Distribution of Extreme Laboratory Values (cont)

Platelet Count (cont)	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
		E	197.000		680.000
		E	254.000		409.000
		E	244.000		525.000
Gamma-Glutamyl Transpep-tidase					
		D	122.000		323.000
		D	93.000		121.000
		D	162.000		283.000
		D	150.000		179.000
ALANINE AMINOTRANSFERASE					
		D	43.000		101.000
		D	61.000		167.000
		D	146.000		210.000
		E	98.000		135.000
ASPARTATE AMINOTRANSFERASE					
		D	61.000		167.000
		D	146.000		210.000
		e	98.000		135.000
ALKALINE PHOSPHOTASE					
		D	107.000		176.000
		D	53.000		176.000
		D	122.000		172.000
BILIRUBIN					
		E	40.700		83.000
HEMATOCRIT					
		D	0.410		0.330
HEMOGLOBIN					
		E	8.760		6.770
		E	8.570		7.270
		E	8.760	8.010	6.460
		E	7.820		6.460
ESINOPHIL COUNT					

	D	0.288		1.715
	E	0.510		1.190
	E	(NO PRE)	0.620	1.610
	E	0.000		1.104
LEUKOCYTE COUNT				
	D	7.650		3.310
URIC ACID				
	D	434.000		595.000
	E	399.000	636.000	595.000
	E	345.000		660.000
	E	150.000		0.250
UREA NITROGEN				
	D	21.100		25.700
CALCIUM				
	D	3.700		4.600
PHOSPHORUS				
	D	0.970		1.260
	E	1.000		2.160
GLUCOSE				
	D	9.200		13.100
	E	6.400	1.600	NO POST
CREATINE PHOSPHOKINASE				
	D	310.000		798.000
	D	281.000		1437.000
	E	119.000		800.000
	E	74.000		2890.000
	E	83.000		3380.000
LEUKOCYTES	D	4.99		18.25
	E	8.72	13.07	
BANDS	D	0		1.03
	D	0.600		1.460
	D	0		1.100
NEUTROPHILS	D	7.46		10.78
	D	2.28		11.32
	E	7.23	10.82	
LYMPHOCYTES	D	1.89		5.39
	E	4.94	7.27	
	E	0.96		5.98

MONOCYTES	D	0.56		1.27
	D	0.44		1.28
	E	0.48		1.16
AST	E	23.0		84.0
ALT	D	79.0		121.0
PHOSPHORUS	D	1.100		1.680

ECG

There were no drug-induced effects on ECG's by either dirithromycin or erythromycin. Changes noted in the ECG's were not clinically significant, comparable in each therapy group, and consisted of minimal changes in heart rate without hemodynamic significance, development or resolution of atrial or ventricular premature contractions, minimal ST-T wave morphologic changes and minimal changes in QRS width or axis. No clinically significant rhythm disturbances, conduction disturbances or electrocardiographic evidence of acute myocardial ischemia or infarction were noted on any ECG.

Medical Officer's Overall Comments:

Efficacy:

Both dirithromycin and erythromycin were effective in the treatment of acute exacerbation of chronic bronchitis caused by the target pathogens.

An overall favorable clinical success rate (cure or improvement) at post-therapy was **86%** (87/101) for the dirithromycin group and **89%** (72/81) for the erythromycin group. At late post-therapy follow-up, it was **89%** (71/80) for the dirithromycin group and **91%** (61/67) for the erythromycin group.

An overall favorable bacteriologic success rate (eradicated/presumed eradicated) at post-therapy was **91%** (85/ 93) for the dirithromycin group and **83.5%** (66/79) for the erythromycin group. At late post-therapy follow-up, it was **92%** (70/76) for the dirithromycin group and **91%** (60/66) for the erythromycin group.

An overall favorable bacteriologic success rate (eradicated/presumed eradicated) by pathogen for evaluable patients at post-therapy was 15/21 (71.4%) for *H. influenzae* , 100% (21/21) for *S. pneumoniae*, 100% (16/16) for *M. catarrhalis* and 100% (10/10) for *H. parainfluenzae* in the dirithromycin group and 20/22 (91%) for *H. influenzae*, 11/13 (84.5%) for *S. pneumoniae*, and 11/12 (91.6%) for *M. catarrhalis* for the erythromycin group.

An overall favorable bacteriologic success rate (eradicated/presumed eradicated) by pathogen for evaluable patients at late post-therapy follow-up was 12/14 (85.7%) for *H. influenzae* , 94% (16/17) for *S. pneumoniae*, 100% (14/14) for *M. catarrhalis* and 100% (5/5) for *H. parainfluenzae* in the dirithromycin group and 16/17 (94%) for *H. influenzae*, 11/12 (91.6%) for *S. pneumoniae*, and 11/11 (100%) for *M. catarrhalis* for the erythromycin group.

Medical Officer's Conclusions:

The clinical and bacteriologic success rate at post therapy and late post-therapy follow-up for both the study drugs appears to be the same, but the eradication rate/presumed eradication rate for *H. influenzae* appears to be superior for the erythromycin group in comparison to the dirithromycin group. In this study, over 70% of the *H. influenzae* isolated were resistant to dirithromycin. These patients were considered to be unevaluable thus were not included in the efficacy analysis.

REVIEW OF PIVOTAL STUDIES:

II. Study B9Z-EW-E002 Synopsis:

Title:	Dirithromycin (LY237216) Versus Erythromycin Base in Bronchitis
Study Centers:	There were 110 study centers (all in Europe).
Dates of Study:	January 1989 through September 1990.
Clinical Phase:	Phase 3.
Objectives:	To compare the efficacy and safety of dirithromycin (LY237216), 500 mg daily, with erythromycin, 1000 mg daily, for the treatment of secondary bacterial infection of acute bronchitis and acute bacterial exacerbation of chronic bronchitis.
Methodology:	Double-blind, randomized, parallel study.
Number of Patients:	Secondary Bacterial Infection of Acute Bronchitis: Dirithromycin: Male 139, Female 128, Total 267; Erythromycin: Male 133, Female 129, Total 262. Acute Bacterial Exacerbation of Chronic Bronchitis: Dirithromycin: Male 194, Female 153 Total 347; Erythromycin: Male 186, Female 160, Total 346.
Diagnosis and Inclusion Criteria:	Diagnosis of secondary bacterial infection of acute bronchitis or acute bacterial exacerbation of chronic bronchitis with cough, productive of purulent sputum, and a chest radiograph free from acute pulmonary infiltrates.
Dosage and Administration:	Test Product Dirithromycin: 500 mg/day, given once daily CT9198-7A, CT9549-9A, CT0009-9A: dirithromycin tablets, 250 mg CT9199-7A, CT9550-9A, CT0010-9A: placebo tablets. Note: Placebo was used to maintain blinding.

	Reference Therapy Erythromycin: 1000 mg/day, given 4 times daily CT9200-7A, CT9200-7A/8B, CT9200-8B, CT9200-9C: erythromycin tablets, 250 mg CT9201-7A, CT9201-7A/8B, CT9201-8B, CT9201-9C: placebo tablets.
Duration of Treatment:	Dirithromycin: 7 days Erythromycin: 7 days
Criteria for Evaluation:	Efficacy--A complete efficacy analysis was to be performed on patients completing at least 5 days of therapy who had positive pretherapy sputum culture, returned for posttherapy evaluation, and who had a clinical response that could be evaluated. Safety--All patients were to be evaluated for safety.
Statistical Methods:	Chi-squared methodology and appropriate continuous data procedures such as two-sample t-test on ranked data were to be used for analysis of laboratory tests.

Study Design:

This was a double-blind, randomized, parallel study. Patients who met the entry criteria and gave informed consent were randomly assigned to one of two antibiotic treatment groups. Randomization was provided by the sponsor. Patients were evaluated for clinical and bacteriological responses to treatment. Safety was to be measured by clinical assessment and laboratory tests. In patients who responded to treatment, the duration of therapy was to be 7 days. The patients were considered evaluable if they received at least 5 days to 7 days of therapy. There was no minimum treatment period for patients who did not respond to therapy. These patients were considered to be evaluable and failures.

A standard dose was selected for the comparator drug erythromycin. The doses selected for dirithromycin were based on pharmacodynamic, pharmacokinetic, and safety data analyses from Phase 1 clinical trials.

Inclusion Criteria

Patients, male and female, aged ≥18 years and ≤65 years, were to be included in the study if they had a clinical diagnosis of secondary bacterial infection of acute bronchitis or acute bacterial exacerbation of chronic bronchitis.

The investigators were to attempt to select those patients who seemed likely to comply with instructions. Each patient was to be asked to sign an ethical committee-approved informed consent form.

Exclusion Criteria

Patients were to be excluded who had a history of renal impairment (serum creatinine 170 μmol/L, 2.0 mg/dL or higher); had any condition, including significant underlying disease or concomitant infection which, in the opinion of the investigator, could have precluded evaluation of response; had an anticipated requirement of systemic antibiotics other than the study antibiotic during-therapy; had received successful or suppressive antimicrobial therapy within 1 week preceding the pretherapy evaluations; had been taking ergotamine; or had used other investigational agents within 3 months prior to entry into study.

Also excluded were patients who were unable to return for follow-up examinations, patients who had hypersensitivity to macrolides, patients who were pregnant, and postpartum/lactating females who were nursing.

Dosing Schedule:

Dirithromycin tablets were to be administered once daily, for a total daily dose of 500 mg. Erythromycin tablets were to be administered four times a day, for a total daily dose of 1000 mg. In the dirithromycin treatment group, a placebo for erythromycin was to be given four times daily; dirithromycin was taken on rising. In the erythromycin group, two placebos for dirithromycin were to be given in the morning.

Evaluation/Procedures:

PROCEDURES FOR EVALUATION OF CLINICAL RESPONSE

Study Visit	Procedure
Pretherapy (Within 24 hours Preceding the First Dose):	A complete history and physical examination (X-ray included) were to be performed.
During Therapy (Days 3-5):	Evaluated clinical response to therapy and assessed patient compliance with instructions for taking medication.
Posttherapy (3-5 Days After Therapy Was Completed):	Physical examination was to be performed to evaluate clinical response to therapy.
Late-Posttherapy (10-14 Days After Therapy was Completed):	Physical examination was to be performed to evaluate clinical response to therapy.

PROCEDURES FOR EVALUATION OF BACTERIOLOGICAL RESPONSE

Study Period	Procedure
Pretherapy (Within 24 Hours Preceding The Start of Therapy):	Gram's stain and culture of expectorated sputum were to be obtained. Susceptibility of the microorganism(s) isolated to both dirithromycin and erythromycin was to be determined by the N.C.C.L.S. methodology for MIC and/or disc diffusion testing. The pathogen had to be susceptible to erythromycin* for the patient to remain in the study.
During Therapy (Days 3-5):	Sputum culture was to be obtained if clinically indicated. If a pathogen was isolated, susceptibility to dirithromycin and erythromycin was to be determined.
Posttherapy (3-5 Days After Therapy Was Completed):	Sputum culture was to be obtained if clinically indicated. If a pathogen was isolated, susceptibility to dirithromycin and erythromycin was to be determined.
Late-Posttherapy (10-14 Days After Therapy Was Completed):	Sputum culture was to be obtained if clinically indicated. If a pathogen was isolated, susceptibility to dirithromycin and erythromycin was to be determined.

* Erythromycin Susceptibility: ≥18 mm zone size; ≤0.5 g/mL MIC

Safety Procedures:

Safety assessments included clinical evaluations and laboratory tests. Selected laboratories were to be used to determine values for the laboratory tests described in the following table. Each study site was provided with laboratory patient kits to collect blood and urine samples for shipment to the selected laboratory. Each study site received a copy of the laboratory results for each testing period. Laboratory values regarded as alarming (predetermined by the sponsor) were to be telephoned to the study site. The test for creatine kinase (CK) isoenzyme was to be performed if the CK isoenzyme was raised by three times the upper limit of normal or more. If the CK isoenzyme fraction of cardiac origin was elevated, the laboratory gave an immediate warning call to the study site and Lilly and the patient was recalled for evaluation.

LABORATORY PROCEDURES TO EVALUATE SAFETY

Study Period	Procedure		
Pretherapy (Within 24 Hours of Receiving the First Dose):	Hematology	Blood Chemistry	Urinalysis
	Hemoglobin	Bilirubin	Appearance
	Hematocrit	Alkaline Phos.	Specific Gravity
	RBC Count	GGT	pH
	MCV	ALT (SGPT)	Protein
	MCH	AST (SGOT)	Glucose
	MCHC	Urea	Ketones
	WBC Count	Creatinine	Bilirubin
	Differential	Uric Acid	Urobilinogen
	Platelet Count	Phosphorus	Blood
		Calcium	Microscopic- WBC
		Total Protein	RBC
		Albumin	Casts
		CK	
		Cholesterol	
During Therapy (Days 3-5):	Laboratory tests were to be repeated as clinically indicated. Urine samples were to be assayed for presence of antimicrobial activity.		

Posttherapy (3-5 Days After Completion of Therapy):	Pretherapy tests were to be repeated. If any abnormal values were found, the tests were to be repeated until values returned to normal or were explained.
Late-Posttherapy (10-14 Days After Completion of Therapy):	Laboratory tests were to be repeated as clinically indicated.

All patients were to be instructed to contact the investigator or clinical personnel by phone if they experienced an adverse event. The investigator was to report all adverse events to the Research Physician by prompt submission of clinical report forms. If the adverse event was alarming, it was to be reported immediately to the Research Physician.

Adverse events were to be recorded on the clinical report form using the patient's words or the investigator's terms (synonym terms). Synonym terms were further classified as Eli Lilly and Company Event Classification Terms (ELECT), which are based on U.S. Food and Drug Administration COSTART definitions. Both synonym terms and ELECT classifications were entered in the Lilly database. Adverse events were to be categorized by body system using the algorithm found in the ELECT dictionary.

Terminations:

A patient was to be discontinued from the study for any one of the following reasons:

- Pathogen isolated from initial culture was resistant to erythromycin.

- Obvious clinical failure of the study antibiotic at any time during treatment. There was no minimum treatment period. The duration of therapy was left to the clinical judgment of the investigator.

- If, in the investigator's opinion, significant adverse event(s) or significant alteration(s) in a laboratory parameter occurred, the study antibiotic was discontinued.

- If the patient or attending physician requested, or the investigator so decided, the patient was withdrawn from the study and the reason stated on the clinical report form. In addition, Lilly could decide to terminate the study.

- Study-drug identity was unblinded for safety reasons.

Patients who discontinued from the study were to have pretherapy laboratory tests and cultures repeated.

Patients who showed a favourable clinical response to treatment but had a negative pretherapy culture may have been continued in the study at the discretion of the clinical investigator. Such patients were qualified for safety evaluation only.

Efficacy Procedures:

CLINICAL RESPONSE DEFINITIONS

Response	Definition of Response
Cure:	Elimination of signs and symptoms of infection with no recurrence in the follow-up period.
Improvement:	Significant but incomplete resolution of signs or symptoms of infection.
Relapse:	Worsening of signs and symptoms of infection following initial improvement.
Failure:	Signs and symptoms did not subside or improve during-therapy. A case requiring the addition of another antibiotic for the treatment of bronchitis was classified as a clinical failure.
Unable to Evaluate:	Unable to evaluate a clinical response due to extenuating circumstances including the concomitant use of a systemic antimicrobial agent for another infection. This response disqualified a case for efficacy analysis. Reasons for these occurrences were specified in the "Comments" section of the clinical report form.

BACTERIOLOGICAL RESPONSE DEFINITIONS

Result	Definition of Response
Pathogen Eliminated:	Eradication of the pathogen at post-therapy and late post-therapy follow-up.
Recurrence Same Pathogen:	Original pathogen eliminated during treatment but recurred during the follow-up period.
Recurrence Same Pathogen, Resistance Developed:	Original pathogen susceptible to the study antibiotic was eliminated during treatment but recurred in the follow-up period and tested as resistant to the study antibiotic.
Recurrence New Pathogen:	Original pathogen susceptible to the study antibiotic was eliminated during treatment but a new pathogen was isolated in the follow-up period.
Failure:	Original pathogen was not eradicated.
Not Applicable:	Term used for patients showing clinical cure or improvement but for whom a repeat culture was impossible and/or not clinically indicated (cough and/or sputum production resolved, presumed elimination of pathogen).
Unable to Evaluate:	Term used when posttherapy culture was not obtained for reasons other than stated above, or when pretherapy culture was negative.

Medical Officer's Comments:

The Medical Officer defined "Not Applicable" as "Presumed Eradicated".

Qualification for Efficacy Analysis:

Cases classified by the sponsor as "qualified" (evaluable) met the following criteria for analysis of **clinical response**: the patient met enrollment criteria; patient completed adequate course of therapy (5-7 days); the pretherapy culture was positive for pathogenic organism(s); a posttherapy clinical evaluation was performed; clinical response (cure, improvement, relapse, or failure) could be evaluated (clinical response of "Unable to Evaluate" disqualified cases for efficacy analysis). Cases classified by the sponsor as "qualified" (evaluable) also met the following criteria for analysis of **bacteriological response**: the patient met enrollment criteria; the patient completed an adequate course of therapy (5-7 days); the pretherapy culture was positive for pathogenic organism(s) with isolated organism(s) susceptible to erythromycin; a posttherapy (3-5 days post-treatment and 10-14 days post treatment) culture was obtained or was "not applicable."

Medical Officer's Comments:

If there was no material obtained for culture at any post-treatment period, the sponsor designated those responses as "Not Applicable", but the Medical Officer's designated those responses as "Presumed Eradicated".

Statistical Methods:

The primary statistical evaluations included all data available from all patients entering the study. The groups of patients, determined by random allocation, were compared by means of chi-square methodology with respect to clinical and bacteriological response rates and with respect to adverse event frequencies. Appropriate continuous data procedures, such as a two-sample t-test on ranked data, were used for analysis of the laboratory monitoring data. Subgroup analyses (efficacy) were performed for the two formulations of study-drug medication utilized in this study. Separate efficacy analyses were performed for patients with acute bronchitis and patients with acute exacerbation of chronic bronchitis.

Investigators:

Study Population
All Patients Consented and/or Randomized

Indication: Secondary Bacterial Infection of Acute Bronchitis

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
F. R. CRANFIELD/GWENT, WALES	1	0	0	0
R. DASGUPTA/LANCASHIRE, ENGLAND	0	1	0	1
A. W. DAVIES/GWENT, WALES	0	1	0	0
J. HOSIE/GLASGOW, SCOTLAND	0	1	0	0
R. J. CHESWORTH/LANCASHIRE, ENGLAND	1	0	0	0
C. E. LANGAN/GLASGOW, SCOTLAND	8	13	2	4
D. G. WOOD/BANGOR, WALES	3	3	2	1
M. W. MUTCH/RENFREWSHIRE, SCOTLAND	2	2	0	0
M. G. SCOTT/GLASGOW, SCOTLAND	1	0	1	0
H. J. DONNACHIE/GLASGOW, SCOTLAND	9	3	2	1
A. W. HARRIS/WEST MIDLANDS, ENGLAND	16	15	4	6
D. WALTON/LANCASHIRE, ENGLAND	3	3	0	0
A. LIENER/SCHWAZ/TIROL, AUSTRIA	2	1	0	0
I. THOMULLER/GRAZ, AUSTRIA	8	8	0	1
K. H. MAYER/WELS, AUSTRIA	0	1	0	0
H. PLEUMEEKERS/ROTTERDAM, THE NETHERLANDS	2	1	2	0
P. W. FUHRING/ROTTERDAM, THE NETHERLANDS	1	2	0	2
C. M. LIMBURG/ROTTERDAM, THE NETHERLANDS	3	2	0	0
C. VAN NOORT/ROTTERDAM, THE NETHERLANDS	1	1	1	0
R. C. HENDRIKS/ROTTERDAM, THE NETHERLANDS	0	1	0	0
G. T. VAN DE POEL/ROTTERDAM, THE NETHERLANDS	0	3	0	3
J. C. VAN MECHELEN/ROTTERDAM, THE NETHERLANDS	1	1	0	0
J. COOPEN/ROTTERDAM, THE NETHERLANDS	2	1	2	1
D. H. SMEETS/ROTTERDAM, THE NETHERLANDS	1	0	0	0
H. FERGUSON/ROTTERDAM, THE NETHERLANDS	3	5	1	1

(continued)

Study Population (continued)
All Patients Consented and/or Randomized

Indication: Secondary Bacterial Infection of Acute Bronchitis

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
J. A. VAN WYNGAARDEN/ROTTERDAM, THE NETHERLANDS	0	1	0	0
D. OOSTHOEK/RIJSSEN, THE NETHERLANDS	4	1	2	0
D. E. PEREZ-TRALLERO/ SAN SABASTIAN, SPAIN	1	0	0	0
F. MARTIN/MADRID, SPAIN	3	0	2	0
A. RODRIGUEZ-NORIEGA/ MADRID, SPAIN	3	3	1	0
A. S. COWIE/WILTSHIRE, ENGLAND	16	16	5	4
P. MCVEY/DUBLIN, IRELAND	10	12	3	2
T. K. KHONG/LEICESTER, ENGLAND	7	8	1	1
E. MAGUIRE/BELFAST, NORTHERN IRELAND	1	1	0	0
B. R. AKHTAR/GWENT, WALES	8	7	0	3
P. LAPPIN/CO. MEATH, IRELAND	4	2	1	0
L. D. MUNOT/DEVON, ENGLAND	4	3	0	0
J. RODGER/LANARKSHIRE, U.K.	1	0	0	0
J. BECKETT/CO. KILKENNY, IRELAND	8	8	2	1
M. MURPHY/CO. CORK, IRELAND	1	1	0	0
J. C. QUIRKE/CO. CORK, IRELAND	5	5	1	0
P. QUINN/CO. MONAGHAN, IRELAND	0	1	0	0
B. SCANLON/LIMERICK, IRELAND	2	1	1	0
J. DRYNAN/CO. KILKENNY, IRELAND	7	9	1	0
J. KEENAN/ROSCOMMON, IRELAND	1	1	1	1
P. NEARY/CO. LOUTH, IRELAND	2	3	0	2
P. O'BRIEN/CO. GALWAY, IRELAND	2	3	1	0
D. B. MURPHY/CO. CORK, IRELAND	2	2	0	0
LONERGAN/CO. KILKENNY, IRELAND	18	19	11	9
D. HERLIHY/CO. CORK, IRELAND	1	1	1	0
FEIGHREY/CO. MEATH, IRELAND	1	1	0	0
M. TIPPINS/BIRMINGHAM, ENGLAND	6	5	0	1
S. SAIKIA/BIRMINGHAM, ENGLAND	2	3	1	1
C. A. HOOD/OXON, ENGLAND	1	0	0	0
F. MCKEAGNEY/CO. LAOIS, IRELAND	1	0	1	0
S. H. SHAH/GWENT, WALES	7	7	1	2
E. SHANAHAN/CO. KERRY, IRELAND	2	0	0	0
D. M. FERNEL/BIRMINGHAM, ENGLAND	1	0	0	0

(continued)

Study Population (concluded)
All Patients Consented and/or Randomized

Indication: Secondary Bacterial Infection of Acute Bronchitis

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
U. K. TEWARI/LANCASHIRE, ENGLAND	2	1	0	0
J. KAY/WEST MIDLANDS, ENGLAND	2	3	2	3
W. BUTLER/CO. MEATH, IRELAND	3	3	0	0
S. J. EDWARDS/CHESHIRE, ENGLAND	0	2	0	0
S. P. WADERA/SUFFOLK, ENGLAND	6	8	0	1
D. COTTER/CO. CORK, IRELAND	3	5	0	0
J. K. KANJILAL/SUFFOLK, ENGLAND	1	1	0	0
A. R. DAWSON/CLEVELAND, ENGLAND	3	0	0	0
C. MCNAMARA/DUBLIN, IRELAND	4	3	2	0
M. V. MALONE/DUBLIN, IRELAND	1	3	0	0
D. DORMAN/CO. SLIGO, IRELAND	1	0	0	0
M. F. RYAN/CORK, IRELAND	1	2	0	0
J. J. LYONS/CO. TIPPERARY, IRELAND	12	11	4	4
F. BRADBURY/KILKENNY, IRELAND	13	14	7	7
E. HARTMANN/CAVAN, IRELAND	3	1	0	0
A. JORDAN/DUBLIN, IRELAND	3	4	0	0
J. E. MOLLOY/LIMERICK, IRELAND	3	2	2	0
R. M. JONES/DURBAN, SOUTH AFRICA	3	1	0	0
E. L. MURRAY/EAST LONDON, SOUTH AFRICA	3	5	1	0
TOTAL	267	262	72	63

Study Population
All Patients Consented and/or Randomized

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
J. K. AGARWALA/LANCASHIRE, ENGLAND	2	2	1	0
Z. AHMAD/MANCHESTER, ENGLAND	5	5	0	1
D. ATKINSON/PRESTON, ENGLAND	2	3	0	1
C. BARAN/DACHAU, GERMANY	4	4	2	4
H. BEUMER/UTRECHT, THE NETHERLANDS	16	16	4	4
M. BRENNAN/CUMBRIA, ENGLAND	2	0	0	0
I. CALDWELL/LANCASHIRE, ENGLAND	6	6	2	2
F. R. CRANFIELD/GWENT, WALES	29	30	9	10
R. DASGUPTA/LANCASHIRE, ENGLAND	9	7	2	1
A. W. DAVIES/GWENT, WALES	10	8	3	2
P. H. DEVICHAND/DYFED, WALES	28	28	6	8
P. M. DEVICHAND/WEST GLAMORGAN, WALES	2	1	2	0
K. K. GARG/LANCASHIRE, ENGLAND	12	12	3	8
J. J. HAMILL/LEICESTER, ENGLAND	2	4	1	3
I. HAQUE/MANCHESTER, ENGLAND	2	4	0	1
D. C. HARGREAVES/SUSSEX, ENGLAND	6	6	2	2
P. R. INGLIS/LANCASHIRE, ENGLAND	12	11	5	3
R. KHANCHANDANI/LUTON BEDS, ENGLAND	2	2	0	0
K. KORLIPARA/LANCASHIRE, ENGLAND	1	0	0	0
F. LUSTMAN/NEWCASTLE-UPON-TYNE, ENGLAND	3	4	1	1
P. MAKSIMCZYK/SOMERSET, U.K.	5	6	2	0
G. MECHIE/LANCASHIRE, ENGLAND	12	10	8	2
T. O'CONNOR/LANCASHIRE, ENGLAND	2	4	0	0
N. PINHEIRO/LANCASHIRE, ENGLAND	16	18	1	7
R. M. RAJAPAKSA/MILTON KEYNES, ENGLAND	6	7	1	3
J. REPPER/ABERDEEN, SCOTLAND	0	2	0	0
C. L. SAIT/SWANSEA, WALES	1	0	0	0
P. SAUL/LANCASHIRE, ENGLAND	2	2	0	1
R. SHORTEN/DACHAU, GERMANY	3	3	1	2
W. WHITING/MANCHESTER, ENGLAND	4	4	1	0
J. ZACHRIAH/BUCKS, ENGLAND	30	30	10	11
J. HOSIE/GLASGOW, SCOTLAND	9	9	1	4

(continued)

Study Population (continued)
All Patients Consented and/or Randomized

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
R. J. CHESWORTH/LANCASHIRE, ENGLAND	3	4	0	1
A. G. WADE/CLYDEBANK, SCOTLAND	6	5	0	1
A. D. BREMNER/GLASGOW, SCOTLAND	4	4	1	1
M. BAUMULLER/DACHAU, GERMANY	2	2	1	2
G. CHROBOK/DACHAU, GERMANY	6	6	3	4
C. E. LANGAN/GLASGOW, SCOTLAND	30	27	8	10
M. G. SCOTT/GLASGOW, SCOTLAND	0	1	0	0
H. J. DONNACHIE/GLASGOW, SCOTLAND	4	9	1	4
A. W. HARRIS/WEST MIDLANDS, ENGLAND	2	2	1	0
D. WALTON/LANCASHIRE, ENGLAND	1	0	0	0
K. H. MAYER/WELS, AUSTRIA	1	0	0	0
H. PLEUMEEKERS/ROTTERDAM, THE NETHERLANDS	0	2	0	1
P. W. FUHRING/ROTTERDAM, THE NETHERLANDS	1	0	0	0
C. M. LIMBURG/ROTTERDAM, THE NETHERLANDS	0	1	0	0
R. C. HENDRIKS/ROTTERDAM, THE NETHERLANDS	0	1	0	0
G. T. VAN DE POEL/ROTTERDAM, THE NETHERLANDS	3	0	0	0
D. H. SMEETS/ROTTERDAM, THE NETHERLANDS	1	0	0	0
H. FERGUSON/ROTTERDAM, THE NETHERLANDS	4	2	2	1
J. A. VAN WYNGAARDEN/ROTTERDAM, THE NETHERLANDS	2	1	0	1
C. J. VOS/ROTTERDAM, THE NETHERLANDS	0	1	0	0
D. OOSTHOEK/RIJSSEN, THE NETHERLANDS	0	3	0	0
D. E. PEREZ-TRALLERO/ SAN SABASTIAN, SPAIN	1	0	0	0
F. MARTIN/MADRID, SPAIN	0	1	0	0
A. S. COWIE/WILTSHIRE, ENGLAND	2	2	0	1
P. MCVEY/DUBLIN, IRELAND	1	0	0	0
T. K. KHONG/LEICESTER, ENGLAND	1	0	0	0

(continued)

Study Population (concluded)
All Patients Consented and/or Randomized

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
E. MAGUIRE/BELFAST, NORTHERN IRELAND	1	0	0	0
B. R. AKHTAR/GWENT, WALES	0	1	0	0
P. LAPPIN/CO. MEATH, IRELAND	0	1	0	1
J. C. QUIRKE/CO. CORK, IRELAND	1	0	0	0
J. DRYNAN/CO. KILKENNY, IRELAND	1	1	1	1
J. KEENAN/ROSCOMMON, IRELAND	1	0	0	0
P. O'BRIEN/CO. GALWAY, IRELAND	1	0	0	0
D. HERLIHY/CO. CORK, IRELAND	0	1	0	0
M. TIPPINS/BIRMINGHAM, ENGLAND	1	1	0	0
S. SAIKIA/BIRMINGHAM, ENGLAND	4	5	1	1
S. H. SHAH/GWENT, WALES	1	1	0	0
U. K. TEWARI/LANCASHIRE, ENGLAND	0	1	0	0
W. BUTLER/CO. MEATH, IRELAND	2	2	0	0
S. J. EDWARDS/CHESHIRE, ENGLAND	1	0	0	0
S. P. WADERA/SUFFOLK, ENGLAND	4	2	1	0
D. COTTER/CO. CORK, IRELAND	4	3	0	0
J. K. KANJILAL/SUFFOLK, ENGLAND	1	0	0	0
C. MCNAMARA/DUBLIN, IRELAND	1	1	1	1
M. V. MALONE/DUBLIN, IRELAND	1	0	0	0
E. HARTMANN/CAVAN, IRELAND	0	1	0	0
J. E. MOLLOY/LIMERICK, IRELAND	0	1	0	0
R. M. JONES/DURBAN, SOUTH AFRICA	1	2	0	1
E. L. MURRAY/EAST LONDON, SOUTH AFRICA	1	0	0	0
TOTAL	347	346	89	113

Medical Officer's Comments:

The Medical Officer concurs with the applicant's evaluability.

