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NDA 50678
DYNABAC

1 OF 8

NDDA50-678

Dynabac

NDA 50-678

Dynabac

Pharm/Tox

AP Ltr

Micro

E-Attch

A/E

Ltr

Chem

FDA Cons

LBL

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Bio

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Clin. Study Report

AP Ltr

6/6/95

LB L

NDA 50-678

JUN 19 1995

**Eli Lilly and Company
Attention: M. W. Talbott, Ph.D.
Director, Medical Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285**

Dear Dr. Talbott:

Please refer to your April 27, 1993, new drug application (NDA) and your resubmission dated February 27, 1995, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Dynabac[®] (dirithromycin tablets) 250-mg tablet for oral administration.

Reference is also made to the Agency's approvable letter dated July 28, 1994. We acknowledge receipt of your additional communications dated August 26, and 31, October 21, December 6, 1994; and January 27, February 24, 1995. Additionally, we acknowledge receipt of your facsimiles of May 15, 18, and 31, and June 12, 1995.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling prepared by the Division of Anti-Infective Drug Products dated June 6, 1995, edited and agreed to by you on June 12, 1995 (copy attached to this letter). For the record, copies of these facsimiles are also attached to this letter. Accordingly, this application is approved effective on the date of this letter.

CHEMISTRY and MANUFACTURING SPECIFICS:

- (1) As agreed in the telephone conversation on May 31, 1995, between Mr. Wayne Millar of Eli Lilly and Ms. Maureen Dillon-Parker of the Division of Anti-infective Drug Products and confirmed by your facsimile of May 31, 1995, we note Eli Lilly accepts the dissolution specification of $Q = NLT \quad \% \text{ in } \quad \text{minutes}$.
- (2) We have determined you have submitted adequate stability data to support an expiration date of 24 months.
- (3) We remind you that only the carton and immediate carton labeling submitted to this NDA are approved with this letter. Please submit any proposed changes to and/or additional carton and immediate container labels for pre-approval as per Title 21 of the Code of Federal Regulations.
- (4) We request that you submit dissolution profiles for the first three commercial manufacturing batches.

MICROBIOLOGY SPECIFICS:

Attached, please find the Microbiology reviewer's recommendations should a future claim be sought for the treatment of specific infection(s) caused by *Haemophilus influenzae* or for the listing of *Haemophilus influenzae* in the *in vitro* section of the approved labeling.

PHASE 4 SPECIFICS:

- (1) We remind you of the Phase 4 commitment specified in your submission dated August 26, 1994, and again confirmed in your facsimile of May 18, 1995. This commitment is to conduct a 600-patient safety study and submit the results to the FDA within 1 year of the approval of this drug. Please note that all protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements relating to this Phase 4 commitment, should be clearly designated "Phase 4 Commitment."
- (2) In addition, we remain concerned about a potential interaction between dirithromycin and terfenadine. We believe the approved labeling presents the data on this issue that is presently available. We do request that, in preparation of your quarterly safety updates, you put special emphasis on this potential interaction and that you highlight a section in your quarterly report dedicated specially to this potential interaction. We would consider any indication that an interaction was occurring to require an expedited report to the FDA and would most likely necessitate a "Dear Health Care Practitioner" letter. We also request that you perform further study of this potential interaction in a manner similar to that suggested in proposed study and submit those data to the FDA within the one year of the approval of this product. The Division of Biopharmaceutics would be happy to work with you on the design of any such further study.

FINAL PRINTED LABELING SPECIFICS:

- (1) The final printed labeling (FPL) for this product must be identical to the enclosed labeling dated June 6, 1995 (including bolding, italicizing, paragraph designation, indentations, and white space). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

- (2) Please submit fifteen copies of the FPL as soon as it is available; in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-678". Approval of this labeling by FDA is not required before it is used.

CONCLUSIONS:

- (1) Should additional information relating to the efficacy and safety of this drug product become available, revision of the labeling may be required.
- (2) Please submit one market package of the drug when it is available.
- (3) We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.
- (4) We remind you of the detailed in your approvable
letter of July 28, 1994 for this product.

Should you have any questions concerning this application, please contact Ms Maureen Dillon-Parker, Project Manager, at 301-443-0257.

Sincerely yours,

MML 6/19/95

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

- ENCLOSURES -**
- **Divisional Labeling dated June 6, 1995 (including changes suggested in 6/12/95 facsimile (21 pages)**
 - **Facsimile May 31, 1995 (1 page)**
 - **Facsimile June 12, 1995 (1 page)**
 - **Microbiology Recommendations (9 pages)**

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Approval letter
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cc: Orig: NDA 50-678

HFD-520

CHI-DO

HFC-130

HFD-82

HFD-473

HFD-500

HFD-735

HFD-240

HF-2

HFD-520/ActgDivDir/Gavrilovich

HFD-520/MO/Moledina NM 6/16/95

HFD-520/MO/Rakowsky

HFD-520/SChem/Roy 6/16/95

HFD-520/Chem/Katagoe 6/16/95

HFD-520/SPharm/Osterberg 6/16/95

HFD-520/Pharm/Joshi

HFD-520/Micro/Creedon 6/16/95

HFD-520/SMicro/Sheldon

HFD-713/Biometrics/Srinivasan

HFD-713/SBiometrics/Harkins 6/16/95

HFD-426/SBiopharm/Pelsor

HFD-426/Biopharm/Ajayi 6/16/95

HFD-521/PMS/DillonParker

mpd: 6/12/95/ndafile\N50678.ap 6/16/95

Concurrence Only:

HFD-520/SMO/Albuerne Mida 6/16/95

HFD-520/SMicro/Sheldon AS 6/16/95

HFD-426/SBio/Pelsor 6/16/95

HFD-521/SPMS/Bona B 6/16/95

APPROVAL

FDA PROPOSED LABEL 6/06/95

DYNABAC[®]

(dirithromycin tablets)

DESCRIPTION

Dynabac[®] (dirithromycin tablets) contain the semi-synthetic macrolide antibiotic dirithromycin for oral administration. It is a pro-drug which is converted non-enzymatically during intestinal absorption into the microbiologically active moiety erythromyclamine.

Chemically, dirithromycin is designated (9*S*)-9-Deoxy-11-deoxy-9,11-[imino[(1*R*)-2-(2-methoxyethoxy)-ethylidene]oxy] erythromycin and has the molecular formula $C_{42}H_{78}N_2O_{14}$. Its molecular weight is 835.09. The structural formula is:

[INSERT FORMULA]

Chemically, erythromyclamine is designated 9-(*S*)-9-amino-9-deoxy-erythromycin and has a molecular formula of $C_{37}H_{70}N_2O_{12}$. Its molecular weight is 743.97. The structural formula is:

[INSERT FORMULA]

Dirithromycin is a basic compound. The free base is poorly soluble in water and readily soluble in polar organic solvents. Dirithromycin is hydrolyzed to erythromyclamine in acidic aqueous solutions; hydrolysis is virtually complete within 2 hours.

