CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-678/SE1-003

MEDICAL REVIEW(S)

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NDA 50-678

MEDICAL OFFICER'S REVIEW OF NDA 50-678

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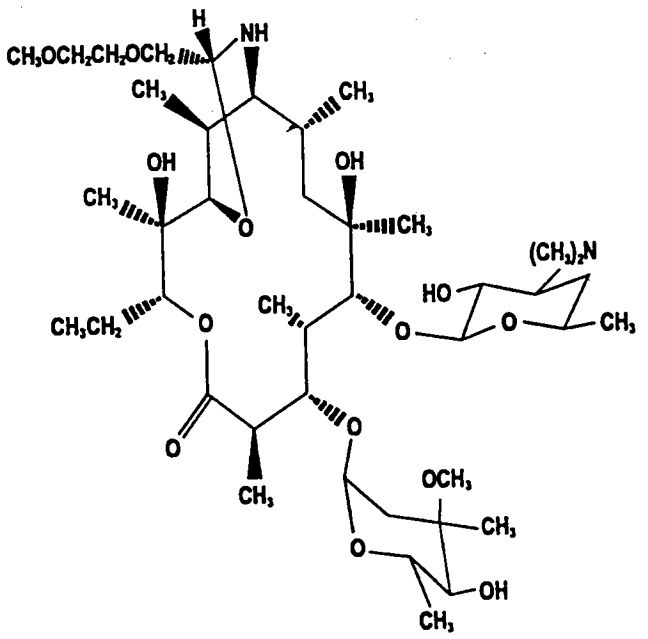
Date Submitted: April 27, 1993.
Amendment #1: February 3, 1994.
MOR Initiated: March 8, 1994.
MOR Completed: July 22, 1994.

APPLICANT: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG:
Generic: Dirithromycin
Trade Name: Dynabac®
Chemical Name: (9*S*)-9-deoxo-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy)ethylidene]oxy] erythromycin

Chemical Structure:



Molecular Formula: $C_{42}H_{78}N_2O_{14}$
Molecular Weight: 835.09

Pharmacologic Category:	Macrolide - Antibiotic
Dosage Form:	250 mg tablet
PROPOSED INDICATIONS:	Treatment of pharyngitis/tonsillitis, skin and skin structure infections, acute exacerbation of chronic bronchitis, superimposed bacterial infection of acute bronchitis and pneumonia caused by various gram-postitive and gram-negative organisms.
SUBMISSION REVIEWED:	Controlled and uncontrolled studies conducted in the US and several foreign countries. Volumes 1.1 to 1.293 reviewed.

MANUCATURING CONTROLS:

Refer to the chemistry review by Dr. Katague.

MICROBIOLOGY REVIEW:

Refer to the microbiology review by Dr. Kathy Creedon.

NONCLINCIAL PHARMOCOLOGY/BIOAVAILABILITY:

Refer to the pharmocology and toxicology review by Dr. Joshi.

HUMAN PHARMACOKINETICS/BIOAVAILABILITY:

Please refer to Dr. Ajayi's review.

SYNOPSIS:

Chemistry

Dirithromycin, a new antibiotic for oral administration, belongs to the macrolide class of antibiotics. Dirithromycin is a 14-membered lactone ring macrolide and is derived from erythromycin. Dirithromycin is the C-9 oxazine derivative of erythromycylamine formed by the condensation of methoxyacetaldehyde and erythromycylamine. Erythromycylamine is formed by the reductive amination of the C-9 ketone of erythromycin. Upon oral administration, dirithromycin is nonenzymatically hydrolyzed to erythromycylamine, which is microbiologically active.

Microbiology

The mode of action of dirithromycin and its metabolite, erythromycylamine, is the same as that of erythromycin and other macrolide antibiotics in that they inhibit RNA-dependent protein synthesis by stimulating the dissociation of peptidyl tRNA from ribosomes [Auckenthaler, Zwahlen, and Waldvogel, 1987]. Macrolide antibiotics reversibly bind to the 50S ribosomal subunit and block the P-site, resulting in impaired transpeptidation and/or translocation. The structure-activity relationship of erythromycin is thought to be due to the 3-dimensional conformation of the entire compound with ribosomal attachment probably involving the 2 sugars and the 2, 3, and 4 carbon atoms of the aglycone ring [Barber, Gyi, and Pye, 1991].

Dirithromycin and erythromycylamine have similar antimicrobial spectrum and potency to erythromycin with activity against *Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Moraxella catarrhalis, Legionella pneumophila, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae* [Counter et al, 1991; Hardy et al, 1988]. The antimicrobial spectrum provides good activity against the most common causes of respiratory and cutaneous infections.

Pharmacology/Toxicology

Preclinical pharmacology studies of dirithromycin were performed in mice, rats, guinea pigs, cats, and dogs. No significant pharmacologic effects were noted on central nervous, gastrointestinal, renal, cardiovascular, hematologic, and immune systems or isolated smooth or cardiac muscle tissue at doses representing significant multiples of the therapeutic doses. The most notable finding in toxicology studies was the development of cardiac and skeletal muscle histopathologic changes associated with high tissue concentrations well above those tissue concentrations observed in man with the intended dose. The tissue concentrations declined and the histopathologic changes reversed with drug discontinuation. No mutagenic, teratogenic, or reproductive effects were seen; lifetime studies to evaluate carcinogenic potential have not been performed.

Pharmacokinetics

Dirithromycin is rapidly absorbed and widely distributed throughout the body. Dirithromycin is rapidly converted by nonenzymatic hydrolysis during absorption to erythromycylamine, which is microbiologically active. Rapid distribution of dirithromycin and erythromycylamine into tissues and high concentrations within cells results in significantly higher concentrations in tissues than in plasma or serum [Bergogne-Berezin, 1992].

In man, following an oral 500-mg dose of dirithromycin, average peak plasma concentrations of μg/mL were observed at 4 hours [Sides et al, 1992]. The area under the plasma concentration versus time curve (AUC_{0-24h}) measured μg·hr/mL. The protein binding of circulating dirithromycin and its metabolite, erythromycylamine, ranged between 15% and 30%. Dirithromycin achieved tissue concentrations of 0.59, 3.47, 3.79, 3.85, 1.70, and 6.52 μg/g in nasal mucosa, tonsil, healthy lung, pathologic lung, bronchial mucosa, and prostate tissue, respectively. Tissue/plasma concentration ratios ranged from

Dirithromycin and erythromycylamine undergo little or no hepatic metabolism. The primary route of elimination is fecal/hepatic, with 81% to 97% of the dose eliminated in this manner. Dirithromycin and erythromycylamine are eliminated in the bile. Approximately 2% of the dose is eliminated renally. Dirithromycin has an elimination half-life of 44 (16 to 65) hours and an apparent volume of distribution (V_{Dss}) of 800 L (504 to 1,041 L) in patients with normal renal function [Bozler et al, 1988]. Dirithromycin does not accumulate in plasma with multiple-dose administration for 21 days [Black et al, 1989].

The sponsor is requesting the approval of the following Indications and Dosage:

Pharyngitis/Tonsillitis due to *Streptococcus pyogenes*

Acute Bacterial Exacerbations of Chronic Bronchitis due to *Moraxella catarrhalis, S. aureus, or Streptococcus pneumoniae*

Secondary Bacterial Infection of Acute Bronchitis due to *H. influenzae, H. parainfluenzae, Moraxella catarrhalis, or Streptococcus pneumoniae*

Pneumonia caused by *Chlamydia pneumoniae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, or Streptococcus pneumoniae*

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus , Staphylococcus epidermidis, or Streptococcus pyogenes* (Abscesses usually require surgical drainage.)

The dose in individuals over 12 years of age is 500 mg (two 250-mg tablets) once a day.

Infection	Duration (Days)
Pharyngitis/Tonsillitis	10
Acute Bacterial Exacerbations of Chronic Bronchitis	7
Secondary Bacterial Infection of Acute Bronchitis	7
Pneumonia	10-14
Uncomplicated Skin and Skin Structure Infections	7

ROUTINE LABORATORY TEST VALUES:

The reference values for the laboratory tests used in all the pivotal studies are given in the table below:

ROUTINE LABORATORY TEST VALUES UPDATE 1988

REFERENCE RANGES

Analyte	Age in years:	Male				Female				Delta Limits	
		Caucasian		Non-Caucasian		Caucasian		Non-Caucasian			
Liver	Units	< 50	>49	< 50	>49	< 50	>49	< 50	>49	Low	High
ALT	U/L	7-112	5-97	5-121	4-84	5-88	5-77	4-46	4-85	-27	27
AST	U/L	10-76	10-79	11-114	7-85	9-65	10-63	9-73	11-71	-25	20
GGT	U/L	6-174	5-149	7-320	5-250	5-123	4-162	5-108	5-113	-28	28
Alk. Phosphatase	U/L	28-135	24-150	33-144	27-146	28-123	25-154	29-135	22-182	-46	28
Bilirubin	µmol/L	3-32	3-32	3-29	3-24	3-22	3-21	3-21	2-19	-16	16
Muscle											
Creatine Kinase	U/L	15-640	5-363	27-1070	15-940	0-243	0-223	13-345	10-453	-279	224
Kidney											
Creatinine	µmol/L	62-141	62-168	71-168	71-186	53-115	53-141	53-124	44-141	-35	35
Urea	mmol/L	2.5-9.3	2.9-11.1	2.1-9.3	2.1-12.1	1.4-7.9	2.5-10.7	1.8-7.1	2.5-11.1	-3.2	3.2
Uric Acid	µmol/L	178-571	196-589	190-607	220-630	101-494	137-547	125-529	167-619	-125	19
Phosphate(i)	mmol/L	0.77-1.58	0.71-1.49	0.77-1.61	0.74-1.58	0.74-1.58	0.81-1.58	0.81-1.55	0.81-1.61	-0.45	39
Calcium	mmol/L	2.12-2.64	2.10-2.62	2.07-2.64	2.10-2.64	2.10-2.62	2.12-2.64	2.05-2.64	2.10-2.59	-0.30	30
Electrolytes											
Sodium	mmol/L	134-147	133-148	135-150	134-149	132-146	134-150	134-150	134-152	-6	8
Potassium	mmol/L	3.4-5.5	3.3-5.4	3.0-5.5	3.0-5.4	3.1-5.3	3.3-5.5	3.1-5.3	3.0-5.3	-1.1	1.1
Chloride	mmol/L	96-112	95-111	96-110	95-111	95-112	94-112	97-112	93-111	-9	8
Bicarbonate	mmol/L	20-35	21-35	21-36	21-36	20-34	21-35	20-35	21-36	-7	8
Nutritional											
Glucose	mmol/L	3.7-11.9	3.9-13.5	3.8-9.5	3.9-14.7	3.9-8.9	3.9-15.2	3.8-15.3	3.9-19.1	-3.1	3.4
Albumin	g/L	36-52	34-50	34-52	33-49	34-50	34-50	33-49	33-49	-7	6
Protein	g/L	62-83	62-82	63-86	62-87	61-83	62-83	64-87	63-86	-11	10
Cholesterol	mmol/L	3.06-6.46	3.49-6.59	2.79-6.51	2.92-6.95	3.13-6.12	3.73-8.31	3.34-7.73	3.78-8.72	-1.84	1.76
HDL Cholesterol	mmol/L	0.44-2.07	0.44-2.17	0.47-2.48	0.41-2.23	0.54-2.72	0.57-2.56	0.52-2.51	0.52-2.64	-0.85	0.80
LDL Cholesterol	mmol/L	1.50-5.95	1.68-6.05	1.22-6.26	1.42-6.43	1.27-5.90	1.81-6.23	1.18-5.82	1.81-6.83	-1.99	1.81
Triglycerides	mmol/L	0.54-10.21	0.53-8.74	0.50-8.99	0.51-6.05	0.40-7.23	0.58-6.21	0.41-6.36	0.52-4.41	-3.09	2.86
Erythrocytes											
Hemoglobin (Fe)	mmol/L	8.00-11.29	7.51-11.40	6.83-11.23	6.60-10.98	6.80-10.30	7.10-10.43	6.21-10.30	6.27-10.18	-1.24	1.24
Erythrocytes	T/L	4.2-6.1	4.0-6.2	3.9-6.4	3.7-6.4	3.8-5.8	3.8-5.7	3.7-5.7	3.5-6.0	-0.7	0.7
Hematocrit	l	0.38-0.55	0.38-0.55	0.34-0.55	0.33-0.54	0.34-0.50	0.34-0.51	0.31-0.51	0.33-0.50	-0.07	0.06
MCV	fL	78-105	78-106	72-105	73-104	78-102	78-105	67-102	72-102	-8	7
MCH (Fe)	fmol	1.60-2.17	1.61-2.23	1.40-2.17	1.37-2.11	1.50-2.11	1.60-2.17	1.24-2.05	1.43-2.11	-0.19	0.20
MCHC (Fe)	mmol/L	19-23	19-23	19-23	18-22	19-23	19-23	18-23	19-22	-2	2
Leukocytes											
Leukocytes	G/L	3.5-13.8	3.4-12.8	2.9-13.5	2.9-11.7	3.5-13.5	3.7-12.4	3.2-13.6	3.1-11.4	-4.0	3.7
Bands	G/L	0-0.74	0-0.76	0-0.33	0-0.36	0-1.06	0-0.81	0-0.39	0-0.20	-0.30	0.28
Neutrophils	G/L	1.82-8.31	1.81-8.93	1.10-9.24	1.25-8.01	1.72-8.90	1.79-8.86	1.18-8.77	1.27-7.60	-3.48	3.15
Lymphocytes	G/L	0.86-4.62	0.84-4.37	0.93-4.95	0.84-4.37	1.02-4.34	0.90-4.47	0.86-4.51	0.95-4.54	-1.63	1.54
Monocytes	G/L	0-0.89	0-0.83	0-0.81	0-0.78	0-0.82	0-0.86	0-0.80	0-0.71	-0.44	0.48
Eosinophils	G/L	0-0.71	0-0.67	0-0.81	0-0.59	0-0.69	0-0.58	0-0.67	0-0.54	-0.39	0.39
Basophils	G/L	0-0.19	0-0.18	0-0.15	0-0.14	0-0.19	0-0.17	0-0.16	0-0.15	-0.13	0.14
Platelets	G/L	136-410	134-432	142-394	139-457	154-461	146-447	148-455	NA	-88	93
Urine											
Specific Gravity	-	1.006-1.036	1.005-1.034	1.007-1.036	1.006-1.036	1.005-1.036	1.005-1.036	1.007-1.037	1.005-1.034	-0.017	0.017
pH	-	5.0-8.0	5.0-8.0	5.0-8.0	5.0-8.0	5.0-8.0	5.0-7.5	5.0-7.5	5.0-8.0	2.0	2.0

CLINICAL STUDIES:

INDICATION: STREPTOCOCCAL PHARYNGITIS/TONSILLITIS

OVERVIEW OF ALL STUDIES:

STUDIES CONDUCTED IN THE U.S.A.:

I. Study B9Z-MC-AQAB: Double blind, randomized, comparative study using erythromycin as the comparative drug.

II. Study B9Z-MC-AQAS: Double blind, randomized, comparative study using erythromycin as the comparative drug.

III. Study B9Z-MC-AQAV: Double blind, randomized, comparative study using penicillin VK as the comparative drug.

FOREIGN STUDIES:

I. Study B9Z-EW-E001: Double blind, randomized, comparative study using erythromycin as the comparative drug.

The sponsor is requesting the following indication and proposed dosage recommendations:

Upper Respiratory Tract Infections:

Pharyngitis/Tonsillitis	Streptococcus pyogenes (Group A β-hemolytic streptococci)	
	Dosage	Normal Duration
	500mg	10 Days

REVIEW OF PIVOTAL STUDIES:

These studies were conducted in the U.S.A.:

I. Study B9Z-MC-AQAB Synopsis:

Title: Dirithromycin versus Erythromycin Base in Streptococcal Pharyngitis/Tonsillitis.

Study Centers: There were 38 active study centers.

Dates of Study: October 7, 1988 - August 8, 1990

Clinical Phase: Phase 2-3

Objectives:
To compare dirithromycin with erythromycin base for effectiveness and safety in the treatment of pharyngitis/tonsillitis caused by group A beta-hemolytic streptococci.

Methodology: Double-blind, double-dummy, randomized, parallel study.

Number of Patients:
Dirithromycin: male 95, female 170, total 265.
Erythromycin: male 107, female 181, total 288.

Diagnosis:
Pharyngitis/tonsillitis with confirmed susceptible group A β-hemolytic streptococcal etiology.

Dosage and Administration:

Test Product
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.

Reference Therapy
Erythromycin Base: 1000 mg/day (one 250- mg tablet q.i.d.)
CT9369, CT9371, CT9966: erythromycin base tablets, 250 mg
CT9370, CT9967: placebo tablets
NOTE: Placebo was used to maintain blinding.

Duration of Treatment: Dirithromycin: 10 days
Erythromycin Base: 10 days

Criteria for Evaluation:

Efficacy--A complete efficacy evaluation was performed on patients completing 10 days of therapy who had positive pretherapy throat culture, returned for the during therapy, posttherapy and the late-posttherapy clinical evaluation and culture, 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:

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 to be 10 days.

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

Inclusion Criteria

Patients were male and female 12 years of age or older, weigh at least 37 kg, and be able to swallow tablets. Patients were to be included if they had a clinical diagnosis of streptococcal pharyngitis/tonsillitis and a positive test with a "rapid strep test" (Hybritech ICON Strep A kits were provided by the sponsor). Patients who had a negative test but a positive culture for group A streptococcus were to be enrolled in the study (consented) if the culture was obtained within 24 hours prior to commencing study drug therapy and the patient had not received treatment with a systemic antimicrobial agent since the initial screening.

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 required to sign an IRB-approved informed consent document.

Exclusion Criteria

Patients were to be excluded if they 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 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 any antimicrobial therapy within 1 week preceding the pretherapy evaluations; or had used other investigational agents within 21 days prior to entry into study.

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

Dosing Schedule:

Patients who were 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 who were 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 were to be performed.
During Therapy (Days 3-5):	Symptomatic response to therapy and patient compliance with instructions for taking medication were to be assessed.
Posttherapy (3-5 Days After Therapy Was Completed):	Physical examination was to be performed to evaluate symptomatic response to therapy.
Late-posttherapy (3-5 Weeks After Therapy Was Completed):	Physical examination was to be performed to evaluate recurrence of pharyngitis or tonsillitis. Failure of a patient to return for this late-posttherapy visit would disqualify the case for evaluation of efficacy.

PROCEDURES FOR EVALUATION OF BACTERIOLOGIC RESPONSE:

Study Visit	Procedure
Pretherapy (Within 24 Hours Preceding Start of Therapy)	All patients were to be screened with a rapid streptest before admission . (Study sites were provided with Hybritech ICON Strep tests by the sponsor.) Only those patients with a positive test (or a negative test but a known positive culture) were to be admitted (consented). For patients entered on the basis of a positive test, the culture at entry must have been positive for group A streptococci for the patient to have qualified for efficacy analysis. If group A streptococci was to be isolated at pretherapy, the isolate was to be saved. If group A streptococci was subsequently isolated at during therapy, posttherapy, or late-posttherapy, the paired isolates were to be sent to a central bacteriology laboratory for serotyping. Patients with only a positive pretherapy culture were not to have isolates sent for serotyping. Serotyping was to be performed to determine if a positive culture in the follow-up period was due to recurrence of the same strain or occurrence of a new strain of streptococcus. For the swab procedure, it was important to use only dacron- or rayon-tipped swabs with plastic shafts; wooden shafts would absorb the extracted samples and cotton tips might interfere with the assay. Materials were supplied by the sponsor. Serum for an antistreptolysin-0 (ASO) titer was to be obtained and sent to the central laboratory during Phase 2.

Study Visit	Procedure
Pretherapy (Within 24 Hours Preceding Start of Therapy) (continued)	Susceptibility of the microorganism(s) isolated to both dirithromycin and erythromycin was to be 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.
Study Period During Therapy (Days 3-5):	Procedure Throat culture was required. If culture was positive for group A streptococci, susceptibility to dirithromycin and erythromycin was to be determined. Subcultures were to be mailed for serotyping of paired isolates.
Posttherapy (3-5 Days After Therapy Was Discontinued):	Throat culture was required. If culture was positive for group A streptococci, susceptibility to dirithromycin and erythromycin was to be determined. Subcultures were to be mailed for serotyping of paired isolates.
Late-posttherapy (3-5 Weeks After Antibiotic Was Discontinued):	Throat culture was required. If culture was positive for group A streptococci, susceptibility to dirithromycin and erythromycin was to be determined. Subcultures were to be mailed for serotyping of paired isolates. Serum for an ASO titer was to be obtained and sent to the central laboratory during Phase 2. Failure of a patient to return for this visit disqualified the case for inclusion in efficacy evaluations (patients that were culture negative and/or symptomatically cured/improved at the posttherapy visit only).
Erythromycin Susceptibility:	≥18 mm zone size; ≤0.5 µg/mL MIC

Safety Procedures:

Safety assessments were to include clinical evaluations and laboratory tests. Electrocardiograms (ECG's) were to be performed during Phase 2. A central laboratory was to be used to determine values for the laboratory tests described below. 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 Hemoglobin Hematocrit RBC Count MCV MCH MCHC WBC Count Differential Count Platelet Count Morphology	Blood Chemistry Phosphorus Calcium Glucose Cholesterol Total Bilirubin Alkaline Phos. GGT ALT (SGPT) AST (SGOT) Urea Nitrogen Creatinine Uric Acid Total Protein Albumin Creatine Kinase*	Urinalysis Appearance Specific Gravity pH Protein Glucose Ketones Bilirubin Urobilinogen Blood Nitrite Leukocyte Esterase Microscopic - WBC RBC Casts
During Therapy (Day 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 (3-5 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 Creatine Kinase (CK) was greater than 1000 U/L, the central laboratory was to notify the site and ran a CK isoenzyme fractionation. The laboratory was to 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 was to 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.

Electrocardiograms (ECG's) were to be taken at the pretherapy and posttherapy visits during the Phase 2 portion of the drug development program. Electrocardiograms were to be mailed to a central site for interpretation. If clinically important abnormalities were noted, ECG's were to be repeated at the late-posttherapy visit or sooner if clinically indicated.

All patients, parents, or guardians 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 Lilly Research Physician by prompt submission of the patient's clinical report form. If any adverse event was alarming, it was to be reported immediately by phone to the Lilly 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 the 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 symptomatic and/or bacteriologic failure of the study antibiotic at any time during treatment.
- 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 to be stated on the clinical report form.
- 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 throat cultures repeated.

Efficacy Procedures:

SYMPTOMATIC RESPONSE DEFINITIONS

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

* The use of failure for cases requiring the addition of another antibiotic was to be 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.

BACTERIOLOGIC RESPONSE DEFINITIONS

Result	Definition of Response
Pathogen Eliminated:	Eradication of the pathogen at post-treatment and late post-treatment periods
Recurrence Same Pathogen:	Original pathogen eliminated during treatment but recurred during the post-treatment and late post-treatment follow-up periods
Recurrence Same Pathogen, Resistance Developed:	Original pathogen susceptible to erythromycin was eliminated during treatment but recurred in the post-treatment and late post-treatment follow-up periods and tested as resistant to erythromycin.
Recurrence New Pathogen (Different Serotype):	Original pathogen susceptible to erythromycin was eliminated during treatment but a new pathogen (serotype) was isolated in the post-treatment and late post-treatment follow-up periods.
Failure:	Original pathogen was not eradicated.
Unable to Evaluate:	Term used when cultures were not obtained, a systemic (nonstudy) antimicrobial agent with activity against group A streptococci was taken, or when a pretherapy culture was negative for group A streptococci.

NOTE: To allow distinction between cases of bacteriologic relapse with the same strain of group A streptococci vs reinfection with a new strain, paired isolates from patients having positive follow-up throat cultures were to be sent to a central laboratory for serotyping. In cases where paired isolates were not serotyped, positive follow-up cultures were to be assumed to represent recurrence of the original infecting strain.

Investigators:

A total of 38 investigators enrolled 553 patients.