Patient disposition (secondary bacterial infection of acute bronchitis) was as follows:

	Dirithromycin	Erythromycin
Patient Enrolled	267	262
Evaluable for Efficacy	72	63
Completed Therapy	70	63
Prematurely Discontinued	2	0
Not Evaluable	195	199
Completed Therapy	1	0
Prematurely Discontinued	194	199

Patient disposition (Acute Bacterial Exacerbation of Chronic Bronchitis) was as follows:

	Dirithromycin	Erythromycin
Patient Enrolled	347	346
Evaluable for Efficacy	89	113
Completed Therapy	87	111
Prematurely Discontinued	2	2
Not Evaluable	258	233
Completed Therapy	0	0
Prematurely Discontinued	258	233

Medical Officer's Comments:

The Medical Officer concurs with the applicant's analysis.

Patient Demographics:

All Patients-Secondary Bacterial Infection of Acute Bronchitis

Age Ranges by Sex
All Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE		MALE		TOTAL		FEMALE		MALE		TOTAL	
	N = 128		N = 139		N = 267		N = 129		N = 133		N = 262	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	9	(7.0%)	18	(12.9%)	27	(10.1%)	11	(8.5%)	15	(11.3%)	26	(9.9%)
	58	(45.3%)	58	(41.7%)	116	(43.4%)	55	(42.6%)	66	(49.6%)	121	(46.2%)
	59	(46.1%)	54	(38.8%)	113	(42.3%)	57	(44.2%)	46	(34.6%)	103	(39.3%)
	2	(1.6%)	9	(6.5%)	11	(4.1%)	6	(4.7%)	6	(4.5%)	12	(4.6%)

Age by Sex - Mean, Median, Minimum and Maximum (in Years)
All Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	128	139	267	129	133	262
MEAN AGE	44.48	42.48	43.44	44.65	42.61	43.61
STD DEV	13.33	14.74	14.09	13.99	14.21	14.11
MEDIAN AGE	43.00	42.00	43.00	44.00	42.00	43.00
MINIMUM AGE						
MAXIMUM AGE						

Origin by Therapy Group
All Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN N = 267		ERYTHROMYCIN N = 262	
	n	(%)	n	(%)
ORIGIN				
CAUCASIAN	261	(97.8%)	256	(97.7%)
BLACK	0		4	(1.5%)
ASIAN	2	(0.7%)	2	(0.8%)
OTHER	4	(1.5%)	0	

Height and Weight at Admission
All Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	HEIGHT IN CM						WEIGHT IN KG					
THERAPY	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	267	0	168.57	10			267	0	71.23	14		
ERYTHROMYCIN	261	1	168.35	9			260	2	71.09	14		

Evaluable Patients - Secondary Bacterial Infection of Acute Bronchitis

Age Ranges by Sex
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE		MALE		TOTAL		FEMALE		MALE		TOTAL	
	N = 33		N = 39		N = 72		N = 26		N = 37		N = 63	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	3	(9.1%)	3	(7.7%)	6	(8.3%)	2	(7.7%)	2	(5.4%)	4	(6.3%)
	11	(33.3%)	16	(41.0%)	27	(37.5%)	13	(50.0%)	18	(48.6%)	31	(49.2%)
	19	(57.6%)	18	(46.2%)	37	(51.4%)	10	(38.5%)	15	(40.5%)	25	(39.7%)
	0		2	(5.1%)	2	(2.8%)	1	(3.8%)	2	(5.4%)	3	(4.8%)

Age By Sex - Mean, Median, Minimum and Maximum
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	33	39	72	26	37	63
MEAN AGE	45.24	43.56	44.33	42.88	45.00	44.13
STD DEV	14.12	13.97	13.96	13.37	13.16	13.18
MEDIAN AGE	49.00	46.00	46.00	43.50	44.00	44.00
MINIMUM AGE						
MAXIMUM AGE						

Origin By Therapy Group
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

ORIGIN	DIRITHROMYCIN N = 72 n	(%)	ERYTHROMYCIN N = 63 n	(%)
CAUCASIAN	71	(98.6%)	62	(98.4%)
ASIAN	0		1	(1.6%)
OTHER	1	(1.4%)	0	

Height and Weight at Admission
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	HEIGHT IN CM						WEIGHT IN KG					
THERAPY	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	72	0	168.70	12			72	0	70.37	15		
ERYTHROMYCIN	63	0	168.66	10			63	0	71.60	17		

All Patients-Acute Bacterial Exacerbation of Chronic Bronchitis

Age Ranges by Sex
All Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE		MALE		TOTAL		FEMALE		MALE		TOTAL	
	N = 153		N = 194		N = 347		N = 160		N = 186		N = 346	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	2	(1.3%)	6	(3.1%)	8	(2.3%)	8	(5.0%)	5	(2.7%)	13	(3.8%)
	35	(22.9%)	41	(21.1%)	76	(21.9%)	32	(20.0%)	41	(22.0%)	73	(21.1%)
	104	(68.0%)	135	(69.6%)	239	(68.9%)	112	(70.0%)	135	(72.6%)	247	(71.4%)
	12	(7.8%)	12	(6.2%)	24	(6.9%)	8	(5.0%)	5	(2.7%)	13	(3.8%)

Age by Sex - Mean, Median, Minimum and Maximum (in Years)
All Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	153	194	347	160	186	346
MEAN AGE	51.54	52.01	51.80	50.27	51.55	50.96
STD DEV	11.22	11.72	11.49	12.92	11.33	12.09
MEDIAN AGE	54.00	55.00	55.00	52.50	54.00	54.00
MINIMUM AGE						
MAXIMUM AGE						

Origin by Therapy Group
All Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN N = 347		ERYTHROMYCIN N = 346	
	n	(%)	n	(%)
ORIGIN				
CAUCASIAN	340	(98.0%)	333	(96.2%)
BLACK	3	(0.9%)	5	(1.4%)
ASIAN	4	(1.2%)	8	(2.3%)

Height and Weight at Admission
All Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	HEIGHT IN CM						WEIGHT IN KG					
THERAPY	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	347	0	167.26	9			347	0	70.74	13		
ERYTHROMYCIN	345	1	167.32	11			345	1	69.81	14		

Evaluable Patients-Acute Bacterial Exacerbation of Chronic Bronchitis

Age by Sex - Ranges
Evaluable Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE		MALE		TOTAL		FEMALE		MALE		TOTAL	
	N = 36		N = 53		N = 89		N = 47		N = 66		N = 113	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
0			2	(3.8%)	2	(2.2%)	3	(6.4%)	2	(3.0%)	5	(4.4%)
9	(25.0%)		13	(24.5%)	22	(24.7%)	10	(21.3%)	11	(16.7%)	21	(18.6%)
25	(69.4%)		35	(66.0%)	60	(67.4%)	32	(68.1%)	51	(77.3%)	83	(73.5%)
2	(5.6%)		3	(5.7%)	5	(5.6%)	2	(4.3%)	2	(3.0%)	4	(3.5%)

Age By Sex - Mean, Median, Minimum and Maximum
Evaluable Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	36	53	89	47	66	113
MEAN AGE	52.31	51.32	51.72	49.57	53.17	51.67
STD DEV	10.34	13.35	12.17	14.12	10.56	12.24
MEDIAN AGE	55.50	57.00	56.00	55.00	57.00	56.00
MINIMUM AGE						
MAXIMUM AGE						

Origin By Therapy Group
Evaluable Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

ORIGIN	DIRITHROMYCIN N = 89 n	(%)	ERYTHROMYCIN N = 113 n	(%)
CAUCASIAN	86	(96.6%)	110	(97.3%)
BLACK	3	(3.4%)	1	(0.9%)
ASIAN	0		2	(1.8%)

Height and Weight at Admission
Evaluable Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

THERAPY	HEIGHT IN CM N	UNK	MEAN	STD DEV	MIN	MAX	WEIGHT IN KG N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	89	0	168.50	10			89	0	72.66	14		
ERYTHROMYCIN	113	0	167.95	10			113	0	71.85	15		

Drug Administration:

All Patients

Exposure to Study Drugs - Mean, Minimum, and Maximum
All Patients

	DIRITHROMYCIN N = 614 DAYS	ERYTHROMYCIN N = 608 DAYS
NUMBER OF PATIENTS	607	599
MEAN DURATION EXPOSURE	7.4	7.4
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	7	9

Summary of Exposure to Study-Drugs
All Patients

	DIRITHROMYCIN N = 614		ERYTHROMYCIN N = 608	
	n	(%)	n	(%)
DAYS OF THERAPY				
PATIENTS WITH INCOMPLETE DATA	7	(1.1%)	9	(1.5%)
1	3	(0.5%)	1	(0.2%)
2	2	(0.3%)	4	(0.7%)
3	0		7	(1.2%)
4	10	(1.6%)	4	(0.7%)
5	4	(0.7%)	7	(1.2%)
6	8	(1.3%)	3	(0.5%)
7	263	(42.8%)	258	(42.4%)
8	297	(48.4%)	304	(50.0%)
9	14	(2.3%)	6	(1.0%)
10	4	(0.7%)	3	(0.5%)
11	2	(0.3%)	1	(0.2%)
12	0		1	(0.2%)

Evaluable Patients-Secondary Bacterial Infection of Acute Bronchitis:

Exposure to Study Drugs - Mean, Minimum, and Maximum
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN N = 72 DAYS	ERYTHROMYCIN N = 63 DAYS
NUMBER OF PATIENTS	72	63
MEAN DURATION EXPOSURE	7.5	7.4
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN N = 72		ERYTHROMYCIN N = 63	
DAYS OF THERAPY	n	(%)	n	(%)
6	1	(1.4%)	0	
7	37	(51.4%)	39	(61.9%)
8	33	(45.8%)	23	(36.5%)
9	1	(1.4%)	1	(1.6%)

Medical Officer's Comments:

Ninety-seven percent of the evaluable patients in the dirithromycin group and 98% of the patients in the erythromycin group were treated for 7-8 days.

Evaluable Patients-Acute Bacterial Exacerbation of Chronic Bronchitis:

Exposure to Study Drugs - Mean, Minimum, and Maximum
Evaluable Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN N = 89 DAYS	ERYTHROMYCIN N = 113 DAYS
NUMBER OF PATIENTS	89	113
MEAN DURATION EXPOSURE	7.5	7.5
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN N = 89		ERYTHROMYCIN N = 113	
DAYS OF THERAPY	n	(%)	n	(%)
2	0		1	(0.9%)
4	1	(1.1%)	0	
5	0		1	(0.9%)
7	42	(47.2%)	48	(42.5%)
8	45	(50.6%)	59	(52.2%)
9	1	(1.1%)	3	(2.7%)
10	0		1	(0.9%)

Medical Officer's Comments:

Ninety-eight percent of the evaluable patients in the dirithromycin group and 95% of the patients in the erythromycin group were treated for 7-8 days.

Unevaluable Patients

Reasons Unevaluable Summary
All Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

REASON UNEVALUABLE	DIRITHROMYCIN N = 267 n	(%)	ERYTHROMYCIN N = 262 n	(%)
ALL UNEVALUABLE PTS.	195	(73.0%)	199	(76.0%)
PRE-CULTURE NEGATIVE	154		158	
UNEVAL. BY INVEST.	13		13	
TIMING OF X-RAY	9		16	
CAUS. ORG. RESISTANT	11		9	
NO POST FOLLOW-UP	9		10	
WRONG AGE	7		7	
INSUFFICIENT THERAPY	6		7	
UNACCEPT. PATHOGEN	6		6	
INITIAL CULT. LATE	3		9	
WRONG DIAGNOSIS	5		5	
NO INITIAL CULTURE	5		4	
SENSITIVITY NOT DONE	3		5	
POST THER. CULT. EARLY	5		2	
LATE CLIN. ASSESSMENT	3		4	
EARLY CLIN. ASSESSMENT	6		1	
NO POST THER. CULTURE	2		3	
POST THER. CULT. LATE	0		4	
NO PRE-THERAPY X-RAY	2		2	
WRONG STUDY DRUG	2		1	
INFILTRATE ON X-RAY	2		1	
NO DURING CULTURE	2		0	
INCOMPLETE DATA	1		1	
PROTOCOL VIOLATED	1		1	
DURING CULTURE EARLY	0		1	
FOLLOW-UP CULT. EARLY	1		0	
FOLLOW-UP CULT. LATE	0		1	
UNDERLYING CONDITION	0		1	
POOR COMPLIANCE	1		0	

Medical Officer's Comments:

Some patients had more than one reason to be considered unevaluable.

Reasons Unevaluable
All Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

REASON UNEVALUABLE	DIRITHROMYCIN N = 347 n	(%)	ERYTHROMYCIN N = 346 n	(%)
ALL UNEVALUABLE PATIENTS	258	(74.4%)	233	(67.3%)
PRE-CULTURE NEGATIVE	163		156	
UNACCEPT. PATHOGEN	31		33	
CAUS. ORG. RESISTANT	31		30	
UNEVAL. BY INVEST.	10		6	
TIMING OF X-RAY	10		6	
WRONG AGE	9		5	
INSUFFICIENT THERAPY	6		3	
NO PRE-THERAPY X-RAY	6		3	
NO POST FOLLOW-UP	4		4	
NO INITIAL CULTURE	4		3	
INFILTRATE ON X-RAY	4		2	
POST-THER. CULT. LATE	3		2	
WRONG DIAGNOSIS	3		2	
PT. STUDIES BEFORE	1		4	
INITIAL CULT. LATE	4		1	
SENSITIVITY NOT DONE	2		2	
INITIAL CULT. EARLY	3		1	
LATE CLIN. ASSESSMENT	2		2	
NO POST THER. CULTURE	2		1	
NEVER ON ACTIVE DRUG	2		1	
NO DURING CULTURE	2		0	
INCOMPLETE DATA	1		1	
EARLY CLIN. ASSESSMENT	2		0	
CONCOMITANT ANTIBIOT.	1		0	
DURING CULTURE EARLY	1		0	
POST THER. CULT. EARLY	1		0	
NO FOLLOW-UP CULTURE	0		1	
FOLLOW-UP CULT. EARLY	1		0	
UNDERLYING CONDITION	1		0	
PROTOCOL VIOLATED	1		0	
POOR COMPLIANCE	0		1	
NO END-THERAPY CULTURE	1		0	
VISIT MISSING	1		0	
PRIMARY DIAGN. MISSING	1		0	
WRONG STUDY DRUG	1		0	

Medical Officer's Comments:
Some patients had more than one reason to be considered unevaluable.

Efficacy Evaluation-Secondary Bacterial Infection of Acute Bronchitis:

Clinical Response-Secondary Bacterial Infection of Acute Bronchitis

The clinical response for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Clinical Response
All Evaluable Patients Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN N = 72		ERYTHROMYCIN N = 63	
RESPONSE	n	(%)	n	(%)
CURE	32	(44.4%)	39	(61.9%)
IMPROVEMENT	35	(48.6%)	21	(33.3%)
RELAPSE	2	(2.8%)	0	
FAILURE	3	(4.2%)	3	(4.8%)

Medical Officer's Comments:

The clinical success (cure or improvement) rate was 93% (67/72) for the dirithromycin group and 95% (60/63) for the erythromycin group.

The clinical response by pathogen for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Clinical Response by Pathogen
All Evaluable Dirithromycin-Treated Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis
Posttherapy

	CURE		IMPROVEMENT		RELAPSE		FAILURE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n
PATHOGENS									
STR PNEUMONIAE	11	(39.2%)	15	(53.5%)	0	0	2	(7.1%)	28
H INFLUENZAE	11	(44.0%)	11	(44.0%)	2	(8.0%)	1	(4.0%)	25
H PARAINFLUENZAE	3	(42.8%)	4	(57.1%)	0	0	0	0	7
MULTIPLE ORGANISMS*	3	(50.0%)	3	(50.0%)	0	0	0	0	6
M CATARRHALIS	2	(66.6%)	1	(33.3%)	0	0	0	0	3
ST AUREUS	1	(50.0%)	1	(50.0%)	0	0	0	0	2
STR GRP A	1	(100.0%)	0	0	0	0	0	0	1

* - These patients had multiple pathogens isolated from the sputum specimens. The following table depicts the clinical and bacteriologic response for patients with polymicrobial infections:

APPEARS THIS WAY
ON ORIGINAL

Clinical and Bacteriological Response
Polymicrobial Infections
Evaluable Dirithromycin-treated patients Posttherapy
Secondary Bacterial Infection of Acute Bronchitis

PATIENT NO.	PATHOGENS	BACTERIOLOGICAL RESPONSE	CLINICAL RESPONSE
	M CATARRHALIS	PATH ELIM	IMPR
	H PARAINFLUENZAE	RECUR SAME	
	M CATARRHALIS	N/A	CURE
	H INFLUENZAE	N/A	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	
	M CATARRHALIS	N/A	IMPR
	S PNEUMONIAE	N/A	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	
	H INFLUENZAE	PATH ELIM	IMPR
	S PNEUMONIAE	PATH ELIM	

N/A - Presumed Eliminated

Clinical Response by Pathogen--All Evaluable Erythromycin-Treated Patients Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

	CURE		IMPROVEMENT		FAILURE		TOTAL
	n	(%)	n	(%)	n	(%)	n
PATHOGENS							
H INFLUENZAE	16	(61.5%)	9	(34.6%)	1	(3.8%)	26
S PNEUMONIAE	12	(66.6%)	6	(33.3%)	0	0	18
H PARAINFLUENZAE	1	(20.0%)	2	(40.0%)	2	(40.0%)	5
ST AUREUS	4	(80.0%)	1	(20.0%)	0	0	5
MULTIPLE ORGANISMS*	3	(60.0%)	2	(40.0%)	0	0	5
M CATARRHALIS	3	(75.0%)	1	(25.0%)	0	0	4

* - These patients had multiple pathogens isolated from the sputum specimens. The following table depicts the clinical and bacteriologic response for patients with polymicrobial infections:

Clinical and Bacteriological response -- Polymicrobial Infections
Evaluable Erythromycin -treated patients Post-therapy
SECONDARY BACTERIAL INFECTION OF ACUTE BRONCHITIS

PATIENT NO.	PATHOGENS	BACTERIOLOGICAL RESPONSE	CLINICAL RESPONSE
	M CATARRHALIS	PATH ELIM	IMPR
	S PNEUMONIAE	RECUR SAME	
	H INFLUENZAE	RECUR SAME	
	H PARAINFLUENZAE	PATH ELIM	CURE
	S PNEUMONIAE	FAILED	
	H INFLUENZAE	N/A	CURE
	S PNEUMONIAE	N/A	
	H INFLUENZA	PATH ELIM	CURE
	S PNEUMONIAE	PATH ELIM	
	H PARAINFLUENZAE	PATH ELIM	IMPR
	S PNEUMONIAE	PATH ELIM	

N/A - Presumed Eliminated

The clinical response for evaluable patients at late-posttherapy (10-14 days) according to the applicant was as follows:

Clinical Response
All Evaluable Patients Late-Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

RESPONSE	DIRITHROMYCIN N = 65 n	(%)	ERYTHROMYCIN N = 59 n	(%)
CURE	52	(80.0%)	48	(81.4%)
IMPROVEMENT	11	(16.9%)	11	(18.6%)
RELAPSE	2	(3.1%)	0	

Medical Officer's Comments:

The clinical success (cure or improvement) rate was 97% (63/65) for the dirithromycin group and 100% (59/59) for the erythromycin group.

The clinical response by pathogen for evaluable patients at late-posttherapy (10-14 days) according to the applicant was as follows:

Clinical Response by Pathogen
All Evaluable Dirithromycin-Treated Patients Late-Posttherapy
Indication: Secondary Bacterial Infection of Acute Bronchitis

	CURE		IMPROVEMENT		RELAPSE		TOTAL
	n	(%)	n	(%)	n	(%)	n
PATHOGENS							
STR PNEUMONIAE	18	(75.0%)	5	(20.8%)	1	(4.1%)	24
H INFLUENZAE	19	(86.3%)	3	(13.6%)	0	0	22
H PARAINFLUENZAE	5	(71.4%)	1	(14.2%)	1	(14.2%)	7
MULTIPLE ORGANISMS*	6	(100.0%)	0	0	0	0	6
M CATARRHALIS	2	(66.6%)	1	(33.3%)	0	0	3
ST AUREUS	1	(50.0%)	1	(50.0%)	0	0	2
STR GRP A	1	(100.0%)	0	0	0	0	1

* - These patients had multiple pathogens isolated from the sputum specimens. The following table depicts the clinical and bacteriologic response for patients with polymicrobial infections:

BACTERIOLOGICAL RESPONSE--POLYMICROBIAL INFECTIONS--
EVALUABLE DIRITHROMYCIN-TREATED PATIENTS LATE-POSTTHERAPY
Indication: Secondary Bacterial Infection of Acute Bronchitis

PATIENT NO.	PATHOGENS	BACTERIOLOGICAL RESPONSE	CLINICAL RESPONSE
	M CATARRHALIS	N/A	CURE
	H PARAINFLUENZAE	N/A	
	M CATARRHALIS	N/A	CURE
	H INFLUENZAE	N/A	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	
	M CATARRHALIS	N/A	CURE
	S PNEUMONIAE	N/A	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	
	H INFLUENZAE	N/A	CURE
	S PNEUMONIAE	N/A	

N/A - Presumed Eliminated

Clinical Response by Pathogen
All Evaluable Erythromycin-Treated Patients Late-Posttherapy
Indication: Secondary Bacterial Infection of Acute Bronchitis

	CURE n	(%)	IMPROVEMENT n	(%)	TOTAL n
PATHOGENS					
H INFLUENZAE	20	(80.0%)	5	(20.0%)	25
STR PNEUMONIAE	15	(78.9%)	4	(21.0%)	19
ST AUREUS	5	(100.0%)	0	0	5
M CATARRHALIS	3	(75.0%)	1	(25.0%)	4
H PARAINFLUENZAE	3	(100.0%)	0	0	3
MULTIPLE ORGANISMS*	2	(66.6%)	1	(33.3%)	3

* - These patients had multiple pathogens isolated from the sputum specimens. The following table depicts the clinical and bacteriologic response for patients with polymicrobial infections:

BACTERIOLOGICAL RESPONSE--POLYMICROBIAL INFECTIONS
EVALUABLE ERY THROMYCIN-TREATED PATIENTS LATE-POSTTHERAPY
Indication: Secondary Bacterial Infection of Acute Bronchitis

PATIENT NO.	PATHOGENS	BACTERIOLOGICAL RESPONSE	CLINICAL RESPONSE
	M CATARRHALIS	PATH ELIM	CURE
	S PNEUMONIAE	RECUR SAME	
	H INFLUENZAE	RECUR SAME	
	H PARAINFLUENZAE	N/A	CURE
	S PNEUMONIAE	N/A	
	H PARAINFLUENZAE	PATH ELIM	IMPR
	S PNEUMONIAE	PATH ELIM	

N/A - Presumed Eliminated

Bacteriologic Response-Secondary Bacterial Infection of Acute Bronchitis

The bacteriologic response for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Bacteriological Response
All Evaluable Patients Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN N = 70		ERYTHROMYCIN N = 63	
RESPONSE	n	(%)	n	(%)
PATHOGEN ELIMINATED	20	(28.6%)	16	(25.4%)
PRESUMED ERADICATED	40	(57.1%)	38	(60.3%)
RECURRENCE SAME	1	(1.4%)	3	(4.8%)
RECURRENCE SAME, RESISTANCE	1	(1.4%)	0	
RECURRENCE NEW	3	(4.3%)	3	(4.8%)
FAILED TO ELIMINATE	5	(7.1%)	3	(4.8%)

The bacteriologic response by pathogen for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Bacteriologic Response by Pathogen

All Evaluable Dirithromycin-Treated Patients Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

	PATHOGEN ELIMINATED		PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE SAME, RESISTANCE		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
PATHOGEN:													
STR PNEUMONIAE	10	(32.3%)	18	(58.1%)	0		0		2	(6.5%)	1	(3.2%)	31
H INFLUENZAE	8	(27.6%)	16	(55.2%)	0		1	(3.4%)	0		4	(13.8%)	29
H PARAINFLUENZAE	3	(37.5%)	3	(37.5%)	1	(12.5%)	0		1	(12.5%)	0		8
M CATARRHALIS	1	(16.7%)	5	(83.3%)	0		0		0		0		6
ST AUREUS	0	0	1	(100.0%)	0		0		0		0		1
STR GRP A	0	0	1	(100.0%)	0		0		0		0		1

Bacteriologic Response by Pathogen
All Evaluable Erythromycin-Treated Patients Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

	PATHOGEN ELIMINATED		PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
PATHOGENS											
H INFLUENZAE	7	(24.1%)	18	(62.1%)	2	(6.9%)	1	(3.4%)	1	(3.4%)	29
STR PNEUMONIAE	6	(25.1%)	11	(47.8%)	2	(8.7%)	2	(8.7%)	2	(8.7%)	23
H PARAINFLUENZAE	4	(57.1%)	3	(60.0%)	0	0	0	0	0	0	7
ST AUREUS	1	(20.0%)	4	(80.0%)	0	0	0	0	0	0	5
M CATARRHALIS	2	(40.0%)	3	(60.0%)	0	0	0	0	0	0	5

The bacteriologic response for evaluable patients at late-posttherapy (10-14 days) according to the applicant was as follows:

Bacteriological Response
All Evaluable Patients Late-Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN N = 64		ERYTHROMYCIN N = 59	
RESPONSE	n	(%)	n	(%)
PATHOGEN ELIMINATED	4	(6.3%)	3	(5.1%)
PRESUMED ERADICATED	58	(90.7%)	51	(86.4%)
RECURRENCE SAME	1	(1.6%)	2	(3.4%)
RECURRENCE NEW	1	(1.6%)	3	(5.1%)

The bacteriologic response by pathogen for evaluable patients at late-posttherapy (10-14 days) according to the applicant was as follows:

Bacteriological Response by Pathogen
All Evaluable Dirithromycin-Treated Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis
Late-Posttherapy

	Pathogen Eliminated n (%)	Presumed Eradication n (%)	Recurrence Same n (%)	Recurrence New n (%)	Total n
PATHOGENS					
STR PNEUMONIAE	2 (7.1%)	25 (89.5%)	0 0	1 (3.6%)	28
H INFLUENZAE	1 (3.8%)	25 (96.2%)	0 0	0 0	26
H PARAINFLUENZAE	1 (12.5%)	6 (75.0%)	1 (12.5%)	0 0	8
M CATARRHALIS	0 0	6 (100.0%)	0 0	0 0	6
ST AUREUS	0 0	1 (100.0%)	0 0	0 0	1
STR GRP A	0 0	1 (100.0%)	0 0	0 0	1

Bacteriological Response by Pathogen
All Evaluable Erythromycin-Treated Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis
Late-Posttherapy

	Pathogen Eliminated		Presumed Eradication		Recurrence Same		Recurrence New		Total
	n	(%)	n	(%)	n	(%)	n	(%)	n
PATHOGENS									
H INFLUENZAE	1	(3.8%)	22	(84.6%)	2	(7.7%)	1	(3.8%)	26
STR PNEUMONIAE	2	(9.1%)	17	(77.3%)	1	(4.5%)	2	(9.1%)	22
ST AUREUS	0	0	5	(100.0%)	0	0	0	0	5
M CATARRHALIS	1	(20.0%)	4	(80.0%)	0	0	0	0	5
H PARAINFLUENZAE	1	(20.0%)	4	(80.0%)	0	0	0	0	5

Efficacy Evaluation- Acute Bacterial Exacerbation of Chronic Bronchitis

Clinical Response- Acute Exacerbation of Chronic Bronchitis

The clinical response for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Clinical Response
All Evaluable Patients Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN N = 89		ERYTHROMYCIN N = 113	
RESPONSE	n	(%)	n	(%)
CURE	50	(56.2%)	56	(49.6%)
IMPROVEMENT	30	(33.7%)	48	(42.5%)
RELAPSE	0		2	(1.8%)
FAILURE	9	(10.1%)	7	(6.2%)

Medical Officer's Comments:

The clinical success (cure or improvement) rate was 90% (80/89) for the dirithromycin group and 92% (104/113) for the erythromycin group.