Dynabac tablets are enteric coated to protect the contents from gastric acid and to permit absorption of the antibiotic in the small intestine. Each enteric-coated tablet contains dirithromycin equivalent to 250 mg and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, magnesium carbonate, magnesium stearate, sodium starch glycolate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol, benzyl alcohol, methacrylic acid copolymer, titanium dioxide, triethyl citrate, and talc.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Absorption--Dirithromycin is rapidly absorbed and converted by nonenzymatic hydrolysis to the microbiologically active compound erythromycylamine. The absolute bioavailability of the oral formulation is approximately 10%. The pharmacokinetic parameters of erythromycylamine in plasma after single- and multiple-dose oral administration of two 250-mg Dynabac tablets once daily for 10 days in 10 fasting healthy subjects (19 to 50 years of age) were as follows:

<u>Pharmacokinetic Parameter</u> (n = 10 subjects)	<u>Mean (1 S.D.)</u>			
	<u>Day 1</u>		<u>Day 10</u>	
C_{max} ($\mu\text{g/mL}$)	0.3	(0.2)	0.4	(0.2)
T_{max} (h)	3.9	(0.9)	4.1	(1.3)
AUC_{0-24h} ($\mu\text{g} \cdot \text{h/mL}$)	0.9	(0.7)	1.8	(1.1)

Distribution--The protein binding of erythromyclamine ranges from 15% to 30%.

Erythromyclamine is widely distributed throughout the body with a mean apparent volume of distribution (V_{Dss}) of 800 L (504 to 1,041 L).

Rapid distribution of erythromyclamine into tissues and high concentrations within cells result in significantly higher concentrations in tissues than in plasma or serum. There are no data available on cerebrospinal fluid penetration.

Table 1

Steady-State Tissue Concentrations of Erythromyclamine Following Two 250-mg Tablets (500 mg) or Dynabac Given Orally Once Daily

Tissue	Time After Last Dose (h)	Mean Tissue Concentration ($\mu\text{g/g}$ or $\mu\text{g}/10^7$ cells)	Corresponding Mean Plasma or Serum Concentration ($\mu\text{g/mL}$)	Tissue/Plasma (Serum) Ratio
Tonsil	14	3.47	0.17	20.4
Healthy lung	12	3.79	0.13	29.2
Pathologic / infected lung	12	3.85	0.13	29.6
Infected bronchial mucosa	12	1.70	0.13	13.1
Alveolar Macrophages	5	0.37	0.35	1.1
High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. Erythromyclamine is concentrated in cell lysosomes, which have a low organelle pH at which drug activity is reduced.				

Metabolism and Excretion--Erythromyclamine is primarily eliminated in the bile and undergoes little or no hepatic metabolism. Thus, the primary route of elimination is fecal/hepatic with 81% to 97% of the dose eliminated in this manner. Approximately 2% of the administered dose is eliminated through the kidney, mainly within the first 36 hours following drug administration.

The mean plasma half-life of erythromyclamine was estimated to be about 8 h (2 to 36 h), while a mean urinary terminal elimination half-life of about 44 h (16 to 65 h) and a mean apparent total body clearance of approximately 23 L/h (20 to 32 L/h) were observed in patients with normal renal function.

Food Effect on Absorption--Dynamac tablets should be administered with food or within an hour of having eaten. The effect of food on the bioavailability of dirithromycin was evaluated following oral administration of two 250-mg Dynamac tablets 1 or 4 hours before food and immediately after a standard breakfast. Results obtained indicated a slight increase in the absorption of erythromyclamine when dirithromycin tablets were administered after food, while a significant decrease in C_{max} (33%) and AUC (31%) occurred when administered 1 hour before food. The effects of high and low fat meals on the bioavailability of dirithromycin were also investigated. The results showed that the amount of dietary fat had little or no effect on the bioavailability of dirithromycin.

Special Populations:

Hepatic Insufficiency--In patients with mild (Child's Grade A) hepatic impairment, mean peak serum concentration, AUC, and volume of distribution increased somewhat with multiple-dose administration; however, based on the magnitude of these changes, no dosage adjustment should be necessary in patients with mildly impaired hepatic function. The pharmacokinetics of dirithromycin in patients with moderate or severe impairment in hepatic function (Child's Grade B or greater) have not been studied.

Renal Insufficiency--The mean peak plasma concentration (C_{max}) and AUC tended to increase as creatinine clearance decreased; however, based on data available to date, no dosage adjustment should be necessary in patients with impaired renal function, including dialysis patients.

Geriatric Patients--In a multiple-dose study in which 19 healthy elderly subjects (65 to 83 years of age) were given two 250-mg Dynabac tablets every day for 10 days, C_{max} and AUC tended to increase with age; however, neither C_{max} nor AUC was statistically or clinically significantly altered with age. Therefore, based on these pharmacokinetic results, no dosage adjustment should be necessary in elderly patients.

Microbiology:

Erythromyclamine, the microbiologically active product of dirithromycin hydrolysis, exerts its activity by binding to the 50S ribosomal subunits of susceptible microorganisms resulting in inhibition of protein synthesis.

Dirithromycin/Erythromyclamine has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Gram-positive aerobes:

Staphylococcus aureus (methicillin-susceptible strains only)

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative aerobes:

Legionella pneumophila

Moraxella catarrhalis

Other bacteria:

Mycoplasma pneumoniae

The following *in vitro* data are available, but their clinical significance is unknown. Dirithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 2 $\mu\text{g/mL}$ or less against most ($\geq 90\%$) strains of the following microorganisms; however, the safety and effectiveness of Dynabac in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive aerobes:

Listeria monocytogenes
Streptococci, groups C, F, and G
Streptococcus agalactiae
Viridans group streptococci

Gram-negative aerobes:

Bordetella pertussis

Anaerobic bacteria:

Propionibacterium acnes

NOTE: Microorganisms that are resistant to other macrolides are cross-resistant to dirithromycin/erythromyclamine. Enterococci and most strains of methicillin-resistant staphylococci are resistant to macrolides. In addition, due to the lack of standardized methodology and interpretive criteria, it is impossible at present to determine if strains of *Haemophilus* are susceptible or are resistant to dirithromycin/erythromyclamine.

Susceptibility Tests:

Dilution Techniques--Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a

dilution method^{1,2} (broth, agar, or microdilution) or equivalent with standardized inoculum concentrations and standardized concentrations of dirithromycin powder.

The MIC values should be interpreted according to the following criteria:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Interpretation</u>
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard dirithromycin powder should provide the following MIC values:

<u>Microorganism</u>	<u>MIC ($\mu\text{g/mL}$)</u>
<i>S. aureus</i> ATCC 29213	1.0 to 4.0

Diffusion Techniques--Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure³ requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15- μ g dirithromycin to test the susceptibility of microorganisms to dirithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15- μ g dirithromycin disk should be interpreted according to the following criteria:

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥ 19	Susceptible (S)
16 to 18	Intermediate (I)
≤ 15	Resistant (R)

Interpretation should be as stated above for results using dilution techniques.

Interpretation involves correlation of the diameter obtained in the disk test with the MIC for dirithromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15- μ g dirithromycin disk should provide the following zone diameters in this laboratory test quality control strain:

<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
<i>S. aureus</i> ATCC 25923	18 to 26

INDICATIONS AND USAGE

Dynabac (dirithromycin tablets) is indicated for the treatment of individuals age 12 years and older with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Dirithromycin should not be used in patients with known, suspected, or potential bacteremias as serum levels are inadequate to provide antibacterial coverage of the blood stream.

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

NOTE: Because the safety and efficacy of dirithromycin in the treatment of respiratory disease secondary to *H. influenzae* have not been demonstrated, Dynabac is NOT indicated for the empiric treatment of acute bacterial exacerbations of chronic or secondary bacterial infection of acute bronchitis. Infections known, suspected, or considered potentially to be caused by *Haemophilus* species should be treated by an antibacterial agent indicated for such treatment.