INVESTIGATOR NAME/LOCATION	NUMBER OF ENROLLED PATIENTS DIR	ERY	NUMBER OF EVALUABLE PATIENTS DIR	ERY
J. M. APPLESTEIN/SAN DIEGO, CA	1	0	1	0
D. H. LEHMAN/SACRAMENTO, CA	4	9	4	7
J. M. SELTZER/SAN DIEGO, CA	8	9	4	2
F. L. BROWN/PHILADELPHIA, PA	1	1	1	1
N. LANG/PHILADELPHIA, PA	6	5	4	4
S. HEATLEY/REDWOOD CITY, CA	2	2	1	1
R. R. STOLTZ/EVANSVILLE, IN	27	22	14	15
D. P. WRIGHT/AUSTIN, TX	3	3	0	0
C. W. WEART/CHARLESTON, SC	11	18	8	10
R. E. SCHNEIDER/CHARLOTTE, NC	7	8	3	2
P. BARDEN/ALBUQUERQUE, NM	1	3	1	1
R. C. HASELBY/MARSHFIELD, WS	14	11	12	9
H. COLLINS/EDISON, NJ	23	20	19	11
C. B. GOSWICK, JR/BRYAN, TX	10	9	7	6
M. S. WAXMAN/NORTH ARLINGTON, NJ	0	1	0	0
B. D. REED/ANN ARBOR, MI	2	2	2	1
M. BARREIRO, BINGHAMTON, NY	3	1	1	0
W. G. GARDNER/AKRON, OH	6	9	3	6
B. I. ASMAR/DETROIT, MI	2	3	1	1
G. M. BREITZER/EAST LANSING, MI	2	1	1	1
L. E. DAVIS/KNOXVILLE, TN	4	4	2	1
E. G. FENNELL/JOHNSON CITY, TN	5	5	3	4
F. P. MICHAEL/DETROIT/MI	7	9	2	4
H. H. MIDDLETON, III/ALBUQUERQUE, NM	2	3	0	0
E. B. SCOTT/PELLETIER/WEST MONROE, LA	0	1	0	0
S. CROSBY/JACKSON, AL	4	6	4	4
B. TUCKER/BIRMINGHAM, AL	5	3	1	1
J. C. ROTSCHAFER/ST. PAUL, MN	14	14	11	10
D. SIMONS-MORTON/HOUSTON, TX	9	13	3	5
P. R. OLSON/ASHEVILLE, NC	1	0	0	0
C. M. HETSKO/MADISON, WI	3	3	3	3
K. C. EDMUNDS/SALEM, VA	10	10	9	8
F. J. GUERRA/EL PASO, TX	5	7	4	3
D. WALLACK/LITTLETON, CO	13	15	8	11
D. G. MILLER/MOORESVILLE, PA	10	13	4	8
D. W. BARTELS/BELVIDERE, IL	10	12	8	8
S. C. PARMAN/MIDDLETOWN, NJ	14	14	12	9
J. M. MCCARTY/FRESNO, CA	16	19	8	10
TOTAL	265	288	169	167

Sponsor's Analysis:

Patient disposition was as follows:

	DIRITH	ERYTH	TOTAL
Patient Enrolled	265	288	553
Evaluable for Efficacy	169	167	336
Completed Therapy	145	149	312
Prematurely Discontinued	24	18	42
Not Evaluable	96	121	217
Completed Therapy	5	6	11
Prematurely Discontinued	91	115	206

Primary diagnosis:	**Pharyngitis**	**Tonsillitis**
Dirithromycin		
All patients	231	34
Evaluable patients	151	18
Erythromycin		
All patients	249	39
Evaluable patients	147	20

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

Patient Demographics:

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

All Patients

AGE RANGES BY SEX - ALL PATIENTS

AGE RANGES	DIRITHROMYCIN FEMALE (N=170) N (%)	DIRITHROMYCIN MALE (N=95) N (%)	DIRITHROMYCIN TOTAL (N=265) N (%)	ERYTHROMYCIN FEMALE (N=181) N (%)	ERYTHROMYCIN MALE (N=107) N (%)	ERYTHROMYCIN TOTAL (N=288) N (%)
	13 (7.6%)	16 (16.8%)	29 (10.9%)	15 (8.3%)	9 (8.4%)	24 (8.3%)
	62 (36.5%)	41 (43.2%)	103 (38.9%)	48 (26.5%)	33 (30.8%)	81 (28.1%)
	82 (48.2%)	37 (38.9%)	119 (44.9%)	102 (56.4%)	59 (55.1%)	161 (55.9%)
	12 (7.1%)	1 (1.1%)	13 (4.9%)	13 (7.2%)	6 (5.6%)	19 (6.6%)
	1 (0.6%)	0	1 (0.4%)	3 (1.7%)	0	3 (1.0%)

AGE BY SEX (YR) - MEAN, MEDIAN, MINIMUM AND MAXIMUM--ALL PATIENTS

	DIRITHROMYCIN FEMALE	DIRITHROMYCIN MALE	DIRITHROMYCIN TOTAL	ERYTHROMYCIN FEMALE	ERYTHROMYCIN MALE	ERYTHROMYCIN TOTAL
NUMBER OF PATIENTS	170	95	265	181	107	288
MEAN AGE	28.75	24.36	27.18	29.66	28.21	29.12
STD DEV	10.60	8.40	10.07	11.14	9.78	10.66
MEDIAN AGE	26.53	22.32	25.11	28.13	27.75	28.03
MINIMUM AGE						
MAXIMUM AGE						

RACIAL ORIGIN BY TREATMENT GROUP--ALL PATIENTS

	DIRITHROMYCIN N=265		ERYTHROMYCIN N=288	
	N	(%)	N	(%)
CAUCASIAN	196	(74.0%)	201	(69.8%)
BLACK	54	(20.4%)	58	(20.1%)
HISPANIC	10	(3.8%)	27	(9.4%)
NATIVE AMERICAN	1	(0.4%)	0	
ASIAN	0		1	(0.3%)
OTHER	4	(1.5%)	1	(0.3%)

HEIGHT AND WEIGHT AT ADMISSION--ALL PATIENTS

	HEIGHT IN CM						WEIGHT IN KG					
	NO.	UNK	MEAN	STD DEV	MIN	MAX	NO.	UNK	MEAN	STD DEV	MIN	MAX
THERAPY												
DIRITHROMYCIN	263	2	168.29	11	144	201	263	2	72.69	18	38	127
ERYTHROMYCIN	284	4	167.75	10	142	193	286	2	74.57	20	41	182

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Evaluable Patients:

Age Ranges by Sex-Evaluable Patients

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE (N = 113)		MALE (N = 56)		TOTAL (N = 169)		FEMALE (N = 111)		MALE (N = 56)		TOTAL (N = 167)	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	7	(6.2%)	9	(16.1%)	16	(9.5%)	11	(9.9%)	5	(8.9%)	16	(9.6%)
	44	(38.9%)	26	(46.4%)	70	(41.4%)	25	(22.5%)	14	(25.0%)	39	(23.4%)
	55	(48.7%)	20	(35.7%)	75	(44.4%)	66	(59.5%)	35	(62.5%)	101	(60.5%)
	7	(6.2%)	1	(1.8%)	8	(4.7%)	8	(7.2%)	2	(3.6%)	10	(6.0%)
	0		0		0		1	(0.9%)	0		1	(0.6%)

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

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	113	56	169	111	56	167
MEAN AGE	28.51	24.33	27.12	29.47	28.19	29.04
STD DEV	9.54	8.64	9.43	10.69	8.55	10.01
MEDIAN AGE	26.37	22.11	24.62	28.89	28.63	28.88
MINIMUM AGE						
MAXIMUM AGE						

Origin By Therapy Group-Evaluable Patients

ORIGIN	DIRITHROMYCIN N = 169 n	(%)	ERYTHROMYCIN N = 167 n	(%)	TOTAL N = 336 n	(%)
CAUCASIAN	130	(76.9%)	126	(75.4%)	256	(76.2%)
BLACK	31	(18.3%)	30	(18.0%)	61	(18.2%)
HISPANIC	4	(2.4%)	11	(6.6%)	15	(4.5%)
NATIVE AMERICAN	1	(0.6%)	0		1	(0.3%)
OTHER	3	(1.8%)	0		3	(0.9%)

Height and Weight at Admission-Evaluable Patients

THERAPY	HEIGHT IN CM N	UNK	MEAN	STD DEV	MIN	MAX	WEIGHT IN KG N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	169	0	167.98	11	144	201	169	0	72.82	18	38	127
ERYTHROMYCIN	167	0	167.62	10	142	190	167	0	74.24	20	41	142

Drug Administration:

All Patients

EXPOSURE TO STUDY DRUGS--
MEAN, MINIMUM, AND MAXIMUM--ALL PATIENTS

	DIRITHROMYCIN N = 265 DAYS	ERYTHROMYCIN N = 288 DAYS
NUMBER OF PATIENTS	258	280
MEAN DURATION EXPOSURE	9.5	9.2
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	7	8

SUMMARY OF EXPOSURE TO STUDY DRUGS--ALL PATIENTS

DAYS OF THERAPY	DIRITHROMYCIN N = 265 n (%)		ERYTHROMYCIN N = 288 n (%)	
PATIENTS WITH INCOMPLETE DATA	7	(2.6%)	8	(2.7%)
1	7	(2.6%)	6	(2.0%)
2	8	(3.0%)	7	(2.4%)
3	10	(3.7%)	10	(3.4%)
4	12	(4.5%)	23	(7.9%)
5	7	(2.6%)	12	(4.1%)
6	5	(1.8%)	8	(2.7%)
7	4	(1.5%)	4	(1.3%)
8	3	(1.1%)	5	(1.7%)
9	2	(0.7%)	3	(1.0%)
10	80	(30.1%)	78	(27.0%)
11	88	(33.2%)	93	(32.2%)
12	11	(4.1%)	11	(3.8%)
13	7	(2.6%)	3	(1.0%)
14	4	(1.5%)	10	(3.4%)
15	7	(2.6%)	3	(1.0%)
16	0		1	(0.3%)
17	2	(0.7%)	1	(0.3%)
18	1	(0.3%)	2	(0.6%)

Evaluable Patients:

The following 2 tables depict the treatment duration for both the study drug and the reference drug:

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

	DIRITHROMYCIN N = 169 DAYS	ERYTHROMYCIN N = 167 DAYS
NUMBER OF PATIENTS	169	167
MEAN DURATION EXPOSURE	10.9	10.9
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs-Evaluable Patients

	DIRITHROMYCIN N = 169		ERYTHROMYCIN N = 167	
DAYS OF THERAPY	n	(%)	n	(%)
2	0		1	(0.6%)
3	1	(0.6%)	0	
4	2	(1.2%)	1	(0.6%)
6	1	(0.6%)	0	
7	1	(0.6%)	0	
9	0		1	(0.6%)
10	62	(36.7%)	59	(35.3%)
11	74	(43.8%)	82	(49.1%)
12	9	(5.3%)	9	(5.4%)
13	7	(4.1%)	3	(1.8%)
14	3	(1.8%)	7	(4.2%)
15	6	(3.6%)	3	(1.8%)
16	0		1	(0.6%)
17	2	(1.2%)	0	
18	1	(0.6%)	0	

Medical Officer's Comment:
80% of the evaluable patients in the dirithromycin group and 84% of the patients in the erythromycin group were treated for 10 - 11 days.

Unevaluable Patients

The folowing patients were excluded from the efficacy analysis, and the reasons for exclusion were as follows:

REASON UNEVALUABLE SUMMARY--ALL PATIENTS

INDICATION: PHARYNGITIS/TONSILLITIS

REASON UNEVALUABLE	DIRITHROMYCIN N = 265 n (%)	ERYTHROMYCIN N = 288 n (%)
PATIENTS WITH =>1 REASON	96 (36.2%)	121 (41.8%)
INSUFFICIENT THERAPY	48	71
CAUS. ORG. UNIDENT.	23	32
UNEVAL. BY INVEST.	24	16
CAUS. ORG. RESISTANT	18	29
SENSITIVITY NOT DONE	16	13
UNACCEPT. PATHOGEN	13	16
NO COLONY COUNT	14	15
NO POST THER. CULTURE	14	14
NO FOLLOW-UP CULTURE	8	10
INCOMPLETE DATA	8	8
SEQUENTIAL THERAPY	1	6
LOW COLONY COUNT	2	5
NO INITIAL CULTURE	2	3
PROTOCOL VIOLATED	4	2
NO POST FOLLOW-UP	1	3
INITIAL CULT. EARLY	2	1
NO THERAPY	1	2
POST THER. CULT. LATE	0	2
BLIND BROKEN	1	0
POOR COMPLIANCE	0	1
BREAK IN THERAPY	0	1

Efficacy Evaluation:

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

RESPONSE	DIRITHROMYCIN N = 169 n (%)	ERYTHROMYCIN N = 167 n (%)
CURE	141 (83.4%)	139 (83.2%)
IMPROVEMENT	18 (10.7%)	19 (11.4%)
RELAPSE	6 (3.6%)	5 (3.0%)
FAILURE	4 (2.4%)	4 (2.4%)

An overall favorable clinical (cure or improvement) was seen in 159/169 (94.1%) dirithromycin-treated patients and in 158/167 (94.6%) erythromycin-treated patients.

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

RESPONSE	DIRITHROMYCIN N = 153 n (%)	ERYTHROMYCIN N = 151 n (%)
CURE	131 (85.6%)	129 (85.4%)
IMPROVEMENT	3 (2.0%)	5 (3.3%)
RELAPSE	19 (12.4%)	17 (11.3%)

An overall favorable clinical (cure or improvement) was seen in 134/153 (87.6%) dirithromycin-treated patients and in 134/151 (88.7%) erythromycin-treated patients.

The clinical response for evaluable patients at termination* according to the applicant as follows:

	THERAPY GROUP										
	DIRITHROMYCIN					ERYTHROMYCIN					
	TERMINATION					TERMINATION					
	FAVOR		UNFAVO		TOTAL	FAVOR		UNFAVO		TOTAL
	N	%	N	%	N	N	%	N	%	N
PROJECT										
AQAB	140	82.8	29	17.2	169	141	84.4	26	15.6	167

* - Termination: This was the evaluation done on all patients entered in the study who were considered to be evaluable at entry, and who were followed up till the study terminated.

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

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Bacteriologic Response

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

RESPONSE	DIRITHROMYCIN N = 167 n (%)	ERYTHROMYCIN N = 165 n (%)
PATHOGEN ELIMINATED	134 (80.2%)	144 (87.3%)
RECURRENCE SAME	15 (8.9%)	12 (7.2%)
RECURRENCE SAME, RESISTANCE	2 (1.2%)	0
RECURRENCE NEW	1 (0.6%)	2 (1.2%)
FAILED TO ELIMINATE	15 (8.9%)	7 (4.2%)

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

RESPONSE	DIRITHROMYCIN N = 151 n (%)	ERYTHROMYCIN N = 150 n (%)
PATHOGEN ELIMINATED	107 (70.8%)	130 (86.6%)
RECURRENCE SAME	35 (23.1%)	13 (8.6%)
RECURRENCE SAME, RESISTANCE	0	3 (2.0%)
RECURRENCE NEW	2 (1.3%)	3 (2.0%)
FAILED TO ELIMINATE	7 (4.6%)	1 (0.7%)

The bacteriologic response for evaluable patients at termination according to the applicant was as follows:

	THERAPY GROUP										
	DIRITHROMYCIN					ERYTHROMYCIN					
	TERMINATION					TERMINATION					
	FAVOR		UNFAV		TOTAL	FAVOR		UNFAV		TOTAL
	N	%	N	%	N	N	%	N	%	N
PROJECT										
AQAB	111	67.3	54	32.7	165	131	79.9	33	20.1	164

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

Susceptibility Results

A total of 225 dirithromycin-treated patients and 237 erythromycin-treated patients had Group A Strep isolated from the pretherapy culture.

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

	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								
STR GRP A	194	9	19	222	206	11	5	222
STR GRP G		1		1	1			1
STREPTOCOCCUS SP			2	2			2	2

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

	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								
ST AUREUS	2			2	2			2
STR GRP A	209	4	20	233	223	5	5	233
STR GRP B	1			1	1			1
STREPTOCOCCUS SP			1	1			1	1

Concomitant Medications:

Prior to study entry, 44.1% of patients from both treated groups combined were receiving some form of drug therapy. Paracetamol (acetaminophen) was the most frequently used drug, taken by 8.7% and 11.5% of dirithromycin-treated and erythromycin-treated patients, respectively. Other frequently used drugs included aspirin, nonsteroidal anti-inflammatory agents, and hormonal agents. Concomitant drug use was comparable between the two treatment groups.

A concomitant agent was prescribed during therapy in 35.8% of dirithromycin-treated patients and 38.5% of erythromycin-treated patients. Paracetamol was again most frequently used. One dirithromycin patient received vancomycin for bloody diarrhea one day after beginning dirithromycin therapy. The bloody diarrhea preceded study enrollment and was not related to study-drug administration. The patient was discontinued early from the study due to the adverse event of diarrhea; the patient did not qualify for efficacy analysis.

Three erythromycin-treated patients received concomitant antimicrobials during the period of study-drug administration. Patient was treated with sulfacetamide topically for conjunctivitis; this patient qualified for efficacy analysis, since a non-systemic antimicrobial was administered. The remaining two erythromycin-treated patients were terminated from the study early; one patient for an adverse event (dehydration) and the second patient for an entry criterion exclusion. Patient was diagnosed with severe dehydration on the first day of the study. Erythromycin was discontinued and the patient was treated with intramuscular benzathine benzylpenicillin. The patient did not qualify for efficacy analysis, since she received less than 24 hours of study-drug. Patient was prescribed phenoxymethyl penicillin for pharyngitis on the second day of the study. Pretherapy culture grew normal flora; therefore, the patient did not qualify for efficacy analysis.

After completion of study-drug therapy, approximately 14% of patients from each treatment group reported taking medication. Again, paracetamol was most frequently used. Four dirithromycin-treated patients received an antibiotic after completion of study-drug therapy. Patient was prescribed cefixime by a non-study physician for symptomatic relapse of pharyngitis between the posttherapy and late-posttherapy periods. No culture was obtained at the time of cefixime prescription or at the subsequent late-posttherapy visit. The patient was qualified for efficacy analysis and was classified as a symptomatic response of "improved" at posttherapy and "relapse" at late-posttherapy. The bacteriologic response was classified as a

"failure to eliminate the pathogen" at posttherapy and "unable to evaluate" at late-posttherapy. A second dirithromycin patient presented with sinusitis at the late-posttherapy visit. A late-posttherapy throat culture was obtained and the patient was then prescribed dicloxacillin. Symptomatically the patient was cured of her pharyngitis and the late-posttherapy throat culture did not grow a pathogen. The patient qualified for efficacy analysis. The sinusitis was reported as an adverse event. A third dirithromycin patient received tetracycline for salpingitis 3 weeks after the last dose of study-drug. The patient did not qualify for efficacy analysis due to an entry criterion exclusion (colony count to confirm at least 10 colonies of group A streptococci was not performed on the pretherapy culture). Dirithromycin patient developed a urinary tract infection four days after the last dose of study-drug and was prescribed trimethoprim/sulfamethoxazole at the posttherapy visit. The patient was classified as a symptomatic response of "cure" and a bacteriologic response of "pathogen eliminated" at the posttherapy visit. The patient was a protocol violation due to the introduction of a new antibiotic for a non-study condition, and did not qualify for efficacy analysis.

Four erythromycin-treated patients received an anti-infective after completion of study-drug therapy. One patient received intravaginal miconazole for moniliasis and a second patient, received oral metronidazole for vaginitis. Both patients qualified for efficacy analysis. Miconazole was considered a non-systemic anti-infective. Oral metronidazole does not possess any clinically relevant antimicrobial activity against group A streptococci; therefore, the patient remained qualified for efficacy analysis. Patient was assigned a symptomatic response of "relapse" and a bacteriologic response of "pathogen eliminated" at the late-posttherapy visit. A third erythromycin patient was prescribed amoxicillin for sinusitis. The patient did not qualify for efficacy analysis due to an entry criterion exclusion (colony count to confirm at least 10 colonies of group A streptococci was not performed on the pretherapy culture). The fourth erythromycin-treated patient was treated with doxycycline and ceftriaxone for gonorrhea (which is categorized as urinary tract infection by the ELECT classification dictionary) between the posttherapy and late-posttherapy visits. The patient was not qualified for efficacy analysis, due to the introduction of the doxycycline and ceftriaxone for a non-study condition.

Safety Results:

Summary of Adverse Events By Body System

FREQUENCY OF ALL TREATMENT-EMERGENT ADVERSE EVENTS BY BODY SYSTEM
BODY AS A WHOLE--ALL PATIENTS

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 265 N (%)	ERYTHROMYCIN N = 288 N (%)	P VALUE
PATIENTS WITH AT LEAST ONE EVENT	64 (24.2%)	69 (24.0%)	0.958
PATIENTS WITH NO EVENT	201 (75.8%)	219 (76.0%)	0.958
HEADACHE	23 (8.7%)	22 (7.6%)	0.655
ABDOMINAL PAIN	20 (7.5%)	32 (11.1%)	0.151
ASTHENIA	9 (3.4%)	7 (2.4%)	0.499
PAIN	6 (2.3%)	2 (0.7%)	0.122
FEVER	4 (1.5%)	5 (1.7%)	0.833
ABSCESS	3 (1.1%)	0 (0.0%)	0.070
BACK PAIN	2 (0.8%)	3 (1.0%)	0.722
CHEST PAIN	2 (0.8%)	2 (0.7%)	0.933
CHILLS	2 (0.8%)	0 (0.0%)	0.140
CHILLS AND FEVER	2 (0.8%)	0 (0.0%)	0.140
INJURY, ACCIDENT	2 (0.8%)	6 (2.1%)	0.191
PELVIC PAIN	2 (0.8%)	0 (0.0%)	0.140
ALLERGIC REACTION	1 (0.4%)	2 (0.7%)	0.612
CYST	1 (0.4%)	0 (0.0%)	0.297
FLU SYNDROME	1 (0.4%)	1 (0.3%)	0.953
MONILIASIS	1 (0.4%)	1 (0.3%)	0.953
NECK PAIN	1 (0.4%)	0 (0.0%)	0.297
SURGICAL PROCEDURE	1 (0.4%)	1 (0.3%)	0.953
ANAPHYLACTOID REACTION	0 (0.0%)	1 (0.3%)	0.337
FACE EDEMA	0 (0.0%)	1 (0.3%)	0.337
INFECTION	0 (0.0%)	1 (0.3%)	0.337

FREQUENCY OF ALL TREATMENT-EMERGENT ADVERSE EVENTS BY BODY SYSTEM
DIGESTIVE SYSTEM--ALL PATIENTS

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 265 N (%)	ERYTHROMYCIN N = 288 N (%)	P VALUE
PATIENTS WITH AT LEAST ONE EVENT	56 (21.1%)	76 (26.4%)	0.147
PATIENTS WITH NO EVENT	209 (78.9%)	212 (73.6%)	0.147
DIARRHEA	25 (9.4%)	27 (9.4%)	0.981
NAUSEA	17 (6.4%)	28 (9.7%)	0.155
VOMITING	8 (3.0%)	10 (3.5%)	0.764
GASTROINTESTINAL DISORDER	5 (1.9%)	3 (1.0%)	0.406
DRY MOUTH	3 (1.1%)	1 (0.3%)	0.277
FLATULENCE	3 (1.1%)	5 (1.7%)	0.552
ANOREXIA	2 (0.8%)	3 (1.0%)	0.722
DYSPEPSIA	2 (0.8%)	3 (1.0%)	0.722
ORAL MONILIASIS	2 (0.8%)	0 (0.0%)	0.140
RECTAL DISORDER	2 (0.8%)	0 (0.0%)	0.140
BLOODY DIARRHEA	1 (0.4%)	0 (0.0%)	0.297
COLITIS	1 (0.4%)	0 (0.0%)	0.297
DYSPHAGIA	1 (0.4%)	1 (0.3%)	0.953
GASTROENTERITIS	1 (0.4%)	0 (0.0%)	0.297
MELENA	1 (0.4%)	0 (0.0%)	0.297
MOUTH ULCERATION	1 (0.4%)	0 (0.0%)	0.297
NAUSEA AND VOMITING	1 (0.4%)	3 (1.0%)	0.357
CONSTIPATION	0 (0.0%)	2 (0.7%)	0.174
ESOPHAGITIS	0 (0.0%)	1 (0.3%)	0.337
NAUSEA VOMITING AND DIARRHEA	0 (0.0%)	1 (0.3%)	0.337
STOMATITIS	0 (0.0%)	1 (0.3%)	0.337
TONGUE DISORDER	0 (0.0%)	1 (0.3%)	0.337
TONGUE EDEMA	0 (0.0%)	1 (0.3%)	0.337

FREQUENCY OF ALL TREATMENT-EMERGENT ADVERSE EVENTS BY BODY SYSTEM
RESPIRATORY SYSTEM--ALL PATIENTS

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 265 N (%)	ERYTHROMYCIN N = 288 N (%)	P VALUE
PATIENTS WITH AT LEAST ONE EVENT	30 (11.3%)	44 (15.3%)	0.172
PATIENTS WITH NO EVENT	235 (88.7%)	244 (84.7%)	0.172
RHINITIS	16 (6.0%)	17 (5.9%)	0.947
COUGH INCREASED	8 (3.0%)	11 (3.8%)	0.606
SINUSITIS	6 (2.3%)	5 (1.7%)	0.657
PHARYNGITIS	5 (1.9%)	5 (1.7%)	0.894
DYSPNEA	1 (0.4%)	2 (0.7%)	0.612
LUNG DISORDER	1 (0.4%)	0 (0.0%)	0.297
ASTHMA	0 (0.0%)	3 (1.0%)	0.096
EPISTAXIS	0 (0.0%)	1 (0.3%)	0.337
HYPERVENTILATION	0 (0.0%)	1 (0.3%)	0.337
RESPIRATORY DISORDER	0 (0.0%)	2 (0.7%)	0.174

FREQUENCY OF ALL TREATMENT-EMERGENT ADVERSE EVENTS BY BODY SYSTEM
SKIN SYSTEM--ALL PATIENTS

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 265 N	(%)	ERYTHROMYCIN N = 288 N	(%)	P VALUE
PATIENTS WITH AT LEAST ONE EVENT	8	(3.0%)	16	(5.6%)	0.144
PATIENTS WITH NO EVENT	257	(97.0%)	272	(94.4%)	0.144
URTICARIA	2	(0.8%)	0	(0.0%)	0.140
CONTACT DERMATITIS	1	(0.4%)	0	(0.0%)	0.297
HERPES ZOSTER	1	(0.4%)	0	(0.0%)	0.297
MACULOPAPULAR RASH	1	(0.4%)	3	(1.0%)	0.357
PSORIASIS	1	(0.4%)	0	(0.0%)	0.297
RASH	1	(0.4%)	8	(2.8%)	0.026
SWEATING	1	(0.4%)	0	(0.0%)	0.297
ACNE	0	(0.0%)	1	(0.3%)	0.337
HERPES SIMPLEX	0	(0.0%)	2	(0.7%)	0.174
PRURITUS	0	(0.0%)	3	(1.0%)	0.096
SKIN BENIGN NEOPLASM	0	(0.0%)	1	(0.3%)	0.337

APPEARS THIS WAY
ON ORIGINAL

Patients Who Died or Discontinued Therapy Due to Adverse Events:

No deaths were reported during the course of this study.

Eight dirithromycin-treated patients and 16 erythromycin-treated patients discontinued early due to adverse events (p=.141). Six of the 8 dirithromycin-treated patients and 8 of the 16 erythromycin-treated patients experienced adverse events related to the gastrointestinal system. No dirithromycin-treated patients and 4 erythromycin-treated patients were discontinued from the study early due to adverse events related to cutaneous rash.