The clinical response by pathogen for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Clinical Response by Pathogen
All Evaluable Dirithromycin-Treated Patients Posttherapy
Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	CURE		IMPROVEMENT		FAILURE		TOTAL
	n	(%)	n	(%)	n	(%)	n
PATHOGENS							
H INFLUENZAE	18	(54.5%)	8	(24.2%)	7	(21.2%)	33
S PNEUMONIAE	12	(48.0%)	12	(48.0%)	1	(4.0%)	25
MULTIPLE ORGANISMS*	7	(53.8%)	6	(46.1%)	0	0	13
M CATARRHALIS	8	(66.6%)	3	(25.0%)	1	(8.3%)	12
ST AUREUS	4	(80.0%)	1	(20.0%)	0	0	5
S GRP F	1	(100.0%)	0	0	0	0	1

* - These patients had multiple pathogens isolated from the sputum specimens. The following table depicts the clinical and bacteriologic response for patients with polymicrobial infections:

Clinical and Bacteriologic Response -- Polymicrobial Infections
All Evaluable Dirithromycin-Treated Patients Posttherapy
Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

PATIENT NO.	PATHOGENS	BACTERIOLOGICAL RESPONSE	CLINICAL RESPONSE
	S PNEUMONIAE H INFLUENZAE	PATH ELIM FAILED	IMPR
	H INFLUENZAE S PNEUMONIAE	PATH ELIM PATH ELIM	IMPR
	S PNEUMONIAE H INFLUENZAE	N/A N/A	CURE
	H PARAINFLUENZAE M CATARRHALIS	N/A N/A	CURE
	H INFLUENZAE S PNEUMONIAE	N/A N/A	CURE
	S GRP A ST AUREUS	N/A N/A	CURE
	M CATARRHALIS H INFLUENZAE S PNEUMONIAE	RECUR SAME RECUR SAME RECUR NEW	IMPR
	H INFLUENZAE S PNEUMONIAE	PATH ELIM RECUR SAME	IMPR
	M CATARRHALIS H INFLUENZAE	PATH ELIM PATH ELIM	CURE
	S GRP A H INFLUENZAE ST AUREUS	PATH ELIM PATH ELIM RECUR NEW	IMPR
	H INFLUENZAE S PNEUMONIAE	N/A N/A	CURE
	H INFLUENZAE S PNEUMONIAE M CATARRHALIS	N/A N/A N/A	IMPR
	H INFLUENZAE S PNEUMONIAE H PARAINFLUENZAE	PATH ELIM PATH ELIM RECUR NEW	CURE

Clinical Response by Pathogen
All Evaluable Erythromycin-Treated Patients Posttherapy
Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	CURE		IMPROVEMENT		RELAPSE		FAILURE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n
PATHOGENS									
H INFLUENZAE	17	(44.7%)	18	(47.3%)	1	(2.6%)	2	(5.2%)	38
S PNEUMONIAE	9	(37.5%)	14	(58.3%)	0	0	1	(4.1%)	24
M CATARRHALIS	14	(70.0%)	6	(30.0%)	0	0	0	0	20
MULTIPLE ORGANISMS*	7	(50.0%)	5	(35.7%)	1	(7.1%)	1	(7.1%)	14
ST AUREUS	6	(75.0%)	2	(25.0%)	0	0	0	0	8
H PARAINFLUENZAE	2	(33.3%)	1	(16.6%)	0	0	3	(50.0%)	6
STR GRP A	1	(50.0%)	1	(50.0%)	0	0	0	0	2
SEPTOCOCCUS SP	0	0	1	(100.0%)	0	0	0	0	1

* - These patients had multiple pathogens isolated from the sputum specimens. The following table depicts the clinical and bacteriologic response for patients with polymicrobial infections:

Clinical and Bacteriologic Response -- Polymicrobial Infections
All Evaluable Erythromycin-Treated Patients Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

PATIENT NO.	PATHOGENS	BACTERIOLOGICAL RESPONSE	CLINICAL RESPONSE
	S GRP B	PATH ELIM	IMPR
	S PNEUMONIAE	PATH ELIM	
	M CATARRHALIS	PATH ELIM	IMPR
	H INFLUENZAE	FAILED	
	S PNEUMONIAE	N/A	CURE
	H PARAINFLUENZAE	N/A	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	
	S PNEUMONIAE	PATH ELIM	IMPR
	H INFLUENZAE	RECUR SAME	
	M CATARRHALIS	N/A	CURE
	S PNEUMONIAE	N/A	
	M CATARRHALIS	N/A	CURE
	H PARAINFLUENZAE	N/A	
	M CATARRHALIS	PATH ELIM	IMPR
	H INFLUENZAE	PATH ELIM	
	S GRP A	PATH ELIM	IMPR
	H INFLUENZAE	PATH ELIM	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	
	H INFLUENZAE	N/A	CURE
	S PNEUMONIAE	N/A	
	S PNEUMONIAE	RECUR SAME	RELAPSE
	H INFLUENZAE	RECUR SAME	
	H INFLUENZAE	UNABLE TO EVAL	FAILURE
	S PNEUMONIAE	UNABLE TO EVAL	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	

The clinical response for evaluable patients at late-posttherapy (10-14 days) according to the applicant was as follows:

Clinical Response
All Evaluable Patients Late-Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN N = 76		ERYTHROMYCIN N = 100	
RESPONSE	n	(%)	n	(%)
CURE	64	(84.2%)	80	(80.0%)
IMPROVEMENT	11	(14.5%)	15	(15.0%)
RELAPSE	1	(1.3%)	5	(5.0%)

Medical Officer's Comments:

The clinical success (cure or improvement) rate was 99% (75/76) for the dirithromycin group and 95% (95/100) for the erythromycin group.

The clinical response by pathogen for evaluable patients at late-posttherapy (10-14 days) according to the applicant was as follows:

Clinical Response by Pathogen
Evaluable Dirithromycin-Treated Patients Late-Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	CURE		IMPROVEMENT		RELAPSE		TOTAL
	n	(%)	n	(%)	n	(%)	n
PATHOGENS							
H INFLUENZAE	23	(92.0%)	2	(8.0%)	0	0	25
S PNEUMONIAE	18	(75.0%)	5	(20.8%)	1	(4.1%)	24
MULTIPLE ORGANISMS*	8	(72.7%)	3	(27.2%)	0	0	11
M CATARRHALIS	10	(100.0%)	0	0	0	0	10
ST AUREUS	4	(80.0%)	1	(20.0%)	0	0	5
STR GRP F	1	(100.0%)	0	0	0	0	1

* - These patients had multiple pathogens isolated from the sputum specimens. The following table depicts the clinical and bacteriologic response for patients with polymicrobial infections:

Clinical and Bacteriologic Response -- Polymicrobial Infections
All Evaluable Dirithromycin-Treated Patients Late-Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

PATIENT NO.	PATHOGENS	BACTERIOLOGICAL RESPONSE	CLINICAL RESPONSE
	S PNEUMONIAE	PATH ELIM	IMPR
	H INFLUENZAE	FAILED	
	H INFLUENZAE	RECUR SAME	IMPR
	S PNEUMONIAE	PATH ELIM	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	
	H PARAINFLUENZAE	N/A	CURE
	M CATARRHALIS	N/A	
	H INFLUENZAE	N/A	CURE
	S PNEUMONIAE	N/A	
	S GRP A	N/A	CURE
	ST AUREUS	N/A	
	M CATARRHALIS	N/A	CURE
	H INFLUENZAE	N/A	
	S GRP A	N/A	CURE
	H INFLUENZAE	N/A	
	H INFLUENZAE	N/A	CURE
	S PNEUMONIAE	N/A	
	H INFLUENZAE	N/A	IMPR
	S PNEUMONIAE	N/A	
	M CATARRHALIS	N/A	
	H INFLUENZAE	RECUR SAME	CURE
	S PNEUMONIAE	PATH ELIM	

Clinical Response by Pathogen
Evaluable Erythromycin-Treated Patients Late-Posttherapy
Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	CURE		IMPROVEMENT		RELAPSE		TOTAL
	n	(%)	n	(%)	n	(%)	n
PATHOGENS							
H INFLUENZAE	24	(70.5%)	6	(17.6%)	4	(11.7%)	34
S PNEUMONIAE	20	(86.9%)	3	(13.0%)	0	0	23
M CATARRHALIS	15	(78.9%)	3	(15.7%)	1	(5.2%)	19
MULTIPLE ORGANISMS*	10	(90.9%)	1	(9.0%)	0	0	11
ST AUREUS	8	(100.0%)	0	0	0	0	8
H PARAINFLUENZAE	3	(100.0%)	0	0	0	0	3
STREPTOCOCCUS SP	0	0	1	(100.0%)	0	0	1
STR GRP A	0	0	1	(100.0%)	0	0	1

* - These patients had multiple pathogens isolated from the sputum specimens. The following table depicts the clinical and bacteriologic response for patients with polymicrobial infections:

Clinical and Bacteriologic Response -- Polymicrobial Infections
All Evaluable Erythromycin-Treated Patients Late-Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

PATIENT NO.	PATHOGENS	BACTERIOLOGICAL RESPONSE	CLINICAL RESPONSE
	S GRP B	N/A	CURE
	S PNEUMONIAE	N/A	
	M CATARRHALIS	N/A	CURE
	H INFLUENZAE	N/A	
	S PNEUMONIAE	N/A	CURE
	H PARAINFLUENZAE	N/A	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	
	S PNEUMONIAE	PATH ELIM	IMPR
	H INFLUENZAE	PATH ELIM	
	M CATARRHALIS	N/A	CURE
	S PNEUMONIAE	N/A	
	M CATARRHALIS	N/A	CURE
	H PARAINFLUENZAE	N/A	
	S GRP A	PATH ELIM	CURE
	H INFLUENZAE	PATH ELIM	
	ST AUREUS	RECUR NEW	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	
	H INFLUENZAE	N/A	CURE
	S PNEUMONIAE	N/A	
	S PNEUMONIAE	N/A	CURE
	H INFLUENZAE	N/A	

Bacteriologic Response-Acute Bacterial Exacerbation of Chronic Bronchitis

The bacteriologic response for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Bacteriologic Response
All Evaluable Patients Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

RESPONSE	DIRITHROMYCIN N = 88 n	(%)	ERYTHROMYCIN N = 110 n	(%)
PATHOGEN ELIMINATED	24	(27.3%)	36	(32.7%)
PRESUMED ERADICATED	43	(48.9%)	49	(44.5%)
RECURRENCE SAME	4	(4.5%)	12	(10.9%)
RECURRENCE SAME, RESISTANCE	0		2	(1.8%)
RECURRENCE NEW	9	(10.2%)	5	(4.5%)
FAILED TO ELIMINATE	8	(9.1%)	6	(5.4%)

The bacteriologic response by pathogen for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Bacteriologic Response by Pathogen
All Evaluable Dirithromycin-Treated Patients Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	PATHOGEN ELIMINATED		PRESUMED ERADICATION		RECURRENCE SAME		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
PATHOGENS											
H INFLUENZAE	11	(25.6%)	22	(51.2%)	3	(7.0%)	1	(2.3%)	6	(14.1%)	43
STR PNEUMONIAE	13	(38.2%)	13	(26.7%)	2	(13.3%)	4	(26.7%)	2	(13.3%)	34
M CATARRHALIS	5	(31.3%)	9	(56.3%)	1	(6.3%)	1	(8.3%)	0	0	16
ST AUREUS	2	(28.6%)	3	(42.9%)	0	0	2	(28.6%)	0	0	7
STR GRP F	1	(33.3%)	2	(66.7%)	0	0	0	0	0	0	3
STR GRP A	1	(50.0%)	1	(50.0%)	0	0	0	0	0	0	2

Bacteriologic Response by Pathogen

All Evaluable Erythromycin-Treated Patients Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	PATHOGEN ELIMINATED n (%)	PRESUMED ELIMINATED n (%)	RECURRENCE SAME n (%)	RECURRENCE SAME, RESISTANCE n (%)	RECURRENCE NEW n (%)	FAILED TO ELIMINATE n (%)	TOTAL n
PATHOGENS							
H INFLUENZAE	14 (30.4%)	16 (34.8%)	6 (15.7%)	2 (4.3%)	0	6 (13.0%)	46
STR PNEUMONIAE	12 (37.5%)	13 (40.6%)	3 (12.5%)	0	3 (9.4%)	0	32
M CATARRHALIS	10 (41.7%)	14 (58.3%)	0	0	0	0	24
ST AUREUS	1 (12.5%)	7 (87.5%)	0	0	0	0	8
H PARAINFLUENZAE	1 (14.3%)	4 (57.1%)	1 (16.6%)	0	1 (14.3)	0	7
STREPTOCOCCUS SP	2 (100.0%)	0 0	0	0	0	0	2
STR GRP A	1 (33.3%)	1 (33.3%)	0	0	1 (33.3%)	0	3

The bacteriologic response for evaluable patients at late-posttherapy (10-14 days) according to the applicant was as follows:

Bacteriological Response
All Evaluable Patients Late-Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

RESPONSE	DIRITHROMYCIN N = 76 n	(%)	ERYTHROMYCIN N = 100 n	(%)
PATHOGEN ELIMINATED	1	(1.3%)	10	(10.0%)
PRESUMED ERADICATED	68	(89.5%)	77	(77.0%)
RECURRENCE SAME	3	(3.9%)	3	(3.0%)
RECURRENCE NEW	3	(3.9%)	8	(8.0%)
FAILED TO ELIMINATE	1	(1.3%)	2	(2.0%)

The bacteriologic response by pathogen for evaluable patients at late-posttherapy (10-14 days) according to the applicant was as follows:

Bacteriologic Response Summary by Pathogen
All Evaluable Dirithromycin-Treated Patients Late-Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	PATHOGEN ELIMINATED		PRESUMED ERADICATION		RECURRENCE SAME		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
PATHOGENS											
STR PNEUMONIAE	3	(10.0%)	25	(83.3%)	1	(4.1%)	1	(3.3%)	0		30
H INFLUENZAE	0		29	(87.9%)	2	(6.1%)	1	(3.0%)	1	(3.0%)	33
ST AUREUS	0		5	(83.3%)	0		1	(16.7%)	0		6
M CATARRHALIS	0		13	(100.0%)	0		0		0		13
STR GRP F	0		3	(100.0%)	0		0		0		3
STR GRP A	0		2	(100.0%)	0		0		0		2

Bacteriologic Response Summary by Pathogen
All Evaluable Erythromycin-Treated Patients Late-Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	PATHOGEN ELIMINATED		PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
PATHOGENS											
H INFLUENZAE	7	(17.1%)	27	(65.9%)	3	(7.3%)	2	(5.8%)	2	(4.9%)	41
STR PNEUMONIAE	2	(6.5%)	27	(87.1%)	0		2	(8.6%)	0		31
M CATARRHALIS	1	(4.5%)	20	(90.9%)	0		1	(5.2%)	0		22
ST AUREUS	1	(11.1%)	7	(77.8%)	0		1	(11.1%)	0		9
STR GRP A	2	(100.0%)	0		0		0		0		2
H PARAINFLUENZAE	0		4	(80.0%)	0		1	(33.3%)	0		5
STREPTOCOCCUS SP	0		1	(50.0%)	0		1	(100.0%)	0		2

SUSCEPTIBILITY RESULTS

Susceptibility Ranges for Pathogens
According to Zone Size Criteria
Therapy Group: Dirithromycin

Bronchitis

	ANTIMIBCROBIAL							
	DIRITHROMYCIN				ERYTHROMCYIN			
PATHOGEN	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
ACINETOBACTER SP			2	2		1	1	2
B CATARRHALIS	29		1	30	30			30
CORYNEBACTERIUM SP	1			1	1			1
E COLI	1		5	6		2	4	6
H INFLUENZAE	83	18	36	137	102	27	8	137
H PARAINFLUENZAE	9	1	3	13	10	2	1	13
K OZAENAE			1	1			1	1
N MENINGITIDIS	1			1	1			1
PR MIRABILIS			1	1			1	1
PR VULGARIS			1	1			1	1
PROTEUS SP			8	8			8	8
PS AERUGINOSA			2	2			2	2
SERRATIA LIQUEFACI			1	1			1	1
ST AUREUS	12		2	14	12		2	14
STR GRP A	4			4	4			4
STR GRP B	2		1	3	2	1		3
STR GRP D	1			1	1			1
STR GRP F	1			1	1			1
STR PNEUMONIAE	85		3	88	86	2		88
STREPTOCOCCUS SP	1			1	1			1

Susceptibility Ranges for Pathogens
According to Zone Size Criteria
Therapy Group: Erythromycin

Bronchitis

	ANTIMIBCROBIAL							
	DIRITHROMYCIN				ERYTHROMCYIN			
	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
PATHOGEN								
ACINETOBACTER SP			1	2	1		1	2
B CATARRHALIS	1			31	31			31
CITROBACTER SP	31		1	1			1	1
E AGGLOMERANS			1	1		1		1
E COLI			2	2			2	2
H INFLUENZAE	75	17	30	122	86	30	6	122
H PARAINFLUENZAE	19	2	1	22	20	2		22
K OXYTOCA			1	1			1	1
M MORGANII			1	1			1	1
PR VULGARIS			1	1			1	1
PROTEUS SP			9	9			9	9
PS AERUGINOSA			3	3			3	3
PS PUTIDA			1	1			1	1
PSEUDOMONAS SP			2	2			2	2
SERRATIA LIQUEFACI			1	1			1	1
ST AUREUS	17		1	18	17		1	18
STR GRP A	4			4	4			4
STR GRP B	1			1	1			1
STR PNEUMONIAE	71		1	72	71	1		72
STREPTOCOCCUS SP	1			1	1			1

Medical Officer's Comments:
About 25.5% (66/259) of the *H. influenzae* isolates were resistent to dirithromycin.

CONCOMITANT MEDICATIONS:

Prior to study entry, 60.8% of dirithromycin-treated and 61.8% of erythromycin-treated patients were receiving some form of drug therapy. Salbutamol was the most frequently used drug, taken by 27.1% and 28.3% of dirithromycin-treated and erythromycin-treated patients, respectively. Other frequently prescribed drugs for each group included beclometasone, theophylline, ipratopium bromide, aminophylline, and prednisolone. Other agents were used by no more than 5% of patients and the distribution of all compounds was well matched between the treatment groups. One dirithromycin-treated patient , received an antibiotic topically for conjunctivitis prior to study entry.

A concomitant agent was prescribed during-therapy in 7.8% of dirithromycin-treated compared with 8.1% of erythromycin-treated patients. Salbutamol was most frequently used. Antitussives, bronchodilators, expectorants, antihistamines, decongestants, and other analgesic agents were also prescribed relatively frequently. One patient in the erythromycin group received an oral antibiotic during-therapy because of continued symptoms. This patient was classified as a qualified patient who completed the protocol. After the database was locked it was found that this patient was not qualified because the causative organism was resistant to erythromycin.

After completion of study-drug therapy, 4.0% of dirithromycin-treated and 4.3% of erythromycin-treated patients reported taking new medications . Two patients in the dirithromycin group received erythromycin for pharyngitis after completion of study-drug therapy. One patient in the erythromycin group received cefaclor in response to a reduced sensitivity to erythromycin.

NDA 50-678
E002 Bronchitis

~~SAFE~~TY RESULTS:

Summary of Adverse Event By Body System Table

Frequency of Treatment Emergent Events
All Patients--All Adverse Events
Body System: Body as a Whole

	DIRITHROMYCIN N = 614		ERYTHROMYCIN N = 608		
	n	(%)	n	(%)	P VALUE
PATIENTS WITH AT LEAST ONE EVENT	29	(4.7%)	31	(5.1%)	0.761
PATIENTS WITH NO EVENT	585	(95.3%)	577	(94.9%)	0.761
EVENT CLASSIFICATION TERM					
ABDOMINAL PAIN	9	(1.5%)	9	(1.5%)	0.983
CHEST PAIN	7	(1.1%)	9	(1.5%)	0.601
HEADACHE	4	(0.7%)	3	(0.5%)	0.714
CHILLS	3	(0.5%)	1	(0.2%)	0.321
ASTHENIA	2	(0.3%)	3	(0.5%)	0.646
INFECTION	2	(0.3%)	0		0.159
PAIN	2	(0.3%)	5	(0.8%)	0.25
CHILLS AND FEVER	1	(0.2%)	0		0.319
FEVER	1	(0.2%)	1	(0.2%)	0.994
MALAISE	1	(0.2%)	0		0.319
MONILIASIS	1	(0.2%)	0		0.319
INJURY, ACCIDENT	0		1	(0.2%)	0.315

Frequency of Treatment Emergent Events
All Patients--Events Starting During Therapy
Body System: Body as a Whole

	DIRITHROMYCIN N = 614		ERYTHROMYCIN N = 608		P VALUE
	n	(%)	n	(%)	
PATIENTS WITH AT LEAST ONE EVENT	18	(2.9%)	25	(4.1%)	0.263
PATIENTS WITH NO EVENT	596	(97.1%)	583	95.9%)	0.263
EVENT CLASSIFICATION TERM					
ABDOMINAL PAIN	8	(1.3%)	8	(1.3%)	0.984
CHEST PAIN	3	(0.5%)	7	(1.2%)	0.199
HEADACHE	3	(0.5%)	2	(0.3%)	0.662
CHILLS	2	(0.3%)	1	(0.2%)	0.569
ASTHENIA	1	(0.2%)	3	(0.5%)	0.312
MALAISE	1	(0.2%)	0		0.319
PAIN	1	(0.2%)	4	(0.7%)	0.175
FEVER	0		1	(0.2%)	0.315

NDA 50-678
E002 Bronchitis

Frequency of Treatment Emergent Events
All Patients--All Adverse Events
Body System: Digestive System

	DIRITHROMYCIN N = 614		ERYTHROMYCIN N = 608		
	n	(%)	n	(%)	P VALUE
PATIENTS WITH AT LEAST ONE EVENT	41	(6.7%)	49	(8.1%)	0.355
PATIENTS WITH NO EVENT	573	(93.3%)	559	(91.9%)	0.355
EVENT CLASSIFICATION TERM					
DIARRHEA	16	(2.6%)	24	(3.9%)	0.188
NAUSEA	13	(2.1%)	10	(1.6%)	0.543
DYSPEPSIA	5	(0.8%)	4	(0.7%)	0.749
FLATULENCE	5	(0.8%)	2	(0.3%)	0.261
VOMITING	5	(0.8%)	5	(0.8%)	0.988
DRY MOUTH	2	(0.3%)	2	(0.3%)	0.992
ANOREXIA	1	(0.2%)	2	(0.3%)	0.557
NAUSEA AND VOMITING	1	(0.2%)	2	(0.3%)	0.557
ORAL MONILIASIS	1	(0.2%)	0		0.319
GASTRITIS	0		1	(0.2%)	0.315
GASTROINTESTINAL DISORDER	0		1	(0.2%)	0.315
JAUNDICE	0		1	(0.2%)	0.315
RECTAL DISORDER	0		1	(0.2%)	0.315

NDA 50-678
E002 Bronchitis

Frequency of Treatment Emergent Events
All Patients--Events Starting During Therapy
Body System: Digestive System

	DIRITHROMYCIN N = 614		ERYTHROMYCIN N = 608		
	n	(%)	n	(%)	P VALUE
PATIENTS WITH AT LEAST ONE EVENT	40	(6.5%)	42	(6.9%)	0.784
PATIENTS WITH NO EVENT	574	(93.5%)	566	(93.1%)	0.784
EVENT CLASSIFICATION TERM					
DIARRHEA	16	(2.6%)	22	(3.6%)	0.308
NAUSEA	13	(2.1%)	9	(1.5%)	0.402
DYSPEPSIA	5	(0.8%)	4	(0.7%)	0.749
FLATULENCE	5	(0.8%)	2	(0.3%)	0.261
VOMITING	5	(0.8%)	4	(0.7%)	0.749
DRY MOUTH	2	(0.3%)	2	(0.3%)	0.992
ANOREXIA	1	(0.2%)	1	(0.2%)	0.994
NAUSEA AND VOMITING	1	(0.2%)	2	(0.3%)	0.557
GASTRITIS	0		1	(0.2%)	0.315
RECTAL DISORDER	0		1	(0.2%)	0.315

NDA 50-678
E002 Bronchitis _ _

Frequency of Treatment Emergent Events
All Patients--All Adverse Events
Body System: Respiratory System

	DIRITHROMYCIN N = 614		ERYTHROMYCIN N = 608		
	n	(%)	n	(%)	P VALUE
PATIENTS WITH AT LEAST ONE EVENT	37	(6.0%)	42	(6.9%)	0.531
PATIENTS WITH NO EVENT	577	(94.0%)	566	(93.1%)	0.531
EVENT CLASSIFICATION TERM					
LUNG DISORDER	15	(2.4%)	12	(2.0%)	0.577
DYSPNEA	12	(2.0%)	7	(1.2%)	0.257
ASTHMA	7	(1.1%)	17	(2.8%)	0.037
HYPERVENTILATION	6	(1.0%)	11	(1.8%)	0.214
PHARYNGITIS	3	(0.5%)	3	(0.5%)	0.99
CARCINOMA OF LUNG	1	(0.2%)	1	(0.2%)	0.994
BRONCHITIS	0		1	(0.2%)	0.315
COUGH INCREASED	0		1	(0.2%)	0.315
LARYNGITIS	0		1	(0.2%)	0.315
RHINITIS	0		1	(0.2%)	0.315

Frequency of Treatment Emergent Events
All Patients--Events Starting During Therapy
Body System: Respiratory System

	DIRITHROMYCIN N = 614		ERYTHROMYCIN N = 608		
	n	(%)	n	(%)	P VALUE
PATIENTS WITH AT LEAST ONE EVENT	26	(4.2%)	26	(4.3%)	0.971
PATIENTS WITH NO EVENT	588	(95.8%)	582	(95.7%)	0.971
EVENT CLASSIFICATION TERM					
LUNG DISORDER	11	(1.8%)	8	(1.3%)	0.502
ASTHMA	7	(1.1%)	10	(1.6%)	0.451
DYSPNEA	7	(1.1%)	5	(0.8%)	0.573
HYPERVENTILATION	6	(1.0%)	7	(1.2%)	0.767
CARCINOMA OF LUNG	1	(0.2%)	1	(0.2%)	0.994
LARYNGITIS	0		1	(0.2%)	0.315
PHARYNGITIS	0		1	(0.2%)	0.315
RHINITIS	0		1	(0.2%)	0.315

Patients Who Died or Discontinued Therapy Due to Adverse Events:

No deaths were reported during the study; however, one patient, 010-1323, who received dirithromycin, was subsequently diagnosed with carcinoma of the lung and died. This death was not thought to have had any relation to study-drug.

Nine patients treated with dirithromycin and 14 patients treated with erythromycin were discontinued early from the study as a result of adverse events. The majority of these events were related to the gastrointestinal system.

Therapy: Dirithromycin

INV	PATIENT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT
012		1	54	FEMALE	CAUCASIAN	4	DIARRHOEA
012		1	30	MALE	CAUCASIAN	6	NAUSEA
034		1	60	FEMALE	CAUCASIAN	4	NAUSEA
050		1	44	MALE	CAUCASIAN	4	LOOSE AND FREQUENT BOWEL MOTIONS
601		1	62	MALE	CAUCASIAN	5	DYSPEPSIA
801		1	55	FEMALE	CAUCASIAN	4	VOMITING
801		1	39	FEMALE	CAUCASIAN	6	DIZZINESS
801		1	21	FEMALE	CAUCASIAN	1	DIARRHOEA
881		1	56	FEMALE	CAUCASIAN	5	ABDOMINAL PAIN

Therapy: Erythromycin

INV	PATIENT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT
026		1	51	FEMALE	CAUCASIAN	7	HOSPITALISED BY B BLOCKER EYE-DROPS
035		1	48	FEMALE	CAUCASIAN	5	DIARRHOEA
037		1	64	FEMALE	CAUCASIAN	2	DIARRHOEA
050		1	64	FEMALE	CAUCASIAN	4	WIND VOMITING AND UPPER ABD PAIN
050		1	57	FEMALE	CAUCASIAN	2	FEELS DREADFUL, POUNDING HEAD
050		1	57	FEMALE	CAUCASIAN	4	SEVERE DYSPEPSIA
050		1	60	FEMALE	CAUCASIAN	3	SICK EMPTY FEELING IN STOMACH
053		1	39	FEMALE	CAUCASIAN	2	NAUSEA, VOMITING
055		1	60	FEMALE	CAUCASIAN	4	PATIENT FELT NAUSEA & GEN. UNWELL
104		1	52	MALE	CAUCASIAN	5	KIDNEY PAIN
801		1	26	FEMALE	CAUCASIAN	3	NAUSEA AND VOMITING
805		1	26	FEMALE	CAUCASIAN	3	ABDOMINAL PAIN
850		1	37	FEMALE	CAUCASIAN	6	ABDOMINAL PAIN
875		1	63	MALE	CAUCASIAN	7	DEBILITATION OF CONDITION - BRONCHITIS

Clinical Laboratory Evaluations:

For the total population, statistically significant changes within groups were seen for several analytes. As would be expected in patients being treated for an acute infectious illness, both treatment groups showed significant reductions in white blood cell (WBC) count and polymorphonuclear neutrophil leukocytes (PMNs). A significant reduction in monocytes was also seen for both treatment groups. With the reduced number of segmented neutrophils, statistically significant increases in lymphocytes were seen in both groups. Both groups showed statistically significant reductions in hematocrit and hemoglobin although the magnitude of these changes was not considered clinically relevant. Platelet counts were significantly increased in both groups, most likely reflecting the phenomenon of reactive thrombocytosis that is frequently seen in recovery from acute infectious illness. No statistically significant difference between the treatment groups was seen for any of the analytes. There were no statistically significant within-group changes that were seen only in the dirithromycin group.

Several blood chemistry analytes showed significant changes within the groups. Alkaline phosphatase, GGT, and total protein showed a statistically significant decrease in both groups. BUN, serum phosphorus, uric acid, and cholesterol all showed statistically significant increases in both groups. Despite the noted rise in BUN for both groups, a statistically significant increase in serum creatinine was seen only in the erythromycin treatment group.

The only analyte for which a statistically significant change was seen only within the dirithromycin group and for which there was a statistically significant between-group difference was an increase in urinary pH. This change was not thought to be of clinical relevance.

When these analytes were analyzed for the frequency with which patients changed status (i.e., normal, low, high) during-therapy, no statistically significant differences were noted.

Distribution of Extreme Laboratory Values

(For Normal laboratory vlaues, see page 5A of MOR)

PLATELETS		Pretherapy	During Therapy	Posttherapy
005-0929	D	397		503
011-1254	D	192		461
017-0790	D	335	674	616
038-1276	D	182		485
043-0933	D	279		531
050-1626	D	370		471
050-1672	D	195		458
051-4101	D	333		564
204-2493	D	204		466
210-2520	D	552		709
801-8030	D	463		635
823-8403	D	296		585
862-8129	D	358		542
874-8334	D	292		473
890-8115	D	456		580
890-8823	D	200		481
004-0683	E	298		462
011-0700	E	248		507
013-1482	E	210		459
028-1163	E	252		462
028-1293	E	347		489
035-1341	E	361		492
043-0926	E	477		608
050-1636	E	291		414
050-4172	E	278		448
050-4174	E	324		477
057-4012	E	308		428
803-8864	E	243		459
805-8414	E	344		451
816-8857	E	306		464
832-8010	E	244		439
870-8164	E	355		508
870-8165	E	339		453
881-8303	E	310		428
891-8411	E	282		451
891-8171	E	395		490

It was observed that some laboratory results were classified as "mixed." This terminology refers to laboratory samples that were handled improperly (hemolyzed) or results in which the test tube containing the preservative EDTA was mixed with the clotted blood sample thus causing contamination. There were 65 of 608 (10.7%) of patients treated with dirithromycin and 57 of 614 (9.3%) patients treated with erythromycin who showed positive delta changes with the posttherapy values of serum phosphorus above the reference range. In most of these patients, this was the only delta change noted. These changes were not thought to be clinically relevant.