Secondary Bacterial Infection of Acute Bronchitis due to *Moraxella catarrhalis* or *Streptococcus pneumoniae*. (See above NOTE.)

Community-Acquired Pneumonia due to *Legionella pneumophila*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae*.

Pharyngitis/Tonsillitis due to *Streptococcus pyogenes*.

NOTE: The usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin. Dynabac generally is effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of Dynabac in the subsequent prevention of rheumatic fever are not available at present.

Uncomplicated Skin and Skin Structure Infections due to *Staphylococcus aureus* (methicillin-susceptible strains). (Abscesses usually require surgical drainage.)

NOTE: Because the safety and efficacy of dirithromycin in the treatment of uncomplicated skin and skin structure infections due to *S. pyogenes* have not been demonstrated, Dynabac is NOT indicated for the empiric treatment of uncomplicated skin and skin structure infections. Infections known, suspected, or potentially caused by *S. pyogenes* should be treated with an antibacterial agent indicated for such treatment.

CONTRAINDICATIONS

Dynabac is contraindicated in patients with known hypersensitivity to dirithromycin, erythromycin, or any other macrolide antibiotic.

WARNINGS

In a prospective study involving 6 healthy male volunteers, dirithromycin did not affect the metabolism of terfenadine. These six volunteers received terfenadine alone (60 mg twice daily) for 8 days, followed by terfenadine in combination with dirithromycin (500 mg once daily) for 10 days. (Both drugs were thus dosed to steady state.) The pharmacokinetics of terfenadine and its acid metabolite and the electrocardiographic QT_c interval were measured during both periods: with terfenadine alone, and with terfenadine plus dirithromycin. In five men, terfenadine levels were undetectable (< 5 ng/mL) throughout the study; in one man, the C_{max} of terfenadine was 8.1 ng/mL with terfenadine alone and 7.2 ng/mL with terfenadine plus dirithromycin. The mean C_{max} , T_{max} and AUC of the acid metabolite of terfenadine were not significantly changed. The mean QT_c interval (msec) was 369 with terfenadine alone and 367 with terfenadine plus dirithromycin.

Serious cardiac dysrhythmias, some resulting in death, have occurred in patients receiving terfenadine concomitantly with other macrolide antibiotics. In addition, most macrolides are contraindicated in patients receiving terfenadine therapy who have pre-existing cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischemic heart disease, congestive heart failure, etc.) or electrolyte disturbances. Until further use data are available, it is prudent to monitor the terfenadine levels when dirithromycin and terfenadine are coadministered. (See terfenadine package insert.)

Dirithromycin should not be used in patients with known, suspected, or potential bacteremias as serum levels are inadequate to provide antibacterial coverage of the blood stream.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including dirithromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

Hepatic Insufficiency--Because dirithromycin/erythromycylamine is principally eliminated via the liver and because no data exist regarding the safety of administering dirithromycin to patients with Child's Grade B or greater hepatic impairment, Dynabac should be administered to such patients only when absolutely necessary. No dosage adjustment should be necessary in patients with mildly impaired hepatic function. (See CLINICAL PHARMACOLOGY section.)

Information to Patients--Dynabac tablets should be taken with food or within one hour of having eaten. They should not be cut, chewed, or crushed.

Drug Interactions:

Terfenadine--See WARNINGS.

Theophylline--Following co-administration of two 250-mg dirithromycin tablets administered once daily with 200-mg theophylline tablets administered twice daily for 10 days to 14 healthy subjects, the steady-state plasma concentration of theophylline was not significantly altered. In general, most patients treated with dirithromycin who are receiving concomitant theophylline therapy *may* not require empiric adjustment of theophylline dosage or monitoring of theophylline plasma concentrations. However, theophylline plasma concentration should be monitored, with dosage adjustment as appropriate, in patients whose pulmonary disease requires maintaining a given theophylline plasma concentration for optimal pulmonary function or in patients with theophylline concentrations at the higher end of the therapeutic range.

Antacids or H₂ receptor antagonists--When dirithromycin is administered immediately following antacids or H₂-receptor antagonists, the absorption of dirithromycin is slightly

enhanced.

The following drug interactions have been reported with erythromycin products. It is presently not known whether these same drug interactions occur with dirithromycin. **Until further data are available regarding the potential interaction of dirithromycin with these compounds, caution should be used during coadministration.**

Triazolam--Erythromycin has been reported to decrease the clearance of triazolam and, thus, may increase the pharmacologic effect of triazolam.

Digoxin--Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

Anticoagulants--There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to a drug interaction with erythromycin may be more pronounced in the elderly.

Ergotamine--Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Other drugs--Drug interactions have been reported with concomitant administration of erythromycin and other medications, including cyclosporine, hexobarbital, carbamazepine, alfentanil, disopyramide, phenytoin, bromocriptine, valproate, astemizole, and lovastatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility--Lifetime studies in animals to evaluate carcinogenic potential have not been performed with dirithromycin.

No mutagenic potential was demonstrated when dirithromycin was used in standard tests of genotoxicity, which included the following bacterial mutation tests *in vitro* and *in vivo* mammalian systems:

- Bacterial Reverse-Mutation Test (Ames test)
- DNA repair (UDS) in rat hepatocytes
- Chinese hamster lung fibroblast (V79) test
- Micronucleus test in mice
- Sister-chromatid exchange - human lymphocytes
- Sister-chromatid exchange - Chinese hamsters
- Mouse Lymphoma Assay

In rats, fertility and reproductive performance were not affected when dirithromycin was administered at doses up to 21 times the maximum recommended human dose on a mg/m² basis.

Pregnancy: Teratogenic Effects. Pregnancy Category C--Teratology studies conducted in rats at doses up to 21 times the maximum recommended human dose on a mg/m² basis and in rabbits at doses up to 4 times the maximum recommended human dose on a mg/m² basis have revealed no evidence of impaired fertility or harm to the fetus due to dirithromycin administration. An additional teratology study in CD-1 mice demonstrated that fetal weight was significantly depressed at the 1000 mg/kg dose (8 times the maximum recommended human dose on a mg/m² basis), and there was an increased occurrence of incomplete ossification among these fetuses - a manifestation of retarded development. This decrease in ossification was also seen in rats given 1000mg/kg/day for 2 weeks prior to mating, throughout the mating period, and throughout gestation.

There are no adequate and well-controlled studies in pregnant women. Dirithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery--Dirithromycin has not been studied for use during labor and delivery. Treatment with dirithromycin should be given during labor and delivery only if clearly needed.

Nursing Mothers--It is not known whether either dirithromycin or erythromyclamide is excreted in human milk. It is known that dirithromycin is excreted in the milk of lactating rodents and that other drugs of this class are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dirithromycin is administered to a nursing woman.

Pediatric Use--Safety and effectiveness in infants and children less than 12 years of age have not been established.

Geriatric Use--In a clinical pharmacology study, 19 healthy geriatric volunteers (65 to 83 years of age) with normal renal and hepatic function had no statistically significant differences in AUC or C_{max} when compared with 10 healthy adult volunteers (19 to 50 years of age). In clinical trials in geriatric patients who received the usual recommended adult dose (500 mg q.d. P.O.), clinical efficacy and safety were comparable with results in non-geriatric adult patients.