REASON DISCONTINUED PATIENT LIST
ALL PATIENTS
THERAPY: DIRITHROMYCIN

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT	CONCOMITANT MEDICATION
006		1	35	MALE	CAUCASIAN	2	DIARRHEA, BLOODY	ASPIRIN BISMUTH SUBSALICYLATE MULTIVITAMINS NICOTINIC ACID VANCOMYCIN
011		1	13	MALE	CAUCASIAN	2	NAUSEA	BROMPHENIRAMINE/PHENYLPROPANOLAMINE PARACETAMOL
018		1	42	FEMALE	BLACK	7	STOMACH PAIN	CHLORTALIDONE IBUPROFEN
064		1	44	FEMALE	BLACK	1	SHORTNESS OF BREATH	PIROXICAM
073		1	14	MALE	BLACK	2	DIARREAL INCONTINENCE	PARACETAMOL
073		1	26	FEMALE	CAUCASIAN	1	STOMACH PAIN	ACICLOVIR ASCORBIC ACID DIETARY SUPPLEMENT ETHINYLESTRADIOL/LEVONORGESTRONE VITAMIN B COMPLEX
104		1	50	FEMALE	CAUCASIAN	7	PERI-TONSILLAR ABSCESS	
115		1	21	MALE	CAUCASIAN	8	GASTROENTERITIS	CALCIUM SALTS ELECTROLYTE SOLUTION MAGNESIUM MULTIVITAMINS PHENOL SALICYLIC ACID

(continued)

REASON DISCONTINUED PATIENT LIST
ALL PATIENTS
THERAPY: ERYTHROMYCIN

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT	CONCOMITANT MEDICATION
006		1	17	MALE	CAUCASIAN	4	STOMACH PAIN	
006		1	30	FEMALE	ASIAN	2	STOMACH CRAMPS	AZATADINE/PSEUDOEPHRINE ETHINYLESTRADIOL/NORGESTRONE TERFENADINE
011		1	25	MALE	CAUCASIAN	4	HEADACHE	
011		1	19	FEMALE	CAUCASIAN	3	STOMACH CRAMPS	PARACETAMOL/CODEINE
016		1	24	FEMALE	BLACK	2	RASH	
028		1	35	MALE	CAUCASIAN	1	VOMITING	PARACETAMOL PARACETAMOL PARACETAMOL/CODEINE PHENYLPROPANOLAMINE/CHLORPHENIRAMINE TRIMETHOBENZAMIDE TRIMETHOBENZAMIDE
028		1	12	FEMALE	CAUCASIAN	4	VOMITING	PARACETAMOL
028		1	18	FEMALE	CAUCASIAN	3	DIARRHEA	PARACETAMOL VITAMINS-MINERALS
046		1	27	MALE	BLACK	2	RASH	

(continued)

REASON DISCONTINUED PATIENT LIST--ALL PATIENTS (continued)

THERAPY: ERYTHROMYCIN

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT	CONCOMITANT MEDICATION
047		1	26	FEMALE	BLACK	8	BAD TASTE IN MOUTH	
047		1	58	FEMALE	BLACK	4	SKIN ERUPTION	
049		1	40	FEMALE	HISPANIC	6	RASH	CLEMASTINE/PHENYLPROPANOLAMINE DEXTROMETHORPHAN/GUAIFENE HYDROCODONE/PSEUDOEPHEDRINE PARACETAMOL PSEUDOEPHEDRINE/CHLORPHENIRAMINE
102		1	20	FEMALE	CAUCASIAN	3	ABDOMINAL PAIN	PARACETAMOL
102		1	16	FEMALE	CAUCASIAN	6	ABDOMINAL PAIN	
104		1	57	MALE	CAUCASIAN	2	DRY MOUTH	IBUPROFEN
115		1	30	FEMALE	BLACK	1	DEHYDRATION	BENZATHINE BENZYLPENICILL ELECTROLYTE SOLUTION PARACETAMOL

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, polymorphonuclear neutrophil leukocytes (PMNs), and bands. A significant reduction in monocytes was also seen for both treatment groups. With the reduced number of segmented neutrophils, statistically significant increases in lymphocytes and eosinophils were seen in both groups. A significant increase in basophils was seen in the dirithromycin treatment group, with no significant difference between the treatment groups. Both groups showed statistically significant reductions in hematocrit, hemoglobin, and red blood cell count. Although the changes in hematocrit, hemoglobin and red blood cell count were statistically significant, the magnitude of the changes were not considered clinically significant. 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 illnesses. A statistically significant difference between the treatment groups was seen only for mean cell volume (MCV). The mean value of the MCV for the dirithromycin group showed a statistically significant decline. The mean MCV for the erythromycin treatment group increased slightly. Although the changes in MCV were statistically different between the treatment groups, the difference is not clinically significant as the posttherapy mean values were well within the reference ranges for the populations studied.

Several blood chemistry analytes showed significant changes within the groups. Total protein and albumin showed a statistically significant decrease in both groups. CPK, BUN, phosphorus, uric acid and cholesterol all showed statistically significant increases in both groups. Despite the noted rise in BUN for both groups, serum creatinine was decreased slightly in both treatment groups.

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

	Pretherapy	During Therapy	Posttherapy
PLATELETS			
016-3102*D	316		463
011-3650 D	267		481
025-0432 D	277		520
028-3210 D	277		597
061-2034 D	297		520
073-2292 D	325		524
086-2753 D	296		427
092-3695 D	384		495
115-3900 D	332		508
002-0005*D	242	365	545
011-3648*D	441		609
016-0261 D	229		113
010-0172 E	286		481
011-3090 E	321		466
009-0150 E	236		443
011-3658 E	239		419
016-3101 E	286		468
025-0434 E	378	486	497
028-0484 E	341		516
047-0859 E	314		520
064-2432 E	326		445
092-3394 E	350		463
102-3501 E	363		477
115-3886 E	257		459
115-4454 E	222		600
115-4985 E	465		623
016-0277 E	311		467
LEUKOCYTES			
011-3648 D	22.63		13.57
NEUTROPHILS			
002-0005 D	5.62	4.70	1.46

	Pretherapy	During Therapy	Posttherapy
CK (U/L)			
011-0199 D	567		2352
011-0200 E	62		2485
011-0193 D	112		475
028-0487 D	80		700
028-2452 D	212		660
028-4383 D	39		332
URINE SP. GRAV.			
016-3102 D	1.005		1.036
GLUCOSE, FASTING (mmol/L)			
016-3102 D	2.800		6.600

* Patient has more than 1 abnormal lab
NOTE: The abnormal laboratory values were followed up till they became normal.

MEDICAL OFFICER'S OVERALL COMMENTS:

Efficacy:

Both dirithromycin and erythromycin were effective in the treatment of pharyngitis/tonsillitis caused by Group A beta-hemolytic streptococci.
The clinical success (cure or improvement) rate at posttherapy (3-5 days) was **94.1%** (159/169) for dirithromycin and **94.6%** (158/167) for the erythromycin group. The clinical (cure or improvement) rate at late-post-treatment (3-5 weeks) was **87.6%** (134/153) for dirithromycin and **88.7%** (134/151) for the erythromycin group. At termination, the clinical (cure or improvement) was **82.8%** (140/169) for the dirithromycin group and **84.4%** (141/167) for the erythromycin group.

The bacteriologic (cure or improvement) rate at posttherapy (3-5 days) was **83.2%** (134/167) for dirithromycin and **87.3%** (144/165) for the erythromycin group. The bacteriologic (cure or improvement) rate at late-post-treatment (3-5 weeks) was **70.8%** (107/151) for dirithromycin and **86.6%** (130/150) for the erythromycin group. At termination, the bacteriologic (cure or improvement) was **67.3%** (111/165) for the dirithromycin group and **79.9%** (131/164) for the erythromycin group.

SAFETY:

Two hundred and sixty-five patients in the dirithromycin group and 288 patients in the erythromycin group were evaluated for safety. The most common adverse events (drug-related or not) in both the treatment groups were in the digestive system. The most common ADRs were nausea, vomiting and abdominal pain in both the treatment groups.

MEDICAL OFFICER'S CONCLUSIONS:

In this study, the Clinical and Bacteriologic (cure or improvement) rates were superior for erythromycin when compared to dirithromycin. The results of this study will be combined with other pivotal studies to recommend the approval of this indication.

REVIEW OF PIVOTAL STUDIES:

II. Study B9Z-MC-AQAS Synopsis:

Title:

Dirithromycin versus Erythromycin Base in Streptococcal Pharyngitis/Tonsillitis.

Study Centers: There were 17 active study centers.

Dates of Study: July 12, 1991 - January 24, 1992

Clinical Phase: Phase 3

Objectives:

To compare dirithromycin with erythromycin base for effectiveness and safety in the treatment of pharyngitis/tonsillitis caused by group A beta-hemolytic streptococci.

Methodology: Double-blind, double-dummy, randomized, parallel study.

Number of Patients:

Dirithromycin: male 54, female 104, Total 158.
Erythromycin: male 51, female 108, Total 159.

Diagnosis and Inclusion Criteria:

Pharyngitis/tonsillitis with confirmed susceptible group A β-hemolytic streptococcal etiology.

Dosage and Administration:

Test Product

Dirithromycin: 500 mg/day (two 250-mg tablets q.d.)
CT00447: dirithromycin tablets, 250 mg
CT00445: placebo tablets
NOTE: Placebo was used to maintain blinding.

Reference Therapy

Erythromycin Base: 1000 mg/day (one 250 mg tablet q.i.d.)
CT00444: erythromycin base tablets, 250 mg
CT00446: lacebo tablets
NOTE: Placebo was used to maintain blinding.

Duration of Treatment:

Dirithromycin: 10 days
Erythromycin Base: 10 days

Criteria for Evaluation:

Efficacy--A complete efficacy evaluation was performed on patients completing 10 days of therapy who had positive pretherapy throat culture, returned for the during therapy, posttherapy and the late-posttherapy clinical evaluation and culture, and for whom the symptomatic response could be evaluated.

Safety--All patients were evaluated for safety.

Statistical Methods:

Chi-square methodology. Appropriate continuous data procedures, such as two-sample t-test on ranked data, were used for analysis of laboratory data.

Study Design:

This was a double-blind, randomized, parallel study. Protocol was identical to Study AQAB.

Investigators:

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
C. M. BRIEFER/ANN ARBOR, MI	4	5	4	2
H. COLLINS/EDISON, NJ	4	2	1	2
D. GINSBERG/HARLEYSVILLE, PA	6	5	6	5
C. B. GOSWICK, JR/BRYAN, TX	12	9	11	7
N. R. PATEL/KETTERING, OH	1	0	1	0
E. H. GUTHRIE/SALT LAKE CITY, UT	33	35	27	31
R. C. HASELBY/MARSHFIELD, WI	5	3	4	1
T. W. LITTLEJOHN, III/WINSTON-SALEM, NC	8	6	4	3
J. W. MALOY/MONTGOMERY, AL	6	8	5	7
J. MCCARTY/FRESNO, CA	15	14	6	11
J. SALISBURY/MIDDLETOWN, NJ	4	6	3	5
J. C. ROTSCHAFER/ST. PAUL, MN	0	1	0	0
G. E. RUOFF/KALAMAZOO, MI	5	7	3	6
P. G. SANDALL/ALBUQUERQUE, NM	5	8	3	7
W. S. MULLICAN/EVANSVILLE, IN	3	6	2	3
H. P. BOTHA/S. AFRICA	16	14	10	6
S. N. FURMAN/S. AFRICA	31	30	21	21
TOTAL	158	159	111	117

Sponsor's Analysis:

Patient disposition was as follows:

	DIRITH	ERYTH	TOTAL
Patient Enrolled	158	159	317
Evaluable for Efficacy	111	117	228
Completed Therapy	93	102	195
Prematurely Discontinued	18	15	33
Not Evaluable	47	42	89
Completed Therapy	2	3	5
Prematurely Discontinued	45	39	84

Primary diagnosis:	**Pharyngitis**	**Tonsillitis**
Dirithromycin		
All patients	77	81
Evaluable patients	50	61
Erythromycin		
All patients	89	70
Evaluable patients	66	51

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

Patient Demographics:
All Patients

Age Ranges By Sex--All Patients

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE (N=104)	MALE (N=54)	TOTAL (N=158)	FEMALE (N=108)	MALE (N=51)	TOTAL (N=159)
N	(%) N	(%) N	(%) N	(%) N	(%)	N (%)
AGE RANGES (YR)						
	9 (8.7%)	11 (20.4%)	20 (12.7%)	8 (7.4%)	3 (5.9%)	11 (6.9%)
	33 (31.7%)	22 (40.7%)	55 (34.8%)	37 (34.3%)	21 (41.2%)	58 (36.5%)
	55 (52.9%)	19 (35.2%)	74 (46.8%)	52 (48.1%)	26 (51.0%)	78 (49.1%)
	6 (5.8%)	1 (1.9%)	7 (4.4%)	9 (8.3%)	1 (2.0%)	10 (6.3%)
	1 (1.0%)	1 (1.9%)	2 (1.3%)	2 (1.9%)	0	2 (1.3%)

Age By Sex Summary--All Patients

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
Number Of Patients	104	54	158	108	51	159
Mean Age	29.03	25.93	27.97	28.76	27.82	28.46
Std Dev	10.87	10.91	10.95	11.15	9.30	10.57
Median Age	28.15	22.54	26.59	26.44	25.44	26.43

Racial Origin By Treatment Group--All Patients

ORIGIN	DIRITHROMYCIN N=158		ERYTHROMYCIN N=159	
	N	(%)	N	(%)
CAUCASIAN	110	(69.6%)	113	(71.1%)
BLACK	18	(11.4%)	23	(14.5%)
HISPANIC	13	(8.2%)	11	(6.9%)
ASIAN	3	(1.9%)	3	(1.9%)
OTHER	14	(8.9%)	9	(5.7%)

Height and Weight At Admission--All Patients

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	157	1	167.77	10			156	2	70.84	17		
ERYTHROMYCIN	159	0	167.57	10			159	0	70.28	17		

Evaluable Patients:

Age Ranges by Sex
Evaluable Patients

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE (N = 78)		MALE (N = 33)		TOTAL (N = 111)		FEMALE (N = 80)		MALE (N = 37)		TOTAL (N = 117)	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	7	(9.0%)	7	(21.2%)	14	(12.6%)	7	(8.8%)	2	(5.4%)	9	(7.7%)
	27	(34.6%)	14	(42.4%)	41	(36.9%)	28	(35.0%)	14	(37.8%)	42	(35.9%)
	39	(50.0%)	11	(33.3%)	50	(45.0%)	37	(46.3%)	20	(54.1%)	57	(48.7%)
	4	(5.1%)	1	(3.0%)	5	(4.5%)	7	(8.8%)	1	(2.7%)	8	(6.8%)
	1	(1.3%)	0		1	(0.9%)	1	(1.3%)	0		1	(0.9%)

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

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	78	33	111	80	37	117
MEAN AGE	28.55	24.92	27.47	28.31	28.74	28.45
STD DEV	10.79	9.60	10.54	10.89	9.57	10.45
MEDIAN AGE	28.15	21.94	26.19	25.93	27.96	26.43
MINIMUM AGE						
MAXIMUM AGE						

Origin By Therapy Group
Evaluable Patients

	DIRITHROMYCIN N = 111		ERYTHROMYCIN N = 117		TOTAL N = 228	
ORIGIN	n	(%)	n	(%)	n	(%)
CAUCASIAN	83	(74.8%)	80	(68.4%)	163	(71.5%)
BLACK	12	(10.8%)	18	(15.4%)	30	(13.2%)
HISPANIC	7	(6.3%)	10	(8.5%)	17	(7.5%)
ASIAN	2	(1.8%)	2	(1.7%)	4	(1.8%)
OTHER	7	(6.3%)	7	(6.0%)	14	(6.1%)

Height and Weight at Admission
Evaluable Patients

THERAPY	HEIGHT IN CM N	UNK	MEAN	STD DEV	MIN	MAX	WEIGHT IN KG N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	111	0	165.73	19			111	0	71.55	17		
ERYTHROMYCIN	117	0	167.49	10			117	0	70.93	18		

Drug Administration:

All Patients

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

	DIRITHROMYCIN N = 158 DAYS	ERYTHROMYCIN N = 159 DAYS
NUMBER OF PATIENTS	157	156
MEAN DURATION EXPOSURE	9.9	9.9
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	1	3

Summary of Exposure To Study Drugs--All Patients

DAYS OF THERAPY	DIRITHROMYCIN N = 158		ERYTHROMYCIN N = 159		TOTAL N = 317	
	N	(%)	N	(%)	N	(%)
PATIENTS WITH INCOMPLETE DATA	1	(0.6%)	3	(1.9%)	4	(1.3%)
1	2	(1.3%)	0		2	(0.6%)
2	3	(1.9%)	4	(2.5%)	7	(2.2%)
3	5	(3.2%)	6	(3.8%)	11	(3.5%)
4	5	(3.2%)	7	(4.4%)	12	(3.8%)
5	6	(3.8%)	2	(1.3%)	8	(2.5%)
6	5	(3.2%)	2	(1.3%)	7	(2.2%)
7	1	(0.6%)	3	(1.9%)	4	(1.3%)
8	1	(0.6%)	3	(1.9%)	4	(1.3%)
9	0		1	(0.6%)	1	(0.3%)
10	26	(16.5%)	38	(23.9%)	64	(20.2%)
11	78	(49.4%)	72	(45.3%)	150	(47.3%)
12	13	(8.2%)	8	(5.0%)	21	(6.6%)
13	8	(5.1%)	2	(1.3%)	10	(3.2%)
14	3	(1.9%)	4	(2.5%)	7	(2.2%)
15	0		3	(1.9%)	3	(0.9%)
16	1	(0.6%)	0		1	(0.3%)
18	0		1	(0.6%)	1	(0.3%)

Evaluable Patients:

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

	DIRITHROMYCIN N = 111 DAYS	ERYTHROMYCIN N = 117 DAYS
NUMBER OF PATIENTS	111	117
MEAN DURATION EXPOSURE	11.0	10.8
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients

DAYS OF THERAPY	DIRITHROMYCIN N = 111 n	(%)	ERYTHROMYCIN N = 117 n	(%)
2	0		2	(1.7%)
3	0		1	(0.9%)
4	1	(0.9%)	0	
5	1	(0.9%)	0	
10	22	(19.8%)	35	(29.9%)
11	68	(61.3%)	63	(53.8%)
12	10	(9.0%)	7	(6.0%)
13	6	(5.4%)	2	(1.7%)
14	2	(1.8%)	4	(3.4%)
15	0		2	(1.7%)
16	1	(0.9%)	0	
18	0		1	(0.9%)

Medical Officer's Comment:

Note that 81% of the evaluable patients in the dirithromycin group and 84% of the patients in the erythromycin group were treated for 10-11 days.

Unevaluable Patients

Reason Unevaluable Summary--All Patients

REASON UNEVALUABLE	DIRITHROMYCIN N = 158 N	(%)	ERYTHROMYCIN N = 159 N	(%)
PATS. WITH => 1 REASON	47	(29.7%)	42	(26.4%)
PATS. WITH > 1 REASON	30	(19.0%)	24	(15.1%)
INSUFFICIENT THERAPY	24	(15.2%)	22	(13.8%)
CAUS. ORG. UNIDENT.	16	(10.1%)	11	(6.9%)
CAUS. ORG. RESISTANT	6	(3.8%)	11	(6.9%)
UNACCEPT. PATHOGEN	9	(5.7%)	5	(3.1%)
UNEVAL. BY INVEST.	5	(3.2%)	4	(2.5%)
NO POST THER. CULTURE	3	(1.9%)	6	(3.8%)
NO FOLLOW-UP CULTURE	3	(1.9%)	4	(2.5%)
SENSITIVITY NOT DONE	3	(1.9%)	3	(1.9%)
CONCOMITANT ANTIBIOT.	2	(1.3%)	1	(0.6%)
INITIAL CULT. EARLY	0		3	(1.9%)
SEQUENTIAL THERAPY	2	(1.3%)	1	(0.6%)
NO DURING CULTURE	2	(1.3%)	0	
POOR COMPLIANCE	2	(1.3%)	0	
LOW COLONY COUNT	2	(1.3%)	0	
VISIT MISSING	2	(1.3%)	0	
PROTOCOL VIOLATED	1	(0.6%)	0	
NO COLONY COUNT	1	(0.6%)	0	
NO END-THERAPY CULTURE	1	(0.6%)	0	
NO POST FOLLOW-UP	0		1	(0.6%)

Efficacy Evaluation:

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

Clinical Response Summary By Therapy Group
All Evaluable Patients Posttherapy

	DIRITHROMYCIN		ERYTHROMYCIN	
RESPONSE	N	(%)	N	(%)
CURE	72	(64.9%)	84	(71.8%)
IMPROVEMENT	34	(30.6%)	29	(24.8%)
RELAPSE	4	(3.6%)	2	(1.7%)
FAILURE	1	(0.9%)	2	(1.7%)

The Clinical Success Rate for the dirithromycin patients was 106/111 (95.5%), and 113/117 (96.6%) for the erythromycin group.

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

Clinical Response Summary by Therapy Group--
All Evaluable Patients Late-Posttherapy

	DIRITHROMYCIN N = 99		ERYTHROMYCIN N = 110	
RESPONSE	N	(%)	N	(%)
CURE	80	(80.8%)	89	(80.9%)
IMPROVEMENT	7	(7.1%)	8	(7.3%)
RELAPSE	12	(12.1%)	13	(11.8%)

The Clinical Success Rate for the dirithromycin group is 87/99 (87.9%), and for the erythromycin group is 97/110 (88.2%).

The clinical response for evaluable patients at termination according to the applicant was as follows:

	THERAPY GROUP										
	DIRITHROMYCIN					ERYTHROMYCIN					
	TERMINATION					TERMINATION					
	FAVOR		UNFAVO			FAVOR		UNFAVO			
	N	%	N	%	N	N	%	N	%	N	
PROJECT											
AQAS	94	84.7	17	15.3	111	100	85.5	17	14.5	117	

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

APPEARS THIS WAY
ON ORIGINAL

Bacteriologic Response

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

Bacteriologic Response Summary By Therapy Group
All Evaluable Patients Posttherapy

	DIRITHROMYCIN N = 110		ERYTHROMYCIN N = 117	
RESPONSE	N	(%)	N	(%)
PATHOGEN ELIMINATED	97	(88.2%)	110	(94.0%)
RECURRENCE SAME	5	(4.5%)	4	(3.4%)
RECURRENCE SAME, RESISTANCE	2	(1.8%)	0	
RECURRENCE NEW	0		1	(0.9%)
FAILED TO ELIMINATE	6	(5.4%)	2	(1.7%)

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

Bacteriologic Response Summary By Therapy Group--
All Evaluable Patients Late-Posttherapy

	DIRITHROMYCIN N = 98		ERYTHROMYCIN N = 110	
RESPONSE	N	(%)	N	(%)
PATHOGEN ELIMINATED	89	(90.8%)	101	(91.8%)
RECURRENCE SAME	9	(9.2%)	7	(6.4%)
RECURRENCE NEW	0		2	(1.8%)

The bacteriologic response for evaluable patients at termination according to the applicant was as follows:

	THERAPY GROUP									
	DIRITHROMYCIN					ERYTHROMYCIN				
	TERMINATION					TERMINATION				
	FAVOR		UNFAVO			FAVOR		UNFAVO		
	N	%	N	%	N	N	%	N	%	N
PROJECT										
AQAS	89	80.9	20	19.1	110	102	87.2	15	12.8	117

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

Susceptibility Results

A total of 134 dirithromycin-treated patients and 138 erythromycin-treated patients had Group A Strep isolated from the pretherapy culture.

APPEARS THIS WAY
ON ORIGINAL

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

	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								
STR GRP A	118	2	11	131	125	2	4	131
STR GRP B	1			1	1			1
STR GRP C	1			1	1			1
STREPTOCOCCUS SP	1			1	1			1

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

	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								
STR GRP A	123	3	10	136	130	3	3	136
STR GRP B	1			1	1			1
STREPTOCOCCUS SP	1			1	1			1

CONCOMITANT MEDICATIONS:

Prior to study entry, 40.7% of patients from both treatment groups combined were receiving some form of drug therapy. Paracetamol was the most frequently used drug, taken by 9.5% and 8.8% of dirithromycin-treated and erythromycin-treated patients, respectively. Concomitant drug use was comparable between the two treatment groups.

A concomitant agent was prescribed during therapy in 49.4% of dirithromycin-treated patients and 49.7% of erythromycin-treated patients. Paracetamol was most frequently used.

After completion of study-drug therapy, 17.7% of dirithromycin-treated patients and 22.0% of erythromycin-treated patients reported taking medication. Paracetamol was most frequently used.

Two dirithromycin-treated patients received an antibiotic after completion of study-drug therapy and before the late-posttherapy visit. Patient was prescribed amoxicillin orally for the treatment of sinusitis. Because the patient received a systemic antibiotic for a non-study related diagnosis, the patient did not qualify for efficacy analysis. At the time of the patient's posttherapy visit, the patient was classified as a symptomatic response of "improvement" and a bacteriologic response of "pathogen eliminated." Patient was treated with chloramphenicol topically for an eye infection; this patient qualified for efficacy analysis, since a non-systemic antibiotic was administered.