Overall Summary of Pivotal Studies

Clinical Response:

Clinical Response Summary
Post-therapy
AQAB/E002
Acute Bacterial Exacerbation of Chronic Bronchitis

Study	Dirithromycin Favorable/Total	Erythromycin Favorable/Total
AQAB	87/101	72/81
E002	80/89	104/113
Total	167/190 (88%)	176/194 (90.7%)

Clinical Response Summary
Late Post-therapy
AQAB/E002
Acute Bacterial Exacerbation of Chronic Bronchitis

Study	Dirithromycin Favorable/Total	Erythromycin Favorable/Total
AQAB	71/80	61/67
E002	75/76	95/100
Total	146/156 (93.6%)	156/167 (93.4%)

Overall Summary

Clinical Response Summary By Target Pathogens
AQAB/ E002
Acute Exacerbation of Chronic Bronchitis

	Posttherapy								Late-Posttherapy							
	Dirithromycin				Erythromycin				Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable	
Pathogen	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
M catarrhalis	23	95.8	1	4.2	26	96.3	1	3.7	21	100	0	0	24	96.0	1	4.0
H influenzae	41	75.9	13	24.1	55	94.8	3	6.2	35	94.6	2	5.4	44	89.8	5	10.2
H parainfluenzae	8	88.9	1	11.1	3	50	3	50	5	83.3	1	16.7	3	100	0	0
Str pneumoniae	39	90.7	4	9.3	34	94.4	2	5.6	37	92.5	3	7.5	32	97.0	1	3.0
Mulitple Pathogens	22	95.7	1	4.3	20	87.0	3	13.0	19	100	0	0	18	94.7	1	5.3

Clinical Response Summary
E002
Secondary Bacterial Infection

	Posttherapy								Late-Posttherapy							
	Dirithromycin				Erythromycin				Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable	
Pathogen	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
M catarrhalis	3	100	-	-	4	100	-	-	3	100	-	-	4	100	-	-
H influenzae	22	88	3	12	25	96.2	1	3.8	22	100	0	0	25	100	0	0
H parainfluenzae	7	100	-	-	3	60	2	40	6	85.7	1	14.3	3	60	2	40
Str pneumoniae	26	92.9	2	7.1	18	100	-	-	23	95.8	1	4.2	19	100	-	-
Mulitple Pathogens	6	100	-	-	5	100	-	-	6	100	-	-	3	100	-	-

Bacteriologic Response Summary
AQAB (US STUDY)
Acute Bacterial Exacerbation of Chronic Bronchitis

	Posttherapy								Late-Posttherapy							
	Dirithromycin				Erythromycin				Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable	
Pathogen	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
M catarrhalis	16	100	0	0	11	91.6	1	8.4	14	100.0	0	0	11	100	0	0
H influenzae	15	71.4	6	28.6	20	91	2	9	12	85.7	2	14.3	16	94	1	6
Str pneumoniae	21	100	0	0	11	84.5	2	15.5	16	94	1	6	11	91.6	1	8.4

Bacteriologic Response Summary
AQAB/ E002
Acute Bacterial Exacerbation of Chronic Bronchitis

	Posttherapy								Late-Posttherapy							
	Dirithromycin				Erythromycin				Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable	
Pathogen	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
M catarrhalis	30	93.8	2	6.2	35	97.2	1	2.8	27	100.0	0	0	32	97.0	1	3.0
H influenzae	48	75.0	16	25.0	50	73.5	18	26.5	43	91.5	4	8.5	50	86.2	8	13.8
Str pneumoniae	47	85.5	8	14.5	36	80.0	9	20.0	44	93.6	3	6.4	40	93.0	3	7.0

Bacteriologic Response Summary
E002 Secondary Bacterial Infection

	Posttherapy								Late-Posttherapy							
	Dirithromycin				Erythromycin				Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable	
Pathogen	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
M catarrhalis	6	100	0		5	100	0		6	100	0		5	100	0	
H influenzae	24	82.8	5	17.2	25	86.2	4	13.8	26	100	0		23	88.5	3	11.5
Str pneumoniae	28	90.3	3	9.7	17	73.9	6	26.1	27	96.4	1	3.6	19	86.3	3	13.7

MEDICAL OFFICER'S CONCLUSIONS:

The overall clinical success rate for dirithromycin was comparable to erythromycin at post-therapy and at late post-therapy. In patients with the diagnosis of Acute Bacterial Exacerbation of Chronic Bronchitis, the bacteriologic success rate at post-therapy for *H. influenzae* was 75.0% (48/64) for the dirithromycin group and 73.5% (50/68) for the erythromycin group. **(NOTE: 38% (137/360) of *H. influenzae* isolated (data from AQAB and E002) were resistant to dirithromycin, thus were considered unevaluable. This success rate only applies to patients who had susceptible organisms.)** The bacteriologic success rate at post-therapy for *S. pneumoniae* was 85.5% (47/55) for dirithromycin group and 80% (36/45) for the erythromycin group. The Bacteriologic success rate at post-therapy for *M. catarrhalis* was 93.8% (30/32) for the dirithromycin group and 97.2% (35/36) for the erythromycin group.
At late post-therapy follow-up, for *H. influenzae* it was 91.5% (43/47) for the dirithromycin group and 86.2% (50/58) for the erythromycin group. The bacteriologic response rate at late post-therapy for *S. pneumoniae* was 93.6% (44/47) for dirithromycin group and 93.0% (40/43) for the erythromycin group. The Bacteriologic success rate at late post-therapy for *M. catarrhalis* was 100% (27/27) for the dirithromycin group and 97.0% (32/33) for the erythromycin group.

There was only one study (E002) which had patients with the primary diagnosis of Secondary Bacterial Infection of Acute Bronchitis. The clinical and bacteriologic outcomes were similar to the chronic bronchitis study results. The target pathogens studied were also identical. The only difference was that patients in the acute bronchitis group did not have any underlying illnesses like the group in chronic bronchitis, thus, they had a milder illness. Based upon that information, the Medical Officer has concluded that the indication, **Secondary Bacterial Infection of Acute Bronchitis** be granted for the same organisms as the Acute Bacterial Exacerbation of Chronic Bronchitis.

~~MEDI~~CAL OFFICER'S RECOMMENDATIONS:

Based upon the data submitted and reviewed , the following recommendations are made:

Dirithromycin is recommended for the treatment of Acute Bacterial Exacerbation of Chronic Bronchitis caused by *S. pneumoniae, or M. catarrhalis.*

Dirithromycin is also recommended for the treatment of Secondary Bacterial Infection of Acute Bronchitis caused by *S. pneumoniae, or M. catarrhalis.*

The bacteriologic response rates in the US study AQAB were lower for dirithromycin when compared to erythromycin (71.4% for dirithromycin versus 91% for erythromycin) for the treatment of *H. influenzae* bronchitis, and *H. influenzae* had more than 38% resistance rate to dirithromycin in both the clinical trials submitted for review. It is recommended that the sponsor study either a higher dosage regimen for the treatment of *H. influenzae* bronchitis or twice a day dosage to eradicate this organism.

The recommended dosage is 500 mg once a day for 7 days.

REVIEW OF PIVOTAL STUDIES:

I. Study B9Z-MC-AQAB Synopsis:

Title:	Dirithromycin versus Erythromycin Base in Bacterial Pneumonia.
Study Centers:	There were 93 active study centers.
Dates of Study:	October 7, 1988 - May 31, 1991
Clinical Phase:	Phase 2-3
Objectives:	To compare dirithromycin with erythromycin base for effectiveness and safety in the treatment of bacterial pneumonia.
Methodology:	Double-blind, double-dummy, randomized, parallel study.
Number of Subjects:	Dirithromycin: Male 130, Female 130, Total 260. Erythromycin: Male 137, Female 120, Total 257.
Diagnosis and Inclusion Criteria:	Pneumonia with confirmed susceptible bacterial etiology or appropriate serology for mycoplasma or legionella.
Dosage and Administration:	<u>Test Product</u> Dirithromycin: 500 mg/day (two 250-mg tablets q.d.) CT9367, CT9964: dirithromycin tablets, 250 mg CT9368, CT9965: placebo tablets NOTE: Placebo was used to maintain blinding. <u>Reference Therapy</u> Erythromycin Base: 1000 mg/day (one 250-mg tablet q.i.d.) CT9369, CT9966: erythromycin base tablets, 250 mg CT9370, CT9967: placebo tablets NOTE: Placebo was used to maintain blinding.
Duration of Treatment:	Dirithromycin: 10-14 days Erythromycin Base: 10-14 days

Criteria for Evaluation:	Efficacy--A complete efficacy evaluation was to be performed on patients completing at least 10 days of therapy who had positive chest x-ray and sputum culture or serology, returned for the during-therapy, posttherapy and the late-posttherapy clinical evaluation (late-posttherapy was required if chest x-ray had not resolved at posttherapy evaluation), and for whom the symptomatic response could be evaluated. Safety--All patients were to be evaluated for safety.
Statistical Methods:	Chi-square tests were to be used for response rates and adverse events. Appropriate continuous data procedures were to be used for analysis of laboratory data. The Type I error was set at 0.05.

Study Design:

This was a double-blind, randomized, parallel study. Patients who met the entry criteria and signed a patient consent form (parent or guardian signed if patient was a minor) were to be assigned by randomization to one of two antibiotic treatment groups. Randomization was provided by the sponsor. Patients were to be evaluated for symptomatic and bacteriologic responses to treatment. Safety was to be measured by clinical assessment and laboratory tests. In patients who responded to treatment, the duration of therapy was 10 to 14 days. There was no minimum treatment period for patients who did not respond to therapy.

Inclusion Criteria

Patients were males and females 12 years of age or older, to weigh at least 37 kg, and to be able to swallow tablets. Patients were to be included if they had a clinical diagnosis of bacterial pneumonia.

The investigators were to attempt to select those patients and parents or guardians who had a history of complying with instructions. Each patient (or parent or guardian for a child) was to be required to sign an informed consent document approved by the Institutional Review Board (IRB).

Exclusion Criteria

Patients were to be excluded who had a history of renal impairment (serum creatinine ≥ 133 μmol/L, 1.5 mg/dL); had any condition, including significant underlying disease or concomitant infection that, in the opinion of the investigator, could have precluded evaluation of response; had an anticipated requirement of systemic antibiotics other than the study antibiotic during therapy; had received any antimicrobial therapy within 1 week preceding the pretherapy evaluation; or had used other investigational agents within 21 days prior to entry into study.

Also excluded were patients who were unable to return for follow-up examinations, patients who had hypersensitivity to macrolides, patients who were pregnant, and postpartum/lactating females who were nursing. Women with child-bearing potential were required to have a negative pregnancy test prior to therapy, and were required to use a reliable birth control method during and for one month after completing therapy.

Dosing Schedule:

Patients randomly allocated to the dirithromycin treatment group received two 250-mg dirithromycin tablets in the morning (total 500 mg) and one tablet of placebo four times daily. The placebo tablet was identical in appearance to the erythromycin tablet.

Patients randomly allocated to the erythromycin treatment group received one 250-mg erythromycin tablet four times daily (total 1000 mg) and two tablets of placebo in the morning. The placebo tablet was identical in appearance to the dirithromycin tablet.

Evaluation/Procedures:

PROCEDURES FOR EVALUATION OF CLINICAL RESPONSE

Study Visit	Procedure
Pretherapy (within 24 hours preceding the first dose):	A complete history and physical examination, including chest roentgenogram to document diagnosis, were to be performed.
During Therapy (Days 3-5):	Evaluated symptomatic response to therapy and assessed patient compliance with instructions for taking medication.
Posttherapy (3-5 days after therapy was completed):	Physical examination was to be performed to evaluate symptomatic response to therapy. Chest roentgenogram was required.
Late-posttherapy (2-3 weeks after therapy was completed):	Physical examination was to be performed to evaluate symptomatic response to therapy. Patients whose chest roentgenogram was not clear at the posttherapy visit required a late-posttherapy chest roentgenogram.

PROCEDURES FOR EVALUATION OF BACTERIOLOGIC RESPONSE

Study Visit	Procedure
Pretherapy (within 24 hours preceding start of therapy)	Expectorated sputum stain (Gram's stain**) and culture; a bacterial culture of blood was performed in duplicate. Susceptibility of the microorganism(s) isolated to both dirithromycin and erythromycin was determined by the FDA standardized disk method and/or MIC determination. The pathogen had to be susceptible to erythromycin* for the patient to remain in the study. All patients were to undergo serologic antibody titer testing for evidence of Mycoplasma or Legionella infection.
During Therapy (Days 3-5):	If pretherapy blood culture was positive, the blood cultures were to be repeated regularly until negative. Gram stain and culture of sputum were to be repeated if clinically indicated.
Posttherapy (3-5 days after therapy was discontinued):	Gram stain and culture of sputum were to be repeated if cough remained productive. Serologic antibody titer testing for evidence of Mycoplasma or Legionella infection were to be done.
Late-posttherapy (2-3 weeks after antibiotic was discontinued):	Gram stain and culture of sputum were to be repeated if cough remained productive. Required for evaluability in patients whose posttherapy chest X-ray had not resolved.

*Erythromycin susceptibility defined as ≥18 mm zone size; ≤0.5 μg/mL MIC.
**Diagnosis was supported by results showing ≥ 25 pmn's/hpf and ≤ 10 epithelial cells/hpf.

Safety Procedures:

Safety assessments were to include clinical evaluations and laboratory tests. Electrocardiograms (ECG's) were performed during Phase 2. A central laboratory was to be used to determine values for the laboratory tests described in the following table. Each study site was provided with laboratory patient kits to collect blood and urine samples for air shipment to the central laboratory.

Each study site received a copy of the laboratory results for each testing period. Laboratory values regarded as alarming (predetermined by the sponsor) were to be telephoned to the study site by the central laboratory.

LABORATORY TESTS TO EVALUATE SAFETY

Study Visit	Procedure		
Pretherapy (Within 24 Hours of Receiving the First Dose):	Hematology	Blood Chemistry	Urinalysis
	Hemoglobin	Phosphorus	Appearance
	Hematocrit	Calcium	Specific Gravity
	RBC Count	Glucose	pH
	MCV	Cholesterol	Protein
	MCH	Total Bilirubin	Glucose
	MCHC	Alkaline Phos.	Ketones
	WBC Count	GGT	Bilirubin
	Differential Count	ALT (SGPT)	Urobilinogen
	Platelet Count	AST (SGOT)	Blood
	Morphology	Urea Nitrogen	Nitrite
		Creatinine	Leukocyte Esterase
		Uric Acid	Microscopic - WBC
		Total Protein	RBC
		Albumin	Casts
		Creatine Kinase*	
During Therapy Urine samples (Days 3-5):	Laboratory tests were to be repeated as clinically indicated. were to be assayed for presence of antimicrobial activity.		
Posttherapy (3-5 Days After Completion of Therapy):	Pretherapy tests were to be repeated. If any abnormal values were found, the tests were to be repeated until values returned to normal or were explained.		
Late-posttherapy (2-3 Weeks After Completion of Therapy):	Laboratory tests were to be repeated during Phase 2. Laboratory tests were to be repeated during Phase 3, if clinically indicated.		

*If CK was greater than 1000 U/L, the central laboratory was to notify the site and perform a CK isoenzyme fractionation. The laboratory then would telephone the study site with the result of the CK isoenzyme fractionation.

If the patient was taking theophylline, carbamazepine, or cyclosporine, the investigator was to request the appropriate drug level at the pretherapy and during-therapy visits. Subsequent levels were to be requested at the posttherapy visit, late-posttherapy visit, or at other times, if clinically indicated. The laboratory would then telephone the study site with the result, if toxic levels were measured. For patients taking warfarin, a prothrombin time was required at the pretherapy and during-therapy visits and was to be done at other times as clinically indicated. This test was to be performed by a local laboratory.

ECG's were to be taken at the pretherapy and posttherapy visits during Phase 2 and were to be mailed to a central site for interpretation. If any abnormality was revealed, ECG's were to be repeated at the late-posttherapy visit or sooner if clinically indicated.

All patients, parents, or guardians were to be questioned at the time of return visits and were to be instructed to contact the investigator, or clinical personnel, by phone if they or their child had an adverse event. The investigator was to report all adverse events to the Research Physician by prompt submission of the patient's CRF. If any adverse event was alarming, it was to be reported immediately by telephone to the Research Physician.

Adverse events were to be recorded on the CRF using the patient's words or the investigator's terms (synonym terms). Synonym terms were further classified as Eli Lilly and Company Event Classification Terms (ELECT), which are based on Food and Drug Administration (FDA) COSTART definitions. Both synonym terms and ELECT classifications were entered in the Lilly database. Adverse events were categorized by body system using the algorithm found in the ELECT dictionary.

Terminations:

A patient was to be discontinued from the study for any one of the following reasons:

Pathogen isolated from initial culture was resistant to erythromycin.

Obvious symptomatic and/or bacteriologic failure of the study antibiotic at any time during treatment. There was no minimum treatment period, and the duration of therapy was left to the clinical judgment of the investigator for patients who were failing.

If, in the investigator's opinion, a significant adverse event or significant alteration in a laboratory test result occurred, the study antibiotic was to be discontinued.

If the patient, parent or guardian, or attending physician requested, or the investigator so decided, the patient was to be withdrawn from the study and the reason was stated on the CRF.

Study drug identity was unblinded for safety reasons.

Pretherapy serum creatinine ≥ 133 μmol/L (1.5 mg/dL).

Patients who discontinued from the study had to have pretherapy laboratory tests and sputum cultures repeated.

Efficacy Procedures:

SYMPTOMATIC RESPONSE DEFINITIONS

Response	Definition
Cure:	Elimination of signs and symptoms of infection at post-therapy with no recurrence in the late post-therapy follow-up period.
Improvement:	Significant, but incomplete, resolution of signs or symptoms of infection at any post-treatment visit.
Relapse:	Worsening of signs and symptoms of infection following initial improvement at any post-treatment visit.
Failure:	Signs and symptoms did not subside or improve during therapy. A case requiring the addition of another antibiotic for the treatment of pneumonia was classified as a symptomatic failure.*
Unable to Evaluate:	Unable to evaluate a symptomatic response due to extenuating circumstances. This response disqualified a case for efficacy analysis only.

* The use of failure for cases requiring the addition of another antibiotic was reserved for those cases where the study-drug medication was purposely discontinued in order to begin a different antibiotic due to worsening or lack of improvement of the patient's clinical condition. If a patient was evaluated posttherapy to be clinically cured or improved but was found to be bacteriologically culture positive for a pathogen and was treated with nonstudy antibiotic, the patient's clinical response remained as assigned, "cure" or "improvement."

BACTERIOLOGIC RESPONSE DEFINITIONS
INDICATION: PNEUMONIA

Result	Definition of Response
Pathogen Eliminated:	Eradication of the pathogen at post-therapy and late post-therapy follow-up.
Recurrence Same Pathogen:	Original pathogen eliminated during treatment but recurred during the follow-up period.
Recurrence Same Pathogen, Resistance Developed:	Original pathogen susceptible to erythromycin was eliminated during treatment but recurred in the follow-up period and tested as resistant to erythromycin.
Recurrence New Pathogen :	Original pathogen susceptible to erythromycin was eliminated during treatment, but a new pathogen was isolated in the follow-up period.
Failure:	Original pathogen was not eradicated.
Not Applicable:	Patient obtained either a cure or improvement clinically, and the follow-up culture was not clinically indicated, or the culture source was eliminated.
Unable to Evaluate:	Term used when cultures were not obtained or when a systemic (nonstudy) antimicrobial agent with activity against respiratory bacterial pathogens was taken. Patients with Mycoplasma and Legionella, whose diagnosis was based on appropriate serologic results, were to be classified under this response heading.

Medical Officer's Comments:

The Medical Officer defined "Not Applicable" as "Presumed Eradicated".

Qualification for Efficacy Analysis:

Cases classified by the sponsor as "qualified" met the following criteria for analysis of efficacy: the patient met the inclusion criteria; the patient completed an adequate course of therapy (10 days if categorized "cure" or "improvement"); the pretherapy culture obtained within 24 hours prior to start of study-drug medication was positive for a respiratory pathogen susceptible to erythromycin; for Mycoplasma and Legionella pneumonia, acute and convalescent antibody titers were obtained. A signficant rise in antibody titers was necessary for the patient to be evaluable for efficacy; posttherapy clinical and microbiological evaluations were performed; and the symptomatic response could be evaluated.

TITERS

MYCOPLASMA: IF EITHER THE IgM OR IgG FLUORESCENT ANTIBODY TEST INDICATES AN INFECTION, THEN THE PATIENT IS CONSIDERED TO HAVE AN INFECTION.

MYCOPLASMA IgM FLUORESCENT ANTIBODY TEST (IFA* TEST BY ZEUS)

IF Fluorescent intensity	AND	Either Pre or Post Titers	THEN	Interpretation
1+ to 4+		≥ 16	Active or recent infection	Infection
2+ to 4+		8	Previous infection	No infection
0 to 1+		8	No infection	No infection

MYCOPLASMA IgG FLUORESCENT ANTIBODY TEST (IFA* TEST BY ZEUS)

IF Fluorescent intensity	AND	Either Pre or Post Titers	THEN	Interpretation
1+ to 4+		≥ 128	Active or recent infection	Infection
2+ to 4+		64	Previous infection	No infection
0 to 1+		64	No infection	No infection

LEGIONELLA FLUORESCENT ANTIBODY TEST (IFA* TEST BY ZEUS)

IF Fluorescent intensity	AND Titers	THEN	Interpretation
≥ 1+	1) any single titers ≥256	Active infection	Infection
≥ 1+	2) convalescent titer ≥128 and convalescent titer ≥4 x acute titer	Active infection	Infection
	3) Not one of the above titer results	No active infection	No infection

Statistical Methods:

The primary statistical evaluations included all data available from all patients entering the study. The groups of patients, determined by random allocation, were compared by means of chi-square methodology with respect to symptomatic and bacteriologic response rates and with respect to adverse event frequencies. Appropriate continuous data procedures, such as a two-sample t-test on ranked data, were used for analysis of the laboratory monitoring data. All analyses examined consistency of results among participating clinics.

Investigators:

Study Population
All Patients Consented and/or Randomized
Indication: Pneumonia

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
D. H. LEHMAN/SACRAMENTO, CA	9	5	3	0
J. M. APPLESTEIN/SAN DIEGO, CA	1	0	1	0
D. H. LEHMAN/SACRAMENTO, CA	5	2	3	1
J. M. SELTZER/SAN DIEGO, CA	0	2	0	0
F. L. BROWN/PHILADELPHIA, PA	1	0	0	0
S. HEATLEY/REDWOOD CITY, CA	1	2	0	2
R. R. STOLTZ/EVANSVILLE, IN	3	9	1	1
C. W. WEART/CHARLESTON, SC	2	0	0	0
R. E. SCHNEIDER/CHARLOTTE, NC	4	2	2	0
J. P. KRAINSON/MIAMI, FL	1	0	0	0
R. C. HASELBY/MARSHFIELD, WI	0	1	0	0
A. D. PUOPOLO/MILFORD, MA	7	8	3	3
H. COLLINS/EDISON, NJ	13	16	9	7
M. S. WAXMAN/NORTH ARLINGTON, NJ	1	1	0	0
C. ORTIZ/ROCHESTER, NY	2	3	0	2
M. BARREIRO/BINGHAMTON, NY	0	2	0	0
E. E. MILLER/COLORADO SPRINGS, CO	2	1	1	0
W. G. GARDNER/AKRON, OH	3	2	3	0
G. E. BERGER/DETROIT, MI	0	2	0	1
R. P. BAUGHMAN/CINCINNATI, OH	1	0	1	0
F. P. MICHAEL/DETROIT, MI	2	1	0	0
M. B. WIENER/DENVER, CO	0	2	0	1
S. R. LINNE/WOODLAND, CA	0	1	0	1
C. KAUFFMAN/ANN ARBOR, MI	0	1	0	0
W. W. SADOWINSKI/WHITTIER, CA	0	1	0	0
B. G. YANGCO/TAMPA, FL	3	2	0	1
B. TUCKER/BIRMINGHAM, AL	6	7	2	1
R. B. GEIGER/VERO BEACH, FL	1	2	0	0
S. A. BRAHIM/TOWSON, MD	1	2	0	0
J. C. ROTSCHAFER/ST. PAUL, MN	1	0	0	0
A. POLLACK/ROCKVILLE, MD	1	1	0	0
T. D. DAVIS/BISMARK, ND	1	0	1	0
J. S. SHEN/ELIZABETH, NJ	3	0	2	0
D. SIMONS-MORTON/HOUSTON, TX	8	11	2	4
J. A. KRAM/OAKLAND, CA	1	1	1	0
F. D. SUTTON, JR/BIRMINGHAM, AL	1	1	0	1
G. H. MEDURI/MEMPHIS, TN	1	0	0	0
C. M. HETSKO/MADISON, WI	7	8	2	3
M. KARETZKY/NEWARK, NJ	2	0	0	0
F. J. GUERRA/EL PASO, TX	22	20	7	10

(continued)

Study Population (continued)
All Patients Consented and/or Randomized
Indication: Pneumonia

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
E. M. BRUNSON/ALABASTER, AL	0	1	0	0
S. J. PADOVE/BIRMINGHAM, AL	8	3	1	0
D. G. MILLER/MOORESVILLE, PA	7	9	3	2
R. A. HACKMAN/MURFREESBORO, TN	0	1	0	1
R. ARANSON/BRIGHTON, MA	2	1	1	0
F. C. WHITTIER/CANTON, OH	4	3	2	1
S. C. PARMAN/MIDDLETOWN, NJ	1	2	0	1
B. A. REED/ANN ARBOR, MI	0	1	0	0
R. BRODIE/BALTIMORE, MD	0	1	0	1
S. G. GEVAS/ARLINGTON, VA	0	1	0	0
S. ZEIG/PEMBROKE PINES, FL	0	2	0	0
J. M. MCCARTY/FRESNO, CA	1	2	1	1
J. M. BUNDY/YUKON, OK	8	9	3	3
T. W. LITTLEJOHN/WINSTON-SALEM, NC	1	1	1	1
D. C. MCCLUSKEY/MOGADORE, OH	5	8	1	2
L. W. WINTER/DANVILLE, IL	1	2	0	0
E. H. GUTHRIE/SALT LAKE CITY, UT	13	14	5	5
H. M. FARIS, JR/GREENVILLE, SC	10	6	1	0
J. COGGESHALL/FRANKLIN, TN	2	1	2	0
G. V. COLLINS/CHARLOTTE, NC	3	2	1	0
C. PIERCE/CHARLOTTE, NC	1	1	0	0
M. L. MEANS/WICHITA, KS	2	1	0	1
L. E. ELLINWOOD/GRAND JUNCTION, CO	3	1	1	0
K. D. JACOBSON/EUGENE, OR	6	5	4	3
W. T. PAUL/COLUMBUS, OH	1	0	0	0
G. WEISMAN/WARMINSTER, PA	10	6	4	2
S. K. ZORN/WEST DES MOINES, IA	2	1	2	0
W. R. MARKEL/BROOMFIELD, CO	0	1	0	0
S. L. GREEN/HAMPTON, VA	2	1	0	1
C. M. SAMET/MANHASSET, NY	1	1	0	0
G. D. BEDSOLE/MONTGOMERY, AL	3	4	0	1
W. M. MOROWITZ/CHERRY HILL, NJ	2	1	1	1
G. E. RUOFF/KALAMAZOO, MI	3	3	1	0
DAUER AND FUTTERMAN/WHITTIER, CA	4	3	0	0
W. J. HENRY/GREER, SC	1	0	0	0
O. E. PERDOMO/ATTALLA, AL	0	2	0	0
A. E. LEE/UNIVERSITY, MS	1	1	0	0
H. M. SERFER/HOLLYWOOD, FL	3	4	0	1
A. R. ROSENTHAL/SOUTH BEND, IN	4	3	0	1
J. D. SANDERS/CHARLESTON, SC	1	0	0	0
C. M. FOGARTY AND W P/SPARTANBURG, SC	5	6	1	3

(continued)

Study Population (concluded)
All Patients Consented and/or Randomized
Indication: Pneumonia

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
G. E. PETERSON/DES MOINES, IA	0	1	0	0
P. H. DIAMOND/MURFREESBORO, TN	1	0	0	0
L. E. MANSFIELD/EL PASO, TX	3	2	1	1
L. K. ALWINE/DOWNINGTON, PA	1	1	0	0
G. D. CARR/HATTIESBURG, MS	1	0	1	0
W. A. BROWN AND P B W/PROVIDENCE, RI	1	0	1	0
R. H. ESHAM AND K CUN/MOBILE, AL	1	1	1	1
S. N. BASS/CLEVELAND, OH	1	2	0	0
W. THERON/KLERKSDORP 2570, REPUBLIC OF SOUTH AFRICA	2	2	1	1
S. F. VAN EERDEN/PARDOW VALLEY, CAPE, S. AFRICA	3	3	2	0
U. G. LALLOO/CONGELLA, NATAL, REPUBLIC OF SOUTH AFRICA	14	12	6	8
R. A. DAVEY/SUNNYSIDE, PRETORIA 0132, REPUBLIC OF SOUTH AFRICA	3	3	0	1
H. T. MATTHEWS/KLERKSDORP 2570, REPUBLIC OF SOUTH AFRICA	0	1	0	1
TOTAL	260	257	90	83

Medical Officer's Comments:

The Medical Officer concurs with the sponsor's evaluability. Note that all investigators had less than 10 evaluable patients in each treatment arm.