ADVERSE REACTIONS

Clinical Trials: In clinical trials, 3299 patients were treated with dirithromycin 500 mg q.d. P.O. for approximately 7 to 14 days. There were no deaths or permanent disabilities thought related directly to drug toxicity. Eighty-seven (2.6%) patients discontinued

medication due to adverse reactions. Thirty-five (40%) of the 87 patients who discontinued therapy did so because of nausea or abdominal pain.

The following adverse clinical and laboratory reactions were reported during the dirithromycin clinical trials conducted in North America (n=1894 patients). (See Tables 2 and 3.)

Table 2
 Adverse Clinical Reactions
 (Incidence equal to or greater than 1%)

Clinical Trials - North America

<u>ADVERSE REACTION</u>	<u>DIRITHROMYCIN</u>	<u>ERYTHROMYCIN</u>
Abdominal pain	9.7%	7.5%
Headache	8.6%	8.2%
Nausea	8.3%	7.5%
Diarrhea	7.7%	7.3%
Vomiting	3.0%	2.8%
Dyspepsia	2.6%	2.1%
Dizziness/vertigo	2.3%	2.3%
Pain (non-specific)	2.2%	1.6%
Asthenia	2.0%	1.9%
Gastrointestinal disorder	1.6%	1.4%
Increased Cough	1.5%	2.6%
Flatulence	1.5%	1.5%
Rash	1.4%	2.6%
Dyspnea	1.2%	1.2%
Pruritus/Urticaria	1.2%	1.0%
Insomnia	1.0%	0.7%

Adverse reactions occurring during the clinical trials with dirithromycin with an incidence of less than 1% but greater than 0.1% included the following (listed alphabetically):

Abnormal stools, allergic reaction (not further defined), amblyopia, anorexia, anxiety, constipation, dehydration, depression, dry mouth, dysmenorrhea,

edema, epistaxis, eye disorder (not further defined), fever, flu syndrome, gastritis, gastroenteritis, hemoptysis, hyperventilation, malaise, mouth ulceration, myalgia, neck pain, nervousness, palpitation, paresthesia, peripheral edema, somnolence, sweating, syncope, taste perversion, thirst, tinnitus, tremor, urinary frequency, vaginal moniliasis, vaginitis, vasodilatation.

Table 3

Adverse Laboratory Reactions
(incidence equal to or greater than 1%)

Clinical Trials - North America

<u>ADVERSE REACTION</u>	<u>DIRITHROMYCIN</u>	<u>ERYTHROMYCIN</u>
Platelet count <i>increased</i>	3.8%	4.8%
Potassium <i>increased</i>	2.6%	0.0%
Bicarbonate <i>decreased</i>	1.4%	2.0%
CPK <i>increased</i>	1.2%	0.9%
Eosinophils <i>increased</i>	1.2%	0.6%
Seg Neutrophils <i>increased</i>	1.2%	1.3%

Adverse laboratory reactions occurring during the clinical trials with dirithromycin with an incidence of less than 1% but greater than 0.1% included the following (listed alphabetically):

Decreased:

Albumin, chloride, hematocrit, hemoglobin, seg neutrophils, phosphorus, platelet count, and total protein.

Increased:

Alkaline phosphatase, ALT, AST, bands, basophils, total bilirubin, creatinine, GGT, leukocyte count, lymphocytes, monocytes, phosphorous, and uric acid.

Macrolide-class adverse reactions--Although not observed in patients treated with dirithromycin in clinical trials, the following adverse reactions and altered laboratory test results have been reported in patients treated with macrolide antibiotics:

Bullous fixed eruptions or serious allergic reactions, including anaphylaxis, have been reported. A few cases of transient deafness have been reported with high doses of oral erythromycin. Rarely, cholestatic hepatitis has been reported. In individuals with prolonged QT intervals, erythromycin has been associated, rarely, with the production of ventricular arrhythmias, including ventricular tachycardia and torsade de pointes.

OVERDOSAGE

The toxic symptoms following an overdose of a macrolide antibiotic may include nausea, vomiting, epigastric distress, and diarrhea. Forced diuresis, peritoneal dialysis, hemodialysis, or hemoperfusion have not been established as beneficial for an overdose of dirithromycin. Hemodialysis has been shown to be ineffective in hastening the elimination of erythromycylamine from plasma in patients with chronic renal failure.

DOSAGE AND ADMINISTRATION

Dynabac (dirithromycin tablets) should be administered with food or within 1 hour of having eaten. (See CLINICAL PHARMACOLOGY, *Food Effect on Absorption*.) Dynabac tablets should not be cut, crushed, or chewed.

Table 4

Recommended Dosage Schedule for Dynabac
 (12 years of age and older)

Infection (Mild to Moderate Severity)	Dose	Frequency	Duration (days)
Acute Bacterial Exacerbations of Chronic Bronchitis due to <i>Moraxella catarrhalis</i> or <i>Streptococcus pneumoniae</i> NOT FOR EMPIRIC THERAPY (See INDICATIONS and USAGE.)	500 mg	q day	7
Secondary Bacterial Infection of Acute Bronchitis due to <i>M. catarrhalis</i> or <i>S. pneumoniae</i> NOT FOR EMPIRIC THERAPY (See INDICATIONS and USAGE.)	500 mg	q day	7
Community-Acquired Pneumonia due to <i>Legionella pneumophila</i> , <i>Mycoplasma pneumoniae</i> , or <i>S. pneumoniae</i>	500 mg	q day	14
Pharyngitis/Tonsillitis due to <i>Streptococcus pyogenes</i>	500 mg	q day	10
Uncomplicated Skin and Skin Structure Infections due to <i>Staphylococcus aureus</i> (methicillin-susceptible) NOT FOR EMPIRIC THERAPY (See INDICATIONS and USAGE.)	500 mg	q day	7

HOW SUPPLIED

Tablets (enteric-coated) (elliptical-shaped) (white)

250 mg (No. 4215)--(60s) NDC 0002-4215-60

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Cardiac and skeletal muscle lesions occurred in rats in studies up to three months by the intravenous route and in six-month studies in the rat and the dog by the oral-route. While no target organ toxicity was identified in these three-month oral studies, both cardiac and skeletal muscles were identified as target tissues after one-month intravenous studies in rats. Histologic changes from oral dosing occurred only after more than four months of treatment in rats and after six months in dogs. These findings were associated with high tissue-to-plasma concentration ratios of antimicrobial activity. The extensive drug uptake by tissues was reversible upon termination of treatment. Lesions in cardiac and skeletal muscle also were reversed upon termination of treatment. Dirithromycin and/or its microbiologically active metabolite appeared to accumulate in tissues with time. Despite the drug uptake in rat tissues at high multiples (approximately 14 times the anticipated clinical dose in mg/m²), there were no lesions in this species until oral treatment was extended beyond four months.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically -- Third Edition*; Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993
2. National Committee for Clinical Laboratory Standards. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria--Third Edition*; Approved Standard NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA, December 1993
3. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests--Fifth Edition*; Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993

NDA 50-678
Package Insert

21

CAUTION

Federal (USA) law prohibits dispensing without prescription.

FDA 6/06/95

AE Ltr 177

Draft LBL 7/28/94

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NDA 50-678

JUL 28 1994

M. W. Talbott, Ph.D.
Director, Medical Regulatory Affairs
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Talbott:

Reference is made to your new drug application (NDA) dated April 27, 1993, submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for Dynabac® (dirithromycin tablets) 250-mg tablet for oral administration.