SAFETY RESULTS:

Summary of Adverse Event By Body System Table

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

	DIRITHROMYCIN N = 158		ERYTHROMYCIN N = 159		
EVENT CLASSIFICATION TERM	N	(%)	N	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	49	(31.0%)	48	(30.2%)	0.874
PATIENTS WITH NO EVENT	109	(69.0%)	111	(69.8%)	0.874
ABDOMINAL PAIN	22	(13.9%)	19	(11.9%)	0.6
HEADACHE	19	(12.0%)	21	(13.2%)	0.751
ASTHENIA	3	(1.9%)	2	(1.3%)	0.647
BACK PAIN	3	(1.9%)	0		0.081
CHILLS	3	(1.9%)	0		0.081
INFECTION	3	(1.9%)	1	(0.6%)	0.311
NECK PAIN	2	(1.3%)	1	(0.6%)	0.558
ABSCESS	1	(0.6%)	0		0.315
ACCIDENTAL OVERDOSE	1	(0.6%)	0		0.315
FEVER	1	(0.6%)	1	(0.6%)	0.996
FLU SYNDROME	1	(0.6%)	3	(1.9%)	0.317
INJURY, ACCIDENT	1	(0.6%)	2	(1.3%)	0.566
MALAISE	1	(0.6%)	0		0.315
SURGICAL PROCEDURE	1	(0.6%)	1	(0.6%)	0.996
CYST	0		1	(0.6%)	0.318
MONILIASIS	0		1	(0.6%)	0.318
NECK RIGIDITY	0		1	(0.6%)	0.318
NEOPLASM	0		1	(0.6%)	0.318

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

	DIRITHROMYCIN N = 158		ERYTHROMYCIN N = 159		
EVENT CLASSIFICATION TERM	N	(%)	N	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	39	(24.7%)	42	(26.4%)	0.724
PATIENTS WITH NO EVENT	119	(75.3%)	117	(73.6%)	0.724
NAUSEA	15	(9.5%)	18	(11.3%)	0.594
DIARRHEA	10	(6.3%)	9	(5.7%)	0.802
GASTROINTESTINAL DISORDER	5	(3.2%)	8	(5.0%)	0.402
VOMITING	5	(3.2%)	4	(2.5%)	0.728
DYSPEPSIA	4	(2.5%)	3	(1.9%)	0.696
NAUSEA AND VOMITING	3	(1.9%)	1	(0.6%)	0.311
ANOREXIA	2	(1.3%)	1	(0.6%)	0.558
GASTRITIS	1	(0.6%)	1	(0.6%)	0.996
MOUTH ULCERATION	1	(0.6%)	0		0.315
ABNORMAL STOOLS	0		1	(0.6%)	0.318
CONSTIPATION	0		1	(0.6%)	0.318
INCREASED APPETITE	0		1	(0.6%)	0.318
NAUSEA VOMITING AND DIARRHEA	0		1	(0.6%)	0.318
STOMATITIS	0		1	(0.6%)	0.318

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

	DIRITHROMYCIN N = 158		ERYTHROMYCIN N = 159		
EVENT CLASSIFICATION TERM	N	(%)	N	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	22	(13.9%)	23	(14.5%)	0.89
PATIENTS WITH NO EVENT	136	(86.1%)	136	(85.5%)	0.89
RHINITIS	13	(8.2%)	14	(8.8%)	0.854
COUGH INCREASED	8	(5.1%)	6	(3.8%)	0.576
SINUSITIS	3	(1.9%)	6	(3.8%)	0.315
PHARYNGITIS	2	(1.3%)	3	(1.9%)	0.657
DYSPNEA	1	(0.6%)	0		0.315
EPISTAXIS	1	(0.6%)	1	(0.6%)	0.996
LUNG DISORDER	1	(0.6%)	1	(0.6%)	0.996
BRONCHITIS	0		1	(0.6%)	0.318
HICCUP	0		1	(0.6%)	0.318

Frequency of Treatment-Emergent Adverse Events
by Body System--Special Senses--All Patients

	DIRITHROMYCIN N = 158		ERYTHROMYCIN N = 159		
EVENT CLASSIFICATION TERM	N	(%)	N	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	11	(7.0%)	6	(3.8%)	0.208
PATIENTS WITH NO EVENT	147	(93.0%)	153	(96.2%)	0.208
EAR PAIN	8	(5.1%)	3	(1.9%)	0.122
AMBLYOPIA	1	(0.6%)	1	(0.6%)	0.996
EAR DISORDER	1	(0.6%)	1	(0.6%)	0.996
EYE DISORDER	1	(0.6%)	0		0.315
TINNITUS	1	(0.6%)	0		0.315
CONJUNCTIVITIS	0		1	(0.6%)	0.318

Frequency of Treatment-Emergent Adverse Events
by Body System--Nervous System--All Patients

	DIRITHROMYCIN N = 158		ERYTHROMYCIN N = 159		
EVENT CLASSIFICATION TERM	N	(%)	N	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	9	(5.7%)	5	(3.1%)	0.269
PATIENTS WITH NO EVENT	149	(94.3%)	154	(96.9%)	0.269
DIZZINESS	3	(1.9%)	2	(1.3%)	0.647
INSOMNIA	2	(1.3%)	2	(1.3%)	0.995
VERTIGO	2	(1.3%)	0		0.155
NEURALGIA	1	(0.6%)	0		0.315
NEUROPATHY	1	(0.6%)	0		0.315
PERSONALITY DISORDER	1	(0.6%)	0		0.315
SOMNOLENCE	1	(0.6%)	0		0.315
AGITATION	0		1	(0.6%)	0.318

Patients Who Died or Discontinued Therapy Due to Adverse Events:

In the dirithromycin group, there were 158 patients exposed; the erythromycin group comprised 159 patients. There were no deaths reported during the study. Seven dirithromycin-treated patients and 4 erythromycin-treated patients discontinued from the study due to an adverse event. Two dirithromycin-treated patients reported events during the course of this study that qualified as serious for regulatory reporting purposes.

Seven dirithromycin patients and 4 erythromycin patients discontinued early due to adverse events; 3 of the 7 dirithromycin patients and all 4 of the erythromycin treated patients experienced adverse events related to the gastrointestinal system. Six of the dirithromycin patients were discontinued from the study due to events related to the body system as a whole.

All Dirithromycin-Treated Patients Who Discontinued
Due To Adverse Events

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT	CONCOMITANT MEDICATION
102		1	17	MALE	CAUCASIAN	10	ABDOMINAL PAIN	ASPIRIN IBUPROFEN IBUPROFEN IBUPROFEN
107		1	14	MALE	CAUCASIAN	5	OVERDOSE ACCIDENTAL	IMIPRAMINE METHYLPHENIDATE
108		1	45	FEMALE	CAUCASIAN	1	VOMITING AND NAUSEA	
111		1	23	FEMALE	HISPANIC	7	ABSCESS-PHARYNGITIS	IBUPROFEN
115		1	21	MALE	HISPANIC	2	SEVERE HEADACHE	ASPIRIN/SODIUM BICARBONATE PARACETAMOL
200		1	66	MALE	CAUCASIAN	1	STOMACH PAIN	BECLOMETASONE SALBUTAMOL
200		2	14	FEMALE	CAUCASIAN	14	SOMNOLENCE	ASPIRIN MULTIVITAMINS

All Erythromycin-Treated Patients Who Discontinued
Due to Adverse Events

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT	CONCOMITANT MEDICATION
107		1	19	FEMALE	CAUCASIAN	3	GASTRITIS	
111		1	48	FEMALE	HISPANIC	3	NAUSEA	ESTROGEN, CONJUGATED
112		1	16	FEMALE	CAUCASIAN	2	VOMITING	PARACETAMOL
116		1	32	FEMALE	CAUCASIAN	3	NAUSEA, VOMITING AND DIARRHEA	ETHINYLESTRADIOL/ LEVONORGESTREL

CLINICAL LABORATORY EVALUATIONS:

For the total population, statistically significant changes within groups were seen for several hematologic parameters. 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 statistically significant reduction in monocytes was also seen for both treatment groups. Increases in lymphocytes and eosinophils were seen in both groups. Both groups showed reductions in hematocrit, hemoglobin, red blood cell count and mean cell volume. 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 illnesses. The mean cell hemoglobin concentration (MCHC) for the erythromycin group showed a statistically significant increase. A statistically significant decrease in mean cell hemoglobin (MCH) was seen in the dirithromycin-treatment group with a significant difference between the treatment groups.

Several blood chemistry analytes were found to have changed significantly within the treatment groups. Total protein and serum creatinine decreased significantly in both groups while CPK, BUN, and phosphorus increased significantly in both groups. The serum creatinine and albumin decline seen among erythromycin-treated patients was greater than that seen among patients receiving dirithromycin. Similarly, a significant increase in serum calcium and cholesterol was noted for the erythromycin-treatment group.

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

Abnormal Labs

	Pretherapy	During Therapy	Posttherapy
PLATELETS			
111-6735 D	394		604
201-6103 D	263		402
105-6586 E	307		443
107-6927 E	316		458
107-6943 E	273		427
114-6805 E	371		537
155-6830 E	352		483
110-6716 E	289		426

NOTE: The abnormal laboratory values were followed up till they were normal.

MEDICAL OFFICER'S OVERALL COMMENTS:

Efficacy:

Both dirithromycin and erythromycin were effective in the treatment of pharyngitis/tonsillitis caused by Group A beta-hemolytic streptococci.
The clinical (cure or improvement) rate at posttherapy (3-5 days) was **95.5%** (106/111) for dirithromycin and **96.6%** (113/ 117) for the erythromycin group. The clinical (cure or improvement) rate at late-post-treatment (3-5 weeks) was **87.9%** (87/ 99) for dirithromycin and **88.2%** (97/110) for the erythromycin group. At termination, the clinical (cure or improvement) was **84.7%** (94/111) for the dirithromycin group and **85.5%** (100/117) for the erythromycin group.

The bacteriologic (cure or improvement) rate at posttherapy (3-5 days) was **88.2%** (97/110) for dirithromycin and **94.0%** (110/117) for the erythromycin group. The bacteriologic (cure or improvement) rate at late-post-treatment (3-5 weeks) was **90.8%** (89/98) for dirithromycin and **91.8%** (101/110) for the erythromycin group. At termination, the bacteriologic (cure or improvement) was **80.9%** (89/110) for the dirithromycin group and **87.2%** (102/117) for the erythromycin group.

SAFETY:

One hundred and fifty-eight patients in the dirithromycin group and 159 patients in the erythromycin group were evaluated for safety. The most common adverse events (drug-related or not) in both the treatment groups were in the digestive system. The most common ADRs were nausea, vomiting and abdominal pain in both the treatment groups.

MEDICAL OFFICER'S CONCLUSIONS:

In this study, the Clinical and Bacteriologic Response rates were comparable for both drugs. The results of this study will be combined with other pivotal studies to recommend the approval of this indication.

REVIEW OF PIVOTAL STUDIES:

III. Study B9Z-MC-AQAV Synopsis:

Title:	Dirithromycin (LY237216) versus Penicillin VK in the Treatment of Streptococcal Pharyngitis and/or Tonsillitis.
Study Centers:	There were 15 active study centers.
Dates of Study:	January 7, 1992 - June 12, 1992
Clinical Phase:	Phase 3
Objectives:	To compare dirithromycin (LY237216) with penicillin VK for effectiveness and safety in the treatment of pharyngitis and/or tonsillitis caused by group A beta-hemolytic streptococci.
Methodology:	Double-blind, double-dummy, randomized, parallel study.
Number of Patients:	Dirithromycin: male 62, female 108, total 170. Penicillin: male 63, female 112, total 175.
Diagnosis and Inclusion Criteria:	Pharyngitis/tonsillitis with confirmation of susceptible group A beta-hemolytic streptococcal etiology.
Dosage and Administration:	<u>Test Product</u> Dirithromycin: 500 mg/day (two 250-mg tablets q.d.) CT01003, CT00634: dirithromycin tablets, 250 mg CT01006, CT00637: placebo capsules NOTE: Placebo was used to maintain blinding. <u>Reference Therapy</u> Penicillin VK: 1000 mg/day (one 250 mg capsule q.i.d.) CT01004, CT00635: penicillin VK capsules, 250 mg CT01005, CT00636: placebo tablets NOTE: Placebo was used to maintain blinding.

Duration of Treatment:	Dirithromycin: 10 days Penicillin VK: 10 days
Criteria for Evaluation:	Efficacy--A complete efficacy evaluation was performed on patients completing 10 days of therapy who had positive pretherapy throat culture, returned for the during therapy, posttherapy and the late-posttherapy clinical evaluation and culture, and for whom the symptomatic response could be evaluated. Safety--All patients were evaluated for safety.
Statistical Methods:	Chi-square methodology. Appropriate continuous data procedures, such as two-sample t-test on ranked data, were used for analysis of laboratory data.

Study Design:

This was a double-blind, double-dummy, randomized, multicenter study with two parallel arms. Protocol is identical to study AQAB except the comparator used in this study was penicillin instead of erythromycin.

Investigators:

Study Population
All Patients Consented and/or Randomized

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	PENICILLIN	DIRITHROMYCIN	PENICILLIN
101 C. M. BRIEFER ANN ARBOR, MI	2	4	1	2
102 H. COLLINS EDISON, NJ	4	5	3	2
104 D. GINSBERG HARLEYSVILLE, PA	10	10	9	10
105 C. B. GOSWICK, JR BRYAN, TX	11	10	9	6
106 N. R. PATEL DAYTON, OH	0	1	0	0
107 E. H. GUTHRIE SALT LAKE CITY, UT	40	40	35	37
108 R. C. HASELBY MARSHFIELD, WI	8	8	7	8
109 T. W. LITTLEJOHN WINSTON-SALE, NC	14	13	12	9
110 J. W. MALOY MONTGOMERY, AL	1	2	1	1
111 J. MCCARTY FRESNO, CA	14	14	10	10
112 J. SALISBURY MIDDLETOWN, NJ	42	44	19	32
113 J. C. ROTSCHAFER ST. PAUL, MN	1	0	1	0
114 G. E. RUOFF KALAMAZOO, MI	6	8	2	6
115 P. G. SANDALL ALBUQUERQUE, NM	11	11	8	10
116 R. R. STOLTZ EVANSVILLE, IN	6	5	4	3
TOTAL	170	175	121	136

Sponsor's Analysis:

Patient disposition was as follows:

	Dirithromycin	Penicillin	Total
Patient Enrolled	170	175	345
Evaluable for Efficacy	121	136	257
Completed Therapy	103	109	212
Prematurely Discontinued	18	27	45
Not Evaluable	49	39	88
Completed Therapy	1	0	1
Prematurely Discontinued	48	39	87

Primary diagnosis:	**Pharyngitis**	**Tonsillitis**
Dirithromycin		
All patients	129	41
Evaluable patients	90	31
Penicillin		
All patients	127	48
Evaluable patients	96	40

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

Patient Demographics:

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

All Patients

Age Ranges By Sex
All Patients

	DIRITHROMYCIN						PENICILLIN					
	FEMALE (N = 108)		MALE (N = 62)		TOTAL (N = 170)		FEMALE (N = 112)		MALE (N = 63)		TOTAL (N = 175)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
AGE RANGES (YR)												
	13	(12.0%)	5	(8.1%)	18	(10.6%)	9	(8.0%)	5	(7.9%)	14	(8.0%)
	28	(25.9%)	23	(37.1%)	51	(30.0%)	24	(21.4%)	20	(31.7%)	44	(25.1%)
	65	(60.2%)	30	(48.4%)	95	(55.9%)	71	(63.4%)	35	(55.6%)	106	(60.6%)
	2	(1.9%)	3	(4.8%)	5	(2.9%)	8	(7.1%)	2	(3.2%)	10	(5.7%)
	0		1	(1.6%)	1	(0.6%)	0		1	(1.6%)	1	(0.6%)

Age By Sex Summary
All Patients

	DIRITHROMYCIN			PENICILLIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	108	62	170	112	63	175
MEAN AGE	28.26	28.34	28.29	29.38	28.39	29.02
STD DEV	9.31	10.34	9.67	9.27	9.75	9.43
MEDIAN AGE	28.14	26.40	27.64	28.74	29.66	28.77
MINIMUM AGE						
MAXIMUM AGE						

Racial Origin By Treatment Group
All Patients

ORIGIN	DIRITHROMYCIN N = 170 n	(%)	PENICILLIN N = 175 n	(%)	TOTAL N = 345 n	(%)
CAUCASIAN	141	(82.9%)	146	(83.4%)	287	(83.2%)
BLACK	13	(7.6%)	8	(4.6%)	21	(6.1%)
HISPANIC	13	(7.6%)	16	(9.1%)	29	(8.4%)
ASIAN	3	(1.8%)	2	(1.1%)	5	(1.4%)
OTHER	0		3	(1.7%)	3	(0.9%)

Height and Weight At Admission
All Patients

THERAPY	HEIGHT IN CM N	UNK	MEAN	STD DEV	MIN	MAX	WEIGHT IN KG N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	169	1	168.05	12			168	2	71.85	18		
PENICILLIN	175	0	168.56	10			175	0	72.31	18		

Evaluable Patients:

Age Ranges by Sex
Evaluable Patients

	DIRITHROMYCIN FEMALE (N = 81) n	(%)	MALE (N = 40) n	(%)	TOTAL (N = 121) n	(%)	PENICILLIN FEMALE (N = 90) n	(%)	MALE (N = 46) n	(%)	TOTAL (N = 136) n	(%)
AGE RANGES (YR)												
	10	(12.3%)	3	(7.5%)	13	(10.7%)	8	(8.9%)	4	(8.7%)	12	(8.8%)
	22	(27.2%)	14	(35.0%)	36	(29.8%)	19	(21.1%)	14	(30.4%)	33	(24.3%)
	48	(59.3%)	22	(55.0%)	70	(57.9%)	58	(64.4%)	27	(58.7%)	85	(62.5%)
	1	(1.2%)	0		1	(0.8%)	5	(5.6%)	1	(2.2%)	6	(4.4%)
	0		1	(2.5%)	1	(0.8%)	0		0		0	

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

	DIRITHROMYCIN			PENICILLIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	81	40	121	90	46	136
MEAN AGE	27.68	27.61	27.66	29.06	27.83	28.65
STD DEV	8.92	9.51	9.08	8.83	8.48	8.70
MEDIAN AGE	27.85	26.51	27.44	28.74	29.62	28.84
MINIMUM AGE						
MAXIMUM AGE						

Origin by Therapy Group
Evaluable Patients

	DIRITHROMYCIN N = 121		PENICILLIN N = 136	
ORIGIN	n	(%)	n	(%)
CAUCASIAN	102	(84.3%)	114	(83.8%)
BLACK	7	(5.8%)	5	(3.7%)
HISPANIC	10	(8.3%)	14	(10.3%)
ASIAN	2	(1.7%)	1	(0.7%)
OTHER	0		2	(1.5%)

Height and Weight at Admission
Evaluable Patients

	HEIGHT IN CM						WEIGHT IN KG					
THERAPY	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	120	1	167.91	13			120	1	71.19	18		
PENICILLIN	136	0	168.65	10			136	0	73.32	19		

Drug Administration:

All Patients

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

	DIRITHROMYCIN N = 170 DAYS	PENICILLIN N = 175 DAYS
NUMBER OF PATIENTS	167	174
MEAN DURATION EXPOSURE	10.3	10.4
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	3	1

Summary of Exposure to Study Drugs
All Patients

DAYS OF THERAPY	DIRITHROMYCIN N = 170 n	(%)	PENICILLIN N = 175 n	(%)
PATIENTS WITH INCOMPLETE DATA	3	(1.8%)	1	(0.6%)
1	2	(1.2%)	1	(0.6%)
2	4	(2.4%)	0	
3	3	(1.8%)	1	(0.6%)
4	3	(1.8%)	4	(2.3%)
5	2	(1.2%)	6	(3.4%)
6	3	(1.8%)	1	(0.6%)
7	1	(0.6%)	2	(1.1%)
8	0		1	(0.6%)
9	1	(0.6%)	1	(0.6%)
10	46	(27.1%)	40	(22.9%)
11	72	(42.4%)	96	(54.9%)
12	14	(8.2%)	8	(4.6%)
13	4	(2.4%)	6	(3.4%)
14	6	(3.5%)	5	(2.9%)
15	3	(1.8%)	2	(1.1%)
16	3	(1.8%)	0	

Evaluable Patients

Summary of Exposure to Study Drugs
Evaluable Patients

DAYS OF THERAPY	DIRITHROMYCIN N = 121 n	(%)	PENICILLIN N = 136 n	(%)
2	2	(1.7%)	0	
4	0		1	(0.7%)
9	1	(0.8%)	0	
10	30	(24.8%)	33	(24.3%)
11	62	(51.2%)	84	(61.8%)
12	11	(9.1%)	7	(5.1%)
13	4	(3.3%)	5	(3.7%)
14	5	(4.1%)	4	(2.9%)
15	3	(2.5%)	2	(1.5%)
16	3	(2.5%)	0	

Medical Officer's Comment:

76% of the evaluable patients in the dirithromycin group and 86% of patients in the penicillin group were treated for 10-11 days.

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

	DIRITHROMYCIN N = 121 DAYS	PENICILLIN N = 136 DAYS
NUMBER OF PATIENTS	121	136
MEAN DURATION EXPOSURE	11.1	11.0
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	0	0

Unevaluable Patients

Reason Unevaluable Summary
All Patients

REASON UNEVALUABLE	DIRITHROMYCIN N = 170 n	(%)	PENICILLIN N = 175 n	(%)
PATS. WITH => 1 REASON	49	(28.8%)	39	(22.3%)
PATS. WITH > 1 REASON	21	(12.4%)	15	(8.6%)
PRE-CULTURE NEGATIVE	22	(12.9%)	19	(10.9%)
INSUFFICIENT THERAPY	13	(7.6%)	12	(6.9%)
NO FOLLOW-UP CULTURE	14	(8.2%)	9	(5.1%)
NO POST THER. CULTURE	12	(7.1%)	5	(2.9%)
VISIT MISSING	11	(6.5%)	5	(2.9%)
NO POST FOLLOW-UP	12	(7.1%)	4	(2.3%)
CAUS. ORG. RESISTAN	5	(2.9%)	2	(1.1%)
CONCOMITANT ANTIBIOT.	3	(1.8%)	2	(1.1%)
LOW COLONY COUNT	1	(0.6%)	3	(1.7%)
BLIND BROKEN	1	(0.6%)	2	(1.1%)
UNEVAL. BY INVEST.	1	(0.6%)	1	(0.6%)
POST THER. CULT. LATE	0		1	(0.6%)

Efficacy Evaluation:

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

Clinical Response Summary By Therapy Group
Evaluable Patients Posttherapy

	DIRITHROMYCIN N = 121		PENICILLIN N = 136	
RESPONSE	n	(%)	n	(%)
CURE	95	(78.5%)	101	(74.3%)
IMPROVEMENT	22	(18.2%)	27	(19.9%)
RELAPSE	2	(1.7%)	7	(5.1%)
FAILURE	2	(1.7%)	1	(0.7%)

The clinical success rate for dirithromycin was 117/121 (96.7%) and 128/136 (94%) for the penicillin group.

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

Clinical Response Summary by Therapy Group
Evaluable Patients Late-Posttherapy

	DIRITHROMYCIN N = 116		PENICILLIN N = 126	
RESPONSE	n	(%)	n	(%)
CURE	95	(81.9%)	98	(77.8%)
IMPROVEMENT	5	(4.3%)	7	(5.6%)
RELAPSE	16	(13.8%)	21	(16.7%)

The clinical success rate for dirithromycin patients was 100/116 (86%) and 105/126 (83%) for the penicillin group.

The clinical response for evaluable patients at termination according to the applicant was as follows:

	THERAPY GROUP									
	DIRITHROMYCIN					PENICILLIN				
	TERMINATION					TERMINATION				
	FAVOR		UNFAVO			FAVOR		UNFAVO		
	N	%	N	%	N	N	%	N	%	N
PROJECT										
AQAV	103	85.1	18	14.9	121	108	79.4	28	20.6	136

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Bacteriologic Response

The bacteriologic response for evaluable patients at posttherapy according to the applicant was as follows:

Bacteriologic Response Summary By Therapy Group
Evaluable Patients Posttherapy

	DIRITHROMYCIN N = 120		PENICILLIN N = 135	
RESPONSE	n	(%)	n	(%)
ERADICATION	109	(90.8%)	123	(90.4%)
RELAPSE	7	(5.8%)	11	(8.1%)
PERSISTENCE	4	(3.3%)	1	(0.7%)

The bacteriologic response for evaluable patients at late-posttherapy according to the applicant was as follows:

Bacteriologic Response Summary by Therapy Group
Evaluable Patients Late-Posttherapy

	DIRITHROMYCIN N = 115		PENICILLIN N = 125	
RESPONSE	n	(%)	n	(%)
ERADICATION	99	(86.1%)	104	(83.2%)
ERADICATION WITH REINFECTION	1	(0.9%)	2	(1.6%)
RELAPSE	11	(9.5%)	18	(14.4%)
PERSISTENCE	4	(3.4%)	1	(0.8%)

The bacteriologic response for evaluable patients at termination according to the applicant was as follows:

	THERAPY GROUP									
	DIRITHROMYCIN					PENICILLIN				
	TERMINATION					TERMINATION				
	FAVOR		UNFAV			FAVOR		UNFAV		
	N	%	N	%	N	N	%	N	%	N
PROJECT										
AQAV	99	82.5	21	17.5	120	106	78.5	29	21.5	135

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

Susceptibility Results

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

Indication: Pharyngitis/Tonsillitis

	ANTIMICROBIAL: DIRITHROMYCIN			PENICILLIN G	
	SUSCEPTIBLE (ZONE>=17) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	TOTAL N
PATHOGEN					
STR GRP A	143	5	148	148	148

Susceptibility Ranges for Pathogens
According to Zone Size Criteria
Therapy: Penicillin

Indication: Pharyngitis/Tonsillitis

	ANTIMICROBIAL: DIRITHROMYCIN			PENICILLIN G		
	SUSCEPTIBLE (ZONE>=17) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	TOTAL N
PATHOGEN						
STR GRP A	155	1	156	155	1	156

Concomitant Medications:

Prior to study entry, 33.0% of the total patient population from both treated groups were receiving some form of drug therapy. Vitamins (ergocalciferol/ascorbic acid, ascorbic acid), oral contraceptives (ethinylestradiol/norethisterone, norethisterone/mestranol, and ethinylestradiol/levonorgestrel), and analgesics (ibuprofen and paracetamol) were the most frequently used drugs.

One or more concomitant agents were used during therapy by 52.9% of dirithromycin-treated patients and 57.1% of penicillin-treated patients. Paracetamol (acetaminophen), the most frequent concomitant medication, was used by 27.1% of dirithromycin and 26.3% of penicillin-treated patients.

After completion of study-drug therapy, 20.6% of dirithromycin-treated patients and 28.0% of penicillin-treated patients reported taking a concomitant medication, with paracetamol being most frequently used. Paracetamol was used by 4.1% of dirithromycin and 6.9% of penicillin-treated patients.

Eighteen dirithromycin-treated patients received another antibiotic after completion of study-drug therapy but before the late-posttherapy visit. Eight of the 18 patients did not qualify for efficacy analysis. Patients had negative or resistant pre-therapy cultures, and were treated with an unspecified antibiotic, penicillin, trimethoprim/sulfamethoxazole, amoxicillin, and penicillin. Patient was not qualified due to a low pretherapy colony count, and was treated with penicillin. Patients were treated with penicillin and cefadroxil, respectively, for reasons other than the study indication, and were thus disqualified due to protocol violation. The 10 qualified patients all had a recurrence of pharyngitis/tonsillitis symptoms and/or were culture-positive for group A beta-hemolytic streptococci after completion of study therapy, and were placed on a second antibiotic due to lack of efficacy of the study drug. The first 7 patients were given cefadroxil, amoxicillin, penicillin, amoxicillin/clavulanate, cefaclor, penicillin G benzathine/penicillin G procaine, and cefprozil, respectively, while the last 3 patients were given an unspecified antibiotic.

In the penicillin-treated group, 20 patients received a second antibiotic after completion of study drug but before the late-posttherapy visit. Two of the patients were terminated for protocol violation due to the use of a concomitant antibiotic. Neither was qualified for efficacy

analysis. Patient was given tetracycline following a vasectomy, and patient self-medicated with amoxicillin after completion of study drug therapy. The remaining 18 patients were all qualified for efficacy analysis. All had recurrence or persistence of pharyngitis/tonsillitis symptoms or were culture positive for group A beta-hemolytic streptococci after completion of study therapy, and were placed on a second antibiotic due to lack of efficacy of the study drug. Patient was given cefaclor. Patients were given erythromycin. Patients were placed on penicillin. Patients were given cephalexin. Patients were given an unspecified antibiotic.