Sponsor's Analysis (Medical Officer concurs with the analysis):

Patient disposition was as follows:

	DIRITH	ERYTH	TOTAL
Patient Enrolled	260	257	517
Evaluable for Efficacy	90	83	173
Completed Therapy	83	82	165
Prematurely Discontinued	7	1	8
Not Evaluable	170	174	344
Completed Therapy	6	5	11
Prematurely Discontinued	164	169	333

Patient Demographics:

The demographics for all patients entered in the study and the evaluable patients are summarized in the tables below:

All Patients

Age by Sex - Ranges
All Patients
Indication: Pneumonia

AGE RANGES	DIRITHROMYCIN FEMALE (N = 130) n	(%)	DIRITHROMYCIN MALE (N = 130) n	(%)	DIRITHROMYCIN TOTAL (N = 260) n	(%)	ERYTHROMYCIN FEMALE (N = 120) n	(%)	ERYTHROMYCIN MALE (N = 137) n	(%)	ERYTHROMYCIN TOTAL (N = 257) n	(%)
	4	(3.1%)	1	(0.8%)	5	(1.9%)	1	(0.8%)	3	(2.2%)	4	(1.6%)
	10	(7.7%)	20	(15.4%)	30	(11.5%)	14	(11.7%)	27	(19.7%)	41	(16.0%)
	59	(45.4%)	68	(52.3%)	127	(48.8%)	52	(43.3%)	54	(39.4%)	106	(41.2%)
	37	(28.5%)	22	(16.9%)	59	(22.7%)	32	(26.7%)	36	(26.3%)	68	(26.5%)
	20	(15.4%)	19	(14.6%)	39	(15.0%)	21	(17.5%)	17	(12.4%)	38	(14.8%)

Age by Sex - Mean, Median, Minimum and Maximum
All Patients
Indication: Pneumonia

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	130	130	260	120	137	257
MEAN AGE	45.23	42.70	43.97	45.32	42.51	43.82
STD DEV	17.87	18.61	18.25	17.92	18.85	18.44
MEDIAN A	40.92	38.33	39.76	42.85	38.60	41.37
MINIMUM AGE						
MAXIMUM AGE						

Origin by Therapy Group
All Patients
Indication: Pneumonia

	DIRITHROMYCIN N = 260		ERYTHROMYCIN N = 257	
ORIGIN	n	(%)	n	(%)
CAUCASIAN	197	(75.8%)	196	(76.3%)
BLACK	43	(16.5%)	39	(15.2%)
HISPANIC	13	(5.0%)	18	(7.0%)
NATIVE AMERICAN	1	(0.4%)	1	(0.4%)
ASIAN	2	(0.8%)	1	(0.4%)
OTHER	4	(1.5%)	2	(0.8%)

Height and Weight at Admission
All Patients
Indication: Pneumonia

	HEIGHT IN CM						WEIGHT IN KG					
THERAPY	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	259	1	169.26	11			258	2	73.10	19		
ERYTHROMYCIN	253	4	169.28	11			252	5	74.53	19		

EVALUABLE PATIENTS:

Age Ranges by Sex
Evaluable Patients
Indication: Pneumonia

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE (N = 51)		MALE (N = 39)		TOTAL (N = 90)		FEMALE (N = 34)		MALE (N = 49)		TOTAL (N = 83)	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	1	(2.0%)	0		1	(1.1%)	1	(2.9%)	1	(2.0%)	2	(2.4%)
	5	(9.8%)	7	(17.9%)	12	(13.3%)	5	(14.7%)	15	(30.6%)	20	(24.1%)
	23	(45.1%)	21	(53.8%)	44	(48.9%)	15	(44.1%)	19	(38.8%)	34	(41.0%)
	16	(31.4%)	5	(12.8%)	21	(23.3%)	7	(20.6%)	10	(20.4%)	17	(20.5%)
	6	(11.8%)	6	(15.4%)	12	(13.3%)	6	(17.6%)	4	(8.2%)	10	(12.0%)

Age By Sex - Mean, Median, Minimum and Maximum
Evaluable Patients
Indication: Pneumonia

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	51	39	90	34	49	83
MEAN AGE	44.40	42.32	43.50	44.91	38.48	41.11
STD DEV	16.91	19.15	17.84	19.01	19.44	19.41
MEDIAN AGE	40.44	39.11	39.56	43.65	35.25	39.07
MINIMUM AGE						
MAXIMUM AGE						

Origin By Therapy Group
Evaluable Patients
Indication: Pneumonia

	DIRITHROMYCIN N = 90		ERYTHROMYCIN N = 83	
ORIGIN	n	(%)	n	(%)
CAUCASIAN	72	(80.0%)	61	(73.5%)
BLACK	11	(12.2%)	16	(19.3%)
HISPANIC	2	(2.2%)	6	(7.2%)
NATIVE AMERICAN	1	(1.1%)	0	
ASIAN	1	(1.1%)	0	
OTHER	3	(3.3%)	0	

Height and Weight at Admission
Evaluable Patients
Indication: Pneumonia

	HEIGHT IN CM						WEIGHT IN KG					
THERAPY	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	90	0	168.89	10			90	0	70.97	18		
ERYTHROMYCIN	83	0	170.10	10			82	1	73.32	18		

Drug Administration:

All Patients

Exposure to Study Drugs - Mean, Minimum, and Maximum
All Patients
Indication: Pneumonia

	DIRITHROMYCIN N = 260 DAYS	ERYTHROMYCIN N = 257 DAYS
NUMBER OF PATIENTS	248	249
MEAN DURATION EXPOSURE	12.8	12.5
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	12	8

Summary of Exposure to Study Drugs
All Patients
Indication: Pneumonia

DAYS OF THERAPY	DIRITHROMYCIN N = 260 n	(%)	ERYTHROMYCIN N = 257 n	(%)
PATIENTS WITH INCOMPLETE DATA	12	(4.6%)	8	(3.1%)
1	1	(0.4%)	3	(1.2%)
2	9	(3.5%)	8	(3.1%)
3	6	(2.3%)	4	(1.6%)
4	6	(2.3%)	12	(4.7%)
5	4	(1.5%)	6	(2.3%)
6	7	(2.7%)	5	(1.9%)
7	4	(1.5%)	4	(1.6%)
8	2	(0.8%)	1	(0.4%)
9	0		5	(1.9%)
10	17	(6.5%)	18	(7.0%)
11	11	(4.2%)	10	(3.9%)
12	7	(2.7%)	4	(1.6%)
13	7	(2.7%)	3	(1.2%)
14	52	(20.0%)	53	(20.6%)
15	88	(33.9%)	81	(31.5%)
16	19	(7.3%)	21	(8.2%)
17	3	(1.2%)	2	(0.8%)
18	2	(0.8%)	1	(0.4%)
19	1	(0.4%)	3	(1.2%)
20	1	(0.4%)	3	(1.2%)
21	1	(0.4%)	0	
22	0		1	(0.4%)
30	0		1	(0.4%)

Evaluable Patients

Exposure to Study Drugs - Mean, Minimum, and Maximum
Evaluable Patients
Indication: Pneumonia

	DIRITHROMYCIN N = 90 DAYS	ERYTHROMYCIN N = 83 DAYS
NUMBER OF PATIENTS	90	83
MEAN DURATION EXPOSURE	14.3	14.5
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients
Indication: Pneumonia

DAYS OF THERAPY	DIRITHROMYCIN N = 90 n	(%)	ERYTHROMYCIN N = 83 n	(%)
7	1	(1.1%)	0	
10	7	(7.8%)	5	(6.0%)
11	2	(2.2%)	3	(3.6%)
12	2	(2.2%)	2	(2.4%)
13	3	(3.3%)	1	(1.2%)
14	23	(25.6%)	25	(30.1%)
15	40	(44.4%)	30	(36.1%)
16	8	(8.9%)	12	(14.5%)
17	1	(1.1%)	1	(1.2%)
18	1	(1.1%)	1	(1.2%)
19	0		2	(2.4%)
20	1	(1.1%)	1	(1.2%)
21	1	(1.1%)	0	

Medical Officer's Comments;

Note that 70% of the evaluable patients in the dirithromycin group and 66% of the evaluable patients in the erythromycin group were treated for 14-15 days.

Unevaluable Patients

Reason Unevaluable Summary
All Patients
Indication: Pneumonia

REASON UNEVALUABLE	DIRITHROMYCIN N = 260 n	(%)	ERYTHROMYCIN N = 257 n	(%)
ALL UNEVALUABLE PATIENTS	170	(65.4%)	174	(67.7%)
CAUS. ORG. UNIDENT.	116		119	
INSUFFICIENT THERAPY	26		41	
NO FOLLOW-UP X-RAY	27		20	
UNEVAL. BY INVEST.	11		19	
CAUS. ORG. RESISTANT	18		12	
NO POST THER. CULTURE	11		14	
UNACCEPT. PATHOGEN	12		9	
NO PRIOR POS. X-RAY	5		10	
SENSITIVITY NOT DONE	5		6	
PROTOCOL VIOLATED	3		5	
SEQUENTIAL THERAPY	1		5	
CLINICAL DIAG. ONLY	1		5	
TIMING OF X-RAY	1		4	
CONCOMITANT ANTIBIOT.	2		2	
INCOMPLETE DATA	1		3	
BACTERIOL. INCOMPLETE	0		3	
NO FOLLOW-UP CULTURE	1		2	
WRONG DIAGNOSIS	1		1	
CONCOMIT. MEDICATION	1		1	
NO INFEC. DEMONSTRATED	1		1	
NO THERAPY	1		0	
INITIAL CULT. EARLY	0		1	

REASON UNEVALUABLE	DIRITHROMYCIN N = 260 n (%)	ERYTHROMYCIN N = 257 n (%)
NO DURING CULTURE	0	1
DURING CULTURE LATE	1	0
POST THER. CULT. EARLY	1	0
POST THER. CULT. LATE	1	0
UNDERLYING CONDITION	1	0
POOR COMPLIANCE	1	0
ALLERGIC TO STUDY DRUG	1	0
WRONG PRIM. DIAGN.	0	1

Medical Officer's Comments:

Some patients had more than one reason to be unevaluable.

Efficacy Evaluation:

The clinical response for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Clinical Response Summary/Therapy Group
All Evaluable Patients - Posttherapy
Indication: Pneumonia

RESPONSE	DIRITHROMYCIN N = 90 n	(%)	ERYTHROMYCIN N = 83 n	(%)
CURE	50	(55.6%)	56	(67.5%)
IMPROVEMENT	35	(38.9%)	27	(32.5%)
RELAPSE	2	(2.2%)	0	
FAILURE	3	(3.3%)	0	

Medical Officer's Comments:

The overall favorable clinical success rate (cure or improvement) was 94% (85/90) for the dirithromycin group and 100% (83/83) for the erythromycin group.

The clinical response by pathogen for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Clinical Response Summary/Pathogen
All Evaluable Patients - Posttherapy
Indication: Pneumonia
Therapy: Dirithromycin

	CURE		IMPROVEMENT		RELAPSE		FAILURE		TOTAL
PATHOGENS	n	(%)	n	(%)	n	(%)	n	(%)	n
MYCOPLASMA	23	(56.0%)	15	(36.5%)	2	(4.8%)	1	(2.4%)	41
L PNEUMOPHILA	12	(85.7%)	2	(14.2%)	0		0		14
STR PNEUMONIAE	5	(38.4%)	8	(61.5%)	0		0		13
H INFLUENZAE	1	(14.2%)	5	(71.4%)	0		1	(14.2%)	7
ST AUREUS	4	(80.0%)	1	(20.0%)	0		0		5
H PARAINFLUENZAE	4	(100.0%)	0		0		0		4
MULTIPLE ORGANISMS*	1	(100.0%)	0		0		0		1
STREPTOCOCCUS SP	0		1	(50.0%)	0		1	(50.0%)	2
M CATARRHALIS	0		2	(100.0%)	0		0		2
S MARCESCENS	0		1	(100.0%)	0		0		1

* - This patient had more than one pathogen isolated from the sputum specimen. The following table depicts the clinical and bacteriologic response for this patient:

Clinical and Bacteriologic Response for Polymicrobial Infections
Evaluable Dirithromycin-treated Patients
Posttherapy

PATIENT NO.	PATHOGENS	BACTERIOLOGIC RESPONSE	CLINICAL RESPONSE
	H. INFLUENZAE S. PNEUMONIAE	N/A	CURE

Clinical Response Summary/Pathogen
All Evaluable Patients - Posttherapy
Indication: Pneumonia
Therapy: Erythromycin

PATHOGENS	CURE n	CURE (%)	IMPROVEMENT n	IMPROVEMENT (%)	TOTAL n
MYCOPLASMA	20	(62.5%)	12	(37.5%)	32
STR PNEUMONIAE	13	(81.2%)	3	(18.7%)	16
L. PNEUMOPHILA	7	(70.0%)	3	(30.0%)	10
H INFLUENZAE	4	(57.1%)	3	(42.8%)	7
MULTIPLE ORGANISMS*	3	(60.0%)	2	(40.0%)	5
ST AUREUS	2	(66.6%)	1	(33.3%)	3
H PARAINFLUENZAE	3	(75.0%)	1	(25.0%)	4
HAEMOPHILUS SP	1	(100.0%)	0		1
M CATARRHALIS	1	(100.0%)	0		1
STREPTOCOCCUS SP	1	(50.0%)	1	(50.0%)	2
STR GRP G	1	(100.0%)	0		1
STR GRP A	0		1	(100.0%)	1

* - These patients had more than one pathogen isolated from the sputum specimen. The following table depicts the clinical and bacteriologic response for these patients:

Clinical and Bacteriologic Response for Polymicrobial Infections
Evaluable Erythromycin-treated Patients
Posttherapy

PATIENT NO	PATHOGENS	BACTERIOLOGIC RESPONSE	CLINICAL RESPONSE
	H. PARAINFLUENZAE H. PARAHEMOLYTICUS	NA	IMPROVED
	S. AUREUS M. CATARRHALIS	NA	IMPROVED
	S. PNEUMONIAS M. CATARRHALIS	NA	CURE
	H. INFLUENZAE M. CATARRHALIS	NA	CURE
	S. PNEUMONIAE GROUP A STREP	FTE	CURE

NA - Presumed Eradicated
FTE - FAILURE TO ELIMINATE

The clinical response for evaluable patients at late-posttherapy (2-3 weeks) according to the applicant was as follows:

Clinical Response Summary/Therapy Group
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia

RESPONSE	DIRITHROMYCIN N = 78 n	(%)	ERYTHROMYCIN N = 77 n	(%)
CURE	70	(89.7%)	67	(87.0%)
IMPROVEMENT	8	(10.3%)	6	(7.8%)
RELAPSE	0		4	(5.2%)

Medical Officer's Comments:

The overall favorable success rate (cure or improvement) was 100% (78/78) for the dirithromycin group and 95% (73/77) for the erythromycin group.

The clinical response by pathogen for evaluable patients at late-posttherapy (2-3 weeks) according to the applicant was as follows:

Clinical Response Summary/Pathogen
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia
Therapy: Dirithromycin

PATHOGENS	CURE n	CURE (%)	IMPROVEMENT n	IMPROVEMENT (%)	TOTAL n
MYCOPLASMA	32	(88.8%)	4	(11.1%)	36
L. PNEUMOPHILA	14	(100.0%)	0		14
STR PNEUMONIAE	11	(84.6%)	2	(15.3%)	13
H INFLUENZAE	3	(75.0%)	1	(25.0%)	4
ST AUREUS	5	(100.0%)	0		5
H PARAINFLUENZAE	4	(100.0%)	0		4
MULTIPLE ORGANISMS*	1	(100.0%)	0		1
M CATARRHALIS	0		1	(100.0%)	1

* - These patients had more than one pathogen isolated from the sputum specimen. The following table depicts the clinical and bacteriologic response for these patients:

Clinical and Bacteriologic Response for Polymicrobial Infections
Evaluable Dirthromycin-treated Patients
Late-Posttherapy

PATIENT NO.	PATHOGENS	BACTERIOLOGIC RESPONSE	CLINICAL RESPONSE
	H. INFLUENZAE S. PNEUMONIAE	NA	CURE

NA - PRESUMED ERADICATION

Clinical Response Summary/Pathogen
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia
Therapy: Erythromycin

PATHOGENS	CURE n	CURE (%)	IMPROVEMENT n	IMPROVEMENT (%)	RELAPSE n	RELAPSE (%)	TOTAL n
MYCOPLASMA	25	(80.6%)	5	(16.1%)	1	(3.2%)	31
STR PNEUMONIAE	15	(100.0%)	0		0		15
L. PNEUMOPHILA	7	(87.5%)	1	(12.5%)	0		8
H INFLUENZAE	6	(85.7%)	0		1	(14.2%)	7
MULTIPLE ORGANISMS*	5	(83.3%)	0		1	(16.6%)	6
H PARAINFLUENZAE	4	(100.0%)	0		0		4
ST AUREUS	1	(50.0%)	0		1	(50.0%)	2
HAEMOPHILUS SP	1	(100.0%)	0		0		1
STR GRP A	1	(100.0%)	0		0		1
STREPTOCOCCUS SP	1	(100.0%)	0		0		1
STR GRP G	1	(100.0%)	0		0		1

* - These patients had more than one pathogen isolated from the sputum specimen. The following table depicts the clinical and bacteriologic response for these patients:

Clinical and Bacteriologic Response for Polymicrobial Infections
Evaluable Erythromycin-treated Patients
Late-Posttherapy

PATIENT NO.	PATHOGENS	BACTERIOLOGIC RESPONSE	CLINICAL RESPONSE
	H. PARAINFLUENZAE H. PARAHEMOLYTICUS	NA	CURE
	S. AUREUS M. CATARRHALIS	NA	CURE
	S. PNEUMONIAE M. CATARRHALIS	NA	CURE
	H. INFLUENZAE M. CATARRHALIS	NA	RELAPSE
	S. PNEUMONIAE GROUP A STREP	FTE	CURE

NA - Presumed Eradicated
FTE - FAILURE TO ELIMINATE

Bacteriologic Response

The bacteriologic response for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Bacteriological Response Summary/Therapy Group
All Evaluable Patients - Posttherapy
Indication: Pneumonia

RESPONSE	DIRITHROMYCIN N = 33 n	(%)	ERYTHROMYCIN N = 41 n	(%)
PATHOGEN ELIMINATED	8	(24.2%)	2	(4.9%)
PRESUMED ERADICATED	24	(72.7%)	34	(82.9%)
RECURRENCE SAME	0		2	(4.9%)
RECURRENCE NEW	0		1	(2.4%)
FAILED TO ELIMINATE	1	(3.0%)	2	(4.9%)

Medical Officer's Comments:

An overall bacteriologic success rate (eradicated/presumed eradiced) at post-therapy was **97%** (32/33) for the dirithromycin group and **87.8%** (36/41) for the erythromycin group.

The bacteriologic response by pathogen for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Bacteriologic Response Summary/Pathogen
All Evaluable Patients
Indication: Pneumonia
Therapy: Dirithromycin

PATHOGENS	PATHOGEN ELIMINATED n	(%)	PRESUMED ERADICATION n	(%)	FAILED TO ELIMINATE n	(%)	TOTAL n
STR PNEUMONIAE	4	(28.6%)	9	(64.3%)	1	(7.1%)	14
H INFLUENZAE	2	(25.0%)	6	(75.0%)	0		8
S AUREUS	2	(40.0%)	3	(60.0%)	0		5
H PARAINFLUENZAE	0		4	(100.0%)	0		4
STREPTOCOCCUS SP	0		1	(100.0%)	0		1
M CATARRHALIS	0		2	(100.0%)	0		2
S MARCESCENS	0		0		0		1

APPEARS THIS WAY
ON ORIGINAL

Bacteriologic Response Summary/Pathogen
All Evaluable Patients
Indication: Pneumonia
Therapy: Erythromycin

PATHOGENS	PATHOGEN ELIMINATED n	(%)	PRESUMED ERADICATION n	(%)	RECURRENCE SAME n	(%)	RECURRENCE NEW n	(%)	FAILED TO ELIMINATE n	(%)	TOTAL n
STR PNEUMONIAE	1	(5.6%)	14	(77.8%)	1	(5.6%)	1	(5.6%)	1	(5.6%)	18
S AUREUS	1	(25.0%)	2	(50.0%)	1	(25.0%)	0		0		4
H INFLUENZAE	0		7	(87.5%)	0		0		1	(12.5%)	8
H PARAINFLUENZAE	0		5	(100.0%)	0		0		0		5
HAEMOPHILUS SP	0		1	(100.0%)	0		0		0		1
STREPTOCOCCUS SP	0		2	(100.0%)	0		0		0		2
STR GRP A	0		1	(50.0%)	0		0		1	(50.0%)	2
M CATARRHALIS	0		4	(100.0%)	0		0		0		4
STR GRP G	0		1	(100.0%)	0		0		0		1

The bacteriologic response for evaluable patients at late-posttherapy (2-3 weeks) according to the applicant was as follows:

Bacteriologic Respone Summary/Therapy Group
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia

RESPONSE	DIRITHROMYCIN N = 27 n	(%)	ERYTHROMYCIN N = 36 n	(%)
PATHOGEN ELIMINATED	3	(11.2%)	0	
PRESUMED ERADICATION	23	(85.2%)	33	(91.7%)
RECURRENCE NEW	0		1	(2.7%)
FAILED TO ELIMINATE	1	(3.7%)	2	(5.6%)

Medical Officer's Comments:

An overall bacteriologic success rate (eradicated/presumed eradicated) at late post-therapy was **96.3%** (26/27) for the dirithromycin group and **91.7%** (33/36) for the erythromycin group.

The bacteriologic response by pathogen for evaluable patients at late-posttherapy (2-3 weeks) according to the applicant was as follows:

Bacteriologic Respone Summary/Pathogen
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia
Therapy: Dirithromycin

PATHOGENS	PATHOGEN ELIMINATED n	(%)	PRESUMED ERADICATION n	(%)	FAILED TO ELIMINATE n	(%)	TOTAL n
STR PNEUMONIAE	3	(21.4%)	10	(71.4%)	1	(7.1%)	14
H INFLUENZAE	0		5	(100.0%)	0		5
ST AUREUS	0		5	(100.0%)	0		5
H PARAINFLUENZAE	0		3	(100.0%)	0		3
M CATARRHALIS	0		1	(100.0%)	0		1

Bacteriologic Respone Summary/Pathogen
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia
Therapy: Erythromycin

PATHOGENS	PRESUMED ERADICATION n	(%)	FAILED TO ELIMINATE n	(%)	TOTAL n
H INFLUENZAE	7	(87.5%)	1	(12.5%)	8
STR PNEUMONIAE	15	(93.8%)	1	(6.3)	16
H PARAINFLUENZAE	5	(100.0%)	0		5
S AUREUS	2	(100.0%)	0		2
HAEMOPHILUS SP	1	(100.0%)	0		1
STR GRP A	1	(50.0%)	1	(50.0)	2
STREPTOCOCCUS SP	1	(100.0%)	0		1
STR GRP G	1	(100.0%)	0		1

Per the protocol, patients with *Mycoplasma pneumoniae, Legionella pneumophilia,* or *Chlamydia pneumoniae* were diagnosed serologically. The favorable clinical response rates for these pathogens are as follows:

Patients with Favorable Clinical Response Posttherapy

	Mycoplasma		Legionella		Chlamydia[b]	
	n/d[a]	(%)	n/d	(%)	n/d	(%)
Dirithromycin:						
AQAB	38/41	(92.7%)	14/14	(100.0%)	NA	
Erythromycin:						
AQAB	32/32	(100.0%)	10/10	(100.0%)	NA	

[a] n = number of patients with favorable response, d = number of evaluable patients
[b] Serologic testing for *Chlamydia pneumoniae* was not performed in AQAB.

Patients with Favorable Clinical Response Late-Posttherapy

	Mycoplasma		Legionella		Chlamydia[b]	
	n/d[a]	(%)	n/d	(%)	n/d	(%)
Dirithromycin:						
AQAB	36/36	(100.0%)	14/14	(100.0%)	NA	
Erythromycin:						
AQAB	30/31	(96.7%)	8/8	(100.0%)	NA	

[a] n = number of patients with favorable response, d = number of evaluable patients
[b] Serologic testing for *Chlamydia pneumoniae* was not performed in AQAB.

X-Ray Summary for AQAB Evaluable Patients

CATEGORY		THERAPY GROUP DIRITHROMYCIN N	ERYTHROMYCIN N
PRETHERAPY	INFILTRATE PRESENT	90	83
DURING THERAPY	IMPROVED	6	6
	RESOLVED	6	3
	UNCHANGED	2	2
	WORSENED	1	1
POSTTHERAPY	IMPROVED	24	22
	RESOLVED	51	53
	UNCHANGED	3	2
	WORSENED	2	
LATE-POSTTHERAPY	IMPROVED	8	4
	RESOLVED	21	23
	UNCHANGED		1

SUSCEPTIBILITY RESULTS

Susceptibility Ranges for Pathogen
According to Zone Size Criteria
Therapy Group: Dirithromycin
Indication: Pneumonia

	ANTIMIBCROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
PATHOGEN	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
B CATARRHALIS	3		2	5	4		1	5
CITROBACTER SP			1	1			1	1
E AEROGENES			1	1			1	1
E COLI	1			1	1			1
H INFLUENZAE	7	1	8	16	10	4	2	16
H PARAINFLUENZAE	4	1	2	7	5	2		7
HAEMOPHILUS SP	3		1	4	3	1		4
K PNEUMONIAE			3	3			3	3
PS AERUGINOSA			1	1			1	1
S MARCESCENS			1	1			1	1
ST AUREUS	6			6	6			6
STAPH COAG-NEG	1			1	1			1
STAPH COAG-POS	1			1	1			1
STR GRP A	1			1	1			1
STR GRP B	2			2	1	1		2
STR PNEUMONIAE	18		2	20	19	1		20
STR VIRIDANS	1		1	2	2			2
STREPTOCOCCUS SP	3			3	3			3

Medical Officer's Comments: 50% (8/16) of *H. influenzae* were resistent to dirithromycin.

Susceptibility Ranges for Pathogen
According to Zone Size Criteria
Therapy Group: Erythromycin
Indication: Pneumonia

	ANTIMIBCROBIAL						
	DIRITHROMYCIN			ERYTHROMYCIN			
PATHOGEN	SUSCEPTIBLE (ZONE>=17) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
B CATARRHALIS	4	1	5	5			5
BACILLUS CEREUS	1		1	1			1
E CLOACAE	1	2	3			3	3
H INFLUENZAE	8	13	21	14	6	1	21
H PARAHEMOLYTICUS	1		1	1			1
H PARAINFLUENZAE	5	1	6	5	1		6
HAEMOPHILUS SP	1		1	1			1
K PNEUMONIAE		1	1			1	1
N SICCA		1	1		1		1
PS AERUGINOSA		2	2			2	2
PSEUDOMONAS SP		1	1			1	1
ST AUREUS	4		4	4			4
STAPH COAG-NEG		1	1	1			1
STAPH COAG-POS	1		1	1			1
STR GRP A	1		1	1			1
STR GRP B	1		1	1			1
STR GRP G	1		1	1			1
STR PNEUMONIAE	26	2	28	28			28
STREPTOCOCCUS SP	4		4	4			4

Medical Officer's comments: 62% (13/21) of the *H. influenzae* were resistent to dirithromycin.

CONCOMITANT MEDICATIONS:

Prior to study entry, 56.2% of dirithromycin-treated patients and 54.9% of erythromycin-treated patients were receiving some form of drug therapy. Paracetamol was the most frequently used drug. Concomitant drug use was comparable between the two treatment groups.

A concomitant agent was prescribed during therapy in 51.2% of dirithromycin-treated patients and 52.5% of erythromycin-treated patients. Paracetamol was most frequently used.

After completion of study-drug therapy, 22.3% of dirithromycin-treated patients and 20.2% of erythromycin-treated patients reported taking medication. Again, paracetamol was most frequently used.

Seventeen patients had concomitant antibiotics listed in the database. All but 5 of these patients were not qualified for efficacy analysis. Of the 12 patients who did not qualify for efficacy analysis, 3 discontinued the study because of protocol violations (Patients 5 patients discontinued because of entry exclusions (Patients 3 because of adverse events (Patients and 1 patient was protocol complete but unevaluable because of negative baseline culture. The 5 patients who qualified for efficacy analysis all started their concomitant antibiotics after completing the protocol requirements. One of the 3 was a clinical failure and was placed on erythromycin therapy after discontinuing the study.