We acknowledge receipt of your additional communications dated June 30, July 13, 29, and 30, August 3, 5, 6, 23, 25, and 27, October 6 and 26, and December 3 and 13, 1993; and January 6, February 3, and June 9, 21, and 22, 1994.

We have completed our review of this new drug application, as amended, and it is approvable. However, before this application may be approved, the following twenty-four pieces of information must be submitted, reviewed, and found acceptable by the FDA:

- (1) Draft final labeling that is identical to the enclosed proposed tentative labeling, dated July 28, 1994, prepared by the Division of Anti-Infective Drug Products, as qualified in the next paragraph.

Please note that there are several areas in the tentative labeling that have been highlighted. You should complete these areas with reference to the location in the NDA where the data that substantiate your completions can be found.

- (2) A full analysis and individual patient line listings of the bacteriological and clinical diagnoses and outcomes.

The susceptibilities (actual numerical MIC or zone size results, preferably both) should be submitted for every pathogen isolated per patient, including pre- and post-therapy isolates.

- (3) A statement of the exact method (or reference method if followed precisely) used to measure the susceptibility of clinical isolates to dirithromycin, erythromyclamine, and erythromycin.

This also should include methods used for fastidious organisms. The citation should include the year, volume, and issue of the reference.

- (4) A description of the methods by which zone diameters were measured for *Haemophilus influenzae* and *H. parainfluenzae* in the clinical trials.

It is clear from the literature that the currently established NCCLS method for agar diffusion does not result in zones of inhibition when testing *Haemophilus* species. Because dilution methods were not used in the clinical trials, it is not possible to establish MIC susceptibility limits for *Haemophilus* species based on the clinical trials.

Furthermore, because the NCCLS diffusion method does not result in zones of inhibition with the dirithromycin 15- μ g disk, no data are available to correlate MIC and zone diameter measurements to test the *in vitro* activity of dirithromycin against *Haemophilus* species.

- (5) Data (as suggested in NCCLS document M23-T2, section 4.0, July 1994) for the development of *in vitro* susceptibility testing criteria and quality control parameters, to compare the broth and agar dilution methods, and the broth microdilution and macrodilution methods.
- (6) A clarification of why (a) each laboratory testing *Staphylococcus aureus* ATCC 25923 did not report the results from 20 repeated tests, (b) *Staphylococcus aureus* ATCC 25923 was not proposed for inclusion in the package insert as a quality control (QC) strain, and (c) no studies were conducted on *Haemophilus influenzae* quality control strains.
- (7) Additional minimum inhibitory concentration (MIC) data on the susceptibility of *Staphylococcus aureus* (penicillin-susceptible and penicillin-resistant) and *Streptococcus pneumoniae* (penicillin-susceptible and penicillin-resistant) to dirithromycin.

The data submitted to the NDA suggest that penicillin-resistant strains have higher MIC 90 values than penicillin-susceptible strains. Penicillin susceptibility data on North American clinical isolates should also be provided.

- (8) Actual data to support the variation ranges provided for all inactive ingredients in the tablet core.

Presently these ranges are unacceptable. You may also propose a range for the lubricant, magnesium stearate. As for the subcoating and enteric coating, you also may propose a range. The range should be expressed as percent of the total weight of the coated tablet.

The issue of minor variations, as discussed in the AAPS Scale-Up Workshop, is not an official position of the agency. When the recommendation from the workshop is adopted, you may submit a supplement to have reasonable variation ranges included in the quantitative composition of the drug product.

- (9) A revision of your drug substance sampling protocol to include sampling from top, middle, and bottom of a drum. The samples may be composited for assay.
- (10) A statement acknowledging that with regards to the dissolution data from the scale-up validation of the to-be-marketed formulation, the dissolution specification (Q) should be set at NLT 70% dissolved in buffer stage in 30 minutes.
- (11) A commitment to conduct the following Phase 4 studies and submit the results to the FDA within 1 year of the approval of this drug:
- a. the pharmacokinetics of dirithromycin in patients with moderate-to-severe hepatic impairment who have a potential for antibacterial therapy;
 - b. the pharmacokinetics of dirithromycin in nursing mothers to assess the degree of excretion into milk;
 - c. a 600-patient safety study with dirithromycin, designed in conjunction with the Division of Anti-Infective Drug Products and the Division of Epidemiology.
- (12) An explanation of whether animals hydrolyze dirithromycin as do humans and whether an assay was used in the animal studies that would allow differentiation between dirithromycin and any microbiologically active other moiety.

- (13) An explanation of whether there are any known medical conditions or other factors that would preclude physiologic hydrolysis of dirithromycin in patients.
- (14) All follow-up data available to you on the two patients in the skin and skin structure infection study that had the extrasystole and alopecia adverse events.
- (15) An explanation of whether patients in the skin and skin structure protocols underwent incision and draining procedures and/or were allowed to use medicated soaps during the trials and, if so, the numbers of patients so treated, and, if not, an explanation of why such information was neither collected nor controlled for during the conduct on these trials.
- (16) The location of the Kopp study site in the skin and skin structure study.
- (17) The reasons for patient discontinuations from study E008 and AQUA (both skin and skin structure infection trials).
- (18) An explanation of how "chronic bronchitis" was defined in the conduct of the trials for acute bacterial exacerbations of chronic bronchitis.
- (19) An explanation of whether the non-North American sites in your protocols used NCCLS microbiologic testing criteria and standards in the performance of and interpretation of the microbiologic tests in the protocols. If not, an explanation of the standards employed by these laboratories and why you believe they should be considered equivalent to North American standards.
- (20) An explanation of why you believe the microbiologic pathogens isolated in the non-North American sites in your protocols have relevance to the American population and why microbiologic data from non-North American sites should be considered able to be extrapolated to the American population. This is especially true for the secondary bacterial infections of acute bronchitis study for which you have submitted at this time only the one European study.
- (21) An explanation of why the serologic interpretive criteria used in connection with the patients allegedly infected with *Legionella* and *Mycoplasma* should be considered clinically valid.

- (22) Copies with English translations of all approved labeling for this product by foreign drug regulatory authorities.
- (23) A list of all countries to which marketing applications for this product have been filed and whether any have been rejected in whole or in part and whether Lilly has withdrawn either the product after approval or the marketing application prior to approval in any country.
- (24) A safety update as required by 21 CFR 314.50(5)(vi)(b).

Please be advised that we reserve further comment on the enclosed July 28, 1994, draft labeling, prepared by the Division of Anti-Infective Drug Products, until all the deficiencies identified have been submitted, reviewed by the Agency, and found adequate. Should additional information relating to the efficacy and safety of this drug product become available, further revisions to the labeling may be required.

Please note that any advertising or promotional labeling for DYNABAC® (dirithromycin tablets) will be considered false and misleading under Section 502 of the Act if it utilizes in vitro microbiologic data to imply clinical efficacy or to imply clinical superiority over other drug products if such indications or clinical superiority have not been established in adequate and well-controlled clinical trials. In vitro microbiologic data establish in vitro microbiologic activity only. Appropriate use of such data in advertising and promotional labeling requires a balanced presentation of how such data should be interpreted in view of the human pharmacokinetic properties and the established clinical efficacy of these drug products.

In addition, any advertising or promotional labeling for DYNABAC^R will be considered false and misleading under Section 502 of the Act if it attempts to minimize, by print size or presentation emphasis, the fact that clinical data from adequate and well-controlled trials are not available establishing efficacy of this drug product in treating diseases due to the organisms contained in the "not clinically supported" (i.e., the second) grouping of organisms in the *Microbiology* subsection of the drug products labeling.