The study populations were further characterized by presenting diagnosis and clinical condition. In the dirithromycin treatment group, 75.9% of patients were diagnosed with pharyngitis and 24.1% with tonsillitis. In the penicillin treatment group, 72.6% of patients were diagnosed with pharyngitis and 27.4% with tonsillitis. Approximately 94.8% of the total patient population presented in "fair" condition and 5.2% in "serious" condition based on the investigators' clinical assessment of the patients' overall symptomatology.

In summary, the randomization procedure resulted in two well-matched treatment groups with respect to patient characteristics, baseline diagnoses, concomitant drug therapy, and clinical condition.

Safety Results:

Summary of Adverse Event By Body System Table

Frequency of Adverse Events
by Body System--Body as a Whole--All Patients

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 170 n	(%)	PENICILLIN N = 175 n	(%)	PVALUE
PATIENTS WITH AT LEAST ONE EVENT	62	(36.5%)	62	(35.4%)	0.84
PATIENTS WITH NO EVENT	108	(63.5%)	113	(64.6%)	0.84
HEADACHE	29	(17.1%)	38	(21.7%)	0.274
ABDOMINAL PAIN	23	(13.5%)	11	(6.3%)	0.024
PAIN	5	(2.9%)	2	(1.1%)	0.236
ASTHENIA	4	(2.4%)	7	(4.0%)	0.384
INFECTION	4	(2.4%)	0		0.041
ACCIDENTAL INJURY	2	(1.2%)	4	(2.3%)	0.431
BACK PAIN	2	(1.2%)	4	(2.3%)	0.431
NECK PAIN	2	(1.2%)	2	(1.1%)	0.977
ABSCESS	1	(0.6%)	0		0.31
CELLULITIS	1	(0.6%)	0		0.31
CHILLS	1	(0.6%)	0		0.31
CHILLS AND FEVER	1	(0.6%)	0		0.31
FEVER	1	(0.6%)	0		0.31
LE SYNDROME	1	(0.6%)	0		0.31
SURGICAL PROCEDURE	1	(0.6%)	3	(1.7%)	0.329
CHEST PAIN	0		3	(1.7%)	0.086
OVERDOSE	0		1	(0.6%)	0.324

Frequency of Adverse Events
by Body System--Digestive System--All Patients

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 170 n	(%)	PENICILLIN N = 175 n	(%)	PVALUE
PATIENTS WITH AT LEAST ONE EVENT	56	(32.9%)	37	(21.1%)	0.014
PATIENTS WITH NO EVENT	114	(67.1%)	138	(78.9%)	0.014
NAUSEA	26	(15.3%)	10	(5.7%)	0.004
DIARRHEA	25	(14.7%)	15	(8.6%)	0.075
DYSPEPSIA	14	(8.2%)	8	(4.6%)	0.164
ANOREXIA	3	(1.8%)	1	(0.6%)	0.301
FLATULENCE	2	(1.2%)	0		0.15
VOMITING	2	(1.2%)	8	(4.6%)	0.06
DRY MOUTH	1	(0.6%)	3	(1.7%)	0.329
ERUCTATION	1	(0.6%)	0		0.31
GASTROENTERITIS	1	(0.6%)	0		0.31
ILEUS	1	(0.6%)	0		0.31
RECTAL DISORDER	1	(0.6%)	0		0.31
GASTRITIS	0		2	(1.1%)	0.162
INCREASED APPETITE	0		1	(0.6%)	0.324
ORAL MONILIASIS	0		1	(0.6%)	0.324
PERIODONTAL ABSCESS	0		1	(0.6%)	0.324
THIRST	0		1	(0.6%)	0.324

Frequency of Adverse Events
by Body System--Respiratory System--All Patients

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 170 n	(%)	PENICILLIN N = 175 n	(%)	PVALUE
PATIENTS WITH AT LEAST ONE EVENT	21	(12.4%)	43	(24.6%)	0.004
PATIENTS WITH NO EVENT	149	(87.6%)	132	(75.4%)	0.004
RHINITIS	10	(5.9%)	30	(17.1%)	0.001
PHARYNGITIS	5	(2.9%)	4	(2.3%)	0.703
COUGH INCREASED	3	(1.8%)	17	(9.7%)	0.002
SPUTUM INCREASED	2	(1.2%)	2	(1.1%)	0.977
ASTHMA	1	(0.6%)	0		0.31
SINUSITIS	1	(0.6%)	4	(2.3%)	0.187
VOICE ALTERATION	1	(0.6%)	0		0.31

Frequency of Adverse Events
by Body System--Skin and Appendages--All Patients

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 170 n	(%)	PENICILLIN N = 175 n	(%)	PVALUE
PATIENTS WITH AT LEAST ONE EVENT	9	(5.3%)	7	(4.0%)	0.568
PATIENTS WITH NO EVENT	161	(94.7%)	168	(96.0%)	0.568
HERPES SIMPLEX	4	(2.4%)	0		0.041
DRY SKIN	1	(0.6%)	1	(0.6%)	0.984
MACULOPAPULAR RASH	1	(0.6%)	1	(0.6%)	0.984
RASH	1	(0.6%)	3	(1.7%)	0.329
SWEATING	1	(0.6%)	1	(0.6%)	0.984
URTICARIA	1	(0.6%)	0		0.31
HERPES ZOSTER	0		1	(0.6%)	0.324

Frequency of Adverse Events
by Body System--Special Senses--All Patients

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 170 n	(%)	PENICILLIN N = 175 n	(%)	PVALUE
PATIENTS WITH AT LEAST ONE EVENT	10	(5.9%)	10	(5.7%)	0.947
PATIENTS WITH NO EVENT	160	(94.1%)	165	(94.3%)	0.947
EAR PAIN	6	(3.5%)	6	(3.4%)	0.959
EAR DISORDER	2	(1.2%)	1	(0.6%)	0.545
TASTE PERVERSION	2	(1.2%)	0		0.15
CONJUNCTIVITIS	0		2	(1.1%)	0.162
OTITIS MEDIA	0		2	(1.1%)	0.162
TINNITUS	0		1	(0.6%)	0.324

Frequency of Adverse Events
by Body System--Urogenital System--All Patients

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 170 n	(%)	PENICILLIN N = 175 n	(%)	PVALUE
PATIENTS WITH AT LEAST ONE EVENT	16	(9.4%)	10	(5.7%)	0.193
PATIENTS WITH NO EVENT	154	(90.6%)	165	(94.3%)	0.193
DYSMENORRHEA	9	(5.3%)	2	(1.1%)	0.028
METRORRHAGIA	2	(1.2%)	1	(0.6%)	0.545
URINARY TRACT INFECTION	2	(1.2%)	1	(0.6%)	0.545
VAGINAL MONILIASIS	2	(1.2%)	3	(1.7%)	0.676
BREAST NEOPLASM	1	(0.6%)	0		0.31
DYSURIA	1	(0.6%)	0		0.31
URINE ABNORMALITY	1	(0.6%)	0		0.31
VAGINITIS	1	(0.6%)	3	(1.7%)	0.329

Patients Who Died or Discontinued Therapy Due to Adverse Events:

No deaths were reported during the course of this study.
Six dirithromycin-treated patients and 9 penicillin-treated patients discontinued early due to an adverse event.

All Dirithromycin-Treated Patients Who Discontinued Due to Adverse Events

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	CAUSE OF ADVERSE EVENT	CONCOMITANT MEDICATION
101		1	21	MALE	CAUCASIAN	2	HIVES	IPHENHYDRAMINE/LIDOCAINE
102		1	26	FEMALE	CAUCASIAN	6	MENSTRUAL CRAMPING	LEVOTHYROXINE SODIUM
								NORETHISTERONE/MESTRANOL
								PARACETAMOL/PSEUDOEPHEDRI
107		1	31	FEMALE	CAUCASIAN	2	ABDOMINAL PAIN	MAGNESIUM/ALUMINIUM HYDRO
								NORETHISTERONE/MESTRANOL
112		1	44	FEMALE	ASIAN	1	HYPERTENSION	ENALAPRIL MALEATE
112		1	45	MALE	CAUCASIAN	7	UPSET STOMACH	ACETYLSALICYLIC ACID/CHLO
								ACETYLSALICYLIC ACID/CHLO
								CODEINE/PARACETAMOL
114		1	44	MALE	CAUCASIAN	1	APPENDECTOMY	BISACODYL
								DICYCLOVERINE HYDROCHLORI
								ERGOCALCIFEROL/ASCORBIC A
								FLUOXETINE HYDROCHLORIDE
								FLUOXETINE HYDROCHLORIDE
								HEPARIN
								HYDROXYZINE HYDROCHLORIDE
								METOCLOPRAMIDE
								NORTRIPTYLINE HYDROCHLORI
								NORTRIPTYLINE HYDROCHLORI
								NORTRIPTYLINE HYDROCHLORI
								PARACETAMOL/OXYCODONE/OXY
								PETHIDINE HYDROCHLORIDE
								SODIUM CITRATE/AMMONIUM/S

All Penicillin-Treated Patients Who Discontinued
Due to Adverse Events

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	CAUSE OF ADVERSE EVENT	CONCOMITANT MEDICATION
101		1	19	FEMALE	CAUCASIAN	5	DIZZINESS	CHLORPHENAMINE MALEATE HYDROXYZINE HYDROCHLORIDE PARACETAMOL PSEUDOEPHEDRINE HYDROCHLO
102		1	19	FEMALE	OTHER	1	RASH	
106		1	33	MALE	CAUCASIAN	5	DIARRHEA	
111		1	26	FEMALE	HISPANIC	4	STOMACH PAIN	GUAIFENESIN IBUPROFEN PARACETAMOL PSEUDOEPHEDRINE HYDROCHLO
112		1	32	FEMALE	CAUCASIAN	5	RASH	
112		1	25	FEMALE	CAUCASIAN	4	VOMITING	
112		1	27	FEMALE	CAUCASIAN	8	URINARY TRACT INFECTION	ERGOCALCIFEROL/ASCORBIC A
114		1	33	FEMALE	CAUCASIAN	5	VAGINAL BACTERIAL INFECTION	ASCORBIC ACID CYCLOBENZAPRINE HYDROCHLO PARACETAMOL PARACETAMOL
114		1	29	MALE	CAUCASIAN	4	NAUSEA	BISMUTH SUBSALICYLATE

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Clinical Laboratory Evaluations:

Statistically significant between-group changes were seen for mean cell hemoglobin (MCH) and serum bilirubin. There was a statistically significant decrease for MCH in the dirithromycin treatment group and a non-significant increase in the penicillin treatment group. There was a statistically significant decrease for bilirubin in both treatment groups; however, the decrease in bilirubin in the penicillin treatment group was greater in magnitude than the decrease in the dirithromycin population.

Statistically significant changes within groups were seen for several hematologic parameters. 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, polymorphonuclear neutrophil leukocytes (PMN's), and bands. A statistically significant reduction in monocytes was also seen for both treatment groups. A decrease in basophils was seen in both treatment groups, but the decrease was statistically significant only among penicillin-treated patients. Significant increases in lymphocytes and eosinophils were seen in both groups. The increase in eosinophils may be due to the large number of patients with allergies. Chronic allergy, or a history of one or more allergic reactions, was reported by 23% of the patient population. In addition, 4 penicillin-treated patients reported onset of mild rhinitis due to allergies during the study period. 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 illnesses. Both groups showed significant reductions in hematocrit (HCT), hemoglobin (HGB), and red blood cell (RBC) count. No patients in either treatment group reported clinically significant episodes of blood loss. Two dirithromycin and one penicillin-treated patients reported metrorrhagia. One penicillin-treated patient reported slightly prolonged bleeding after a pin prick (classified in COSTART as coagulation time increased). The penicillin-treated patient was not receiving anti-coagulants and no coagulation tests were performed.

Several blood chemistry analytes were found to have statistically significant within-group changes. Total protein decreased significantly in both groups while CPK, BUN, phosphorus, uric acid, and cholesterol increased significantly in both groups. With respect to liver function tests, there were statistically significant within-group decreases in alkaline phosphatase in both treatment groups.

Urine tests showed a significant decrease in urine specific gravity for patients receiving penicillin, and a significant decrease in urine pH for patients in the dirithromycin-treated group.

In summary, statistically significant changes within the two treatment groups were noted for many of the analytes, but in the absence of placebo control patients it is impossible to ascribe these changes to drug treatment. A statistically significant difference between treatment groups was noted only for mean cell hemoglobin (MCH) and total bilirubin. None of the mean changes for any analyte approached a level that would be considered of clinical significance.

Distribution of Extreme Laboratory Values

No clinically significant depressions in leukocyte count or other hematologic parameters, and no clinically significant elevations in liver function tests were noted in this group of patients. The two patients in this group that exhibited hyper-eosinophilia did not have symptoms suggestive of drug allergy.

Medical Officer's Recommendations:

Efficacy:

Both dirithromycin and penicillin were effective in the treatment of pharyngitis/tonsillitis caused by Group A beta-hemolytic streptococci.

The clinical (cure or improvement) rate at posttherapy (3-5 days) was **96.7%** (117/121) for dirithromycin and **94.0%** (128/136) for the penicillin group. The clinical (cure or improvement) rate at late-post-treatment (3-5 weeks) was **86.0%** (100/116) for dirithromycin and **83.0%** (105/126) for the penicillin group. At termination, the clinical (cure or improvement) was **85.1%** (103/121) for the dirithromycin group and **79.4%** (108/136) for the erythromycin group.

The bacteriologic (cure or improvement) rate at posttherapy (3-5 days) was **90.8%** (109/120) for dirithromycin and **90.4%** (123/135) for the penicillin group. The bacteriologic (cure or improvement) rate at late-post-treatment (3-5 weeks) was **86.1%** (99/115) for dirithromycin and **83.2%** (104/125) for the penicillin group. At termination, the bacteriologic (cure or improvement) was **82.5%** (99/120) for the dirithromycin group and **78.5%** (106/135) for the penicillin group.

SAFETY:

One hundred and seventy patients in the dirithromycin group and 175 patients in the penicillin group were evaluated for safety. The most common adverse events (drug-related or not) in both the treatment groups were in the digestive system. The most common ADRs were nausea, vomiting and abdominal pain in both the treatment groups.

MEDICAL OFFICER'S CONCLUSIONS:

In this study, the Clinical and Bacteriologic Response rates were comparable for dirithromycin and penicillin. The results of this study will be combined with other pivotal studies to recommend the approval of this indication.

Overall Summary:

Clinical Response
Posttherapy

	THERAPY GROUP															
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN					
	POST THERAPY					POST THERAPY					POST THERAPY					
	FAVORA		UNFAV			FAVORA		UNFAV			FAVORA		UNFAV			
	N	%	N	%	N	N	%	N	%	N	N	%	N	%	N
PROJECT																
AQAB	159	94.1	10	5.9	169	158	94.6	9	5.4	167	.	.	.	.	.
AQAS	106	95.5	5	4.5	111	113	96.6	4	3.4	117	.	.	.	.	.
AQAV	117	96.7	4	3.3	121	.	.	.	.	.	128	94.1	8	5.9	136
ALL	382	95.3	19	4.7	401	271	95.4	13	4.6	284	128	94.1	8	5.9	136

Clinical Response
Late-Posttherapy

	THERAPY GROUP														
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN				
	LATEPOST THERAPY					LATEPOST THERAPY					LATEPOST THERAPY				
	FAVORA		UNFAV			FAVORA		UNFAV			FAVORA		UNFAV		
PROJECT	N	%	N	%	N	N	%	N	%	N	N	%	N	%	N
AQAB	134	79.3	35	20.7	169	134	80.2	33	19.8	167	.	.	.	.	.
AQAS	87	78.4	24	21.6	111	97	82.9	20	17.1	117	.	.	.	.	.
AQAV	100	82.6	21	17.4	121	.	.	.	.	.	105	77.2	31	22.8	136
ALL	321	80.0	80	20.0	401	231	81.3	53	18.7	284	105	77.2	31	22.8	136

Clinical Response
Termination

	THERAPY GROUP															
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN					
	TERMINATION					TERMINATION					TERMINATION					
	FAVOR		UNFAV			FAVOR		UNFAV			FAVOR		UNFAV			
	N	%	N	%	N	N	%	N	%	N	N	%	N	%	N
PROJECT																
AQAB	140	82.8	29	17.2	169	141	84.4	26	15.6	167	.	.	.	.	.
AQAS	94	84.7	17	15.3	111	100	85.5	17	14.5	117	.	.	.	.	.
AQAV	103	85.1	18	14.9	121	.	.	.	.	.	108	79.4	28	20.6	136
ALL	337	84.0	64	16.0	401	241	84.9	43	15.1	284	108	79.4	28	20.6	136

Bacteriologic Response
Posttherapy

	THERAPY GROUP															
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN					
	POST THERAPY					POST THERAPY					POST THERAPY					
	FAVOR		UNFAV			FAVOR		UNFAV			FAVOR		UNFAV			
	N	%	N	%	N	N	%	N	%	N	N	%	N	%	N
PROJECT																
AQAB	134	79.3	35	20.7	169	144	86.2	23	13.8	167	.	.	.	.	.
AQAS	97	87.4	14	12.6	111	110	94.0	7	6.0	117	.	.	.	.	.
AQAV	109	90.1	12	9.9	121	.	.	.	.	.	123	90.4	13	9.6	136
ALL	340	84.8	61	15.2	401	254	89.4	30	10.6	284	123	90.4	13	9.6	136

Bacteriologic Response
Late-Posttherapy

	THERAPY GROUP															
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN					
	LATEPOST THERAPY					LATEPOST THERAPY					LATEPOST THERAPY					
	FAVOR		UNFAV			FAVOR		UNFAV			FAVOR		UNFAV			
	N	%	N	%	N	N	%	N	%	N	N	%	N	%	N
PROJECT																
AQAB	107	63.3	62	36.7	169	130	77.8	37	22.2	167	.	.	.	.	.
AQAS	89	80.2	22	19.8	111	101	86.3	16	13.7	117	.	.	.	.	.
AQAV	99	81.8	22	18.2	121	.	.	.	.	.	104	76.5	32	23.5	136
ALL	295	73.6	106	26.4	401	231	81.3	53	18.7	284	104	76.5	32	23.5	136

Bacteriologic Response
Termination

	THERAPY GROUP															
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN					
	TERMINATION					TERMINATION					TERMINATION					
	FAVOR		UNFAVO			FAVOR		UNFAVO			FAVOR		UNFAVO			
PROJECT	N	%	N	%	N	N	%	N	%	N	N	%	N	%	N
AQAB	111	67.3	54	32.7	165	131	79.9	33	20.1	164	.	.	.	.	.
AQAS	89	81.7	20	18.3	109	102	87.2	15	12.8	117	.	.	.	.	.
AQAV	99	82.5	21	17.5	120	.	.	.	.	.	106	78.5	29	21.5	135
ALL	299	75.9	95	24.1	394	233	82.9	48	17.1	281	106	78.5	29	21.5	135

MEDICAL OFFICER'S OVERALL COMMENTS:

Efficacy:

Dirithromycin, Erythromycin and Penicillin were effective in the treatment of pharyngitis/tonsillitis caused by Group A beta-hemolytic streptococci.

The overall clinical (cure or improvement) rate at posttherapy (3-5 days) was **95.3%** (382/401) for dirithromycin, **95.4%** (271/284) for the erythromycin group and **94.1%** (128/136) for the penicillin group. The overall clinical (cure or improvement) rate at late-post-treatment (3-5 weeks) was **80.0%** (321/401) for dirithromycin, **81.3%** (231/284) for the erythromycin group, and **77.2%** (105/136) for the penicillin group. At termination, the overall clinical (cure or improvement) was **84.0%** (337/401) for the dirithromycin group, **84.9%** (241/284) for the erythromycin group, and **79.4%** (108/136) for the penicillin group.

The overall bacteriologic (cure or improvement) rate at posttherapy (3-5 days) was **84.8%** (340/401) for dirithromycin, **89.4%** (254/284) for the erythromycin group and **90.4%** (123/136) for the penicillin group. The overall bacteriologic (cure or improvement) rate at late-post-treatment (3-5 weeks) was **73.6%** (295/401) for dirithromycin, **81.3%** (231/284) for the erythromycin group, and **76.5%** (104/136) for the penicillin group. At termination, the overall bacteriologic (cure or improvement) was **75.9%** (299/394) for the dirithromycin group, **82.9%** (233/281) for the erythromycin group, and **78.5%** (106/135) for the penicillin group.

REVIEW OF FOREIGN STUDIES:

I. Study B9Z-EW-E001 Synopsis:

Title:	Dirithromycin (LY237216) Versus Erythromycin Base in Streptococcal Pharyngitis/Tonsillitis
Study Centers:	There were 40 study centers (all in Europe).
Dates of Study:	May 1988 through November 1990.
Clinical Phase:	Phase 2 and 3.
Objectives:	To compare the effectiveness and safety of dirithromycin with erythromycin in the treatment of pharyngitis/tonsillitis.
Methodology:	Double-blind, randomized, parallel study
Number of Patients:	Dirithromycin: Male 76, Female 117, Total 193 Erythromycin: Male 84, Female 112, Total 196.
Diagnosis and Inclusion Criteria:	Diagnosis of streptococcal pharyngitis/tonsillitis by positive culture or "rapid strep test."
Dosage and Administration:	<u>Test Product</u> Dirithromycin: 500 mg/day, given once daily CT9198-7A, CT0009-9A, CT9549-9A: dirithromycin tablets, 250 mg CT9199-7A, CT-0010-9A, CT-9550-9A: placebo tablets NOTE: Placebo was used to maintain blinding. <u>Reference Therapy</u> Erythromycin 1000 mg/day, given four times daily CT9200-7A, CT9200-9C, CT9200-7A, CT9200-8B: erythromycin base tablets, 250 mg CT9201-7A, CT-9201-9C, CT9201-7A, CT9201-8B: placebo tablets NOTE: Placebo was used to maintain blinding.
Duration of Treatment:	Dirithromycin: 10 days Erythromycin Base: 10 days

Criteria for Evaluation: Efficacy--A complete efficacy analysis was performed on patients completing 10 days of therapy who had a positive pretherapy throat culture, who returned for during-therapy, posttherapy, and late-posttherapy clinical evaluation and culture, and for whom the symptomatic response could be evaluated.

Safety--All patients were evaluated for safety.

Statistical Methods: Chi-squared methodology was applied to response rates and adverse events. Appropriate continuous data procedures, such as two-sample t-test on ranked data were 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. Protocol was identical to AQAB.

Investigators:

INVESTIGATOR NAME/LOCATION	NUMBER OF ENROLLED PTS. DIRITH	ERYTH	NUMBER OF EVALUABLE PTS. DIRITH	ERYTH
D. G. WOOD/BANGOR, WALES	1	1	1	0
M. G. SCOTT/GLASGOW, SCOTLAND	1	2	1	0
M. J. DONNACHIE/GLASGOW, SCOTLAND	5	3	2	1
A. W. HARRIS/SUTTON COLDFIELD, ENGLAND	4	4	1	2
T. E. JONES/GWYNEDD, WALES	1	2	1	0
J. STADLER/GARTENSTRASSE, SWITZERLAND	0	2	0	0
H. D. WERDENBERG/PORRENTRUY, SWITZERLAND	0	1	0	0
S. WEISS/BERN, SWITZERLAND	2	0	0	0
R. DEUMIER/MONTMORENCY, FRANCE	0	2	0	2
F. HERRY/SAINT POL DE LEON, FRANCE	1	0	0	0
H. PORTIER/DIJON, FRANCE	1	1	0	0
O. MULLER/LAMBRECHT, GERMANY	30	30	23	20
P. REYES/MADRID, SPAIN	3	3	0	0
B. H. CARLSEN/BALLERUP, DENMARK	0	1	0	0
M. RISHOEJ/ROEDOVRE, DENMARK	6	4	5	2
B. T. KEPP/RODOVRE, DENMARK	1	2	1	2
A. S. COWIE/CORSHAM, ENGLAND	11	10	5	6
R. L. BHATKAR/AUCHINLECK, SCOTLAND	4	4	3	3
A. A. SANDERSON/SPENNYMOOR, ENGLAND	5	4	0	2
T. K. KHONG/LEICESTER, ENGLAND	10	10	2	4
J. A. BOCHSLER/LONDON, ENGLAND	5	5	1	2
M. R. GOLD/ENGLAND	5	5	1	2
B. R. AKHTAR/ABERTILLERY, WALES	2	2	1	1
D. A. LANGRIDGE/DIDCOT, ENGLAND	0	2	0	0
A. E. SENSIER/SPENNYMOOR, ENGLAND	2	1	2	0
S. H. SHAH/GWENT, WALES	7	8	2	4
M. CLARKE/CASTLEBLAYNEY, IRELAND	0	2	0	0
J. C. WILLIAMSON/RUNCORN CHESHIRE, ENGLAND	1	0	0	0
W. BUTLER/NAVAN, IRELAND	14	14	11	12
D. COTTER/BANTRY, IRELAND	3	4	0	3
C. MCNAMARA/DUBLIN, IRELAND	6	6	4	2
SULLIVAN/CLONMEL, IRELAND	6	5	4	3
S. KIERNAN/NAVAN, IRELAND	2	2	2	2
M. F. RYAN/CORK, IRELAND	10	9	4	4
F. BRADBURY/KILKENNY, IRELAND	9	9	3	4
P. MCGARRY/LONGFORD, IRELAND	6	6	3	5
E. HARTMANN/CAVAN, IRELAND	3	4	2	2
L. MCENTEE/TRIM, IRELAND	6	6	1	2
M. CASEY/MOATE, IRELAND	8	8	4	3
M. SMYTH/DUBLIN, IRELAND	4	4	1	0
TOTAL	193	196	97	99

Sponsor's Analysis:

Patient disposition was as follows:

	DIRITH	ERYTH	TOTAL
Patient Enrolled	193	196	389
Evaluable for Efficacy	97	99	196
Completed Therapy	93	97	190
Prematurely Discontinued	4	2	6
Not Evaluable	96	97	193
Completed Therapy	22	12	34
Prematurely Discontinued	74	85	159

Primary diagnosis:	**Pharyngitis**	**Tonsillitis**
Dirithromycin		
All patients	41	152
Evaluable patients	19	78
Erythromycin		
All patients	49	147
Evaluable patients	25	74

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

Patient Demographics:

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

AGE BY SEX - SUMMARY (IN YEARS)