SAFETY RESULTS:

Summary of Adverse Event By Body System Table

Frequency of Treatment Emergent Events
All Patients - All Adverse Events
Body System: Body as a Whole
Indication: Pneumonia

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 260 n	(%)	ERYTHROMYCIN N = 257 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	72	(27.7%)	63	(24.5%)	0.411
PATIENTS WITH NO EVENT	188	(72.3%)	194	(75.5%)	0.411
ABDOMINAL PAIN	32	(12.3%)	15	(5.8%)	0.01
HEADACHE	17	(6.5%)	17	(6.6%)	0.972
ASTHENIA	9	(3.5%)	7	(2.7%)	0.628
CHEST PAIN	7	(2.7%)	7	(2.7%)	0.982
BACK PAIN	6	(2.3%)	5	(1.9%)	0.775
PAIN	6	(2.3%)	6	(2.3%)	0.984
INJURY, ACCIDENT	4	(1.5%)	4	(1.6%)	0.987
CHILLS	3	(1.2%)	1	(0.4%)	0.321
SURGICAL PROCEDURE	3	(1.2%)	3	(1.2%)	0.989
NEOPLASM	2	(0.8%)	0		0.159
ABSCESS	1	(0.4%)	0		0.32
FEVER	1	(0.4%)	2	(0.8%)	0.556
FLU SYNDROME	1	(0.4%)	1	(0.4%)	0.993
INFECTION	1	(0.4%)	2	(0.8%)	0.556
MALAISE	1	(0.4%)	2	(0.8%)	0.556
NECK PAIN	1	(0.4%)	1	(0.4%)	0.993
CYST	0		1	(0.4%)	0.314
FACE EDEMA	0		1	(0.4%)	0.314
MONILIASIS	0		1	(0.4%)	0.314
PELVIC PAIN	0		1	(0.4%)	0.314

Frequency of Treatment Emergent Events
All Patients - All Adverse Events
Body System: Digestive System
Indication: Pneumonia

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 260 n	(%)	ERYTHROMYCIN N = 257 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	58	(22.3%)	53	(20.6%)	0.641
PATIENTS WITH NO EVENT	202	(77.7%)	204	(79.4%)	0.641
DIARRHEA	21	(8.1%)	20	(7.8%)	0.901
NAUSEA	20	(7.7%)	19	(7.4%)	0.897
CONSTIPATION	5	(1.9%)	1	(0.4%)	0.103
VOMITING	5	(1.9%)	6	(2.3%)	0.746
DYSPEPSIA	4	(1.5%)	4	(1.6%)	0.987
FLATULENCE	4	(1.5%)	4	(1.6%)	0.987
NAUSEA AND VOMITING	4	(1.5%)	1	(0.4%)	0.182
GASTROINTESTINAL DISORDER	3	(1.2%)	1	(0.4%)	0.321
ANOREXIA	2	(0.8%)	5	(1.9%)	0.247
RECTAL DISORDER	2	(0.8%)	0		0.159
STOMATITIS	2	(0.8%)	1	(0.4%)	0.569
DRY MOUTH	1	(0.4%)	0		0.32
GINGIVITIS	1	(0.4%)	0		0.32
LIVER DAMAGE	1	(0.4%)	0		0.32
PSEUDOMEMBRANOUS COLITIS	1	(0.4%)	0		0.32
SALIVARY GLAND ENLARGEMENT	1	(0.4%)	0		0.32
THIRST	1	(0.4%)	0		0.32
TONGUE DISORDER	1	(0.4%)	0		0.32
DYSPHAGIA	0		1	(0.4%)	0.314
GASTRITIS	0		1	(0.4%)	0.314
GLOSSITIS	0		1	(0.4%)	0.314
TONGUE EDEMA	0		1	(0.4%)	0.314
TOOTH DISORDER	0		1	(0.4%)	0.314

Frequency of Treatment Emergent Events
All Patients - All Adverse Events
Body System: Nervous System
Indication: Pneumonia

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 260 n	(%)	ERYTHROMYCIN N = 257 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	15	(5.8%)	15	(5.8%)	0.974
PATIENTS WITH NO EVENT	245	(94.2%)	242	(94.2%)	0.974
DIZZINESS	4	(1.5%)	6	(2.3%)	0.511
INSOMNIA	4	(1.5%)	3	(1.2%)	0.715
ANXIETY	3	(1.2%)	0		0.084
SOMNOLENCE	2	(0.8%)	0		0.159
TREMOR	2	(0.8%)	2	(0.8%)	0.991
ABNORMAL DREAMS	1	(0.4%)	0		0.32
DEPRESSION	1	(0.4%)	1	(0.4%)	0.993
PARESTHESIA	1	(0.4%)	1	(0.4%)	0.993
PERIPHERAL NEURITIS	1	(0.4%)	0		0.32
VERTIGO	1	(0.4%)	0		0.32
AGITATION	0		1	(0.4%)	0.314
CONFUSION	0		1	(0.4%)	0.314
NERVOUSNESS	0		1	(0.4%)	0.314
SPEECH DISORDER	0		1	(0.4%)	0.314

Frequency of Treatment Emergent Events
All Patients - All Adverse Events
Body System: Respiratory System
Indication: Pneumonia

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 260 n	(%)	ERYTHROMYCIN N = 257 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	64	(24.6%)	65	(25.3%)	0.859
PATIENTS WITH NO EVENT	196	(75.4%)	192	(74.7%)	0.859
LUNG DISORDER	17	(6.5%)	16	(6.2%)	0.884
PHARYNGITIS	12	(4.6%)	9	(3.5%)	0.521
DYSPNEA	8	(3.1%)	10	(3.9%)	0.614
RHINITIS	7	(2.7%)	14	(5.4%)	0.113
ASTHMA	5	(1.9%)	11	(4.3%)	0.122
SINUSITIS	5	(1.9%)	10	(3.9%)	0.183
SPUTUM INCREASED	4	(1.5%)	8	(3.1%)	0.235
HYPERVENTILATION	3	(1.2%)	2	(0.8%)	0.663
PLEURAL EFFUSION	3	(1.2%)	0		0.084
COUGH INCREASED	2	(0.8%)	2	(0.8%)	0.991
HEMOPTYSIS	2	(0.8%)	2	(0.8%)	0.991
PNEUMONIA	2	(0.8%)	1	(0.4%)	0.569
RESPIRATORY DISORDER	2	(0.8%)	1	(0.4%)	0.569
BRONCHITIS	1	(0.4%)	3	(1.2%)	0.31
CARCINOMA OF LUNG	1	(0.4%)	4	(1.6%)	0.173
PLEURAL DISORDER	1	(0.4%)	0		0.32
LARYNGITIS	0		1	(0.4%)	0.314
PULMONARY TUBERCULOSIS AGGRAVATED	0		1	(0.4%)	0.314
STRIDOR	0		1	(0.4%)	0.314

Frequency of Treatment Emergent Events
All Patients - All Adverse Events
Body System: Respiratory System
Indication: Pneumonia

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 260 n	(%)	ERYTHROMYCIN N = 257 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	13	(5.0%)	14	(5.4%)	0.819
PATIENTS WITH NO EVENT	247	(95.0%)	243	(94.6%)	0.819
RASH	4	(1.5%)	8	(3.1%)	0.235
SWEATING	3	(1.2%)	2	(0.8%)	0.663
MACULOPAPULAR RASH	2	(0.8%)	1	(0.4%)	0.569
PRURITUS	2	(0.8%)	0		0.159
HERPES SIMPLEX	1	(0.4%)	1	(0.4%)	0.993
HERPES ZOSTER	1	(0.4%)	0		0.32
URTICARIA	1	(0.4%)	0		0.32
ACNE	0		1	(0.4%)	0.314
SUBCUTANEOUS NODULE	0		1	(0.4%)	0.314

Patients Who Died or Discontinued Therapy Due to Adverse Events:

Although no deaths were reported during the course of this study, 6 patients were reported to have died after discontinuation from the study. These patients are listed in the table below.

Summary of Patient Deaths

Age (yrs)	Protocol Number	Patient Number	Diagnosis	Days of Rx	Chronic Illnesses	Cause of Death	Relative Day[a]
Dirithromycin-Treated Patients							
62	AQAB		Pneumonia	1	CHF,COPD,HTN	CHF, ASHD	45
65	AQAB		Pneumonia	7	SLE, HPOTHY	SLE	28
78	AQAB		Pneumonia	9	CAD,HTN,ARTH	Carcinoma	35
Comparator-Treated Patients							
46	AQAB		Pneumonia	7	Depression	Lung Carcinoma	46
62	AQAB		Pneumonia	5	Bronchitis	Respiratory Failure	52
61	AQAB		Pneumonia	1	DM,CAD	Death, cause unknown	52

[a]Day of death, relative to date of study-drug therapy completion. Last day of study-drug therapy = relative day 0.

There were 23 events reported during the course of this study that qualified as serious for regulatory reporting purposes. Nine of these patients were discussed in the serious adverse event summaries and will not be discussed here. Their patient numbers are:

Fourteen dirithromycin-treated patients and 14 erythromycin-treated patients discontinued early due to adverse events. Seven of the 14 dirithromycin-treated patients and 5 of the 14 erythromycin-treated patients experienced adverse events related to the gastrointestinal system.

THERAPY: DIRITHROMYCIN

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT
004		1	65	FEMALE	NATIVE AMERICAN	7	INCREASED DYSPNEA
016		1	33	MALE	CAUCASIAN	2	ABDOMINAL CRAMPS
028		1	34	MALE	CAUCASIAN	7	NAUSEA
032		1	30	MALE	BLACK	14	EMPYEMA
041		1	57	FEMALE	CAUCASIAN	10	EXACERBATION OF COPD
047		1	39	MALE	CAUCASIAN	2	SKIN ERUPTION
101		1	62	FEMALE	CAUCASIAN	1	PNEUMONIA WORSENED
116		1	28	FEMALE	CAUCASIAN	2	NAUSEA
116		1	32	MALE	CAUCASIAN	3	NAUSEA
122		2	28	FEMALE	CAUCASIAN	12	NAUSEA AND VOMITTING
150		1	79	FEMALE	CAUCASIAN	4	DIARRHEA
175		1	37	MALE	CAUCASIAN	2	VOMITING
176		1	63	MALE	HISPANIC	2	NAUSEA AND VOMITING
202		1	40	MALE	BLACK	15	EXTENSION OF PNEUMONIA & ABSCESS DEVELOPMENT

THERAPY: ERYTHROMYCIN

011		2	28	FEMALE	CAUCASIAN	14	PHARYNGITIS
063		1	64	FEMALE	CAUCASIAN	4	SUPRAPUBIC RASH
073		1	36	FEMALE	HISPANIC	2	DIARRHEA
073		1	62	FEMALE	HISPANIC	4	EPIGASTRIC DISTRESS
086		1	21	FEMALE	CAUCASIAN	3	NAUSEA AND VOMITING
086		1	22	MALE	CAUCASIAN	16	SPUTUM, YELLOW
090		1	38	FEMALE	CAUCASIAN	6	RASH
092		1	35	FEMALE	CAUCASIAN	15	COLD SYMPTOMS
101		1	55	FEMALE	BLACK	4	NAUSEA
118		1	59	FEMALE	CAUCASIAN	10	HOMOGENEOUS MASS LEFT LUNG
120		1	25	MALE	CAUCASIAN	7	INSPIRATORY WHEEZING
120		1	71	MALE	CAUCASIAN	6	BLADDER CARCINOMA
128		1	60	FEMALE	CAUCASIAN	2	INCREASED ABDOMINAL PAIN
131		1	54	MALE	CAUCASIAN	4	EXACERBATION OF PNEUMONIA

CLINICAL LABORATORY EVALUATIONS:

None of the changes were of a magnitude that would approach clinical significance.

Distribution of Extreme Laboratory Values

(For Normal Laboratory Values, see page 5A of the MOR)

ANALYTE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Platelet Count					
		D	692.000		867.000
		D	333.000		502.000
		D	514.000		658.000
		D	547.000		754.000
		D	359.000		470.000
		D	370.000		494.000
		D	243.000		464.000
		D	219.000		483.000
		D	356.000		567.000
		D	280.000		509.000
		D	368.000		613.000
		D	239.000		440.000
		D	382.000		561.000
		D	356.000		491.000
		D	376.000		604.000
		D	98.000		466.000
		D	378.000		481.000
		D	384.000		890.000
		D	204.000		481.000
		D	204.000		510.000
		D	308.000		802.000
		D	253.000		501.000
		D	415.000		520.000
		D	269.000		467.000
		D	246.000		437.000
		E	404.000		549.000
		E	314.000	447.000	573.000
		E	297.000		488.000
		E	359.000		607.000
		E	366.000		563.000
		E	299.000		497.000
		E	188.000	336.000	499.000
		E	371.000		664.000
		E	276.000		888.000

Platelet Count (cont)	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
		E	270.000		539.000
		E	420.000		556.000
		E	272.000		439.000
		E	655.000		762.000
		E	476.000		595.000
		E	311.000		473.000
		E	416.000		584.000
		E	371.000	481.000	
		E	464.000		946.000
		E	249.000	504.000	
		E	342.000		447.000
		E	392.000		488.000
		E	276.000		467.000
		E	521.000		928.000
		E	304.000		490.000
		E	273.000		546.000
		E	197.000		680.000
		E	254.000		409.000
		E	244.000		525.000
Gamma-Glutamyl Transpep-tidase					
		D	122.000		323.000
		D	93.000		121.000
		D	162.000		283.000
		D	150.000		179.000
ALANINE AMINOTRANSFERASE					
		D	43.000		101.000
		D	61.000		167.000
		D	146.000		210.000
		E	98.000		135.000
ASPARTATE AMINOTRANSFERASE					
		D	61.000		167.000
		D	146.000		210.000
		e	98.000		135.000

ALKALINE PHOSPHOTASE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
		D	107.000		176.000
		D	53.000		176.000
		D	122.000		172.000
BILIRUBIN					
		E	40.700		83.000
HEMATOCRIT					
		D	0.410		0.330
HEMOGLOBIN					
		E	8.760		6.770
		E	8.570		7.270
		E	8.760	8.010	6.460
		E	7.820		6.460
ESINOPHIL COUNT					
		D	0.288		1.715
		E	0.510		1.190
		E	(NO PRE)	0.620	1.610
		E	0.000		1.104
LEUKOCYTE COUNT					
		D	7.650		3.310
URIC ACID					
		D	434.000		595.000
		E	399.000	636.000	595.000
		E	345.000		660.000
		E	150.000		0.250
UREA NITROGEN					
		D	21.100		25.700
CALCIUM					
		D	3.700		4.600
PHOSPHORUS					
		D	0.970		1.260
		E	1.000		2.160

GLUCOSE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
		D	9.200		13.100
		E	6.400	1.600	NO POST
CREATINE PHOSPHOKINASE					
		D	310.000		798.000
		D	281.000		1437.000
		E	119.000		800.000
		E	74.000		2890.000
		E	83.000		3380.000
LEUKOCYTES		D	4.99		18.25
		E	8.72	13.07	
BANDS		D	0		1.03
		D	0.600		1.460
		D	0		1.100
NEUTROPHILS		D	7.46		10.78
		D	2.28		11.32
		E	7.23	10.82	
LYMPHOCYTES		D	1.89		5.39
		E	4.94	7.27	
		E	0.96		5.98
MONOCYTES		D	0.56		1.27
		D	0.44		1.28
		E	0.48		1.16
AST		E	23.0		84.0
ALT		D	79.0		121.0
PHOSPHORUS		D	1.100		1.680

Medical Officer's Overall Comments:

Efficacy:

Both dirithromycin and erythromycin were effective in the treatment of pneumonia caused by the target pathogens.

The Clinical Cure or improvement rate at post-therapy was **94%** (85/90) for the dirithromycin group and **100%** (83/83) for the erythromycin group. The Clinical Cure or improvement rate at late post-therapy was **100%** (78/78) for the dirithromycin group and **95%** (73/77) for the erythromycin group.

The Bacteriologic Cure or improvement rate at post-therapy was **97%** (32/33) for the dirithromycin group and **87.8%** (36/41) for the erythromycin group. The Bacteriologic Cure or improvement rate at late post-therapy was **96.3%** (26/27) for the dirithromycin group and **91.7%** (33/36) for the erythromycin group.

The Bacteriologic Cure or improvement by pathogen for evaluable patients at post-therapy was 8/8 (100%) for *H. influenzae* , 92.8% (13/14) for *S. pneumoniae*, 100% (2/2) for *M. catarrhalis* and 100% (4/4) for *H. parainfluenzae* in the dirithromycin group and 7/8 (87.5%) for *H. influenzae*, 15/18 (83.3%) for *S. pneumoniae*, and 4/4 (100%) for *M. catarrhalis* for the erythromycin group.

The Bacteriologic Cure or improvement by pathogen for evaluable patients at late post-therapy was 5/5 (100%) for *H. influenzae* , 92.8% (13/14) for *S. pneumoniae*, 100% (1/1) for *M. catarrhalis* and 100% (3/3) for *H. parainfluenzae* in the dirithromycin group and 7/8 (87.5%) for *H. influenzae*, 15/16 (93.8%) for *S. pneumoniae*, and 5/5 (100%) for *H. parainfluenzae* for the erythromycin group.

In patients who were diagnosed only by serology for the atypical microorganisms, the clinical outcome at post-therapy was 38/41 (92.7%) for *M. pneumoniae*, and 14/14 (100%) for *L. pneumophila* in the dirithromycin group, and 32/32 (100%) for *M. pneumoniae* and 10/10 (100%) for *L. pneumophila* in the erythromycin group.

The clinical outcome at late post-therapy was 36/36 (100%) for *M. pneumoniae*, and 14/14 (100%) for *L. pneumophila* in the dirithromycin group, and 30/31 (96.7%) for *M. pneumoniae* and 8/8 (100%) for *L. pneumophila* in the erythromycin group.

Medical Officer's Conclusions:

The clinical and bacteriologic cure or improvement rate at post therapy and late post-therapy for both the study drugs appears to be the same, but the eradication rate/presumed eradication rate for *H. influenzae* appears to be better for the dirithromycin group in comparison to the erythromycin group. Fifty-seven percent (21/37) of the *H. influenzae* isolates were resistent to dirithromycin.

REVIEW OF PIVOTAL STUDIES:

II. Study B9Z-EW-E003 Synopsis:

Title:	Dirithromycin versus Erythromycin Base in Bacterial Pneumonia.
Study Centers:	There were 76 active study centers.
Dates of Study:	October 25, 1988 - November 12, 1991
Clinical Phase:	Phase 2-3
Objectives:	To compare dirithromycin with erythromycin base for effectiveness and safety in the treatment of bacterial pneumonia.
Methodology:	Double-blind, double-dummy, randomized, parallel study.
Number of Patients:	Dirithromycin: Male 190, Female 105, Total 295. Erythromycin: Male 177, Female 119, Total 296.
Diagnosis and Inclusion Criteria:	Pneumonia with confirmed susceptible bacterial etiology or appropriate serology for mycoplasma, legionella or chlamydia.
Dosage and Administration:	<u>Test Product</u> Dirithromycin: 500 mg/day (two 250-mg tablets q.d.) CT9198, CT9549, CT0009, CT00047, CT00564: dirithromycin tablets, 250 mg CT9199; CT9550, CT0010, CT00042, CT00565: placebo tablets NOTE: Placebo was used to maintain blinding. <u>Reference Therapy</u> Erythromycin Base: 1000 mg/day (one 250-mg tablet q.i.d.) CT9200, CT9220, CT00040, CT00566: erythromycin base tablets, 250 mg CT9201, CT00041 CT00567: placebo tablets NOTE: Placebo was used to maintain blinding.

Duration of Treatment:	Dirithromycin: 10-14 days Erythromycin Base: 10-14 days
Criteria for Evaluation:	Efficacy--A complete efficacy evaluation was to be performed on patients completing at least 10 days of therapy who had positive chest x-ray and sputum culture or serology, returned for the during-therapy, posttherapy and the late-posttherapy clinical evaluation (late-posttherapy was required if chest x-ray had not resolved at posttherapy evaluation), and for whom the symptomatic response could be evaluated. Safety--All patients were evaluated for safety.
Statistical Methods:	Chi-square tests were used for response rates and adverse events. Appropriate continuous data procedures were used for analysis of laboratory data. The Type I error was set at 0.05.

Study Design:

The North American study, AQAB, and the European study, E003, were both randomized, parallel studies comparing dirithromycin given orally 500 mg daily with erythromycin in the treatment of bacterial pneumonia. Study AQAB was double-blind, involved 93 U.S. centers, and was conducted between October, 1988 and May, 1991. Study E003 was double-blind, involved 76 centers worldwide, and was conducted from October, 1988, to November, 1991. AQAB studied 517 patients and E003 studied 591 patients. Both studies were performed in very similar fashions. The protocol differences are shown in the table below. The principal difference between the studies was the inclusion of *Chlamydia pneumoniae* as an accepted pathogen in the E003 study.

Comparison of Protocols
Studies: B9Z-MC-AQAB and B9Z-EW-E003
Indication: Pneumonia

Parameter	B9Z-MC-AQAB	B9Z-EW-E003
Comparator	Erythromycin base 250 mg QID	Erythromycin base 250 mg QID
Blinding	Double	Double
Inclusion criterion for weight	≥37 kg	None
Inclusion criterion for age	>12 years	≥16 years, ≤75 years
Exclusion criterion for creatinine	≥133 µmol/L	≥170 µmol/L
Exclusion criterion for hypersensitivity	Hypersensitivity to macrolides not allowed	Hypersensitivity to macrolides not allowed
Acceptable duration of therapy	10-14 days	10-14 days
Bacteriologic assessment	Positive culture within 24 hours pretherapy or positive serologic criteria	Positive culture within 24 hours pretherapy or positive serologic criteria
Diagnoses	Bronchopneumonia, Lobar pneumonia, Mycoplasma pneumonia, Legionella pneumonia	Bronchopneumonia, Lobar pneumonia, Mycoplasma pneumonia, Chlamydia pneumonia, Legionella pneumonia
Radiologic assessment	Positive for infiltrate pretherapy	Positive for infiltrate pretherapy
Concomitant therapy	Systemic antibiotics not allowed	Systemic antibiotics, ergotamine not allowed

Both studies used similar evaluation criteria for clinical and bacteriologic response and similar statistical methodology. Both studies included patient groups that were similar with regard to age, height, weight, gender distribution, and origin. For purposes of examining the overall efficacy of dirithromycin in treating bacterial pneumonia, it is reasonable to pool the data obtained for dirithromycin and for erythromycin in these two studies.

Investigators:

Study Population
All Patients Consented and/or Randomized
Indication: Pneumonia

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
J. K. AGARWALA/LANCASHIRE, ENGLAND	4	5	2	3
R. B. BAGDIJIAN R B/LANCASHIRE, ENGLAND	2	2	1	1
J. QUALTROUGH/BLACKPOOLL, ENGLAND	1	2	0	0
A. G. WADE/CLYDEBANK, SCOTLAND	2	0	0	0
S. P. WADERA/SUFFOLK, ENGLAND	0	1	0	0
P. MAKSIMEZYK/SOMERSET, U.K.	2	1	2	0
N. PINHERIO/LANCASHIRE, ENGLAND	6	6	5	4
J. NANKANI/WREXHAM, U.K.	4	2	3	0
K. H. MAYER/WELS, AUSTRIA	3	2	2	0
W. GRAF/HOLENACKERSTR, SWITZERLAND	5	6	2	1
S. WEISS/BERN, SWITZERLAND	8	10	1	1
J. P. ZELLWEGER/FRIBOURG, SWITZERLAND	1	3	0	0
A. STALDER/BERN, SWITZERLAND	3	2	3	1
G. SIDOROFF/NATTERS, AUSTRIA	5	3	3	1
K. HESS/HANOVER, GERMANY	2	3	0	0
I. THOMULLER/GRAZ, AUSTRIA	5	9	1	3
A. PRUDHOMME/TARBES CEDEX, FRANCE	5	4	2	1
VIVES/GAUDENS CEDEX, FRANCE	6	6	1	1
TAYTARD/PESSAC, FRANCE	2	1	0	0
MACQUET/TOURCOING, FRANCE	4	5	0	2
M. A. FISCHER/MONTAUBAN, FRANCE	2	2	1	2
MOTTIER/BREST CEDEX, FRANCE	1	3	0	2
H. J. GELLERMANN/BREMERHAVEN, GERMANY	6	6	3	3
J. HIRSCH/KAUFBEUREN-NEUGABLONZ, GERMANY	1	0	0	0
E. WINDRICH/BALINGEN, GERMANY	0	1	0	0
O. J. BRUECKNER/MUNCHEN, GERMANY	1	1	0	0
O. MUELLER/LAMBRECHT, GERMANY	15	14	6	6
J. M. BUNDY/YUKON, OK, U.S.A.	1	1	0	0
H. COLLINS/EDISON, NJ, U.S.A.	0	1	0	1
F. J. GUERRA/EL PASO, TX, U.S.A.	4	2	3	1
E. H. GUTHRIE/SALT LAKE CITY, UT, U.S.A.	25	26	10	18
C. M. HETSKO/MADISON, WI, U.S.A.	1	1	0	0
K. D. JACOBSON/EUGENE, OR, U.S.A.	2	1	2	1
D. C. MCCLUSKEY/MOGADORE, OH, U.S.A.	1	1	0	0
A. D. PUOPOLO/MILFORD, MA, U.S.A.	2	4	1	2
D. SIMONS-MORTON/HOUSTON, TX, U.S.A.	1	2	1	1
R. R. STOLTZ/EVANSVILLE, IN, U.S.A.	2	1	1	1
G. WEISMAN/WARMINSTER, PA, U.S.A.	1	2	0	0
D. E. PEREZ-TRALLERO/SAN SABASTIN, SPAIN	1	2	0	0

(continued)

Study Population (continued)
All Patients Consented and/or Randomized
Indication: Pneumonia

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
E. TALA/PREITILA, FINLAND	22	22	8	9
P. SAARELAINEN/HELSINKI, FINLAND	7	8	4	4
S. ELLE/ELVERUM, NORWAY	0	2	0	0
L. HENRIKSEN/HALDEN, NORWAY	1	1	0	0
O. STARHEIM/ARENDAL, NORWAY	2	1	0	0
O. F. LEHN/HALDEN, NORWAY	9	7	0	1
E. G. ROGAN/DUBLIN, IRELAND	1	1	1	0
P. LAPPIN/CO. MEATH, IRELAND	3	1	0	0
K. K. GARG/LANCASHIRE, ENGLAND	3	5	1	3
J. J. HAMILL/LEICESTER, ENGLAND	1	1	0	1
J. ZACHARIAH/BUCKS, ENGLAND	4	5	4	2
M. KANSAGRA/MILTON KEYNES, U.K.	6	6	4	5
LONERGAN/CO. KILKENNY, IRELAND	3	2	0	1
G. C. HALDAR/MILTON KEYNES, U.K.	1	0	1	0
J. HOSIE/GLASGOW, SCOTLAND	6	5	4	2
S. P. WADERA/SUFFOLK, ENGLAND	1	0	1	0
D. COTTER/CO CORK, IRELAND	0	1	0	0
KIERNAN S/CO. MEATH, IRELAND	1	0	1	0
M. F. RYAN/BALLINCOLLIG, IRELAND	3	0	2	0
F. BRADBURY/KILKENNY, IRELAND	2	4	1	3
P. MCGARRY/LONGFORD, IRELAND	4	6	1	1
J. E. MOLLOY/LIMERICK, IRELAND	2	3	1	2
R. AVILA/LISBON, PORTUGAL	16	16	9	7
D. J. WEICH/BLOEMFONTEIN, SOUTH AFRICA	8	5	5	1
C. D. MORRIS/EAST LONDON, SOUTH AFRICA	3	3	3	3
E. L. MURRAY/EAST LONDON, SOUTH AFRICA	1	2	0	0
T. D. WILTON/GERMISTON, SOUTH AFRICA	2	2	0	0
A. R. VAN DER WATT/BENONI, SOUTH AFRICA	1	0	0	0
R. SPAMMER/PAROW, SOUTH AFRICA	1	2	1	0
G. PROMINITZ/ANSFERE, SOUTH AFRICA	4	3	1	1
T. UYS/LIBANON, SOUTH AFRICA	9	9	0	0
J. C. KALLMEYER/NATAL, SOUTH AFRICA	3	3	0	0
W. L. SIELING/TYGERBERG, SOUTH AFRICA	2	1	2	0
U. G. LALLOO/NATAL, SOUTH AFRICA	6	5	3	2
M. V. VAN VUOREN/BLOEMFONTEIN, SOUTH AFRICA	6	4	5	4
BRUDERMAN I/TEL AVIV, ISRAEL	6	8	2	3
M. TOPILSKY/RAMAT AVIV, ISRAEL	8	8	6	6
TOTAL	295	296	127	118

Medical Officer's Comments: The Medical Officer concurs with the sponsor's evaluability. Only one investigator (Guthrie) had at least 10 evaluable patients in each treatment group.

Sponsor's Analysis:

Patient disposition was as follows:

	DIRITH	ERYTH	TOTAL
Patient Enrolled	295	296	591
Evaluable for Efficacy	127	118	245
Completed Therapy	122	112	234
Prematurely Discontinued	5	6	11
Not Evaluable	168	178	346
Completed Therapy	1	0	1
Prematurely Discontinued	167	178	345

Medical Officer's Comments:

The Medical Officer concurs with the sponsor's analysis.