Finally, any advertisement or promotional labeling for DYNABAC^R will be considered false and misleading under the Act if it does

not include the entire INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the labeling when referring to the indications or dosing regimens for which this product is approved. The "NOTES" and other added statements in these sections are considered integral parts of the approved indication and dosing regimens and may not be deleted or edited. In advertising or promotional labeling, the "NOTES" and other added statements may not be spatially separated from the wording in the initial part of the INDICATIONS AND USAGE or DOSAGE AND ADMINISTRATION sections so as to minimize their impact. Such information must be presented in advertising or promotional pieces in at least the same print size and with at least the same impact as any other information from this section of the labeling.

This guidance constitutes notice of activities that may be considered to be violations of the Act. Failure to comply with this guidance may result in regulatory action without further notice.

Please submit, in triplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Anti-Infective Drug Products, and the remaining copies to the Division of Drug Marketing, Advertising, and Communications, HFD-240, Room 17B-06, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FDA 2253 for this submission; that form is for routine use, not proposed materials.

Within 10 days of the date of this letter, you are required to amend the application, or notify us of an intent to file and amendment, or follow one of the other alternatives described in 21 CFR 314.110. In the absence of such action on your part, the Food and Drug Administration may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial response will not be processed as a major amendment ("user fee resubmission"), and therefore, the user fee review clock for the "resubmission" will not be activated. -

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

NDA 50-678

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Should you have any questions concerning this application, please contact Ms. Maureen Dillon-Parker, Project Manager, at 301-443-6797.

Sincerely yours,

MML 7/28/94

Murray M. Lumpkin, M.D.
Deputy Director for Center Review Management
Center for Drug Evaluation and Research

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cc: Orig: NDA 50-678

HFD-520

CHI-DO

HFC-130

HFD-82

HFD-473

HFD-500

HFD-735

HFD-240

HF-2

HFD-520/ActgDivDir/Gavrilovich

HFD-520/MO/Moledina NM 7/28/94

HFD-520/MO/Rakowsky RR 7/28/94

HFD-520/SPharm/Osterberg

HFD-520/Pharm/Joshi

HFD-520/Micro/Creedon KA 7/28/94

HFD-520/SMicro/Sheldon

HFD-713/Biometrics/Srinivasan

HFD-713/SBiometrics/Harkins

HFD-426/SBiopharm/Pelso

HFD-426/Biopharm/Ajayi

HFD-521/PMS/DillonParker

mpd: 7/27/94/ae\N50678.ae/ft 7/28/94

Concurrence Only:

HFD-520/SMO/Albuerne

HFD-520/SMicro/Sheldon

HFD-426/SBio/Pelso

HFD-521/ASPMS/DeSantis

msk 7/28/94

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APPROVABLE

Draft Labeling

DYNABAC®
(dirithromycin tablets)**DESCRIPTION**

Dirithromycin is a semi-synthetic macrolide antibiotic for oral administration. It is a prodrug which is converted non-enzymatically during intestinal absorption into the microbiologically active moiety erythromyclamine.

Chemically, dirithromycin is designated (9S)-9-Deoxy-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy)-ethylidene]oxy] erythromycin and has the molecular formula $C_{42}H_{73}N_2O_{14}$. Its molecular weight is 835.09. The structural formula is:

INSERT FORMULA HERE

Chemically, erythromyclamine is designated _____ and has a molecular formula of _____. Its molecular weight is _____. The structural formula is:

INSERT FORMULA HERE

Dirithromycin is a basic compound. The free base is poorly soluble in water and readily soluble in polar organic solvents. Dirithromycin is hydrolysed to erythromyclamine in acidic aqueous solutions; hydrolysis is virtually complete within 2 hours.

DYNABAC tablets are enteric coated to protect the contents from gastric acid and to permit absorption of the antibiotic in the small intestine. Each enteric-coated tablet contains dirithromycin equivalent to 250 mg and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, magnesium carbonate, magnesium stearate, sodium starch glycolate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol, benzyl alcohol, methacrylic acid copolymer, titanium dioxide, triethyl citrate, and talc.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Absorption:

Dirithromycin is rapidly absorbed and converted to the microbiologically active compound erythromyclamine by nonenzymatic hydrolysis. The absolute bioavailability of the oral formulation is approximately 10%. The pharmacokinetic parameters of erythromyclamine in plasma after single- and multiple-dose oral administration of two 250-mg DYNABAC tablets once daily for 10 days in 10 fasting healthy subjects (19 to 50 years of age) were as follows:

Pharmacokinetic Parameters

	Mean (1 S.D.)	
	Day 1	Day 10
C_{max} ($\mu\text{g/mL}$)	0.3 (0.2)	0.4 (0.2)
T_{max} (h)	3.9 (0.9)	4.1 (1.3)
AUC_{0-24h} ($\mu\text{g h/mL}$)	0.9 (0.7)	1.8 (1.1)

Distribution: The protein binding of erythromyclamine ranges between 15% to 30%. Erythromyclamine is widely distributed throughout the body with a mean apparent volume of distribution ($V_{D_{ss}}$) of 800 L (..SD supplied by sponsor). Rapid distribution of erythromyclamine into tissues and high concentrations within cells result in significantly higher concentrations in tissues than in plasma or serum. There are no data available on cerebrospinal fluid penetration.

TABLE 1

Tissue Concentrations of Erythromyclamine Following Two 250-mg tablets (500 mg) Dirithromycin Orally Once Daily

Tissue	Time After Last Dose (h)	Mean Tissue Concentration ($\mu\text{g/g}$ or $\mu\text{g}/10^7$ cells)	Corresponding Mean Plasma or Serum Concentration ($\mu\text{g/mL}$)	Tissue/Plasma Serum Ratio
Tonsil	14	3.47	0.17	20.4
Healthy Lung	12	3.79	0.13	29.2
Pathologic Lung	12	3.85	0.13	29.6
Bronchial mucosa	12	1.70	0.13	13.1
Alveolar Macrophages	5	0.37	0.35	1.1

High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. Erythromyclamine is concentrated in cell lysosomes, which have a low organelle pH at which drug activity is reduced.

Metabolism and Excretion:

Erythromyclamine is primarily eliminated in the bile and undergoes little or no hepatic metabolism. Thus, the primary route of elimination is fecal/hepatic with 81% to 97% of the dose eliminated in this manner. Approximately 2% of the administered dose is eliminated through the kidney, mainly within the first 36 hours following drug administration.

The mean plasma half-life of erythromyclamine was estimated to be about 8 h (..SD supplied by sponsor); while a mean urinary terminal elimination half-life of about 44 h (..SD supplied by sponsor) and a mean apparent total body clearance of approximately 23 L/min (..SD supplied by sponsor) were observed in patients with normal renal function.

Food Effect on Absorption:

The effect of food on the bioavailability of dirithromycin was evaluated following oral administration of two 250 mg SYNABAC tablets 1 or 4 hours before food and immediately after a standard breakfast. Results obtained indicated a slight increase in the absorption of erythromycylamine when dirithromycin tablets were administered after food; while a significant decrease in C_{max} (33%) and AUC (31%) occurred when administered 1 hour before food. The effects of high and low fat meals on the bioavailability of dirithromycin were also investigated. The results showed that the amount of dietary fat had little or no effect on the bioavailability of dirithromycin.