ALL PATIENTS

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	117	76	193	112	84	196
MEAN AGE	30.55	30.21	30.41	32.58	29.48	31.25
STD DEV	10.79	12.34	11.40	11.56	11.13	11.46
MEDIAN AGE	29.00	27.50	29.00	30.00	28.00	29.00
MINIMUM AGE						
MAXIMUM AGE						

RACIAL ORIGIN BY TREATMENT GROUP

ALL PATIENTS

	DIRITHROMYCIN N=193		ERYTHROMYCIN N=196	
	n	(%)	n	(%)
RACIAL ORIGIN				
CAUCASIAN.	192	(99.5%)	195	(99.5%)
BLACK	1	(0.5%)	0	
ASIAN	0		1	(0.5%)

HEIGHT AND WEIGHT AT ADMISSION

ALL PATIENTS

	HEIGHT IN CM							WEIGHT IN KG						
	N	UNK	MEAN	STD DEV	MIN	MAX		N	UNK	MEAN	STD DEV	MIN	MAX	
THERAPY														
DIRITHROMYCIN	193	0	167.66	9				193	0	67.99	13			
ERYTHROMYCIN	196	0	168.57	11				195	1	69.40	14			

EVALUABLE PATIENTS:

Age Ranges by Sex
Evaluable Patients

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE (N = 64)		MALE (N = 33)		TOTAL (N = 97)		FEMALE (N = 67)		MALE (N = 32)		TOTAL (N = 99)	
AGE RANGES	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	18	(28.1%)	16	(48.5%)	34	(35.1%)	13	(19.4%)	16	(50.0%)	29	(29.3%)
	37	(57.8%)	12	(36.4%)	49	(50.5%)	43	(64.2%)	13	(40.6%)	56	(56.6%)
	9	(14.1%)	5	(15.2%)	14	(14.4%)	10	(14.9%)	3	(9.4%)	13	(13.1%)
	0		0		0		1	(1.5%)	0		1	(1.0%)

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

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	64	33	97	67	32	99
MEAN AGE	31.11	30.39	30.87	33.43	27.25	31.43
STD DEV	11.98	14.11	12.67	11.65	10.05	11.48
MEDIAN AGE	29.50	25.00	27.00	30.00	25.00	28.00
MINIMUM AGE						
MAXIMUM AGE						

Origin By Therapy Group
Evaluable Patients

ORIGIN	DIRITHROMYCIN N = 97 n	(%)	ERYTHROMYCIN N = 99 n	(%)	TOTAL N = 196 n	(%)
CAUCASIAN	96	(99.0%)	98	(99.0%)	194	(99.0%)
BLACK	1	(1.0%)	0		1	(0.5%)
ASIAN	0		1	(1.0%)	1	(0.5%)

Height and Weight at Admission
Evaluable Patients

THERAPY	HEIGHT IN CM N	UNK	MEAN	STD DEV	MIN	MAX	WEIGHT IN KG N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	97	0	168.52	9			97	0	67.93	12		
ERYTHROMYCIN	99	0	167.55	8			99	0	67.32	12		

Drug Administration:

All Patients

EXPOSURE TO STUDY DRUGS--
MEAN, MINIMUM, AND MAXIMUM
ALL PATIENTS

	DIRITHROMYCIN N = 193	ERYTHROMYCIN N = 196
NUMBER OF PATIENTS	189	190
MEAN DURATION EXPOSURE, DAYS	10.2	10.2
MINIMUM EXPOSURE, DAYS		
MAXIMUM EXPOSURE, DAYS		
PATIENTS WITH INCOMPLETE DATA	4	6

SUMMARY OF EXPOSURE TO STUDY DRUGS

ALL PATIENTS

DAYS OF THERAPY	DIRITHROMYCIN N = 193 n	(%)	ERYTHROMYCIN N = 196 n	(%)
PATIENTS WITH INCOMPLETE DATA	4	(2.1%)	6	(3.1%)
2	3	(1.6%)	2	(1.0%)
3	1	(0.5%)	2	(1.0%)
4	1	(0.5%)	4	(2.0%)
5	1	(0.5%)	1	(0.5%)
6	4	(2.1%)	1	(0.5%)
7	2	(1.0%)	0	
8	1	(0.5%)	0	
9	3	(1.6%)	5	(2.6%)
10	91	(47.2%)	83	(42.3%)
11	75	(38.9%)	81	(41.3%)
12	4	(2.1%)	8	(4.1%)
13	0		2	(1.0%)
14	1	(0.5%)	0	
15	1	(0.5%)	0	
16	1	(0.5%)	1	(0.5%)

Evaluable Patients

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

	DIRITHROMYCIN N = 97 DAYS	ERYTHROMYCIN N = 99 DAYS
NUMBER OF PATIENTS	97	99
MEAN DURATION EXPOSURE	10.3	10.4
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients

DAYS OF THERAPY	DIRITHROMYCIN N = 97 n	(%)	ERYTHROMYCIN N = 99 n	(%)
2	0		1	(1.0%)
3	1	(1.0%)	0	
4	1	(1.0%)	0	
6	1	(1.0%)	0	
9	1	(1.0%)	0	
10	51	(52.6%)	50	(50.5%)
11	41	(42.3%)	46	(46.5%)
12	0		2	(2.0%)
14	1	(1.0%)	0	

Medical Officer's Comments:
94% of the evaluable patients in the dirithromycin group and 96% of patients in the erythromycin group were treated for 10-11 days.

Unevaluable Patients

REASON UNEVALUABLE	DIRITHROMYCIN N = 193 n	(%)	ERYTHROMYCIN N = 196 n	(%)	TOTAL N = 389 n	(%)
ALL UNEVALUABLE PATS.	96	(49.7%)	97	(49.5%)	193	(49.6%)
PATS. WITH > 1 REASON	43	(22.3%)	44	(22.4%)	87	(22.4%)
PRE-CULTURE NEGATIVE	27	(14.0%)	25	(12.8%)	52	(13.4%)
LATE CLIN. ASSESSMENT	19	(9.8%)	13	(6.6%)	32	(8.2%)
NO FOLLOW-UP CULTURE	16	(8.3%)	15	(7.7%)	31	(8.0%)
INSUFFICIENT THERAPY	12	(6.2%)	16	(8.2%)	28	(7.2%)
NO POST FOLLOW-UP	11	(5.7%)	12	(6.1%)	23	(5.9%)
NO POST THER. CULTURE	4	(2.1%)	12	(6.1%)	16	(4.1%)
POST THER. CULT. LATE	9	(4.7%)	6	(3.1%)	15	(3.9%)
CAUS. ORG. RESISTANT	6	(3.1%)	8	(4.1%)	14	(3.6%)
UNACCEPT. PATHOGEN	5	(2.6%)	6	(3.1%)	11	(2.8%)
EARLY CLIN. ASSESSMENT	5	(2.6%)	4	(2.0%)	9	(2.3%)
VISIT MISSING	3	(1.6%)	5	(2.6%)	8	(2.1%)
UNEVAL. BY INVEST.	6	(3.1%)	1	(0.5%)	7	(1.8%)
NO DURING CULTURE	3	(1.6%)	4	(2.0%)	7	(1.8%)
POOR COMPLIANCE	4	(2.1%)	3	(1.5%)	7	(1.8%)
POST THER. CULT. EARLY	3	(1.6%)	1	(0.5%)	4	(1.0%)
FOLLOW-UP CULT. LATE	3	(1.6%)	1	(0.5%)	4	(1.0%)
INCOMPLETE DATA	1	(0.5%)	3	(1.5%)	4	(1.0%)
LOW COLONY COUNT	2	(1.0%)	2	(1.0%)	4	(1.0%)
NO COLONY COUNT	1	(0.5%)	3	(1.5%)	4	(1.0%)
CONCOMIT. MEDICATION	1	(0.5%)	2	(1.0%)	3	(0.8%)
BREAK IN THERAPY	0		3	(1.5%)	3	(0.8%)
CONCOMITANT ANTIBIOT.	1	(0.5%)	1	(0.5%)	2	(0.5%)
NO INITIAL CULTURE	2	(1.0%)	0		2	(0.5%)
DURING CULTURE LATE	2	(1.0%)	0		2	(0.5%)
WRONG AGE	1	(0.5%)	1	(0.5%)	2	(0.5%)
SENSITIVITY NOT DONE	0		1	(0.5%)	1	(0.3%)
INITIAL CULT. EARLY	0		1	(0.5%)	1	(0.3%)
DURING CULTURE EARLY	1	(0.5%)	0		1	(0.3%)
PROLONGED THERAPY	1	(0.5%)	0		1	(0.3%)

Efficacy Evaluation:

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

CLINICAL RESPONSE SUMMARY BY THERAPY GROUP
ALL EVALUABLE PATIENTS POSTTHERAPY

RESPONSE	DIRITHROMYCIN N = 97 n	(%)	ERYTHROMYCIN N = 99 n	(%)
CURE	78	(80.4%)	82	(82.8%)
IMPROVEMENT	11	(11.3%)	11	(11.1%)
RELAPSE	2	(2.1%)	4	(4.0%)
FAILURE	6	(6.2%)	2	(2.0%)

An overall favorable symptomatic (cure or improvement) (cure or improvement) was achieved in 91.7% (89/97) of dirithromycin-treated patients and 93.9% (93/99) of erythromycin-treated patients.

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

CLINICAL RESPONSE SUMMARY BY THERAPY GROUP LATE-POSTTHERAPY
ALL EVALUABLE PATIENTS

RESPONSE	DIRITHROMYCIN N = 89 n	(%)	ERYTHROMYCIN N = 93 n	(%)
CURE	81	(91.0%)	90	(96.8%)
IMPROVEMENT	1	(1.1%)	0	
RELAPSE	7	(7.9%)	3	(3.2%)

An overall clinical success rate was 82/89 (92%) for the dirithromycin patients and 90/93 (96.8%) for the erythromycin patients.

The clinical response for evaluable patients at termination according to the applicant was as follows:

Clinical Response at Termination
E001 Pharyngitis/Tonsillitis
Evaluable Patients

Termination

	Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable	
Project	N	%	N	%	N	%	N	%
E001	82	84.5	15	15.5	90	90.9	9	9.1

Bacteriologic Response

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

BACTERIOLOGIC RESPONSE SUMMARY BY THERAPY GROUP
ALL EVALUABLE PATIENTS POSTTHERAPY

RESPONSE	DIRITHROMYCIN N = 95 n	(%)	ERYTHROMYCIN N = 98 n	(%)
PATHOGEN ELIMINATED	79	(83.2%)	86	(87.8%)
RECURRENCE SAME	7	(7.3%)	9	(9.2%)
FAILED TO ELIMINATE	9	(9.5%)	3	(3.0%)

Posttherapy throat cultures that were negative for group A streptococci were obtained from 79 of 95 (83.2%) dirithromycin-treated patients, compared with 86 of 98 (87.8%) erythromycin-treated patients.

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

BACTERIOLOGIC RESPONSE SUMMARY BY THERAPY GROUP

ALL EVALUABLE PATIENTS

	DIRITHROMYCIN N = 89		ERYTHROMYCIN N = 92	
RESPONSE	n	(%)	n	(%)
PATHOGEN ELIMINATED	77	(86.5%)	84	(91.3%)
RECURRENCE SAME	10	(11.2%)	7	(7.6%)
FAILED TO ELIMINATE	2	(2.2%)	1	(1.1%)

In the dirithromycin group, 77 of the 89 qualified patients (86.5%) had negative throat cultures at the late-posttherapy evaluation. In the erythromycin group, 84 of the 92 (91.3%) qualified patients seen at the late-posttherapy evaluation had negative late-posttherapy throat cultures.

The bacteriologic response for evaluable patients at termination according to the applicant was as follows:

Bacteriological Response at Termination
E001 Pharyngitis/Tonsillitis
Evaluable Patients

	Termination							
	Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable	
Project	N	%	N	%	N	%	N	%
E001	78	80.4	19	19.6	85	85.9	14	14.1

Susceptibility Results

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

	ANTIMIBCROBIAL						
	DIRITHROMYCIN				ERYTHROMCYIN		
	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	RESISTANT (ZONE<=13) N	TOTAL N
PATHOGEN							
STR GRP A	149	1	9	159	153	6	159

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

	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								
STR GRP A	150	5	9	164	156	2	6	164

CONCOMITANT MEDICATIONS:

Prior to study entry, approximately 20% of patients in each treatment group were receiving some form of drug therapy. Levonorgestrel/ethinylestradiol was the most frequently used drug, taken by 5.7% and 5.1% of the dirithromycin-treated and erythromycin-treated patients, respectively. Other frequently used drugs included nonsteroidal anti-inflammatory agents and hormonal agents.

Fourteen (7.3%) dirithromycin- and 23 (11.7%) erythromycin-treated patients received concomitant drug therapy during the period of study drug administration. Two erythromycin patients used chloramphenicol eye drops for conjunctivitis during the study. Neither of these patients qualified for efficacy. One patient did not have a pathogen at pretherapy and discontinued the study as an entry criteria exclusion. The other patient was above the acceptable age limit of the study. Paracetamol was the most frequently used non-study drug medication in both treatment groups.

After completion of study-drug therapy, approximately 3% of patients (4.1% dirithromycin and 1.5% erythromycin) reported taking concomitant medications. Again, paracetamol was most frequently used. Two patients received an antibiotic between the posttherapy and late-posttherapy visits. One dirithromycin patient was prescribed erythromycin for symptoms of acute bronchitis. The acute bronchitis was reported as an adverse event and had a duration of 8 days. The patient was not qualified for efficacy analysis due to the introduction of another antibiotic. Similarly, one erythromycin patient was prescribed amoxicillin for the treatment of otitis media. The otitis media was reported as an adverse event and had a duration of 5 days. The patient was not qualified for efficacy analysis due to the introduction of another antibiotic.

SAFETY RESULTS:

Summary of Adverse Event By Body System Table

FREQUENCY OF TREATMENT-EMERGENT EVENTS
ALL ADVERSE EVENTS
BODY SYSTEM: BODY AS A WHOLE
ALL PATIENTS

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 193 n	(%)	ERYTHROMYCIN N = 196 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	13	(6.7%)	17	(8.7%)	0.474
PATIENTS WITH NO EVENT	180	(93.3%)	179	(91.3%)	0.474
ABDOMINAL PAIN	4	(2.1%)	7	(3.6%)	0.373
HEADACHE	4	(2.1%)	3	(1.5%)	0.688
INJURY, ACCIDENT	2	(1.0%)	1	(0.5%)	0.553
PAIN	2	(1.0%)	2	(1.0%)	0.988
ASTHENIA	1	(0.5%)	3	(1.5%)	0.322
BACK PAIN	1	(0.5%)	0		0.313
SURGICAL PROCEDURE	1	(0.5%)	0		0.313
MALAISE	0		1	(0.5%)	0.320
NECK PAIN	0		1	(0.5%)	0.320

FREQUENCY OF TREATMENT-EMERGENT EVENTS

EVENTS STARTING DURING THERAPY

BODY SYSTEM: BODY AS A WHOLE

ALL PATIENTS

EVENT CLASSIFICATION TERM	DIRITHROMYCIN n = 193 N	(%)	ERYTHROMYCIN n = 196 N	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	9	(4.7%)	15	(7.7%)	0.220
PATIENTS WITH NO EVENT	184	(95.3%)	181	(92.3%)	0.220
ABDOMINAL PAIN	3	(1.6%)	7	(3.6%)	0.209
HEADACHE	3	(1.6%)	2	(1.0%)	0.640
PAIN	2	(1.0%)	1	(0.5%)	0.553
ASTHENIA	1	(0.5%)	3	(1.5%)	0.322
BACK PAIN	1	(0.5%)	0		0.310
INJURY, ACCIDENT	1	(0.5%)	1	(0.5%)	0.991
MALAISE	0		1	(0.5%)	0.320
NECK PAIN	0		1	(0.5%)	0.320

FREQUENCY OF TREATMENT-EMERGENT EVENTS

ALL ADVERSE EVENTS

BODY SYSTEM: DIGESTIVE SYSTEM

ALL PATIENTS

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 193 n	(%)	ERYTHROMYCIN N = 196 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	19	(9.8%)	28	(14.3%)	0.179
PATIENTS WITH NO EVENT	174	(90.2%)	168	(85.7%)	0.179
DIARRHEA	9	(4.7%)	9	(4.6%)	0.973
VOMITING	4	(2.1%)	4	(2.0%)	0.982
NAUSEA	3	(1.6%)	13	(6.6%)	0.012
GASTROINTESTINAL DISORDER	2	(1.0%)	2	(1.0%)	0.988
BLOODY DIARRHEA	1	(0.5%)	0		0.313
CONSTIPATION	1	(0.5%)	0		0.313
DYSPEPSIA	1	(0.5%)	0		0.313
DYSPHAGIA	1	(0.5%)	1	(0.5%)	0.991
GASTRITIS	1	(0.5%)	2	(1.0%)	0.571
ENTERITIS	0		1	(0.5%)	0.320
FLATULENCE	0		1	(0.5%)	0.320
GASTROENTERITIS	0		1	(0.5%)	0.320
GINGIVITIS	0		1	(0.5%)	0.320
MOUTH ULCERATION	0		1	(0.5%)	0.320
NAUSEA AND VOMITING	0		1	(0.5%)	0.320

FREQUENCY OF TREATMENT-EMERGENT EVENTS
EVENTS STARTING DURING THERAPY
BODY SYSTEM: DIGESTIVE SYSTEM
ALL PATIENTS

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 193 n	(%)	ERYTHROMYCIN N = 196 n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	16	(8.3%)	28	(14.3%)	0.062
PATIENTS WITH NO EVENT	177	(91.7%)	168	(85.7%)	0.062
DIARRHEA	7	(3.6%)	9	(4.6%)	0.632
NAUSEA	3	(1.6%)	13	(6.6%)	0.012
VOMITING	3	(1.6%)	4	(2.0%)	0.718
GASTROINTESTINAL DISORDER	2	(1.0%)	2	(1.0%)	0.988
BLOODY DIARRHEA	1	(0.5%)	0		0.313
CONSTIPATION	1	(0.5%)	0		0.313
DYSPEPSIA	1	(0.5%)	0		0.313
GASTRITIS	1	(0.5%)	2	(1.0%)	0.571
DYSPHAGIA	0		1	(0.5%)	0.320
ENTERITIS	0		1	(0.5%)	0.320
FLATULENCE	0		1	(0.5%)	0.320
GASTROENTERITIS	0		1	(0.5%)	0.320
GINGIVITIS	0		1	(0.5%)	0.320
MOUTH ULCERATION	0		1	(0.5%)	0.320
NAUSEA AND VOMITING	0		1	(0.5%)	0.320

Patients Who Died or Discontinued Therapy Due to Adverse Events:

There were no deaths reported during the study. There were 4 events (3 dirithromycin-treated patients and 1 erythromycin-treated patient) reported during the course of this study that qualified as serious for regulatory reporting purposes. Each of the events reported in dirithromycin patients occurred after completion of the drug therapy.Five dirithromycin patients and 7 erythromycin patients discontinued early due to adverse events; 4 of the 5 dirithromycin patients and 5 of the 7 erythromycin patients experienced adverse events related to the gastrointestinal system. One dirithromycin patient was discontinued from the study early due to adverse events related to a cutaneous rash; no erythromycin patients were discontinued from the study due to rash. In addition, 1 erythromycin patient discontinued early with complaints of malaise.

PATIENTS DISCONTINUED BECAUSE OF ADVERSE EVENTS

ALL DIRITHROMYCIN-TREATED PATIENTS

PHARYNGITIS/TONSILLITIS INDICATION

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT	CONCOMITANT MEDICATION
402		1	18	MALE	CAUCASIAN	6	GENERALISED ALLERGIC EXANTHEMA	BETAMETHASONE/ DEXCHLORPHENIRAMINE
801		1	29	FEMALE	CAUCASIAN	2	DIARRHOEA	
805		1	30	FEMALE	CAUCASIAN	2	DIARRHOEA	
862		1	42	FEMALE	CAUCASIAN	7	VOMITING	
894		1	16	FEMALE	CAUCASIAN	2	VOMITING	

PATIENTS DISCONTINUED BECAUSE OF ADVERSE EVENTS

ALL ERYTHROMYCIN-TREATED PATIENTS

INV	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT	CONCOMITANT MEDICATION
402		1	30	MALE	CAUCASIAN	4	NAUSEA	CISAPRIDE
801		1	31	MALE	CAUCASIAN	4	GENERAL MALAISE	PARACETAMOL
804		1	23	MALE	CAUCASIAN	5	DIARRHOEA	
805		1	34	FEMALE	CAUCASIAN	3	NAUSEA	LOFEPRAMINE
862		1	19	FEMALE	CAUCASIAN	6	SICKNESS	TEMAZEPAM
866		1	28	FEMALE	CAUCASIAN	2	DIARRHOEA	
871		1	34	FEMALE	CAUCASIAN	3	ABDOMINAL CRAMPS	

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, polymorphonuclear neutrophil leukocytes (PMNs), and bands. 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, hemoglobin and red blood cell count. Although the changes in hematocrit, hemoglobin and red blood cell count were statistically significant, the magnitude of the changes were not considered clinically significant. 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 illnesses. No statistically significant difference between the treatment groups were seen for any of the analytes. There were no statistically significant changes within seen only for the dirithromycin group. The mean value of the MCH for the erythromycin group showed a statistically significant increase.

Several blood chemistry analytes showed significant changes within the groups. Alkaline phosphatase showed a statistically significant decrease in both groups. CPK, BUN, phosphorus, and cholesterol all showed statistically significant increases in both groups. Despite the noted rise in BUN for both groups, serum creatinine was significantly decreased slightly in only the erythromycin treatment group.

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

E001 Pharyngitis
Abnormal Labs

	Pretherapy	During Therapy	Posttherapy
PLATELETS			
054-4077 D		237	494
055-4089*D	417		609
057-4047 D	308		402
801-8194 D	399		508
810-8151 D	545		656
871-8104 D	285		415
871-8209 D	352	299	448
891-8122 D	382		526
896-8133 D	355		562
812-8089 E	240		411
871-8211 E	312		425
886-8179 E	307		424
894-8163 E	317		484
MCV (fL)			
055-4089	88.6		105
PHOSPHORUS (mmol/L)			
055-4089	1.29		1.86

All abnormal laboratory values were followed up till they were normal.

MEDICAL OFFICER'S OVERALL COMMENTS:

Efficacy:

Both dirithromycin and erythromycin were effective in the treatment of pharyngitis/tonsillitis caused by Group A beta-hemolytic streptococci.
The clinical (cure or improvement) rate at posttherapy (3-5 days) was **91.7%** (89/97) for dirithromycin and **93.9%** (93/ 99) for the erythromycin group. The clinical (cure or improvement) rate at late-post-treatment (3-5 weeks) was **92%** (82/ 89) for dirithromycin and **96.8%** (90/93) for the erythromycin group. At termination, the clinical (cure or improvement) was **84.5%** (82/97) for the dirithromycin group and **90.9%** (90/99) for the erythromycin group.

The bacteriologic (cure or improvement) rate at posttherapy (3-5 days) was **83.2%** (79/95) for dirithromycin and **87.8%** (86/98) for the erythromycin group. The bacteriologic (cure or improvement) rate at late-post-treatment (3-5 weeks) was **86.5%** (77/89) for dirithromycin and **91.3%** (84/92) for the erythromycin group. At termination, the bacteriologic (cure or improvement) was **80.42%** (78/95) for the dirithromycin group and **85.9%** (85/99) for the erythromycin group.

SAFETY:

One hundred and ninety -three patients in the dirithromycin group and 19659 patients in the erythromycin group were evaluated for safety. The most common adverse events (drug-related or not) in both the treatment groups were in the digestive system. The most common ADRs were nausea, vomiting and abdominal pain in both the treatment groups.

Medical Officer's Conclusions

In this study, the Clinical and Bacteriologic Response rates were comparable for both drugs. The results of this study will be combined with other pivotal studies to recommend the approval of this indication.

OVERALL MEDICAL OFFICER'S CONCLUSIONS

The overall Clinical and Bacteriologic Response rates in the two pivotal studies AQAS and AQAV were comparable for dirithromycin and the control drugs. In one pivotal study (AQAB), response rates for erythromycin were better than dirithromycin. The Europeon study which followed the same protocol as the US studies was used as a supportive study for this indication, had comparable clinical (cure or improvement) rates for dirithromycin and erythromycin. Thus, data of three out of four studies showed that clinical and bacteriolgic (cure or improvement) rates for dirithromycin were comparable to the control drugs.

MEDICAL OFFICER'S RECOMMENDATIONS

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

Dirithromycin is recommended for approval for the treatment of pharyngitis/tonsillitis caused by *Streptococcus pyogenes.*

The recommended dosage is 500 mg once a day for 10 days.

REVIEW OF PIVOTAL STUDIES:

I. Study B9Z-MC-AQAB Synopsis:

Title:	Dirithromycin (LY237216) Versus Erythromycin Base in Acute Bacterial Exacerbation of Chronic Bronchitis
Study Centers:	There were 98 study centers (All in North America)
Dates of Study:	October 1988 through May 1991
Clinical Phase:	Phase 2 and 3
Objectives:	To compare the effectiveness and safety of dirithromycin with erythromycin in the treatment of acute bacterial exacerbation of chronic bronchitis.
Methodology:	Double-blind, randomized, parallel study.
Number of Subjects:	Dirithromycin: Male 179, Female 214, Total 393. Erythromycin: Male 183, Female 226, Total 409.
Diagnosis and Inclusion Criteria:	Diagnosis of acute bacterial exacerbation of chronic bronchitis with cough, purulent sputum, and a chest radiograph free from acute pulmonary infiltrates.
Dosage and Administration:	<u>Test Product</u> Dirithromycin: 500 mg, given once daily CT9367,CT9964: dirithromycin tablets,250 mg CT9368,CT9965: placebo tablets Note: placebo was used to maintain blinding <u>Reference Therapy</u> Erythromycin: 1000 mg/day, 250/mg given four times daily CT9369,CT9966: erythromycin tablets, 250 mg CT9370,CT9967: 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 post-therapy evaluation, and who had a symptomatic response that could be evaluated. Safety--All patients were to be evaluated for safety.
Statistical Methods:	Chi-square methodology was applied to response rates and adverse events. Appropriate continuous data procedures, such as two-sample t-tests on ranked data, were to be used for analysis of laboratory data.

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 to be 7 days. There was no minimum treatment period for patients who did not respond to therapy.

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

Inclusion Criteria

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

The investigators attempted 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 asked to sign an IRB-approved informed consent document.