Patient Demographics:

The patient demographics for all patients entered in the study and the evaluable patients are summarized in the tables below:

All Patients

Age by Sex - Ranges
All Patients
Indication: Pneumonia

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE N = 105		MALE N = 190		TOTAL N = 295		FEMALE N = 119		MALE N = 177		TOTAL N = 296	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	0		0		0		1	(0.8%)	0		1	(0.3%)
	13	(12.4%)	20	(10.5%)	33	(11.2%)	15	(12.6%)	18	(10.2%)	33	(11.1%)
	44	(41.9%)	70	(36.8%)	114	(38.6%)	37	(31.1%)	72	(40.7%)	109	(36.8%)
	37	(35.2%)	78	(41.1%)	115	(39.0%)	51	(42.9%)	64	(36.2%)	115	(38.9%)
	11	(10.5%)	22	(11.6%)	33	(11.2%)	15	(12.6%)	23	(13.0%)	38	(12.8%)

Age by Sex - Mean, Median, Minimum and Maximum
All Patients
Indication: Pneumonia

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	105	190	295	119	177	296
MEAN AGE	43.92	45.88	45.19	45.61	46.27	46.00
STD DEV	15.78	15.99	15.92	16.38	16.09	16.18
MEDIAN AGE	43.00	46.50	45.00	48.00	44.00	46.00
MINIMUM AGE						
MAXIMUM AGE						

Origin by Therapy Group
All Patients
Indication: Pneumonia

	DIRITHROMYCIN N = 295		ERYTHROMYCIN N = 296		TOTAL N = 591	
ORIGIN	n	(%)	n	(%)	n	(%)
CAUCASIAN	252	(85.4%)	256	(86.5%)	508	(86.0%)
BLACK	32	(10.8%)	31	(10.5%)	63	(10.7%)
ASIAN	1	(0.3%)	3	(1.0%)	4	(0.7%)
OTHER	10	(3.4%)	6	(2.0%)	16	(2.7%)

Height and Weight at Admission
All Patients
Indication: Pneumonia

	HEIGHT IN CM						WEIGHT IN KG					
THERAPY	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	295	0	168.87	9			295	0	68.94	15		
ERYTHROMYCIN	296	0	168.99	9			295	1	69.13	15		

EVALUABLE PATIENTS:

Age By Sex - Ranges
Evaluable Patients
Indication: Pneumonia

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE (N = 44)		MALE (N = 83)		TOTAL (N = 127)		FEMALE (N = 47)		MALE (N = 71)		TOTAL (N = 118)	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	6	(13.6%)	11	(13.3%)	17	(13.4%)	6	(12.8%)	11	(15.5%)	17	(14.4%)
	19	(43.2%)	35	(42.2%)	54	(42.5%)	18	(38.3%)	32	(45.1%)	50	(42.4%)
	13	(29.5%)	29	(34.9%)	42	(33.1%)	21	(44.7%)	25	(35.2%)	46	(39.0%)
	6	(13.6%)	8	(9.6%)	14	(11.0%)	2	(4.3%)	3	(4.2%)	5	(4.2%)

Age By Sex - Mean, Median, Minimum and Maximum
Evaluable Patients
E003: Pneumonia Indication

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	44	83	127	47	71	118
MEAN AGE	43.05	42.82	42.90	43.19	42.85	42.98
STD DEV	16.69	16.06	16.22	14.69	14.61	14.58
MEDIAN AGE	42.50	39.00	42.00	44.00	41.00	41.00
MINIMUM AGE						
MAXIMUM AGE						

Origin By Therapy Group
Evaluable Patients
Indication: Pneumonia

ORIGIN	DIRITHROMYCIN N = 127		ERYTHROMYCIN N = 118		TOTAL N = 245	
	n	(%)	n	(%)	n	(%)
CAUCASIAN	103	(81.1%)	104	(88.1%)	207	(84.5%)
BLACK	16	(12.6%)	11	(9.3%)	27	(11.0%)
ASIAN	1	(0.8%)	1	(0.8%)	2	(0.8%)
OTHER	7	(5.5%)	2	(1.7%)	9	(3.7%)

Height and Weight at Admission
Evaluable Patients
Indication: Pneumonia

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	127	0	168.87	10			127	0	68.54	15		
ERYTHROMYCIN	118	0	170.94	10			118	0	69.93	15		

Drug Administration:

All Patients

Exposure to Study Drugs - Mean, Minimum, and Maximum
All Patients
Indication: Pneumonia

	DIRITHROMYCIN N = 295 DAYS	ERYTHROMYCIN N = 296 DAYS
PATIENTS WITH COMPLETE DATA	290	294
MEAN DURATION EXPOSURE	12.3	12.5
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	5	2

Summary of Exposure to Study Drugs
All Patients
Indication: Pneumonia

DAYS OF THERAPY	DIRITHROMYCIN N = 295		ERYTHROMYCIN N = 296		TOTAL N = 591	
	n	(%)	n	(%)	n	(%)
PATIENTS WITH INCOMPLETE DATA	5	(1.7%)	2	(0.7%)	7	(1.2%)
1	3	(1.0%)	2	(0.7%)	5	(0.8%)
2	4	(1.4%)	7	(2.4%)	11	(1.9%)
3	5	(1.7%)	7	(2.4%)	12	(2.0%)
4	5	(1.7%)	4	(1.4%)	9	(1.5%)
5	7	(2.4%)	0		7	(1.2%)
6	4	(1.4%)	4	(1.4%)	8	(1.4%)
7	4	(1.4%)	5	(1.7%)	9	(1.5%)
8	4	(1.4%)	1	(0.3%)	5	(0.8%)
9	6	(2.0%)	4	(1.4%)	10	(1.7%)
10	22	(7.5%)	18	(6.1%)	40	(6.8%)
11	28	(9.5%)	32	(10.8%)	60	(10.2%)
12	17	(5.8%)	25	(8.4%)	42	(7.1%)
13	15	(5.1%)	9	(3.0%)	24	(4.1%)
14	68	(23.1%)	68	(23.0%)	136	(23.0%)
15	91	(30.8%)	98	(33.1%)	189	(32.0%)
16	4	(1.4%)	9	(3.0%)	13	(2.2%)
17	1	(0.3%)	0		1	(0.2%)
18	2	(0.7%)	1	(0.3%)	3	(0.5%)

Evaluable Patients

Exposure to Study Drugs - Mean, Minimum, and Maximum
Evaluable Patients
Indication: Pneumonia

	DIRITHROMYCIN N = 127 DAYS	ERYTHROMYCIN N = 118 DAYS
NUMBER OF PATIENTS	127	118
MEAN DURATION EXPOSURE	13.1	13.6
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients
Indication: Pneumonia

DAYS OF THERAPY	DIRITHROMYCIN N = 127		ERYTHROMYCIN N = 118		TOTAL N = 245	
	n	(%)	n	(%)	n	(%)
3	1	(0.8%)	2	(1.7%)	3	(1.2%)
4	1	(0.8%)	1	(0.8%)	2	(0.8%)
5	3	(2.4%)	0		3	(1.2%)
6	1	(0.8%)	0		1	(0.4%)
9	1	(0.8%)	1	(0.8%)	2	(0.8%)
10	11	(8.7%)	6	(5.1%)	17	(6.9%)
11	13	(10.2%)	7	(5.9%)	20	(8.2%)
12	8	(6.3%)	9	(7.6%)	17	(6.9%)
13	5	(3.9%)	6	(5.1%)	11	(4.5%)
14	33	(26.0%)	30	(25.4%)	63	(25.7%)
15	48	(37.8%)	52	(44.1%)	100	(40.8%)
16	1	(0.8%)	3	(2.5%)	4	(1.6%)
18	1	(0.8%)	1	(0.8%)	2	(0.8%)

Unevaluable Patients

Reason Unevaluable Summary
All Patients
Indication: Pneumonia

REASON UNEVALUABLE	DIRITHROMYCIN N = 295		ERYTHROMYCIN N = 296		TOTAL N = 591	
	n	(%)	n	(%)	n	(%)
PATS. WITH => 1 REASON	168	(56.9%)	178	(60.1%)	346	(58.5%)
PATS. WITH > 1 REASON	69	(23.4%)	65	(22.0%)	134	(22.7%)
PRE-CULTURE NEGATIVE	84	(28.5%)	75	(25.3%)	159	(26.9%)
NO INITIAL CULTURE	23	(7.8%)	31	(10.5%)	54	(9.1%)
INSUFFICIENT THERAPY	23	(7.8%)	18	(6.1%)	41	(6.9%)
TIMING OF X-RAY	18	(6.1%)	14	(4.7%)	32	(5.4%)
CAUS. ORG. RESISTANT	16	(5.4%)	15	(5.1%)	31	(5.2%)
UNEVAL. BY INVEST.	13	(4.4%)	15	(5.1%)	28	(4.7%)
UNACCEPT. PATHOGEN	8	(2.7%)	20	(6.8%)	28	(4.7%)
WRONG AGE	10	(3.4%)	12	(4.1%)	22	(3.7%)
EARLY CLIN. ASSESSMENT	10	(3.4%)	12	(4.1%)	22	(3.7%)
NO POST THER. CULTURE	10	(3.4%)	9	(3.0%)	19	(3.2%)
UNDERLYING CONDITION	10	(3.4%)	9	(3.0%)	19	(3.2%)
SENSITIVITY NOT DONE	5	(1.7%)	9	(3.0%)	14	(2.4%)
WRONG DIAGNOSIS	7	(2.4%)	6	(2.0%)	13	(2.2%)
NO FOLLOW-UP X-RAY	6	(2.0%)	6	(2.0%)	12	(2.0%)
POST THER. CULT. EARLY	6	(2.0%)	4	(1.4%)	10	(1.7%)
LATE CLIN. ASSESSMENT	7	(2.4%)	3	(1.0%)	10	(1.7%)
CONCOMITANT ANTIBIOT.	5	(1.7%)	4	(1.4%)	9	(1.5%)
NO POST FOLLOW-UP	4	(1.4%)	4	(1.4%)	8	(1.4%)
NO DURING CULTURE	3	(1.0%)	1	(0.3%)	4	(0.7%)
BLIND BROKEN	0		3	(1.0%)	3	(0.5%)
INITIAL CULT. EARLY	1	(0.3%)	2	(0.7%)	3	(0.5%)
VISIT MISSING	0		3	(1.0%)	3	(0.5%)
DURING CULTURE LATE	0		2	(0.7%)	2	(0.3%)
PROTOCOL VIOLATED	0		2	(0.7%)	2	(0.3%)
SEQUENTIAL THERAPY	0		2	(0.7%)	2	(0.3%)
POOR COMPLIANCE	1	(0.3%)	1	(0.3%)	2	(0.3%)
ALLERGIC TO STUDY DRUG	0		2	(0.7%)	2	(0.3%)
NEVER ON ACTIVE DRUG	1	(0.3%)	1	(0.3%)	2	(0.3%)
DURING CULTURE EARLY	1	(0.3%)	0		1	(0.2%)
POST THER. CULT. LATE	1	(0.3%)	0		1	(0.2%)
INCOMPLETE DATA	0		1	(0.3%)	1	(0.2%)
CONCOMIT. MEDICATION	0		1	(0.3%)	1	(0.2%)
PROLONGED THERAPY	0		1	(0.3%)	1	(0.2%)
WRONG WEIGHT	1	(0.3%)	0		1	(0.2%)

Medical Officer's Comments: Some patients had more than one reason to be considered unevaluable.

Efficacy Evaluation:

The clinical response for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Clinical Response Summary/Therapy Group
All Evaluable Patients - Posttherapy
Indication: Pneumonia

RESPONSE	DIRITHROMYCIN N = 127 n	(%)	ERYTHROMYCIN N = 118 n	(%)
CURE	70	(55.1%)	66	(55.9%)
IMPROVEMENT	47	(37.0%)	42	(35.6%)
RELAPSE	2	(1.6%)	1	(0.8%)
FAILURE	8	(6.3%)	9	(7.6%)

Medical Officer's Comments:

An overall favorable clinical success (cure or improvement) rate was 117/127 (92%) for dirithromycin and 108/118 (91.5%) for the erythromycin group.

The clinical response by pathogen for evaluable patients at posttherapy according to the applicant was as follows:

Clinical Response Summary/Pathogen
All Evaluable Patients - Posttherapy
Therapy: Dirithromycin

PATHOGENS	CURE n	(%)	IMPROVEMENT n	(%)	RELAPSE n	(%)	FAILURE n	(%)	TOTAL n
S PNEUMONIAE	23	(57.5%)	16	(40.0%)	1	(2.5%)	0		40
H INFLUENZAE	14	(66.6%)	4	(19.0%)	0		3	(14.2%)	21
MULTIPLE ORGANISMS	13	(65.0%)	5	(25.0%)	0		2	(10.0%)	20
M. PNEUMONIAE	10	(52.6%)	7	(36.8%)	0		2	(10.5%)	19
C. PNEUMONIAE SP	5	(33.3%)	9	(60.0%)	0		1	(6.6%)	15
S AUREUS	3	(100.0%)	0		0		0		3
H PARAINFLUENZAE	1	(50.0%)	1	(50.0%)	0		0		2
GRP A STREP	1	(50.0%)	1	(50.0%)	0		0		2
M CATARRHALIS	0		2	(66.6%)	1	(33.3%)	0		3
L PNEUMOPHILA	0		2	(100.0%)	0		0		2

Clinical and Bacteriologic Response for Polymicrobial Infections
Evaluable Dirithromycin-treated Patients
Posttherapy

Patient No.	Pathogens	Individual Bact. Response	Overall Bact. Response	Clinical Response
	S. aureus	PE	PE	FAIL
	S. pneumoniae	PE		
	S. aureus.	NA	UTE	CURE
	M pneumonia	UTE		
	H. influenzae	NA	UTE	CURE
	C. pneumoniae sp.	UTE		
	M. pneumoniae	UTE	UTE	CURE
	C. pneumoniae			
	S. pneumoniae	NA	UTE	CURE
	C. pneumoniae sp.	UTE		
	Streptococcus sp	NA	NA	CURE
	Group F strep	NA		
	S. aureus	NA	NA	CURE
	S. pneumoniae	NA		
	H. influenzae	NA	NA	CURE
	S. pneumoniae	NA		
	C. pneumoniae sp.	UTE	UTE	CURE
	M. pneumoniae	UTE		
	H. influenzae	SR	SR	IMP
	S. pneumoniae	PE		
	H. influenzae	PE	PE	IMP
	S. pneumoniae	PE		
	H. influenzae	NA	UTE	CURE
	M. pneumoniae	UTE		
	Group A strep	PE	PE	IMP
	M. catarrhalis	PE		
	K. pneumoniae	NA	NA	IMP
	S. pneumoniae	NA		
	S. pneumoniae	NA	UTE	CURE
	M. pneumoniae	UTE		

(cont)

Clinical and Bacteriologic Response for Polymicrobial Infections
Evaluable Dirithromycin-treated Patients
Posttherapy

Patient No.	Pathogens	Individual Bact. Response	Overall Bact. Response	Clinical Response
	H. influenzae	PE	UTE	IMP
	L. pneumophila	UTE		
	M. pneumoniae	UTE		
	H. influenzae	FEP	FEP	FAIL
	S. aureus	PE		
	H. influenzae	NA	NA	CURE
	Streptococcus MG	NA		
	H. influenzae	NA	NA	CURE
	S. pneumoniae	NA		
	H. parainfluenzae	NA	NA	CURE
	S. pneumoniae	NA		

Abbreviation:
PE = Pathogen eliminated
UTE = unable to evaluate
NA = not applicable
SR = recurrence same, resistant
FEP = failure to eliminate pathogen
IMP = improved

Clinical Response Summary/Pathogen
All Evaluable Patients - Posttherapy
Indication: Pneumonia
Therapy: Erythromycin

PATHOGENS	CURE n	CURE (%)	IMPROVEMENT n	IMPROVEMENT (%)	RELAPSE n	RELAPSE (%)	FAILURE n	FAILURE (%)	TOTAL n
S PNEUMONIAE	16	(69.5%)	6	(26.0%)	1	(4.3%)	0		23
MULTIPLE ORGANISMS	13	(59.0%)	7	(31.8%)	0		2	(9.0%)	22
C. PNEUMONIAE SP	7	(36.8%)	11	(57.8%)	0		1	(5.2%)	19
M. PNEUMONIAE	10	(55.5%)	6	(33.3%)	0		2	(11.1%)	18
H INFLUENZAE	8	(47.0%)	7	(41.1%)	0		2	(11.7%)	17
S AUREUS	4	(57.1%)	2	(28.5%)	0		1	(14.2%)	7
M CATARRHALIS	5	(83.3%)	1	(16.6%)	0		0		6
H PARAINFLUENZAE	1	(33.3%)	1	(33.3%)	0		1	(33.3%)	3
GRP A STREP	1	(100.0%)	0		0		0		1
L PNEUMOPHILA	1	(100.0%)	0		0		0		1
GRP F STREP	0		1	(100.0%)	0		0		1

Clinical and Bacteriologic Response for Polymicrobial Infections
Evaluable Erythromycin-treated Patients
Posttherapy

Patient No.	Pathogens	Individual Bact. Response	Overall Bact. Response	Clinical Response
	H. parainfluenzae	UTE	UTE	FAIL
	S. aureus	UTE		
	S. pneumoniae	UTE		
	Haemophilus sp.	FEP	FEP	CURE
	S. aureus	FEP		
	H. influenzae	PE	PE	CURE
	S. pneumoniae	PE		
	M. catarrhalis	PE		
	H. influenzae	NA	NA	CURE
	S. aureus	NA		
	H. parainfluenzae	SP	SP	IMP
	S. pneumoniae	PE		
	H. influenzae	PE	UTE	CURE
	M. pneumoniae	UTE		
	H. parainfluenzae	PE	UTE	IMP
	M. pneumoniae	UTE		
	H. influenzae	UTE	UTE	FAIL
	C. pneumoniae sp.	UTE		
	H. influenzae	NA	UTE	CURE
	C. pneumoniae sp.	UTE		
	C. pneumoniae sp.	UTE	UTE	IMP
	M. pneumoniae	UTE		
	S. pneumoniae	NA	NA	CURE
	Grp. C strep	NA		
	H. influenzae	PE	PE	CURE
	S. pneumoniae	PE		
	M. catarrhalis	PE		
	H. influenzae	FEP	FEP	CURE
	S. pneumoniae	PE		
	H. influenzae	PE	PE	IMP
	S. pneumoniae	PE		
	C. pneumoniae sp.	UTE	UTE	CURE
	M. pneumoniae	UTE		
	S. pneumoniae	PE	PE	CURE
	Grp. A strep	PE		
	C. pneumoniae sp.	UTE	UTE	CURE
	M. catarrhalis	NA		
	H. influenzae	PE	PE	IMP
	S. pneumoniae	PE		

Patient No.	Pathogens	Individual Bact. Response	Overall Bact. Response	Clinical Response
	H. parainfluenzae	NA	UTE	CURE
	M. pneumoniae	UTE		
	H. influenzae	PE	UTE	IMP
	L. pneumophila	UTE		
	H. influenzae	NA	NA	IMP
	S. pneumoniae	NA		
	Klebsiella sp.	NA	UTE	CURE
	M. pneumoniae	UTE		

Abbreviation:
PE = Pathogen eliminated
UTE = unable to evaluate
NA = not applicable
SR = recurrence same, resistant
FEP = failure to eliminate pathogen
IMP = improved

The clinical response for evaluable patients at late-posttherapy (2-3 weeks) according to the applicant was as follows:

Clinical Response Summary/Therapy Group
All Evaluable Patients -Late-Posttherapy
Indication: Pneumonia

	DIRITHROMYCIN N = 110		ERYTHROMYCIN N = 98	
RESPONSE	n	(%)	n	(%)
CURE	96	(87.3%)	84	(85.7%)
IMPROVEMENT	8	(7.3%)	9	(9.2%)
RELAPSE	6	(5.5%)	5	(5.1%)

Medical Officer's Comments:

An overall favorable clinical success (cure or improvement) rate was 104/110 (94.5%) for dirithromycin and 93/98 (95.0%) for the erythromycin group.

The clinical response by pathogen for evaluable patients at late-posttherapy (2-3 weeks) according to the applicant was as follows:

Clinical Response Summary/Pathogen
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia
Therapy: Dirithromycin

	CURE		IMPROVEMENT		RELAPSE		TOTAL
PATHOGENS	n	(%)	n	(%)	n	(%)	n
S PNEUMONIAE	31	(83.7%)	4	(10.8%)	2	(5.4%)	37
MULTIPLE ORGANISMS	15	(88.2%)	2	(11.7%)	0		17
H INFLUENZAE	15	(93.7%)	0		1	(6.2%)	16
M. PNEUMONIAE	15	(93.7%)	1	(6.2%)	0		16
C. PNEUMONIAE SP	12	(85.7%)	1	(7.1%)	1	(7.1%)	14
S AUREUS	3	(100.0%)	0		0		3
H PARAINFLUENZAE	1	(50.0%)	0		1	(50.0%)	2
GRP A STREP	1	(50.0%)	0		1	(50.0%)	2
M CATARRHALIS	2	(100.0%)	0		0		2
L PNEUMOPHILA	1	(100.0%)	0		0		1

Clinical and Bacteriologic Response for Polymicrobial Infections
Evaluable Dirithromycin-treated Patients
Late-Posttherapy

Patient No.	Pathogens	Individual Bact. Response	Overall Bact. Response	Clinical Response
	S. aureus	NA	UTE	CURE
	M. pneumoniae	UTE		
	H. influenzae	NA	UTE	CURE
	C. pneumoniae sp.	UTE		
	M. pneumoniae	UTE	UTE	CURE
	C. pneumoniae sp.		UTE	
	S. pneumoniae	NA	UTE	CURE
	C. pneumoniae sp.	UTE		
	Streptococcus sp.	NA	NA	CURE
	Strep. Grp. F	NA		
	S. aureus	NA	NA	CURE
	S. pneumoniae	NA		
	H. influenzae	NA	NA	CURE
	S. pneumoniae	NA		
	C. pneumoniae sp.	UTE	UTE	CURE
	M. pneumoniae	UTE		
	H. influenzae	PE	PE	IMP
	S. pneumoniae	PE		
	H. influenzae	UTE	UTE	IMP
	C. pneumoniae.	UTE		
	H. influenzae	NA	UTE	CURE
	M. pneumoniae	UTE		
	K. pneumoniae	NA	NA	CURE
	S. pneumoniae	NA		
	S. pneumoniae	NA	UTE	CURE
	M. pneumoniae	UTE		
	H. influenzae	NA	UTE	CURE
	L. pneumophila	UTE		
	M. pneumoniae	UTE		
	H. influenzae	NA	NA	CURE
	Streptococcus MG	NA		
	H. influenzae	NA	NA	CURE
	S. pneumoniae	NA		
	H. parainfluenzae	NA	NA	CURE
	S. pneumoniae	NA		

Abbreviations:
NA = not applicable
UTE = unable to evaluate
PE = pathogen eliminated
IMP = improved

Clinical Response Summary/Pathogen
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia
Therapy: Erythromycin

PATHOGENS	CURE n	CURE (%)	IMPROVEMENT n	IMPROVEMENT (%)	RELAPSE n	RELAPSE (%)	TOTAL n
S PNEUMONIAE	20	(90.9%)	0		2	(9.0%)	22
MULTIPLE ORGANISMS	14	(77.7%)	1	(5.5%)	3	(16.6%)	18
C. PNEUMONIAE	13	(86.5%)	2	(12.5%)	0		15
M. PNEUMONIAE	13	(86.6%)	2	(13.3%)	0		15
H INFLUENZAE	10	(71.4%)	4	(28.5%)	0		14
M CATARRHALIS	5	(100%)	0		0		5
S AUREUS	4	(100%)	0		0		4
H PARAINFLUENZAE	2	(100.0%)	0		0		2
GRP A STREP	1	(100.0%)	0		0		1
L PNEUMOPHILA	1	(100.0%)	0		0		1
GRP F STREP	1	(100.0%)	0		0		1

Clinical and Bacteriologic Response for Polymicrobial Infections
Evaluable Erythromycin-treated Patients
Late-Posttherapy

Patient No.	Pathogens	Individual Bact. Response	Overall Bact. Response	Clinical Response
	Haemophilus sp.	NA	NA	CURE
	S. aureus	NA		
	H. influenzae	NA	NA	CURE
	S. pneumoniae	NA		
	M. catarrhalis	NA		
	H. influenzae	NA	NA	CURE
	S. aureus	NA		
	H. influenzae	NA	UTE	CURE
	M. pneumoniae	UTE		
	H. parainfluenzae	UTE	UTE	RELAPSE
	M. pneumoniae	UTE		
	H. influenzae	NA	UTE	CURE
	C. pneumoniae.	UTE		
	C. pneumoniae.	UTE	UTE	RELAPSE
	M. pneumoniae	UTE		
	S. pneumoniae	NA	NA	CURE
	Strep. grp. C	NA		
	H. influenzae	UTE	UTE	RELAPSE
	M. pneumoniae	UTE		
	H. influenzae	NA	NA	CURE
	S. pneumoniae	NA		
	M. catarrhalis	NA		
	H. influenzae	NA	NA	CURE
	S. pneumoniae	NA		
	H. influenzae	NA	PE	CURE
	S. pneumoniae	NA		
	C. pneumoniae.	UTE	UTE	CURE
	M. pneumoniae	UTE		
	S. pneumoniae	NA	NA	CURE
	Strep. grp. A	NA		
	C. pneumoniae.	UTE	UTE	CURE
	M. catarrhalis	NA		
	H. influenzae	NA	NA	CURE
	S. pneumoniae	NA		
	H. influenzae	NA	NA	IMP
	S. pneumoniae	NA		
	Klebsiella sp.	NA	UTE	CURE
	M. pneumoniae	UTE		

* Overall response for Patient 848-5679 should be NA since culture source was unavailable at late-posttherapy. Pathogen elimination was confirmed by culture at posttherapy.

Abbreviations: NA = not applicable; PE = pathogen eliminated; UTE = unable to evaluate; IMP = improved

Bacteriologic Response

The bacteriologic response for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Bacteriologic Response Summary/Therapy Group -
All Evaluable Patients - Posttherapy
Indication: Pneumonia

	DIRITHROMYCIN N = 81		ERYTHROMYCIN N = 67	
RESPONSE	n	(%)	n	(%)
PATHOGEN ELIMINATED	25	(30.9%)	19	(28.3%)
PRESUMED ERADICATION	44	(54.3%)	40	(59.7%)
RECURRENCE SAME	2	(2.5%)	3	(4.5%)
RECURRENCE SAME, RESISTANCE	1	(1.2%)	0	
RECURRENCE NEW	5	(6.2%)	0	
FAILED TO ELIMINATE	4	(4.9%)	5	(7.5%)

Medical Officer's Comments:

The bacteriologic favorable success (eradicated/presumed eradicated) rate was 69/81 (85.2%) for dirithromycin group and 59/67 (88.1%) for the erythromycin group.

The bacteriologic response by pathogen for evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Bacteriologic Response Summary/Pathogen
All Evaluable Patients
Indication: Pneumonia
Therapy: Dirithromycin

PATHOGENS	PATHOGEN ELIMINATED n	(%)	PRESUMED ERADICATION n	(%)	RECURRENCE RECURRENCE SAME n	(%)	SAME, RESISTANCE n	(%)	RECURRENCE NEW n	(%)	FAILED TO ELIMINATE n	(%)	TOTAL n
S PNEUMONIAE	16	(32.7%)	30	(61.2%)	0		0		3	(6.1%)	0		49
H INFLUENZAE	11	(39.3%)	11	(39.3%)	2	(7.1)	3	(10.7%)	0		1	(3.6%)	28
M CATARRHALIS	1	(25.0%)	2	(50.0%)	0		0		1	(25.0%)	0		4
GRP A STREP	1	(33.3%)	1	(33.3%)	0		0		1	(33.3%)	0		3
H PARAINFLUENZAE	0		2	(66.7%)	0		0		0		1	(33.3%)	3
S AUREUS	2	(28.6)	5	(71.4%)	0		0		0		0		7

Bacteriologic Response Summary/Pathogen
All Evaluable Patients
Indication: Pneumonia
Therapy: Erythromycin

PATHOGENS	PATHOGEN ELIMINATED n	(%)	PRESUMED ERADICATION n	(%)	RECURRENCE SAME n	(%)	FAILED TO ELIMINATE n	(%)	TOTAL n
S PNEUMONIAE	11	(34.4%)	21	(65.6%)	0		0		32
H INFLUENZAE	14	(51.9%)	7	(25.9%)	2	(7.4%)	4	(14.8%)	27
S AUREUS	1	(12.5%)	6	(75.0%)	0		1	(12.5)	8
M CATARRHALIS	2	(25.0%)	6	(75.0)	0		0		8
H PARAINFLUENZAE	1	(20.0%)	3	(60.0%)	1	(20.0)	0		5
GRP A STREP	1	(50.0%)	1	(50.0%)	0		0		2
GRP F STREP	0		1	(100.0%)	0		0		1

The bacteriologic response for evaluable patients at late-posttherapy (2-3 weeks) according to the applicant was as follows:

Bacteriologic Response Summary/Therapy Group
All Evaluable Patients - Late Posttherapy
Indication: Pneumonia

	DIRITHROMYCIN N = 68		ERYTHROMYCIN N = 58	
RESPONSE	n	(%)	n	(%)
PATHOGEN ELIMINATED	6	(8.8%)	4	(6.9%)
PRESUMED ERADICATED	60	(88.2%)	52	(89.9%)
RECURRENCE SAME	1	(1.5%)	0	
RECURRENCE SAME, RESISTANCE	0		1	(1.7%)
RECURRENCE NEW	1	(1.5%)	0	
FAILED TO ELIMINATE	0		1	(1.7%)

Medical Officer's Comments:

The bacteriologic success (eradicated/presumed eradicated) rate was 66/68 (97.0%) for dirithromycin group and 56/58 (96.6%) for the erythromycin group.

The bacteriologic response by pathogen for evaluable patients at late-posttherapy (2-3 weeks) according to the applicant was as follows:

Bacteriologic Response Summary/Pathogen
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia
Therapy: Dirithromycin

	PATHOGEN ELIMINATED		PRESUMED ERADICATION		RECURRENCE SAME		RECURRENCE NEW		TOTAL
PATHOGENS	n	(%)	n	(%)	n	(%)	n	(%)	n
STR PNEUMONIAE	5	(11.1%)	39	(86.7%)	1	(2.2%)	0		45
H INFLUENZAE	2	(9.1%)	20	(90.9%)	0		0		22
H PARAINFLUENZAE	0		2	(66.7%)	0		1	(33.3%)	3
S AUREUS	0		5	(100.0%)	0		0		5
STR GRP A	0		1	(100.0%)	0		0		1
M CATARRHALIS	0		2	(100.0%)	0		0		2

Bacteriologic Response Summary/Pathogen
All Evaluable Patients - Late-Posttherapy
Indication: Pneumonia
Therapy: Erythromycin

PATHOGENS	PATHOGEN ELIMINATED n	(%)	PRESUMED ERADICATION n	(%)	RECURRENCE SAME, RESISTANCE n	(%)	FAILED TO ELIMINATE n	(%)	TOTAL n
STR PNEUMONIAE	2	(6.9%)	26	(89.7%)	1	(3.4%)	0		29
H INFLUENZAE	1	(4.5%)	20	(90.0%)	0		1	(4.5%)	22
M CATARRHALIS	0		8	(100.0%)	0		0		8
ST AUREUS	0		6	(100.0%)	0		0		6
H PARAINFLUENZAE	0		2	(100.0%)	0		0		2
STR GRP A	0		2	(100.0%)	0		0		2
STR GRP F	0		1	(100.0%)	0		0		1

Per the protocol, patients with *Mycoplasma pneumoniae, Legionella pneumophilia,* or *Chlamydia pneumoniae* were diagnosed serologically. The favorable clinical response rates for these pathogens are as follows:

Patients with Favorable Clinical Response Posttherapy

	Mycoplasma		Legionella		Chlamydia#	
	n/d[a]	(%)	n/d	(%)	n/d	(%)
Dirithromycin:						
E003	21/23	(91.3%)	3/3	(100.0%)	17/18	(94.4%)
Erythromycin:						
E003	21/23	(91.3%)	2/2	(100.0%)	21/23	(91.3%)

[a] n = number of patients with favorable response, d = number of evaluable patients

 # - NOTE: 8 patients in the dirithromycin group and 15 patients in the erythromycin group were enrolled by investigators in the US.
7/8 patients in the dirithromycin group and 13/15 in the erythromycin group had a favorable outcome.

Patients with Favorable Clinical Response Late-Posttherapy

	Mycoplasma		Legionella		Chlamydia#	
	n/d[a]	(%)	n/d	(%)	n/d	(%)
Dirithromycin:						
E003	20/20	(100.0%)	2/2	(100.0%)	16/17	(94.1%)
Erythromycin:						
E003	18/19	(94.7%)	1/1	(100.0%)	17/19	(89.5%)

[a] n = number of patients with favorable response, d = number of evaluable patients

- 7/7 patients in the dirithromycin group and 10/12 in the erythomycin group had a favorable outcome.

