After review of the data the Agency does not agree that there is enough bacterial eradication and clinical cure data from studies to support these breakpoints. The Agency feels that there is only data to provide a breakpoint that characterizes *S. aureus* isolates as susceptible to telithromycin and therefore the following interpretive criteria are appropriate.

Interpretive Category	MIC (µg/mL)	Zone of Inhibition (mm)
Susceptible	0.25	≥22

The bacterial eradication and clinical outcome rates for all indications with infections caused by *S. aureus* with telithromycin MICs of ≤ 0.25 µg/mL were 84% (57/68) and 81% (55/68) respectively. There were 31 isolates from CAP, 5 from AECB and 22 from ABS.

The regression analysis data for determining the zone sizes based on MICs for *S. aureus* is seen in the following graph (provided by Aventis in e-mail of 17 mar 04). This analysis is based on the MIC and zone size determinations for all isolates (bmITT population). The applicant calculated the error rates based on their proposed interpretive criteria of

. The "Very Major" (VM), "Major" (M), and "Minor" (m) error rates provided by the applicant meet the criteria established by the NCCLS (3). The Agency feels the more appropriate breakpoint is ≤0.25 µg/mL = susceptible with no intermediate or resistant breakpoints determined because of the lack of data to determine these breakpoints. Because of the lack of data it is not possible to calculate accurate error rates for the breakpoint of ≤0.25 µg/mL = susceptible.

Table 31. Bacterial eradication and clinical cure rates for *S. aureus* from all indications

+

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Table 1 Bacteriological eradication rates and clinical cure rates at Posttherapy/TOC according to MIC values for HMR 3647 by causative pathogen for all indications combined without centers excluded by FDA - PPb population [a]□ (Continued)

			HMR 3647								
			Bacteriological outcome [c] No. (%)						Clinical outcome [d] No. (%)		
Pathogen [b]	MIC (µg/ml)	N	Eradication		Persistence		Recurrence		Cure		Failure
Staphylococcus aureus											
	0.06	9	7	(77.8)	2	(22.2)	0	(0.0)	7	(77.8)	2 (22.2)
	0.12	50	42	(84.0)	7	(14.0)	1	(2.0)	40	(80.0)	10 (20.0)
	0.25	9	8	(88.9)	1	(11.1)	0	(0.0)	8	(88.9)	1 (11.1)
	8	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0 (0.0)
	N/A	15	14	(93.3)	1	(6.7)	0	(0.0)	14	(93.3)	1 (6.7)
	Total	84	72	(85.7)	11	(13.1)	1	(1.2)	70	(83.3)	14 (16.7)
Staphylococcus aureus (OXA-R)											
	0.12	3	2	(66.7)	1	(33.3)	0	(0.0)	2	(66.7)	1 (33.3)
	8	1	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)	0 (0.0)
	Total	4	3	(75.0)	1	(25.0)	0	(0.0)	3	(75.0)	1 (25.0)

The regression analysis data based on all isolates of *S. aureus* (bmITT) are shown below followed by regression analysis done on the oxacillin-susceptible and –resistant populations of *S. aureus*.

Figure 10. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***S. aureus*, All Strains Combined (n=139)**

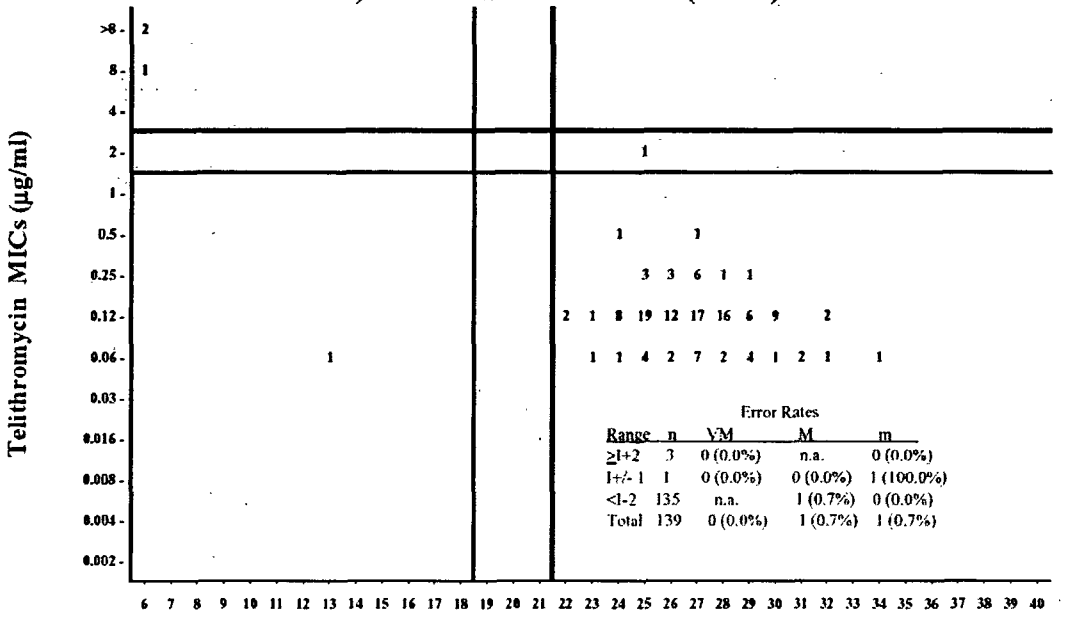


Figure 11. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Staphylococcus aureus*, Oxacillin-Susceptible (n=130)**