Exclusion Criteria

Patients were to be excluded if they:

- 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 hypersensitivity to the macrolide class of antibiotics;
- 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;
- were unable to return for follow-up examinations;
- were pregnant, or postpartum females who were nursing.

Women with child-bearing potential were to have a negative pregnancy test prior to therapy. They were also required to use a reliable method of birth control during and for one month following completion of therapy.

Dosing Schedule:

Patients randomly allocated to the dirithromycin treatment group received two 250-mg dirithromycin tablets in the morning (total daily dosage 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 daily dosage 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 were to be performed. Blood chemistries, complete blood count (CBC) and urinalysis were to be performed.
During-Therapy (Days 3-5)	Symptomatic response to therapy was to be evaluated. Patient compliance with instructions for taking medication was to be assessed. Laboratory tests were to be repeated as clinically indicated.
Posttherapy (3-5 days after therapy was completed)	Physical examination was to be performed to evaluate symptomatic response to therapy. Blood chemistries, CBC, and urinalysis were to be performed.
Late-posttherapy (10-14 days after therapy was completed)	Physical examination was to be performed to evaluate symptomatic response to therapy. Laboratory tests were to be repeated if clinically indicated.

PROCEDURES FOR EVALUATION OF BACTERIOLOGIC RESPONSE

Study Visit	Procedure
Pretherapy (Within 24 hours preceding start of therapy):	Culture and Gram's stain of expectorated sputum. Susceptibility to both dirithromycin and erythromycin of the isolated microorganism(s) was to be determined by the FDA standardized disk method and/or MIC determination. The pathogen had to be susceptible to erythromycin.*
During-Therapy (Days 3-5):	Urine sample for antibiotic presence.
Posttherapy (3-5 days after therapy was discontinued):	Gram's stain and culture of sputum if productive cough continued.
Late-posttherapy (10-14 days after therapy was discontinued):	Gram's stain and culture of sputum if production of sputum continued.

* Erythromycin susceptibility defined as ≥18 mm zone diameter or ≤0.5 µg/mL MIC

Safety Procedures:

Safety assessments included clinical evaluations and laboratory tests. Electrocardiograms (ECG's) were to be performed during Phase 2 Studies. A central laboratory was used to determine values for the laboratory tests. Each study site was provided with 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. If creatine kinase (CK) was >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.

LABORATORY TESTS TO EVALUATE SAFETY

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*	

*If CK was >1000 U/L, the central laboratory was to notify the site and run a CK isoenzyme fractionation. The laboratory then telephoned 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 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 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. These 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, or parents, and/or guardians 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 clinical report form. If any

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 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 discontinued from the study for any one of the following reasons:

- The 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.
- If the patient, parent or guardian, or attending physician requested, or the investigator so decided, the patient was withdrawn from the study and the reason was to be stated on the clinical report form.
- Study drug identity was unblinded for safety reasons.
- Pretherapy serum creatinine ≥133 μmol/L (1.5 mg/dL).

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

Efficacy Procedures:

SYMPTOMATIC RESPONSE DEFINITIONS

Response	Definition
Cure:	Elimination of signs and symptoms of infection with no recurrence in the post-treatment or late post-treatment follow-up periods.
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 the infection 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 but not safety analysis.

* 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, e.g., if a patient presenting at the posttherapy evaluation was clinically cured or improved, but bacteriologically culture-positive for a respiratory pathogen and was treated with an antibiotic, the patient's symptomatic response was categorized as "cure" or "improvement".

Medical Officer's Comments:

The Medical Officer concurs with the above definitions.

BACTERIOLOGIC RESPONSE DEFINITIONS

Response	Definition
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 post-treatment or late post-treatment follow-up periods.
Recurrence Same Pathogen, Resistance Developed:	Original pathogen susceptible to erythromycin was eliminated during treatment, but recurred in the post-treatment or late post-treatment follow-up periods 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 sputum was no longer being produced.
Unable to Evaluate:	Cultures were not obtained or a systemic (non-study) antimicrobial agent with activity against respiratory bacterial pathogens was taken.

Medical Officer's Comments:

The response "Not Applicable" was defined as "Presumed Eradicated" by the Medical Officer.

Qualification for Efficacy Analysis:

Cases classified by the sponsor as "qualified" (evaluable) met the following criteria for analysis of symptomatic 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).
- A posttherapy clinical evaluation was performed.
- Symptomatic response (cure, improvement, relapse, or failure) could be evaluated (symptomatic response of "Unable to Evaluate" disqualified cases for efficacy analysis).

Cases classified by the sponsor as "qualified" (evaluable) for analysis of bacteriologic response also met the following criteria:

- The pretherapy culture was positive for pathogenic organism(s) with isolated organism(s) susceptible to erythromycin.
- A posttherapy culture was obtained or was "not applicable." **(Note: The Medical Officer defined this as presumed eradicated.)**

Any patient who did not meet the qualification criteria for both symptomatic and bacteriologic responses was, unevaluable.

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 to be 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 to be used for analysis of the laboratory monitoring data. All analyses examined consistency of results among participating clinics. Subgroup analyses (safety and efficacy) were to be performed for the two formulations of study-drug medication utilized in this study.

Investigators:

Study Population
All Patients Consented and/or Randomized

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
J. M. APPLESTEIN/SAN DIEGO, CA	2	4	0	1
J. S. SPINDLER/HOUSTON, TX	1	0	0	0
D. H. LEHMAN/SACRAMENTO, CA	8	9	1	2
J. M. SELTZER/SAN DIEGO, CA	1	1	0	0
S. HEATLEY/REDWOOD CITY, CA	6	2	2	0
R. R. STOLTZ/EVANSVILLE, IN	17	11	5	4
D. P. WRIGHT/AUSTIN, TX	0	1	0	0
C. W. WEART/CHARLESTON, SC	2	1	0	0
G. B. FISHER/PENSACOLA, FL	5	3	0	0
R. E. SCHNEIDER/CHARLOTTE, NC	1	1	0	0
J. P. KRAINSON/MIAMI, FL	1	2	0	0
P. BARDEN/ALBUQUERQUE, NM	1	1	0	0
R. C. HASELBY/MARSHFIELD, WI	1	0	1	0
H. COLLINS/EDISON, NJ	4	2	0	1
M. S. WAXMAN/NORTH ARLINGTON, NJ	4	5	0	0
C. ORTIZ/ROCHESTER, NY	3	1	2	0
J. M. KOHAN/NEW HARTFORD, NY	5	5	0	0
M. BARREIRO/BINGHAMTON, NY	3	2	0	0
E. E. MILLER/COLORADO SPRINGS, CO	13	1	4	1
W. G. GARDNER/AKRON, OH	2	1	1	0
G. E. BERGER/DETROIT, MI	10	9	5	0
R. P. BAUGHMAN/CINCINNATI, OH	23	24	15	18
E. G. FENNELL/JOHNSON CITY, TN	1	2	0	1
F. P. MICHAEL/DETROIT, MI	1	2	0	0
C. F. KUPFERER/ALBUQUERQUE, NM	0	1	0	0
E. B. SCOTT/PELLETIER/ WEST MONROE, LA	2	2	0	0
S. CROSBY/JACKSON, AL	1	1	0	1
R. W. ZIERING/VISTA, CA	1	2	0	0
M. B. WIENER/DENVER, CO	3	2	0	1
S. R. LINNE/WOODLAND, CA	4	3	0	0

(continued)

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

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
C. KAUFFMAN/ANN ARBOR, MI	3	1	0	0
B. G. YANGCO/TAMPA, FL	4	5	0	0
B. TUCKER/BIRMINGHAM, AL	13	14	1	0
R. B. GEIGER/VERO BEACH, FL	6	1	1	0
S. A. BRAHIM/TOWSON, MD	5	4	0	0
J. C. ROTSCHAFER/ST. PAUL, MN	4	6	0	0
A. POLLACK/ROCKVILLE, MD	1	1	0	0
J. A. PIERCE/ST. LOUIS, MO	2	2	0	0
T. D. DAVIS/BISMARK, ND	1	2	0	0
J. S. SHEN/ELIZABETH, NJ	0	3	0	0
D. SIMONS-MORTON/HOUSTON, TX	11	13	1	1
J. A. KRAM/OAKLAND, CA	5	4	2	2
P. R. OLSON/ASHEVILLE, NC	1	2	0	0
F. D. SUTTON, JR/BIRMINGHAM, AL	7	8	2	2
G. H. MEDURI/MEMPHIS, TN	4	5	2	3
D. D. BLEVINS/SALEM, VA	2	4	0	1
M. KARETZKY/NEWARK, NJ	7	8	2	2
S. J. PADOVE/BIRMINGHAM, AL	0	3	0	0
D. G. MILLER/MOORESVILLE, PA	3	6	0	0
G. F. SANTOS/MIAMI, FL	2	3	0	0
M. A. NAKAO/ALBANY, NY	1	2	0	1
R. A. HACKMAN/MURFREESBORO, TN	1	0	0	0
R. ARANSON/BRIGHTON, MA	1	3	0	0
F. C. WHITTIER/CANTON, OH	3	6	0	0
D. W. BARTELS/BELVIDERE, IL	2	1	1	0
K. L. RICE/MINNEAPOLIS, MN	4	3	0	0
B. A. REED/ANN ARBOR, MI	3	2	1	0
G. A. SCHMIDT/CHICAGO, IL	0	1	0	0
R. BRODIE/BALTIMORE, MD	4	3	2	0
S. G. GEVAS/ARLINGTON, VA	2	2	1	1
P. A. D'HEMECOURT/BETHESDA, MD	2	3	1	0
S. ZEIG/PEMBROKE PINES, FL	9	7	4	1
J. M. MCCARTY/FRESNO, CA	0	1	0	0
T. W. LITTLEJOHN/WINSTON-SALEM, NC	4	4	2	0
D. C. MCCLUSKEY/MOGADORE, OH	18	15	4	0
L. W. WINTER/DANVILLE, IL	1	1	0	0
H. M. FARIS, JR/GREENVILLE, SC	2	6	0	1

(continued)

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

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
J. COGGESHALL/FRANKLIN, TN	1	1	0	1
C. PIERCE/CHARLOTTE, NC	9	8	5	1
K. D. JACOBSON/EUGENE, OR	1	1	1	1
W. T. PAUL/COLUMBUS, OH	2	2	0	0
G. WEISMAN/WARMINSTER, PA	4	8	1	0
S. K. ZORN/WEST DES MOINES, IA	16	18	5	6
W. L. MASTERJOHN/BELLFLOWER, CA	2	2	0	0
C. M. SAMET/MANHASSET, NY	1	0	0	0
G. D. BEDSOLE/MONTGOMERY, AL	12	13	1	1
W. M. MOROWITZ/CHERRY HILL, NJ	15	17	3	3
DAUER AND FUTTERMAN/WHITTIER, CA	2	3	0	0
J. L. ZAREMBA/BIRMINGHAM, AL	8	7	4	4
W. J. HENRY/GREER, SC	4	5	0	0
A. C. DEGRAFF/HARTFORD, CT	3	3	1	0
S. SMITH/MONROEVILLE, AL	1	2	1	0
O. E. PERDOMO/ATTALLA, AL	4	2	0	1
A. E. LEE/UNIVERSITY, MS	5	5	5	4
H. M. SERFER/UNIVERSITY, MS	1	1	0	0
G. C. SCOTT/COLUMBIA, MO	4	4	1	0
A. R. ROSENTHAL/SOUTH BEND, IN	1	3	0	1
J. D. SANDERS/CHARLESTON, SC	0	1	0	1
SPILLER K/LAFAYETTE, LA	2	2	1	0
C. M. FOGARTY AND W P/ SPARTANBURG, SC	5	5	1	2
M. L. BARNARD/FLORENCE, SC	1	0	0	0
G. E. PETERSON/DES MOINES, IA	6	5	1	2
S. C. BOWMAN/SAFETY HARBOR, FL	1	2	0	1
G. J. PROSCH/BIRMINGHAM, AL	3	4	2	2
L. E. MANSFIELD/EL PASO, TX	9	9	5	2
L. K. ALWINE/DOWNINGTON, PA	4	3	0	2
G. D. CARR/HATTIESBURG, MS	1	2	0	0
W. A. BROWN AND P B W/ PROVIDENCE, RI	1	2	0	1
TOTAL	393	409	101	81

Medical Officer's Comments:

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

Sponsor's Analysis:

Patient disposition was as follows:

	Dirithromycin	Erythromycin
Patient Enrolled	393	409
Evaluable for Efficacy	101	81
Completed Therapy	80	70
Prematurely Discontinued	21	11
Not Evaluable	292	328
Completed Therapy	0	0
Prematurely Discontinued	292	328

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 Ranges by Sex
All Patients

	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE		MALE		TOTAL		FEMALE		MALE		TOTAL	
	N = 214		N = 179		N = 393		N = 226		N = 183		N = 409	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
AGE RANGES (YR)												
0			1	(0.6%)	1	(0.3%)	0		1	(0.5%)	1	(0.2%)
12	12	(5.6%)	6	(3.4%)	18	(4.6%)	10	(4.4%)	2	(1.1%)	12	(2.9%)
81	81	(37.9%)	38	(21.2%)	119	(30.3%)	63	(27.9%)	45	(24.6%)	108	(26.4%)
87	87	(40.7%)	65	(36.3%)	152	(38.7%)	94	(41.6%)	67	(36.6%)	161	(39.4%)
34	34	(15.9%)	69	(38.5%)	103	(26.2%)	59	(26.1%)	68	(37.2%)	127	(31.1%)

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

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	214	179	393	226	183	409
MEAN AGE	48.59	56.95	52.39	53.02	56.60	54.62
STD DEV	15.39	16.60	16.47	16.15	15.99	16.16
MEDIAN AGE	48.66	61.52	54.08	55.04	60.12	57.46
MINIMUM AGE						
MAXIMUM AGE						

Orgin by Therapy Group
All Patients

	DIRITHROMYCIN N = 393		ERYTHROMYCIN N = 409	
	n	(%)	n	(%)
CAUCASIAN	319	(81.2%)	336	(82.2%)
BLACK	57	(14.5%)	60	(14.7%)
HISPANIC	16	(4.1%)	12	(2.9%)
NATIVE AMERICAN	1	(0.3%)	0	
ASIAN	0		1	(0.2%)

Height and Weight At Admission
All Patients

THERAPY	HEIGHT IN CM N	UNK	MEAN	STD DEV	MIN	MAX	WEIGHT IN KG N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	392	1	168.67	10			391	2	76.57	20		
ERYTHROMYCIN	406	3	168.01	10			409	0	75.33	19		

Evaluable Patients:

Age Ranges by Sex
Evaluable Patients

AGE RANGES	DIRITHROMYCIN FEMALE N = 56 n	(%)	MALE N = 45 n	(%)	TOTAL N = 101 n	(%)	ERYTHROMYCIN FEMALE N = 48 n	(%)	MALE N = 33 n	(%)	TOTAL N = 81 n	(%)
	0		1	(2.2%)	1	(1.0%)	0		0		0	
	5	(8.9%)	2	(4.4%)	7	(6.9%)	1	(2.1%)	1	(3.0%)	2	(2.5%)
	17	(30.4%)	11	(24.4%)	28	(27.7%)	11	(22.9%)	8	(24.2%)	19	(23.5%)
	27	(48.2%)	20	(44.4%)	47	(46.5%)	27	(56.3%)	7	(21.2%)	34	(42.0%)
	7	(12.5%)	11	(24.4%)	18	(17.8%)	9	(18.8%)	17	(51.5%)	26	(32.1%)

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

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	56	45	101	48	33	81
MEAN AGE	48.10	52.25	49.95	54.24	58.40	55.93
STD DEV	15.16	16.25	15.71	13.71	16.29	14.86
MEDIAN AGE	48.97	53.85	50.79	57.09	65.11	60.26
MINIMUM AGE						
MAXIMUM AGE						

Origin By Therapy Group
Evaluable Patients

ORIGIN	DIRITHROMYCIN N = 101 n	(%)	ERYTHROMYCIN N = 81 n	(%)
CAUCASIAN	79	(78.2%)	57	(70.4%)
BLACK	19	(18.8%)	23	(28.4%)
HISPANIC	3	(3.0%)	1	(1.2%)

Height and Weight at Admission
Evaluable Patients

	HEIGHT IN CM						WEIGHT IN KG					
THERAPY	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	101	0	167.82	10			100	1	77.38	23		
ERYTHROMYCIN	81	0	167.25	10			81	0	76.55	24		

Drug Administration:

All Patients

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

	DIRITHROMYCIN N = 393	ERYTHROMYCIN N = 409
NUMBER OF PATIENTS	385	403
MEAN DURATION EXPOSURE DAYS	6.9	6.9
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	8	6

Summary of Exposure to Study Drugs
All Patients

	DIRITHROMYCIN N = 393		ERYTHROMYCIN N = 409	
DAYS OF THERAPY	n	(%)	n	(%)
PATIENTS WITH INCOMPLETE DATA	8	(2.0%)	6	(1.5%)
1	4	(1.0%)	4	(1.0%)
2	10	(2.5%)	5	(1.2%)
3	18	(4.6%)	20	(4.9%)
4	43	(10.9%)	60	(14.7%)
5	39	(9.9%)	46	(11.2%)
6	25	(6.4%)	23	(5.6%)
7	105	(26.7%)	99	(24.2%)
8	83	(21.1%)	77	(18.8%)
9	12	(3.1%)	16	(3.9%)
0	11	(2.8%)	10	(2.4%)
1	9	(2.3%)	10	(2.4%)
2	13	(3.3%)	10	(2.4%)
3	2	(0.5%)	4	(1.0%)
4	3	(0.8%)	7	(1.7%)
5	7	(1.8%)	10	(2.4%)
6	0		1	(0.2%)
17	0		1	(0.2%)
18	1	(0.3%)	0	

Evaluable Patients

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

	DIRITHROMYCIN N = 101 DAYS	ERYTHROMYCIN N = 81 DAYS
NUMBER OF PATIENTS	101	81
MEAN DURATION EXPOSURE	7.9	8.6
MINIMUM EXPOSURE DAYS		
MAXIMUM EXPOSURE DAYS		
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients

DAYS OF THERAPY	DIRITHROMYCIN N = 101 n	(%)	ERYTHROMYCIN N = 81 n	(%)
3	3	(3.0%)	0	
4	1	(1.0%)	0	
6	4	(4.0%)	1	(1.2%)
7	41	(40.6%)	33	(40.7%)
8	33	(32.7%)	23	(28.4%)
9	5	(5.0%)	6	(7.4%)
10	6	(5.9%)	6	(7.4%)
11	1	(1.0%)	3	(3.7%)
12	4	(4.0%)	1	(1.2%)
13	1	(1.0%)	2	(2.5%)
14	0		2	(2.5%)
15	2	(2.0%)	4	(4.9%)

Medical Officer's Comments:
73% of the evaluable patients in the dirithromycin group and 69% of patients in the erythromycin group were treated for 7-8 days.

Unevaluable Patients

Reason Unevaluable Summary
All Patients

REASON UNEVALUABLE	DIRITHROMYCIN N= 393 n	(%)	ERYTHROMYCIN N = 409 n	(%)
ALL UNEVALUABLE PATIENTS.	292	(74.3%)	328	(80.2%)
CAUS. ORG. UNIDENT.	179		201	
CAUS. ORG. RESISTANT	63		78	
INSUFFICIENT THERAPY	52		70	
UNACCEPT. PATHOGEN	26		39	
UNEVAL. BY INVEST.	25		17	
SENSITIVITY NOT DONE	19		7	
NO POSTTHER. CULTURE	7		13	
PROTOCOL VIOLATED	8		7	
SEQUENTIAL THERAPY	6		2	
NO DURING CULTURE	2		5	
NO INITIAL CULTURE	3		2	
NO FOLLOW-UP CULTURE	3		2	
TIMING OF X-RAY	2		2	
BACTERIOL. INCOMPLETE	2		1	
NO THERAPY	0		3	
UNDERLYING CONDITION	0		3	
NO PRETHERAPY X-RAY	2		1	
BLIND BROKEN	1		1	
WRONG DIAGNOSIS	1		1	
CAUS. ORG. UNAPPROVED	1		0	
PRIN. INF. UNAPPROVED	0		1	
INITIAL CULT. EARLY	1		0	
POST THER. CULT. LATE	1		0	
UNDERLYING DISEASE	1		0	
POOR COMPLIANCE	0		1	
LATE CLIN. ASSESSMENT	0		1	
NO POST FOLLOW-UP	1		0	

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

	DIRITHROMYCIN N = 101		ERYTHROMYCIN N = 81	
RESPONSE	n	(%)	n	(%)
CURE	55	(54.5%)	45	(55.6%)
IMPROVEMENT	32	(31.7%)	27	(33.3%)
RELAPSE	4	(4.0%)	2	(2.5%)
FAILURE	10	(9.9%)	7	(8.6%)

An overall favorable symptomatic response (cure or improvement) was achieved in 86% of dirithromycin-treated patients and 89% of erythromycin-treated patients.

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
THERAPY: DIRITHROMYCIN

PATHOGENS	CURE n	CURE (%)	IMPROVEMENT n	IMPROVEMENT (%)	RELAPSE n	RELAPSE (%)	FAILURE n	FAILURE (%)	TOTAL N
H INFLUENZAE	7	(33.3%)	8	(38.0%)	1	(4.7%)	5	(23.8%)	21
S PNEUMONIAE	8	(44.4%)	7	(38.8%)	1	(5.5%)	2	(11.1%)	18
STREP SP	11	(68.7%)	4	(25.0%)	0	0	1	(6.2%)	16
M CATARRHALIS	10	(83.3%)	2	(16.6%)	0	0	0		12
S AUREUS	6	(54.5%)	3	(27.2%)	0	0	2	(18.1%)	11
MULTIPLE ORGANISM*	7	(70.0%)	2	(20.0%)	1	(10.0%)	0		10
H PARAINFLUENZAE	4	(44.4%)	4	(44.4%)	1	(11.1%)	0		9
GRP A STREP	2	(100.0%)	0	0	0		0		2
E COLI	0		1	(100.0%)	0		0		1
K PNEUMONIAE	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 for Polymicrobial Infections
Evaluable Dirithromycin-treated Patients
Posttherapy

PATIENT NO.	PATHOGENS	BACTERIOLOGIC RESPONSE	CLINICAL RESPONSE
	H Influenzae S Pneumoniae	PE PE	Relapse
	S Aureus Group A Strep	NA NA	Cure
	S Aureus H Parainfluenzae	NA NA	Cure
	S Aureus S Pneumoniae	NA NA	Cure
	H Influenzae M Catarrhalis	PE PE	Cure
	S Aureus Strep Sp	NA NA	Improvement
	H Influenzae S Pneumoniae	RSR PE	Improvement
	S Pneumoniae M Catarrhalis	PE	Cure
	Strep Sp M Catarrhalis	NA NA	Cure
	S Pneumoniae Strep Sp M Catarrhalis	NA NA NA	Cure

PE = Pathogen Eliminated
NA = Presumed Eliminated
RSR = Recurrence Same, Resistance

CLINICAL RESPONSE SUMMARY/PATHOGEN
ALL EVALUABLE PATIENTS
POSTTHERAPY
THERAPY: ERYTHROMYCIN

PATHOGENS	CURE n	CURE (%)	IMPROVEMENT n	IMPROVEMENT (%)	RELAPSE n	RELAPSE (%)	FAILURE n	FAILURE (%)	TOTAL N
H INFLUENZAE	10	(50.0%)	10	(50.0%)	0		0		20
STREP SP	10	(55.5%)	2	(11.1%)	1	(5.5%)	5	(27.7%)	18
S AUREUS	7	(58.3%)	5	(41.6%)	0		0		12
S PNEUMONIAE	6	(50.0%)	5	(41.6%)	1	(8.3%)	0		12
MULTIPLE ORGANISMS*	6	(66.6%)	2	(22.2%)	0		1	(11.1%)	9
M CATARRHALIS	5	(71.4%)	1	(14.2%)	0		1	(14.2%)	7
GRP G STREP	1	(50.0%)	1	(50.0%)	0		0		2
S VIRIDANS	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 for Polymicrobial Infections
Evaluable Erythromycin-treated Patients
Posttherapy

PATIENT NO.	PATHOGENS	BACTERIOLOGIC RESPONSE	CLINICAL RESPONSE
	Group C Strep	NA	Improvement
	M Catarrhalis	NA	
	Strep Sp	NA	Cure
	M Catarrhalis	NA	
	S Aureus	NA	Cure
	Grp A Strep	NA	
	H Influenzae	NA	Cure
	M Catarrhalis	NA	
	H Influenzae	UTE	Failure
	H Parainfluenzae	UTE	
	H Influenzae	FEP	Improvement
	S Aureus	FEP	
	S Pneumoniae	NA	Cure
	Strep Sp	NA	
	Strep Sp	NA	Cure
	M Catarrhalis	NA	
	Strep Sp	NA	Cure
	M Catarrhalis	NA	

NA=Presumed Eliminated
UTE=Unable to Evaluate
FEP=Failure to Eliminate Pathogen

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

Clinical Response Summary/Therapy Group
All Evaluable Patients-Late-posttherapy

RESPONSE	DIRITHROMYCIN N = 80 n	(%)	ERYTHROMYCIN N = 67 n	(%)
CURE	58	(72.5%)	49	(73.1%)
IMPROVEMENT	13	(16.3%)	12	(17.9%)
RELAPSE	8	(10.0%)	6	(9.0%)
FAILURE	1	(1.3%)	0	

Medical Officer's Comments:

An overall favorable symptomatic response (cure or improvement) was achieved in 89% (71/80) of the dirithromycin patients and in 91% (61/67) of the erythromycin patients.