X-Ray Summary for E003 Evaluable Patients

CATEGORY		THERAPY GROUP IRITHROMYCIN N	ERYTHROMYCIN N
PRETHERAPY	PRESENT	126	117
DURING THERAPY	IMPROVED	3	3
	PRESENT	1	1
	RESOLVED	4	1
POSTTHERAPY	IMPROVED	36	35
	RESOLVED	64	64
	UNCHANGED	8	5
	WORSENED		5
LATE-POSTTHERAPY	IMPROVED	8	4
	RESOLVED	27	23
	UNCHANGED	4	2
	WORSENED	2	

SUSCEPTIBILITY RESULTS

Susceptibility Ranges for Pathogen
According to Zone Size Criteria
Therapy Group: Dirithromycin
Indication: Pneumonia

	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
PATHOGEN	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
M CATARRHALIS	5			5	5			5
E COLI			1	1			1	1
ENTEROBACTER SP			2	2			2	2
H INFLUENZAE	19	5	18	42	32	7	3	42
H PARAINFLUENZAE	3		2	5	5			5
HAEMOPHILUS SP			1	1		1		1
K PNEUMONIAE	3		1	4	2		2	4
PS AERUGINOSA			1	1			1	1
ST AUREUS	9			9	9			9
STAPHYLOCOCCUS SP	1			1			1	1
STR GRP A	4		1	5	4		1	5
STR PNEUMONIAE	65	1	5	71	69	1	1	71
STR VIRIDANS	1		1	2	2			2
STREPTOCOCCUS MG	1			1	1			1
STREPTOCOCCUS SP	1			1	1			1

Medical Officer's Comments:
Forty-three percent (18/42) of the *H. influenzae* isolated were resistent to dirithromycin.

Susceptibility Ranges for Pathogen
According to Zone Size Criteria
Therapy Group: Erythromycin
Indication: Pneumonia

	ANTIMIBCROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
PATHOGEN	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
ACINETOBACTER SP	1			1	1			1
M CATARRHALIS	11		1	12	11	1		12
E COLI			2	2			2	2
H INFLUENZAE	18	3	18	39	28	6	5	39
H PARAINFLUENZAE	1	1	6	8	6	1	1	8
HAEMOPHILUS SP	1			1	1			1
K PNEUMONIAE	2			2	1	1		2
KLEBSIELLA SP			1	1		1		1
NEISSERIA SP			1	1	1			1
PR MIRABILIS	1			1			1	1
PROTEUS SP			1	1			1	1
PS AERUGINOSA			3	3			3	3
PS FLUORESCENS			1	1			1	1
ST AUREUS	11	1		12	12			12
ST EPIDERMIDIS	1			1	1			1
STAPH COAG-NEG	2			2	2			2
STAPHYLOCOCCUS SP			1	1		1		1
STR GRP A	3		1	4	3		1	4
STR GRP C	1			1	1			1
STR GRP F	1			1	1			1

(continued)

Medical Officer's Comments:
46% (18/39) of the *H. influenzae* isolated were resistent to dirithromycin.

Susceptibility Ranges for Pathogen (continued)
According to Zone Size Criteria
Therapy Group: Erythromycin
Indication: Pneumonia

	ANTIMIBCROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
PATHOGEN	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
STR PNEUMONIAE	48		3	51	49	1	1	51
STR VIRIDANS			1	1	1			1
STREPTOCOCCUS SP			1	1			1	1

CONCOMITANT MEDICATIONS:

Prior to study entry, 33.9% of dirithromycin-treated patients and 33.4% of erythromycin-treated patients were receiving some form of drug therapy. Salbutamol was the most frequently used drug. Concomitant drug use was comparable between the two treatment groups.

A concomitant agent was prescribed during therapy in 39.3% of dirithromycin-treated patients and 40.5 of erythromycin-treated patients. Paracetamol was most frequently used.

After completion of study-drug therapy, 8.1% of dirithromycin-treated patients and 8.4% of erythromycin-treated patients reported taking medication. Again, salbutamol was most frequently used.

SAFETY RESULTS:

Summary of Adverse Event By Body System Table

Frequency of Treatment-Emergent Events
All Patients - All Adverse Events
Body System: Body as a Whole
Indication: Pneumonia

	DIRITHROMYCIN N = 295		ERYTHROMYCIN N = 296		
EVENT CLASSIFICATION TERM	n	(%)	n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	34	(11.5%)	33	(11.1%)	0.885
PATIENTS WITH NO EVENT	261	(88.5%)	263	(88.9%)	0.885
CHEST PAIN	8	(2.7%)	8	(2.7%)	0.995
ASTHENIA	5	(1.7%)	1	(0.3%)	0.1
HEADACHE	5	(1.7%)	10	(3.4%)	0.193
ABDOMINAL PAIN	4	(1.4%)	4	(1.4%)	0.996
FEVER	4	(1.4%)	5	(1.7%)	0.741
CHILLS	3	(1.0%)	2	(0.7%)	0.651
INJURY, ACCIDENT	2	(0.7%)	1	(0.3%)	0.561
MALAISE	2	(0.7%)	0		0.156
SURGICAL PROCEDURE	2	(0.7%)	1	(0.3%)	0.561
ABSCESS	1	(0.3%)	1	(0.3%)	0.998
ALLERGIC REACTION	1	(0.3%)	0		0.316
DRUG LEVEL INCREASED	1	(0.3%)	0		0.316
INFECTION	1	(0.3%)	0		0.316
PAIN	1	(0.3%)	2	(0.7%)	0.565
SEPSIS	1	(0.3%)	1	(0.3%)	0.998
ANAPHYLACTOID REACTION	0		1	(0.3%)	0.318
CARCINOMA	0		1	(0.3%)	0.318
CHEST PAIN SUBSTERNAL	0		1	(0.3%)	0.318
INFECTION SUPERIMPOSED	0		1	(0.3%)	0.318
MONILIASIS	0		1	(0.3%)	0.318

Frequency of Treatment-Emergent Events
All Patients - All Adverse Events
Body System: Digestive System
Indication: Pneumonia

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 295 n	(%)	ERYTHROMYCIN N = 296 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	30	(10.2%)	35	(11.8%)	0.52
PATIENTS WITH NO EVENT	265	(89.8%)	261	(88.2%)	0.52
DIARRHEA	14	(4.7%)	6	(2.0%)	0.068
NAUSEA	7	(2.4%)	12	(4.1%)	0.247
GASTRITIS	3	(1.0%)	3	(1.0%)	0.997
GASTROINTESTINAL DISORDER	2	(0.7%)	2	(0.7%)	0.997
VOMITING	2	(0.7%)	3	(1.0%)	0.656
ANOREXIA	1	(0.3%)	1	(0.3%)	0.998
DRY MOUTH	1	(0.3%)	0		0.316
DYSPEPSIA	1	(0.3%)	1	(0.3%)	0.998
HEMATEMESIS	1	(0.3%)	0		0.316
NAUSEA AND VOMITING	1	(0.3%)	3	(1.0%)	0.317
TOOTH DISORDER	1	(0.3%)	0		0.316
APHTHOUS STOMATITIS	0		1	(0.3%)	0.318
CONSTIPATION	0		1	(0.3%)	0.318
FLATULENCE	0		1	(0.3%)	0.318
GASTROENTERITIS	0		1	(0.3%)	0.318
HYPERCHLORHYDRIA	0		1	(0.3%)	0.318
MELENA	0		1	(0.3%)	0.318
MOUTH ULCERATION	0		1	(0.3%)	0.318

Frequency of Treatment-Emergent Events
All Patients - All Adverse Events
Body System: Respiratory System
Indication: Pneumonia

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 295 n	(%)	ERYTHROMYCIN N = 296 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	53	(18.0%)	55	(18.6%)	0.847
PATIENTS WITH NO EVENT	242	(82.0%)	241	(81.4%)	0.847
LUNG DISORDER	19	(6.4%)	19	(6.4%)	0.991
DYSPNEA	8	(2.7%)	10	(3.4%)	0.637
HYPERVENTILATION	8	(2.7%)	3	(1.0%)	0.127
PLEURAL EFFUSION	6	(2.0%)	4	(1.4%)	0.52
SPUTUM INCREASED	6	(2.0%)	15	(5.1%)	0.046
PNEUMONIA	5	(1.7%)	1	(0.3%)	0.1
CARCINOMA OF LUNG	4	(1.4%)	4	(1.4%)	0.996
ASTHMA	2	(0.7%)	0		0.156
COUGH INCREASED	2	(0.7%)	2	(0.7%)	0.997
LARYNGITIS	1	(0.3%)	1	(0.3%)	0.998
PLEURAL DISORDER	1	(0.3%)	0		0.316
RHINITIS	1	(0.3%)	1	(0.3%)	0.998
SINUSITIS	1	(0.3%)	1	(0.3%)	0.998
EPISTAXIS	0		1	(0.3%)	0.318
HICCUP	0		1	(0.3%)	0.318
HYPOXIA	0		1	(0.3%)	0.318
LUNG FIBROSIS	0		1	(0.3%)	0.318
PHARYNGITIS	0		1	(0.3%)	0.318
PNEUMOTHORAX	0		1	(0.3%)	0.318

Patients Who Died or Discontinued Therapy Due to Adverse Events:

There was one death reported in the erythromycin group during the study period. He was a 58 year old male who received therapy for 10 days, and developed septicemia. Eighteen patients in the dirithromycin group and 20 patients in the erythromycin group discontinued therapy because of adverse events. The details of those discontinuations are listed in the tables below:

THERAPY: DIRITHROMYCIN

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT
102		1	62	MALE	CAUCASIAN	4	HAEMOPHILUS SEPTICAEMIA
198		1	66	MALE	CAUCASIAN	5	PULMONARY TUBERCULOSIS
301		1	37	MALE	CAUCASIAN	7	PERICARDITIS
305		1	42	MALE	CAUCASIAN	7	PULMONARY ABSCESS
401		1	59	MALE	CAUCASIAN	3	EXACERBATION OF PNEUMONIA
503		1	21	FEMALE	OTHER	3	RASH
504		1	68	MALE	CAUCASIAN	5	PULMONARY EMBOLUS
504		1	43	FEMALE	CAUCASIAN	3	RASH
504		1	71	FEMALE	CAUCASIAN	4	DYSPNEA M
504		1	18	MALE	CAUCASIAN	2	GASTRITIS
509		1	73	MALE	ASIAN	6	EXERTIONAL DYSPNEA
701		1	61	FEMALE	CAUCASIAN	1	ALLERGIC REACTION - EXANTHEMA AND U
701		1	63	MALE	CAUCASIAN	9	PULMONARY EMBOLISM
901		1	34	MALE	CAUCASIAN	14	ACTIVE PULMONARY TUBERCULOSIS MILAR
930		1	36	MALE	BLACK	7	CONTINUOUS PYREXIA
931		1	40	FEMALE	CAUCASIAN	1	SEVERE HYPOTENSION
932		1	32	MALE	OTHER	5	(RISE IN TEMP, POOR RESPONSE TO ANTIBIOTIC)
941		1	67	MALE	CAUCASIAN	3	ERYSIPELAS, NOT DUE TO THE DRUG

THERAPY: ERYTHROMYCIN

007	1	67	FEMALE	CAUCASIAN	2	LUNG DISORDER (SUSPECTED CARCINOMA)
101	1	54	MALE	CAUCASIAN	12	DETECTION OF KIDNEY TUMOR
101	1	53	MALE	CAUCASIAN	12	BRONCHIAL CARCINOMA
102	1	64	MALE	CAUCASIAN	3	VERTIGO
104	1	37	MALE	CAUCASIAN	1	SHOCK
198	1	19	FEMALE	CAUCASIAN	2	ALBUMINURIA
504	1	38	FEMALE	CAUCASIAN	15	OTITIS MEDIA
504	1	25	FEMALE	CAUCASIAN	3	URTICARIA
504	1	46	MALE	CAUCASIAN	13	URTICARIA
505	1	32	FEMALE	CAUCASIAN	14	IMPETIGO RESULTING FROM SEVERE SUNBURN
508	1	60	MALE	CAUCASIAN	10	NAUSEA
509	1	46	FEMALE	BLACK	2	NAUSEA
701	1	32	MALE	CAUCASIAN	4	MENINGITIS
762	1	35	MALE	CAUCASIAN	11	VOMITING
850	1	24	MALE	CAUCASIAN	6	VOMITING AND NAUSEA
901	1	58	MALE	CAUCASIAN	15	PULMONARY CANCER EPIDERMOIDE TYPE)
921	1	46	MALE	BLACK	11	DEVELOPMENT OF LUNG ABSCESS
930	1	31	MALE	BLACK	8	GLOMERULITIS
930	1	31	MALE	BLACK	7	PYREXIA AFTER 3 DAYS
941	1	31	MALE	CAUCASIAN	3	NAUSEA

CLINICAL LABORATORY EVALUATIONS:

Three approaches to the analysis and depiction of clinical laboratory data are presented in this section. The first examines changes in central tendency and compares changes in mean values for each analyte for each treatment population. This analysis is designed to evaluate the following: 1) whether drug treatment has resulted in an overall change in a particular analyte compared to baseline for each treatment population, 2) whether the treatment groups differ with regard to endpoint means and overall change from baseline, and 3) whether the changes from baseline on average for a treatment population are notably positive or negative for each analyte. This analysis is limited to laboratory values with numeric values; urinalysis dipstick and microscopic examination results cannot be analyzed in this manner, and the analysis of these results is performed in the "categorical analysis," described later in this section.

Distribution of Extreme Laboratory Values
(For Normal Laboratory Values, see page 5A of the MOR)

Analyte	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Platelet Count		D	134.000		534.000
		D	175.000		468.000
		D	175.000		472.000
		D	203.000		399.000
		D	205.000		514.000
		D	208.000		625.000
		D	184.000		457.000
		D	207.000		553.000
		D	266.000		411.000
		D	239.000		524.000
		D	133.000		395.000
		D	219.000		486.000
		E	294.000		522.000
		E	246.000		669.000
		E	175.000		504.000
		E	320.000		451.000
		E	195.000		679.000
		E	240.000		409.000
		E	260.000		812.000
		E	232.000		457.000
		E	467.000		1080.000
		E	150.000		478.000
		E	133.000		400.000
		E	216.000		412.000
		E	192.000		490.000
		E	210.000		554.000
TBILI		D	21.000		42.000
GGT		D	440.000		796.000
ALKPH		D	196.000		449.000
		D	141.000		339.000
AST		D	31.000		145.000
ALT		D	91.000		362.000
HCT		D	0.396		0.287
		D	0.425		0.248
		D	0.440		0.730
		E	0.430		0.310

Analyte	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
HGB		D	8.378		5.585
		D	9.185		4.903
		D	8.502		14.150
		E	8.502		6.144
EOSN		E	0.400		1.500
UR AC		E	221.00		618.00
CREAT		E	82.00		148.00
		E	100.00		156.00
PHOS		D	1.100		2.700
		D	2.920		8.090
		D	2.350		0.610
		D	1.100	1.000	1.860
		D	1.310		3.880
		D	0.940		2.600*
		D	1.000		2.200
		D	0.800		3.000
		E	1.300		3.900
		E	0.960		1.690
		E		1.120	1.610
		E	1.300		2.670
		E	1.450		1.910
CHOL		D	4.600		2.600
CALC		E	2.330		0.590
CPK		D	7.400		2166.000

**Late-post

In summary, most of the laboratory changes were minor and not clinically significant. None of the laboratory notables could be clearly attributed to either of the study medications. The distribution of laboratory abnormalities among both study groups was similar.

Medical Officer's Overall Comments:

Efficacy:

Both dirithromycin and erythromycin were effective in the treatment of pneumonia caused by the target pathogens.

The overall clinical success (cure or improvement) rate at post-therapy was **92%** (117/127) for the dirithromycin group and **91.5%** (108/118) for the erythromycin group. At late post-therapy follow-up, it was **94.5%** (104/110) for the dirithromycin group and **95%** (93/98) for the erythromycin group.

The bacteriologic success (eradicated/presumed eradicated) rate at post-therapy was **85.2%** (69/81) for the dirithromycin group and **88.1%** (59/67) for the erythromycin group. At late post-therapy follow-up, it was **97.0%** (66/68) for the dirithromycin group and **96.6%** (56/58) for the erythromycin group.

The bacteriologic success (eradicated/presumed eradicated) rate by pathogen for evaluable patients at post-therapy was 22/28 (78.6%) for *H. influenzae* , 93.9% (46/49) for *S. pneumoniae*, 75% (3/4) for *M. catarrhalis* and 66.7% (2/3) for *H. parainfluenzae* in the dirithromycin group and 21/27 (77.8%) for *H. influenzae*, 32/32 (100%) for *S. pneumoniae*, 8/8 (100%) for *M. catarrhalis, and 80% (*4/5) for *H. parainfluenzae* for the erythromycin group.

The bacteriologic success (eradicated/presumed eradicated) rate by pathogen for evaluable patients at late post-therapy was 22/22 (100%) for *H. influenzae* , 97.8% (44/45) for *S. pneumoniae*, 100% (2/2) for *M. catarrhalis* and 66.7% (2/3) for *H. parainfluenzae* in the dirithromycin group and 21/22 (95.5%) for *H. influenzae*, 28/29 (96.6%) for *S. pneumoniae*, 8/8 (100%) for *M. catarrhalis* and 2/2 (100%) for *H. parainfluenzae* for the erythromycin group.

In patients who were diagnosed only by serology for the atypical microorganisms, the clinical success rate at post-therapy was 21/23 (91.3%) for *M. pneumoniae*, 17/18 (94.4%) for *C. pneumoniae* and 3/3 (100%) for *L. pneumophila* in the dirithromycin group, and 21/23 (91.3%) for *M. pneumoniae* , 21/23 (91.3%) for *C. pneumoniae* and 2/2 (100%) for *L. pneumophila* in the erythromycin group.
In patients who were diagnosed only by serology for the atypical microorganisms, the clinical success rate at late post-therapy was 20/20 (100%) for *M. pneumoniae*, 16/17 (94.1%) for *C. pneumoniae* and 2/2 (100%) for *L. pneumophila* in the dirithromycin group, and 18/19 (94.7%) for *M. pneumoniae* , 17/19 (89.5%) for *C. pneumoniae* and 1/1 (100%) for *L. pneumophila* in the erythromycin group.

Medical Officer's Conclusions:

The clinical and bacteriologic response rate at post therapy and late post-therapy for both the study drugs appears to be the same, but the eradication rate/presumed eradication rate for *H. influenzae* appears to be better for the dirithromycin group in comparison to the erythromycin group. Forty-four percent of the *H. influenzae* isolates were resistent to dirithromycin.

Overall Summary of Pivotal Studies

Clinical Response:

Clinical Response Summary
Post-therapy
AQAB/E003
Pneumonia

Study	Dirithromycin Favorable/Total	Erythromycin Favorable/Total
AQAB	85/90	83/83
E003	117/127	108/118
Total	**202/217 (93%)**	**191/201 (95%)**

Clinical Response Summary
Late Post-therapy
AQAB/E003
Pneumonia

Study	Dirithromycin Favorable/Total	Erythromycin Favorable/Total
AQAB	78/78	73/77
E003	104/110	93/98
Total	**182/188 (96.8%)**	**166/175 (95%)**

Clinical Response Summary by Target Pathogens
AQAB/ E003 Pneumonia

	Posttherapy								Late-Posttherapy							
	Dirithromycin				Erythromycin				Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable	
Pathogen	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
M catarrhalis	4	100	0	0	7	100	-	-	3	100	0	0	5	83.3	1	16.7
C. pneumoniae	14	93.3	1	6.7	18	94.7	1	5.3	15	93.8	1	6.2	13	92.9	1	7.1
L Pneumophilia	16	100	-	-	11	100	-	-	15	100	-	-	9	100	-	-
M.pneumoniae	55	91.7	5	8.3	48	96.0	2	4.0	52	100	-	-	45	97.8	1	2.2
H influenzae	24	85.7	4	14.3	22	91.7	2	8.3	19	95	1	5	20	95.2	1	4.8
Str pneumonia	52	98.1	1	1.9	38	97.4	1	2.6	48	96	2	4	35	94.6	2	5.4
Multiple Pathogens	19	90.5	2	9.5	25	92.6	2	7.4	17	100	-	-	20	83.3	4	16.7

Bacteriologic Response

Bacteriologic Response Summary of Target Pathogens
AQAB/E003
Pneumonia

	Posttherapy								Late-Posttherapy							
	Dirithromycin				Erythromycin				Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable		Favorable		Unfavorable	
Pathogen	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
M catarrhalis	5	83.3	1	16.7	12	100	-	-	3	100	-	-	8	100	-	-
H. influenzae	30	83.3	6	16.7	28	80	7	20	27	96.4	1	3.6	28	93.3	2	6.7
Str pneumonia	59	93.7	4	6.3	47	94	3	6	57	96.6	2	3.4	43	95.6	2	4.4

Serologic Response

Patients with Favorable Clinical Response Posttherapy
AQAB/E003

	Mycoplasma		Legionella		Chlamydia	
	n/d[a]	(%)	n/d	(%)	n/d	(%)
Dirithromycin:						
E003	21/23	(91.3%)	3/3	(100.0%)	17/18	(94.4%)
AQAB	38/41	(92.7%)	14/14	(100%)	N/A	N/A
TOTAL	**59/64**	**(92.2%)**	**17/17**	**(100%)**	**17/18**	**(94.4%)**
Erythromycin:						
E003	21/23	(91.3%)	2/2	(100.0%)	21/23	(91.3%)
AQAB	32/32	(100%)	10/10	(100%)	N/A	N/A
TOTAL	**53/55**	**(96.4%)**	**12/12**	**(100%)**	**21/23**	**(91.3%)**

[a] n = number of patients with favorable response, d = number of evaluable patients

Patients with Favorable Clinical Response Late-Posttherapy
AQAB/E003

	Mycoplasma		Legionella		Chlamydia	
	n/d[a]	(%)	n/d	(%)	n/d	(%)
Dirithromycin:						
E003	20/20	(100.0%)	2/2	(100.0%)	16/17	(94.1%)
AQAB	36/36	(100%)	14/14	(100%)	N/A	N/A
TOTAL	**56/56**	**(100%)**	**16/16**	**(100%)**	**16/17**	**(94.1%)**
Erythromycin:						
E003	18/19	(94.7%)	1/1	(100.0%)	17/19	(89.5%)
AQAB	30/31	(96.7%)	8/8	(100%)	N/A	N/A
TOTAL	**48/50**	**(96%)**	**9/9**	**(100%)**	**17/19**	**(89.5%)**

[a] n = number of patients with favorable response, d = number of evaluable patients

MEDICAL OFFICER'S CONCLUSIONS:

The overall clinical success rate for dirithromycin was comparable to erythromycin at post-therapy and at late post-therapy. The bacteriologic success rate at post-therapy for *H. influenzae* was 83.3% (30/36) for dirithromycin group and 80% (28/35) for the erythromycin group. **(NOTE: 44% of *H. influenzae* were resistant to dirithromycin, thus were considered unevaluable. This success rate only applies to patients who had susceptible organisms.)** The bacteriologic success rate at post-therapy for *S. pneumoniae* was 93.7% (59/63) for dirithromycin group and 94% (47/50) for the erythromycin group. At late post-therapy follow-up, for *H. influenzae* it was 96.4% (27/28) for the dirithromycin group and 93.3% (28/30) for the erythromycin group. The bacteriologic response rate at late post-therapy for *S. pneumoniae* was 96.6% (57/59) for dirithromycin group and 95.6% (43/45) for the erythromycin group.

In patients who were diagnosed only by serology for the atypical microorganisms, the clinical success rate at post-therapy was 59/64 (92.2%) for *M. pneumoniae*, 17/18 (94.4%) for *C. pneumoniae (7/8 of the patients enrolled in the US)* and 17/17 (100%) for *L. pneumophila* in the dirithromycin group, and 53/55 (96.4%) for *M. pneumoniae* , 21/23 (91.3%) for *C. pneumoniae (13/15 of the patients enrolled in the US)* and 12/12 (100%) for *L. pneumophila* in the erythromycin group.
In patients who were diagnosed only by serology for the atypical microorganisms, the clinical success rate at late post-therapy was 56/56 (100%) for *M. pneumoniae*, 16/17 (94.1%) for *C. pneumoniae (7/7 in the US)* and 16/16 (100%) for *L. pneumophila* in the dirithromycin group, and 48/50 (96.0%) for *M. pneumoniae* , 17/19 (89.5%) for *C. pneumoniae (10/12 in the US)* and 9/9 (100%) for *L. pneumophila* in the erythromycin group.

MEDICAL OFFICER'S RECOMMENDATIONS:

Based upon the data submitted and reviewed , the following recommendations are made:

Dirithromycin is recommended for the treatment of pneumonia caused by *S. pneumoniae, M. catarrhalis, M. pneumoniae, L.pneumophila or C. pneumoniae.*

(The total number of patients with pneumonia caused by *M. catarrhalis* were small, but since the cure rate was acceptable, and this organism was also studied in patients with chronic bronchitis, it is recommended for approval.)

Though the clinical and bacteriologic response rates were acceptable for the treatment of *H. influenzae* pneumonia, that organism had more than 44% resistance rate in both the clinical trials submitted for review. It is recommended that the sponsor study either a higher dosage regimen for the treatment of *H. influenzae* pneumonia or twice a day dosage to eradicate this organism.

The recommended dosage is 500 mg once a day for 14 days.

OVERALL SAFETY

A total of 3469 dirithromycin patients , 3106 erythromycin patients and 175 penicillin patients were evaluated for safety.

Frequency of All Adverse Events
Integrated Safety Database Population

	Dirithromycin N = 3469		Macrolide Comparators N = 3106		Pen VK N = 175	
	n	%	n	%	n	%
Patients With At Least One Event	1262	(36.4%)	1071	(34.5%)	118	(67.4
Patients With No Event	2207	(63.6%)	2035	(65.5%)	57	(32.6
Events with a Frequency ≥ 0.5% in the Dirithromycin Treatment Group						
Abdominal Pain	212	(6.1%)	148	(4.8%)	11	(6.3%
Nausea	192	(5.5%)	164	(5.3%)	10	(5.7%
Diarrhea	191	(5.5%)	160	(5.2%)	15	(8.6%
Headache	182	(5.2%)	121	(3.9%)	38	(21.7
Lung Disorder	84	(2.4%)	62	(2.0%)	0	
Rhinitis	74	(2.1%)	67	(2.2%)	30	(17.1
Dyspepsia	57	(1.6%)	37	(1.2%)	8	(4.6%
Vomiting	51	(1.5%)	47	(1.5%)	0	
Chest Pain	46	(1.3%)	43	(1.4%)	0	
Dyspnea	43	(1.2%)	38	(1.2%)	0	
Pain	43	(1.2%)	34	(1.1%)	0	
Asthenia	42	(1.2%)	32	(1.0%)	0	
Pharyngitis	41	(1.2%)	24	(0.8%)	0	
Dizziness	40	(1.2%)	39	(1.3%)	0	
Gastrointestinal Disorder	35	(1.0%)	32	(1.0%)	0	
Asthma	34	(1.0%)	43	(1.4%)	0	
Flatulence	33	(1.0%)	32	(1.0%)	0	
Cough Increased	28	(0.8%)	31	(1.0%)	0	
Back Pain	26	(0.7%)	16	(0.5%)	0	
Rash	26	(0.7%)	39	(1.3%)	0	
Sinusitis	26	(0.7%)	28	(0.9%)	0	
Chills	24	(0.7%)	17	(0.5%)	0	
Pruritus	22	(0.6%)	19	(0.6%)	0	
Hyperventilation	21	(0.6%)	24	(0.8%)	0	
Insomnia	19	(0.5%)	12	(0.4%)	0	
Surgical Procedure	19	(0.5%)	10	(0.3%)	0	
Fever	18	(0.5%)	19	(0.6%)	0	
Ear Pain	17	(0.5%)	11	(0.4%)	0	
Nausea and Vomiting	17	(0.5%)	16	(0.5%)	0	
Injury, Accident	16	(0.5%)	21	(0.7%)	0	
Urinary Tract Infection	15	(0.4%)	8	(0.3%)	0	

Medical Officer's Comments:

Based upon the review of safety data submitted, the adverse events associated with dirithromycin are primarily GI- related. These adverse events are also seen with other macrolides and the frequency is also not unusual.

Medical Officer's Recommendations:

The adverse events related to the GI system should be appropriately addressed in the package insert. The following recommendations are made:

GI tract: Abdominal pain 6%; diarrhea 5.5%; nausea 5.5%; vomiting 1.5%; dyspepsia 1.6%; flatulence 1.0%.

CNS: Headache 5.2%; dizziness 1.2%.

Body as a Whole: Asthenia 1.2%.

There were other adverse events reported with incidence rates of less than 1% . These included insomnia, somnolence, hypersensitivity reactions, and anorexia .

The Medical Officer has addressed the labeling changes in a separate review. Please refer to the MOR dated 7/25/94.

Nasim Moledina, M.D.
Medical Officer, FDA.

cc: Orig NDA 50-678
HFD-340
HFD-520
HFD-520/MO/NMoledina
HFD-520/Pharm/SJoshi
HFD-520/Micro/KCreedon
HFD-520/Chem/DKatague
HFD-520/PMS/MDParker
nm/7/25/94/7/28/94.

Concurrence Only:
HFD-520/ActingDirDir/LGavrilovich
HFD-520/SMO/MSAlbuerne

7/28/94
7/28/94

REVIEW OF THE DRAFT PACKAGE INSERT OF NDA 50-678

Date Submitted: July 20, 1994
Date Review Initiated: July 25, 1994

The review of this package insert was accomplished by the dirithromycin review team of the Division of Anti-Infective Drug Products, and the Division of Biopharmaceutics.

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confidential

commercial

information

Medical Officer's Comments:

A copy of the labeling, identical to the one above, should be supplied to the sponsor with the action letter.

Nasim Moledina, M.D.
Medical Officer, FDA.

cc: Orig NDA 50-678
HFD-340
HFD-520
HFD-520/MO/NMoledina
HFD-520/Pharm/SJoshi
HFD-520/Micro/KCreedon
HFD-520/Chem/DKatague
HFD-520/PMS/MDParker
nm/7/26/94/rev 7/27/94.

Concurrence Only:
HFD-520/ActingDirDir/LGavrilovich
HFD-520/SMO/MSAlbuerne 7/27/94