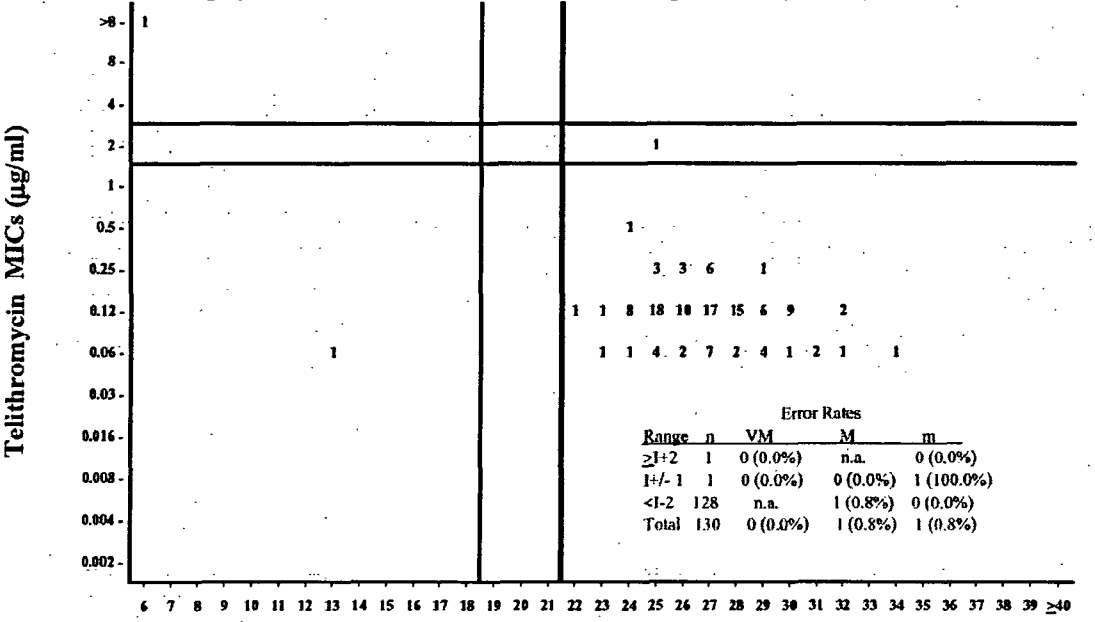
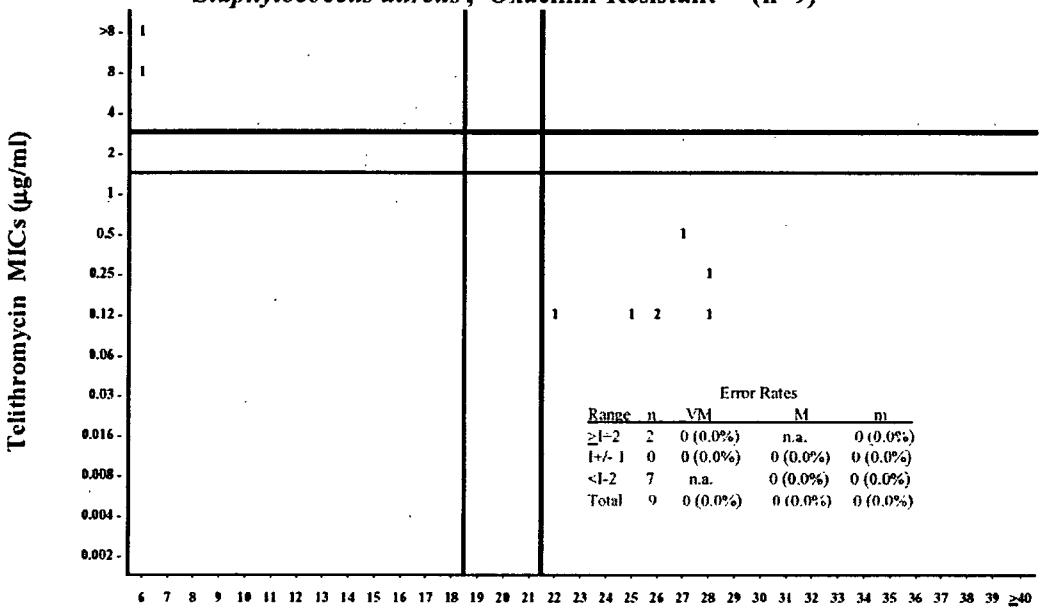


Figure 12. Telithromycin MICs vs. Zone Diameter (15 µg Disks) bmITT Population

***Staphylococcus aureus*, Oxacillin-Resistant (n=9)**



QUALITY CONTROL ORGANISMS AND THEIR MIC AND DISC DIFFUSION RANGES FOR TELITHROMYCIN SUSCEPTIBILITY TESTING:

The Agency concurs with the telithromycin quality control ranges in Table 32.

Table 32. Quality control ranges for telithromycin

QC strain	Minimal Inhibitory concentration (µg/mL)	Disk Diffusion (Zone size in mm)
Staphylococcus aureus ATCC® 29213	0.06 - 0.25	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	24 - 30
Streptococcus pneumoniae ATCC 49619	0.004 - 0.03	27 - 33
Haemophilus influenzae ATCC 49247	1.0 - 4.0	17 - 23

ATCC = American Type Culture Collection

CONCLUSION

Susceptibility Test Interpretive Criteria

The in vitro susceptibility breakpoints proposed by the applicant for *S. pneumoniae*, and *H. influenzae* are appropriate for inclusion in the package insert for telithromycin.