Special Populations:

Hepatic Insufficiency:

Mean peak serum concentration, AUC, and volume of distribution increased somewhat with multiple-dose administration; however, based on the magnitude of these changes, no dosage adjustment should be necessary in patients with mildly impaired hepatic function. The pharmacokinetics of dirithromycin in patients with moderate or severe impairment in hepatic function have not been studied.

Renal Insufficiency:

The mean peak plasma concentration (C_{max}) and AUC tended to increase as creatinine clearance decreased; however, no dosage adjustment should be necessary in patients with impaired renal function, including dialysis patients.

Geriatric Patients:

In a multiple-dose study in which 19 healthy elderly subjects (age 65 to 83 years old) were given two 250-mg DYNABAC® tablets every day for 10 days, C_{max} and AUC tended to increase with age; however, neither C_{max} nor AUC were statistically significantly altered with age. Therefore, based on these pharmacokinetic results, no dosage adjustment should be necessary in elderly patients.

Microbiology:

Dirithromycin and its hydrolytic product, erythromycylamine, exert their antibacterial action by binding to the 50S ribosomal subunits of susceptible microorganisms resulting in inhibition of protein synthesis.

Dirithromycin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Gram-positive aerobes:

Staphylococcus aureus (methicillin-sensitive strains only)

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative aerobes:

Moraxella catarrhalis

Other bacteria:

Mycoplasma pneumoniae

The following *in vitro* data are available, but their clinical significance is unknown. Dirithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 2 μ /mL or less against most ($\geq 90\%$) strains of the following microorganisms; however, the safety and effectiveness of dirithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive aerobes:

Listeria monocytogenes
Streptococci, groups C, F, and G
Streptococcus agalactiae
Viridans group streptococci

Gram-negative aerobes:

Bordetella pertussis
Legionella pneumophila

Anaerobic bacteria:

Propionibacterium acnes

NOTE: Many strains of staphylococci and *Haemophilus influenzae* have demonstrated resistance to dirithromycin. Enterococci and most strains of methicillin-resistant staphylococci are resistant to macrolides including dirithromycin. Microorganisms that are resistant to other macrolides are cross-resistant to dirithromycin.

Susceptibility Tests:

Dilution Techniques:

Quantitative methods that are used to determine minimum inhibitory concentrations (MICs) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method (broth, agar, or microdilution) or equivalent with dirithromycin powder. The MIC values obtained should be interpreted according to the following criteria:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Interpretation</u>
≤ 2	(S) Susceptible
4	(I) Intermediate
≥ 8	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by dirithromycin monotherapy. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable drug concentrations are unlikely to be inhibitory, and that other therapy should be selected.

Measurement of MIC or minimum bactericidal concentration (MBC) and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **CLINICAL PHARMACOLOGY** section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standard susceptibility test procedures require the use of laboratory control microorganisms. Standard dirithromycin powder should provide the following MIC values:

<u>Organism</u>	<u>MIC Range ($\mu\text{g/mL}$)</u>
<i>S. aureus</i> ATCC 29213	1-4

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² which has been recommended for use with disks to test susceptibility of microorganisms to dirithromycin uses the 15- μg dirithromycin disk. Interpretation involves the correlation of the diameter obtained in the disk test with the MIC for dirithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with the 15- μg dirithromycin disk should be interpreted according to the following criteria:

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥ 19	(S) Susceptible
16-18	(I) Intermediate
≤ 15	(R) Resistant

As with standardized dilution techniques, susceptibility test procedures require the use of laboratory control microorganisms. The 15- μg dirithromycin disk should give the following zone diameters in the laboratory test quality control strain:

<u>Organism</u>	<u>Zone Diameter (mm)</u>
<i>S. aureus</i> ATCC 25923	18-26

INDICATIONS AND USAGE

DYNABAC (dirithromycin tablets) is indicated for the treatment of mild-to-moderate infections (See **WARNINGS**) caused by susceptible strains of the designated microorganisms in the conditions listed below. **(Due to the low serum levels, dirithromycin should not be used in patients who are judged to be inappropriate for outpatient oral therapy, such as patients with known or suspected bacteremias.)**

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

NOTE: DYNABAC is NOT indicated for the empiric treatment of acute bacterial exacerbations of chronic or secondary bacterial infection of acute bronchitis. Over 70% of clinical isolates of *H. influenzae* isolated in acute bacterial exacerbation of chronic bronchitis clinical trials exhibited *in vitro* resistance to dirithromycin. The safety and efficacy of dirithromycin in the empiric treatment of patients with acute bacterial exacerbation of chronic bronchitis caused by *H. influenzae* have not been demonstrated.

Secondary Bacterial Infection of Acute Bronchitis due to *Moraxella catarrhalis* or *Streptococcus pneumoniae*. (See above **NOTE**.)

Community-Acquired Pneumonia due to *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*.

Pharyngitis/Tonsillitis due to *Streptococcus pyogenes*.

NOTE: The usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the intramuscular or the oral route. Dirithromycin generally is effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of dirithromycin in the subsequent prevention of rheumatic fever are not available at present.

Uncomplicated Skin and Skin Structure Infections due to *Staphylococcus aureus*.
(Abscesses usually require surgical drainage.)

NOTE: Dirithromycin is NOT indicated for the empiric therapy of uncomplicated skin and skin structure infections without the aid of a culture as data are insufficient to recommend treatment of skin and skin structure infections due to *S. pyogenes*. Infections known or suspected to be caused by this microorganism should be treated with a known effective antibacterial agent.

CONTRAINDICATIONS

Dirithromycin is contraindicated in patients with known hypersensitivity to dirithromycin, erythromycin, or any of the macrolide antibiotics.

Dirithromycin is contraindicated in patients receiving terfenadine therapy who have preexisting cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischemic heart disease, congestive heart failure, etc.) or electrolyte disturbances.

WARNINGS

Due to the low serum levels, dirithromycin should not be used in patients who are judged to be inappropriate for outpatient oral therapy, such as patients with known or suspected bacteremias.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including dirithromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

Information to Patients:

DYNABAC tablets may be administered on an empty stomach or coadministered with food. (See CLINICAL PHARMACOLOGY, *Food Effect on Absorption*.)

Drug Interactions:

Terfenadine: See CONTRAINDICATIONS.

Theophylline: Following co-administration of two-250 mg dirithromycin tablets once daily with theophylline tablets 200 mg twice daily for 10 days to 14 healthy subjects, the steady-state plasma concentration of theophylline was not significantly altered. In general, most patients treated with dirithromycin who are receiving concomitant theophylline therapy do not require empiric adjustment of theophylline dosage or monitoring of theophylline plasma concentrations. However, theophylline plasma concentrations should be monitored, with dosage adjustment as appropriate, in patients with severe pulmonary disease who are dependent on maintaining a given plasma

theophylline concentration for optimal pulmonary function or for patients with theophylline concentrations at the higher end of the therapeutic range.

Antacids or H₂ receptor antagonists:

When dirithromycin is administered immediately following antacids or H₂-receptor antagonists, the absorption of dirithromycin is slightly enhanced.

The following drug interactions have been reported with erythromycin products. It is presently not known whether these same drug interactions occur with dirithromycin.

Until further data are available regarding the potential interaction of dirithromycin with these compounds, caution should be used during coadministration.

Triazolam:

Erythromycin has been reported to decrease the clearance of triazolam and, thus, may increase the pharmacologic effect of triazolam.