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

CLINICAL RESPONSE SUMMARY/PATHOGEN
ALL EVALUABLE PATIENTS -- LATE-POSTTHERAPY

THERAPY: DIRITHROMYCIN

	CURE		IMPROVEMENT		RELAPSE		FAILURE		TOTAL
PATHOGENS	n	(%)	n	(%)	n	(%)	n	(%)	N
S PNEUMONIAE	9	(56.2%)	5	(31.2%)	1	(6.2%)	1	(6.2%)	16
H INFLUENZAE	8	(66.6%)	2	(16.6%)	2	(16.6%)	0		12
STREP SP	10	(76.9%)	1	(7.6%)	2	(15.3%)	0		13
M CATARRHALIS	10	(90.9%)	1	(9.0%)	0		0		11
S AUREUS	6	(66.6%)	1	(11.1%)	2	(22.2%)	0		9
MULTIPLE ORGANISMS*	7	(87.5%)	1	(12.5%)	0		0		8
H PARAINFLUENZAE	4	(66.6%)	1	(16.6%)	1	(16.6%)	0		6
GRP A STREP	2	(100.0%)	0		0		0		2
E COLI	1	(100.0%)	0		0		0		1
NO CULTURE TAKEN	1	(100.0%)	0		0		0		1
K PNEUMONIAE	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 for Polymicrobial Infections
Evaluable Dirithromycin-treated Patients
Late-Posttherapy

PATIENT NO.	PATHOGENS	BACTERIOLOGIC RESPONSE	CLINICAL RESPONSE
	S Aureus	NA	Cure
	Group A Strep	NA	
	Strep Sp	NA	Cure
	K Pneumoniae	NA	
	H Influenzae	NA	Cure
	M Catarrhalis	NA	
	S Aureus	NA	Cure
	Strep Sp	NA	
	H Influenzae	NA	Improvement
	S Pneumoniae	NA	
	S Pneumoniae	PE	Cure
	M Catarrhalis	PE	
	Strep Sp	NA	Cure
	M Catarrhalis	NA	

NA = Presumed Eliminated
PE = Pathogen Eliminated

CLINICAL RESPONSE SUMMARY/PATHOGEN
ALL EVALUABLE PATIENTS -- LATE-POSTTHERAPY

THERAPY: ERYTHROMYCIN

PATHOGENS	CURE n	CURE (%)	IMPROVEMENT n	IMPROVEMENT (%)	RELAPSE n	RELAPSE (%)	TOTAL N
H INFLUENZAE	11	(73.3%)	3	(20.0%)	1	(6.6%)	15
S AUREUS	9	(75.0%)	2	(16.6%)	1	(8.3%)	12
S PNEUMONIAE	7	(70.0%)	2	(20.0%)	1	(10.0%)	10
STREP SP	10	(100.0%)	0		0		10
MULTIPLE ORGANISMS#	5	(62.5%)	2	(25.0%)	1	(12.5%)	8
M [illegible]RHALIS	6	(100.0%)	0		0		6
GRP G STREP	1	(50.0%)	1	(50.0%)	0		2
S VIRIDANS	0		1	(100.0%)	0		1
*	0		1	(100.0%)	0		1
GRP A STREP	0		0		1	(100.0%)	1
NO CULTURE TAKEN	0		0		1	(100.0%)	1

*The organism name was not entered into the database and the patient appears in tables by clinical response but not in tables cross-tabulating clinical and bacteriologic response.

- 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 for Polymicrobial Infections
Evaluable Erythromycin-treated Patients
Late-Posttherapy

PATIENT NO.	PATHOGENS	BACTERIOLOGIC RESPONSE	CLINICAL RESPONSE
	Group A Strep	PE	Relapse
	M Catarrhalis	PE	
	Strep Sp	NA	Cure
	M Catarrhalis	NA	
	M Catarrhalis	NA	Cure
	H Influenzae	NA	
	H Influenzae	PE	Improvement
	S Pneumoniae	PE	
	S Pneumoniae	NA	Cure
	Strep Sp	NA	
	Strep Sp	NA	Cure
	M Catarrhalis	NA	
	Strep Sp	NA	Cure
	M Catarrhalis	NA	

NA = No cultures perfomed post-therapy/Presumed Eliminated
PE = Presumed Eliminated

Bacteriologic Response

The bacteriologic response for 172 evaluable patients at posttherapy (3-5 days) according to the applicant was as follows:

Bacteriological Response Summary/Therapy Group
All Evaluable Patients Posttherapy

	DIRITHROMYCIN N = 93		ERYTHROMYCIN N = 79	
RESPONSE	n	(%)	n	(%)
PATHOGEN ELIMINATED	16	(17.2%)	6	(7.6%)
PRESUMED ELIMINATED	69	(74.2%)	60	(76.0%)
RECURRENCE SAME	2	(2.1)	1	(1.2%)
RECURRENCE SAME, RESISTANCE	1	(1.1%)		
RECURRENCE NEW	0		4	(5.1%)
FAILED TO ELIMINATE	5	(5.4%)	8	(10.1%)

Medical Officer's Comments:

There was a favorable bacteriologic response (pathogen eliminated or presumed eliminated) in 85 of 93 (91%) of patients treated with dirithromycin and 66 of 79 (83.5%) of patients treated with erythromycin. Ten patients that were clinically evaluable (8 in dirithromycin group and 2 in the erythromycin group) were not bacteriological evaluable.

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

POSTTHERAPY

THERAPY: DIRITHROMYCIN

	PATHOGEN ELIMINATED		PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
PATHOGENS											
H INFLUENZAE	6	(28.5%)	9	(42.8%)	3	(14.3%)	0		3	(14.3%)	21
S PNEUMONIAE	6	(28.5%)	15	(71.5%)	0		0		0		21
M CATARRHALIS	1	(6.3%)	15	(93.7%)	0		0		0		16
S AUREUS	2	(15.4%)	11	(84.6%)	0		0		0		13
H PARAINFLUENZAE	3	(30.0%)	7	(70.0%)	0		0		0		10
STREP SP	0		16	(88.9%)	0		0		2	(11.1%)	18
GRP A STREP	0		3	(100.0%)	0		0		0		3
E COLI	0		1	(100.0%)	0		0		0		1
K PNEUMONIAE	0		1	(100.0%)	0		0		0		1

BACTERIOLOGIC RESPONSE SUMMARY/PATHOGEN
ALL EVALUABLE PATIENTS
POSTTHERAPY

THERAPY: ERYTHROMYCIN

	PATHOGEN ELIMINATED n (%)	PRESUMED ELIMINATED n (%)	RECURRENCE SAME n (%)	RECURRENCE NEW n (%)	FAILED TO ELIMINATE n (%)	TOTAL n
PATHOGENS						
H INFLUENZAE	3 (13.6%)	17 (77.3%)	1 (4.5%)	0	1 (4.5%)	22
S PNEUMONIAE	3 (23.0%)	8 (61.5%)	0	2 (15.5%)	0	13
M CATARRHALIS	0	11 (91.6%)	0	1 (8.4%)	0	12
S AUREUS	0	13 (92.8%)	0	0	1 (7.2%)	14
STREP VIRIDANS	0	0	0	0	1 (100%)	1
STREP SP	0	14 (66.7%)	0	1	6 (33.3%)	21
GRP A STREP	0	1 (100.0%)	0	0	0	1
GROUP C STREP	0	1 (100.0%)	0	0	0	1
GROUP G STREP	0	2 (100.0%)	0	0	0	2

CONCOMITANT MEDICATIONS:

Prior to study entry, 81.4% of patients in both groups were receiving some form of drug therapy. Drugs used to treat pulmonary disease including theophylline, salbutamol, oral and inhaled steroids, ipratropium and orciprenaline were the most frequently used. Drug use was comparable between the two treatment groups. A concomitant agent was prescribed during therapy in 38.7% of dirithromycin patients and 38.4% of erythromycin patients. Theophylline, prednisone and salbutamol were most frequently used. Four patients, 2 from each treatment arm, received oral antibiotic therapy other than study drug during the study period. None of these patients were qualified for efficacy analysis because of entry exclusions (unacceptable pathogen or pathogen resistant to erythromycin). After completion of study-drug therapy, 13.2% and 14.9% of the dirithromycin and erythromycin groups, respectively, started new medications. Again, theophylline, prednisone and salbutamol were most frequently used. Two patients in the dirithromycin arm received antibiotics posttherapy because of continued symptoms. Likewise, two patients in the erythromycin arm received antibiotics posttherapy because of continued symptoms.

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

	DIRITHROMYCIN N = 393		ERYTHROMYCIN N = 409		
	n	(%)	n	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	83	(21.1%)	81	(19.8%)	0.644
PATIENTS WITH NO EVENT	310	(78.9%)	328	(80.2%)	0.644
CLASSIFICATION TERM					
ABDOMINAL PAIN	32	(8.1%)	31	(7.6%)	0.767
HEADACHE	23	(5.9%)	20	(4.9%)	0.545
CHEST PAIN	15	(3.8%)	12	(2.9%)	0.488
PAIN	8	(2.0%)	6	(1.5%)	0.539
CHILLS	6	(1.5%)	12	(2.9%)	0.179
ASTHENIA	5	(1.3%)	6	(1.5%)	0.813
BACK PAIN	4	(1.0%)	4	(1.0%)	0.955
DRUG LEVEL INCREASED	2	(0.5%)	0		0.149
INJURY, ACCIDENT	2	(0.5%)	3	(0.7%)	0.686
NECK PAIN	2	(0.5%)	1	(0.2%)	0.54
ALLERGIC REACTION	1	(0.3%)	0		0.307
CHILLS AND FEVER	1	(0.3%)	1	(0.2%)	0.977
FEVER	1	(0.3%)	4	(1.0%)	0.193
FLU SYNDROME	1	(0.3%)	1	(0.2%)	0.977
INJECTION SITE HEMORRHAGE	1	(0.3%)	0		0.307
MALAISE	1	(0.3%)	0		0.307
PELVIC PAIN	1	(0.3%)	1	(0.2%)	0.977
SURGICAL PROCEDURE	1	(0.3%)	3	(0.7%)	0.336
FACE EDEMA	0		1	(0.2%)	0.327
INFECTION	0		1	(0.2%)	0.327
INJECTION SITE INFLAMMATION	0		1	(0.2%)	0.327

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

	DIRITHROMYCIN N = 393		ERYTHROMYCIN N = 409		
	N	(%)	N	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	71	(18.1%)	84	(20.5%)	0.376
PATIENTS WITH NO EVENT	322	(81.9%)	325	(79.5%)	0.376
EVENT CLASSIFICATION TERM					
NAUSEA	30	(7.6%)	24	(5.9%)	0.319
DIARRHEA	16	(4.1%)	38	(9.3%)	0.003
DYSPEPSIA	9	(2.3%)	7	(1.7%)	0.558
VOMITING	9	(2.3%)	6	(1.5%)	0.39
FLATULENCE	4	(1.0%)	3	(0.7%)	0.665
GASTROINTESTINAL DISORDER	4	(1.0%)	6	(1.5%)	0.567
CONSTIPATION	3	(0.8%)	1	(0.2%)	0.297
NAUSEA AND VOMITING	3	(0.8%)	3	(0.7%)	0.961
INCREASED APPETITE	2	(0.5%)	0		0.149
RECTAL HEMORRHAGE	2	(0.5%)	0		0.149
DRY MOUTH	1	(0.3%)	4	(1.0%)	0.193
DUODENAL ULCER	1	(0.3%)	0		0.307
GASTRITIS	1	(0.3%)	2	(0.5%)	0.586
GASTROENTERITIS	1	(0.3%)	0		0.307
HEPATOMEGALY	1	(0.3%)	0		0.307
MELENA	1	(0.3%)	1	(0.2%)	0.977
MOUTH ULCERATION	1	(0.3%)	0		0.307
RECTAL DISORDER	1	(0.3%)	0		0.307
ANOREXIA	0		3	(0.7%)	0.089
DYSPHAGIA	0		1	(0.2%)	0.327
ERUCTATION	0		1	(0.2%)	0.327
THIRST	0		1	(0.2%)	0.327

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

	DIRITHROMYCIN N = 393		ERYTHROMYCIN N = 409		
	N	(%)	N	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	70	(17.8%)	47	(11.5%)	0.011
PATIENTS WITH NO EVENT	323	(82.2%)	362	(88.5%)	0.011
EVENT CLASSIFICATION TERM					
LUNG DISORDER	23	(5.9%)	12	(2.9%)	0.043
ASTHMA	16	(4.1%)	10	(2.4%)	0.194
RHINITIS	11	(2.8%)	5	(1.2%)	0.11
DYSPNEA	10	(2.5%)	9	(2.2%)	0.749
SINUSITIS	5	(1.3%)	3	(0.7%)	0.443
HYPERVENTILATION	3	(0.8%)	6	(1.5%)	0.344
PHARYNGITIS	3	(0.8%)	1	(0.2%)	0.297
RESPIRATORY DISORDER	3	(0.8%)	1	(0.2%)	0.297
EPISTAXIS	2	(0.5%)	0		0.149
HEMOPTYSIS	1	(0.3%)	1	(0.2%)	0.977
LARYNGITIS	1	(0.3%)	1	(0.2%)	0.977
LUNG EDEMA	1	(0.3%)	0		0.307
SPUTUM INCREASED	1	(0.3%)	2	(0.5%)	0.586
BRONCHITIS	0		1	(0.2%)	0.327
COUGH INCREASED	0		5	(1.2%)	0.028
PNEUMONIA	0		3	(0.7%)	0.089
STRIDOR	0		1	(0.2%)	0.327

Frequency of Treatment Emergent Events
All Patients - All Adverse Events
Body System: Skin and Appendages

	DIRITHROMYCIN N = 393		ERYTHROMYCIN N = 409		
	N	(%)	N	(%)	P-VALUE
PATIENTS WITH AT LEAST ONE EVENT	15	(3.8%)	21	(5.1%)	0.368
PATIENTS WITH NO EVENT	78	(96.2%)	388	(94.9%)	0.368
EVENT CLAS...ATION TERM					
PRURITUS	5	(1.3%)	3	(0.7%)	0.443
RASH	4	(1.0%)	7	(1.7%)	0.398
SWEATING	4	(1.0%)	6	(1.5%)	0.567
ACNE	1	(0.3%)	1	(0.2%)	0.977
ERYTHEMA NODOSUM	1	(0.3%)	0		0.307
MACULOPAPULAR RASH	1	(0.3%)	3	(0.7%)	0.336
URTICARIA	1	(0.3%)	1	(0.2%)	0.977
PUSTULAR RASH	0		1	(0.2%)	0.327
VESICULOBULLOUS RASH	0		1	(0.2%)	0.327

Patients Who Died or Discontinued Therapy Due to Adverse Events:

There were 4 deaths reported among patients enrolled in the study. Given the age and severity of illness in the patients studied in this trial, this finding is not surprising and none of the deaths were directly attributable to study drugs.

Age (yrs)	Protocol Number	Patient Number	Diagnosis	Days of Rx	Chronic Illnesses	Cause of Death
DIRITHROMYCIN-TREATED PATIENTS						
75	AQAB		Bronchitis	2	ASHD, COPD, HTN	Cardiogenic Shock
50	AQAB		Bronchitis	2	COPD, HTN	Cirrhosis
68	AQAB		Bronchitis	4	COPD, HTN, AS	Respiratory Failure
81	AQAB		Bronchitis	7	CHF, VHD, AF, COPD	Lung edema

Nineteen (19) dirithromycin- and 21 erythromycin-treated patients discontinued early due to adverse events, (7 of which were classified as serious). Eleven (11) of the 19 dirithromycin-treated patients and 11 of the 21 erythromycin-treated patients experienced adverse events related to the gastrointestinal system.

THERAPY DIRITHROMYCIN

INV	PATIENT	VISIT	AGE	SEX	DAYS OF THERAPY	ADVERSE EVENT
011		1	35	F	1	Nausea
018		1	39	F	5	Abdominal Cramps
037		1	24	F	7	Vaginitis
041		1	35	F	4	Nausea & Vomiting
041		1	28	M	1	Nausea
041		1	60	F	3	Itching
041		1	54	M	4	Acute Exac. of COPD
053		1	32	F	6	Strep Throat
054		1	29	F	5	Nausea
063		1	60	M	1	Nausea
103		1	70	M	1	Chest Tightness
111		1	21	F	4	Abdominal Cramps
118		1	46	F	4	Hives
118		1	43	F	3	Vomiting
154		1	40	F	4	Nausea
169		1	67	M	4	Loose Suture from Prev. Lung Surgery
176		1	24	F	2	Stomach Ache
176		1	12	M	3	Stomach Cramps
178		1	69	M	2	Repiratory Failure

APPEARS THIS WAY
ON ORIGINAL

THERAPY: ERYTHROMYCIN

0004	1	71	F	5	Abdominal Pain
017	1	57	F	3	Nausea
033	1	61	M	8	Redness on Hands and Feet
035	1	68	M	3	Epigastric Pain
035	1	31	F	4	Vomiting
037	1	30	F	4	Rash Macular
041	1	51	M	4	Diarrhea
0061	1	63	F	4	Weakness
073	1	48	M	4	Nausea
073	1	61	F	8	Stomach Cramping
076	1	44	F	5	Lobar Pneumonia
079	1	41	F	3	Diarrhea
081	1	22	F	2	Epigastric Distress
090	1	81	M	4	Rash-Dermatitis
105	1	32	F	5	Rash
131	1	63	M	3	Increased SOB
150	1	78	M	5	Pneumonia
153	1	49	F	2	Stomach Discomfort
160	1	31	F	2	Asthma
176	1	43	F	3	Nausea and Vomiting
181	1	44	F	1	Dog Bite (Lip Laceration)

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. The erythromycin group showed statistically significant reductions in hematocrit, hemoglobin and red blood cell count. Although the changes in hematocrit, hemoglobin and red blood cell count were statistically significant, the magnitude of the changes were not considered clinically significant. 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 illnesses. A statistically significant difference between the treatment groups was seen only for hematocrit (HCT), hemoglobin (HGB), red blood cell count (RBC) and lymphocytes (LYMPHS). In general, the hematologic parameters decreased in erythromycin-treated patients while they increased in the dirithromycin-treated patients. The mean changes were very small and, while statistically significant, are not clinically important. The lymphocyte count increased slightly more in patients in the dirithromycin group than in the erythromycin group. The increase in lymphocytes represents the normal recovery process after an acute illness.

Several blood chemistry analytes showed significant changes within the groups. Total protein (TPROT) showed a statistically significant decrease in both groups. Albumin and CK all fell in the erythromycin group but only the change in albumin and CK were statistically significantly different than those seen in the dirithromycin group. Despite the noted rise in BUN for both groups, serum creatinine was decreased in the dirithromycin group and only slightly increased in the erythromycin group. Serum uric acid showed a statistically significant increase in both groups but the increases were quite small and not clinically significant.

With respect to liver function studies, there were statistically significant decreases in alkaline phosphatase in both treatment groups. GGT showed a statistically significant increase only in the erythromycin treatment group with no significant difference between the groups.

In summary, statistically significant differences within the two treatment groups were noted for many of the analytes, but, in the absence of untreated control patients, it is impossible to ascribe these changes to drug treatment. A statistically significant difference between treatment groups was noted only for several hematologic parameters as well as albumin and CK but these changes were small and did not approach clinical significance.

When these analytes were analyzed for the frequency with which patients changed status during therapy (i.e., normal, low, high), statistically significant differences between the treatment groups were noted for fasting blood glucose and urine glucose. Seven (7) patients in the erythromycin group had blood glucose levels which changed from normal to high, while no dirithromycin-treated patients had such a transition (Fisher's exact test, 2-tailed, $p<0.016$). Similarly, urine glucose changed from normal (negative) to abnormal (glucose present) more often in patients receiving erythromycin than in those receiving dirithromycin.

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

ANALYTE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Hematocrit					
		D	0.520		0.590
		D	0.430		0.310
		E	0.450	0.450	0.370
		E	0 480		0.560
Hemoglobin					
		E	9.600	9.700	9.700
		D	8.010		6.460
Mean Cell Volume					
		D	109.000		117.000
		E	96.000	95.000	104.000
		E	104.000		114.000
		E	96.000	96.000	104.000
Leukocyte Count					
		D	6.140		13.690
		D	8.530		15.000
		D		8.810	13.060
		D	11.780	6.510	9.260
		D	10.150	11.510	17.480*
		D	8.760	9.480	13.100
		D	8.090	17.730	

	D	12.100	14.290	21.170
	D	15.410		19.410
	D	10.650		15.120
	D	9.330	11.540	17.380
	E	13.730	19.520	14.690
	E	10.760	9.040	10.760
	E	15.250	15.710	21.230
	E	14.130	18.240	17.210
	E	11.450	12.690	15.260
	E	6.640	5.960	18.820
	E	8.990	16.480	17.080
	E	10.790		14.740
	E	10.830		15.810
	E	10.380		15.230
	E	5.140		13.830
	E	11.550		17.200

*Value is from late-posttherapy, since it was notable and posttherapy was not.

Distribution of Extreme Laboratory Values (cont)

ANALYTE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Segmented Neutrophil Count					
		D	3.700		9.580
		D	5.570		12.370
		D		7.350	11.620
		D	6.820		10.290
		D	6.330	7.140	14.860*
		D	4.930		9.380
		D	7.570	8.400	12.050
		D	5.170		9.880
		D	5.180	14.700	
		D	10.850	9.480	16.920
		D	5.320		9.850
		D	6.880		10.270
		D	10.790		14.730
		D	7.040		11.290
		D	5.090		9.100
		D	5.700		11.750
		D	11.470		15.090
		D	8.540		11.000
		E	6.740	6.030	10.020
		E	5.370	7.870	9.080
		E	2.040	4.710	9.850
		E	6.450	4.350	6.450
		E	9.610	9.380	14.990
		E	3.770	3.350	10.890
		E	8.480	14.430	13.430
		E	6.870*	9.420	10.560
		E	4.010	2.920	16.300
		E	6.100	11.570	8.050
		E	8.540		12.290
		E	7.740	13.390	15.090
		E	4.290		8.080
		E	8.810		13.700
		E	9.950		13.740
		E	7.720		11.190
		E	7.100		10.530
Lymphocyte Count					
		D	2.730		5.210
		D	3.030		0.740
		E	3.290	0.740	1.090
		E	3.960		5.530

Distribution of Extreme Laboratory Values (cont)

ANALYTE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Monocyte Count					
		D	0.170	0.950	0.470
		D	0.230		1.050
		D	0.280		0.910
		E	0.420	1.070	1.360
		E	0.350	0.570	0.920*
		E	0.220		1.020
		E	0.500	1.050	0.860
Eosinophil Count					
		D	0.230	0.680	0.780
		D	0.220	0.750	0.320
		D	0.080	0.650	0.960
		D	0.140	0.130	0.760
		D	0.680	1.360	0.170
		D	0.160		1.560
		D	0.030	1.070	1.510
		E	0.620	1.070	0.550
		E	0.760	1.370	1.620
Basophil Count					
		D	0.020	0.110	0.200
		E	0.020		0.330
		E	0.080	0.280	0.030
		E	0.000		0.240
Platelet Count					
		D	317.000	243.000	521.000
		D	323.000	304.000	448.000
		D	325.000	387.000	465.000
		D	383.000		508.000
		D	300.000		428.000
		D	312.000	388.000	439.000
		D	421.000		521.000
		D	348.000		534.000
		D	387.000		704.000
		D	445.000		539.000
		D	417.000		607.000
		D	368.000		467.000
		D	372.000		120.000
		D	437.000		548.000
		E	381.000	561.000	700.000
		E	378.000	555.000	658.000

	E	283.000		581.000
	E	339.000	448.000	472.000
	E	328.000	362.000	453.000
	E	172.000	212.000	563.000
	E	227.000		509.000

Distribution of Extreme Laboratory Values (cont)

ANALYTE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Platelet Count (cont)		E	355.000		483.000
		E	371.000		498.000
		E	268.000		121.000
		E	428.000		569.000
		E	317.000		445.000
Aspartate Aminotrans-ferase					
		D	20.000		116.000
		D	10.000		103.000
		E	83.000		111.000
		E	152.000		203.000
		E	34.000	42.000	58.000
		E	44.000		92.000
		E	23.000		122.000
Alanine Aminotrans-ferase					
		D	98.000	92.000	114.000
		D	9.000		142.000
		E	320.000		397.000
		E	82.000	135.000	60.000
		E	53.000		175.000
		E	16.000		153.000
		E	31.000		79.000
Alkaline Phosphatase					
		D	129.000	121.000	122.000
		D	258.000		379.000
		E	89.000		149.000
		E	56.000		174.000
Gamma-Glutamyl Transpep-tidase					
		D	110.000		146.000
		D	168.000	168.000	201.000
		E	631.000		692.000
		E	205.000	238.000	176.000
		E	82.000	78.000	76.000
		E	693.000		988.000
		E	113.000		247.000
		E	229.000	217.000	296.000
		E	45.000		113.000

Distribution of Extreme Laboratory Values (cont)

ANALYTE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Bilirubin					
		D	12.000		26.000
		E	14.000		29.000
		E	15.000		31.000
Albumin					
		D	42.000		33.000
		E	36.000	31.000	26.000
		E	46.000	42.000	37.000
		E	43.000		32.000
Total Protein					
		D	72.000	63.000	58.000
		D	71.000		58.000
		D	70.000		86.000
		E	73.000	60.000	68.000
		E	71.000		88.000
Creatinine					
		D	80.000	80.000	124.000*
		D	97.000	124.000	133.000
		D	80.000		133.000
		E	97.000	177.000	97.000
		E	115.000	168.000	115.000
Creatine Phosphokinase					
		D	239.000		481.000
		D	100.000	151.000	478.000
		D	155.000		738.000
		D	428.000		830.000
		D	167.000		819.000
		E	417.000	726.000	536.000
		E	133.000	159.000	1038.000
		E	940.000		17.000
Calcium					
		D	2.370	2.050	2.270
		E	2.420	2.370	2.400

Distribution of Extreme Laboratory Values (cont)

ANALYTE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Inorganic Phosphorus					
		D	0.900	0.900	2.390
		D	1.360		0.680
		D	1.030		0.550
		D	1.290		0.610
		E	1.160	1.130	1.610
		E	0.970		1.650
		E	0.900	1.420	1.680
		E	1.160	0.480	1.000
		E	1.160	0.650	0.650
		E	0.840		1.580
		E	1.190	0.740	0.520
		E	1.230		0.710
		E	1.160		1.610
		E	1.070		1.650
		E	1.130		1.680
		E	1.420	0.710	
		E	1.000		1.710
Glucose					
		D	5.100	10.400	4.800
		E	5.300	6.500	10.000
		E	10.300		21.600
		E	9.400		3.600
		E	6.100	4.800	10.100
		E	12.500	20.300	19.700
		E	16.200	21.900	20.400
		E	13.500	28.700	9.800
		E	8.700		16.500
		E	5.300		18.300
Uric Acid					
		D	517.000	666.000	684.000
		D	470.000		636.000
		E	446.000	494.000	601.000
Cholesterol					
		E	4.370	4.970	13.400
Urine Specific Gravity					
		D	1.015		1.044
		D	1.011	1.036	1.037
		D	1.024		1.004
		E	1.016		1.036

	E	1.015	1.042
Urine Ph			
	E	5.000	6.000	8.000

APPEARS THIS WAY
ON ORIGINAL

Distribution of Extreme Laboratory Values (cont)

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
		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