Digoxin:

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

Anticoagulants: There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to this drug interaction may be more pronounced in the elderly.

Ergotamine: Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Other drugs: Drug interactions have been reported with concomitant administration of erythromycin and other medications, including cyclosporin, hexobarbital, carbamazepine, alfentanil, disopyramide, phenytoin, bromocriptine, valproate, astemizole, and lovastatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Lifetime studies in animals to evaluate carcinogenic potential have not been performed with dirithromycin. No mutagenic potential was demonstrated for dirithromycin in standard tests of genotoxicity, which included the following bacterial mutation tests *in vitro* and *in vivo* mammalian systems: .

- Bacterial Reverse-Mutation Test (Ames test)
- DNA repair (UDS) in rat hepatocytes
- Chinese hamster lung fibroblast (V79) test
- Micronucleus test in mice
- Sister-chromatid exchange - human lymphocytes
- Sister-chromatid exchange - Chinese hamsters
- Mouse Lymphoma Assay

In rats, fertility and reproductive performance were not affected by dirithromycin at doses up to 21 times the maximum recommended human dose on a mg/m² basis.

Pregnancy: Teratogenic Effects. Pregnancy Category B.

Teratology studies conducted in rats at doses up to 21 times the maximum recommended human dose on a mg/m² basis and in rabbits at doses up to 4 times the maximum recommended human dose on a mg/m² basis have revealed no evidence of impaired fertility or harm to the fetus due to dirithromycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

Dirithromycin has not been studied for use during labor and delivery. Treatment should be given only if clearly needed.

Nursing Mothers:

It is not known whether dirithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dirithromycin is administered to a nursing woman. Dirithromycin is excreted in rat milk.

Pediatric Use:

Safety and effectiveness in infants and children less than 12 years of age have not been established.

Geriatric Use:

In a clinical pharmacology study, healthy geriatric volunteers (65 to 83 years of age) with normal renal and hepatic function had no statistically significant differences in AUC or C_{max} when compared with healthy adult volunteers (19 to 50 years of age). In clinical trials in geriatric patients who received the usual recommended adult dose (500 mg QD PO), clinical efficacy and safety were comparable with results in nongeriatric adult patients.

ADVERSE REACTIONS

In Clinical Trials:

In clinical trials using multiple doses of dirithromycin, ___ patients were treated with the recommended dosage of dirithromycin (500 mg QD PO). There were ___ deaths or permanent disabilities thought related to drug toxicity. _____ (___%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. _____ (___%) of the ___ patients who discontinued therapy did so because of (list major reasons for discontinuation).

The following adverse events were thought to be possibly, probably, or almost certainly related to dirithromycin during evaluation in clinical trials conducted in North America (n= ___ dirithromycin-treated patients).

TABLE 2

ADVERSE CLINICAL REACTIONS DIRITHROMYCIN MULTIPLE-DOSE DOSING REGIMENS CLINICAL TRIALS - NORTH AMERICA	
<i>INCIDENCE EQUAL TO OR GREATER THAN 1%</i>	LIST REACTIONS IN A COLUMN WITH PERCENTAGES FROM HIGHEST PERCENTAGE TO LOWEST
<i>INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%</i>	LIST REACTIONS IN A COLUMN ALPHABETICALLY

TABLE 3

ADVERSE LABORATORY REACTIONS DIRITHROMYCIN MULTIPLE DOSE DOSING REGIMENS CLINICAL TRIALS - NORTH AMERICA	
<i>INCIDENCE EQUAL TO OR GREATER THAN 1%</i>	LIST REACTIONS IN A COLUMN WITH PERCENTAGES FROM HIGHEST PERCENTAGE TO LOWEST
<i>INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%</i>	LIST REACTIONS IN A COLUMN ALPHABETICALLY

In Postmarketing Experience: (DELETE IF NOT APPLICABLE)

In addition to the events reported during North American clinical trials with dirithromycin, the following adverse experiences have been reported from foreign sources during worldwide postmarketing experience:

(List any adverse events reported in postmarketing surveillance not covered by the previous clinical trials listing)

Macrolide-class adverse reactions:

Although not observed in patients treated with dirithromycin in clinical trials, the following adverse reactions and altered laboratory test results have been reported in patients treated with macrolide antibiotics:

Bullous fixed eruptions, or serious allergic reactions, including anaphylaxis, have been reported. A few cases of transient deafness have been reported with high doses of oral erythromycin. Rarely, cholestatic hepatitis has been reported. In individuals with prolonged QT intervals, erythromycin has been associated, rarely, with the production of ventricular arrhythmias, including ventricular tachycardia and torsade de pointes.

OVERDOSAGE

The toxic symptoms following an overdose of a macrolide antibiotic may include nausea, vomiting, epigastric distress, and diarrhea. Forced diuresis, peritoneal dialysis, hemodialysis, or hemoperfusion have not been established as beneficial for an overdose of dirithromycin. Hemodialysis has been shown to be ineffective in hastening the elimination of dirithromycin from plasma in patients with chronic renal failure.

DOSAGE AND ADMINISTRATION

DYNABAC (dirithromycin tablets) may be administered on an empty stomach or coadministered with food. (See **CLINICAL PHARMACOLOGY**, *Food Effect on Absorption*.)

TABLE 4
Recommended Dosage Schedule for DYNABAC
(13 years of age and older)

Site and Type of Infection (Mild to Moderate Severity)	Dose	Frequency	Duration (days)
Acute Bacterial Exacerbations of Chronic Bronchitis due to <i>Moraxella</i> <i>catarrhalis</i> or <i>Streptococcus</i> <i>pneumoniae</i> . NOT FOR EMPIRIC THERAPY. (See INDICATIONS AND USAGE.)	500 mg	q day	7
Secondary Bacterial Infection of Acute Bronchitis due to <i>M. catarrhalis</i> or <i>S.</i> <i>pneumoniae</i> . NOT FOR EMPIRIC THERAPY. (See INDICATIONS AND USAGE.)	500 mg	q day	7
Community-Acquired Pneumonia due to <i>Mycoplasma pneumoniae</i> or <i>S.</i> <i>pneumoniae</i> .	500 mg	q day	14
Pharyngitis/Tonsillitis due to <i>Streptococcus pyogenes</i> .	500 mg	q day	10

Site and Type of Infection	Dose	Frequency	Duration (days)
Uncomplicated Skin and Skin Structure Infections due to <i>Staphylococcus aureus</i> . NOT FOR EMPIRIC THERAPY. (See INDICATIONS AND USAGE.)	500 mg	q day	7

HOW SUPPLIED

Tablets (enteric-coated) (elliptical-shaped) (white)

250 mg (No. 4215)--(60's) NDC 0002-4215-60

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Lesions in cardiac and skeletal muscle occurred in rats in studies up to three months by the intravenous route, and in six month studies in the rat and the dog by the oral route. These findings were associated with high tissue-to-plasma concentration ratios of antimicrobial activity. The extensive drug uptake by tissues was reversible upon termination of treatment. Lesions in cardiac and skeletal muscle also were reversed upon termination of treatment. Dirithromycin and/or its microbiologically active metabolites appeared to accumulate in tissues with time. Despite the drug uptake in rat tissues at high multiples (approximately 16 times the anticipated clinical dose in mg/m²), there were no lesions in this species until oral treatment was extended beyond four months.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically -- Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests -- Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

Eli Lilly and Company

ADDRESS

DATE

(7/28/94)

Review Draft PI

7/20/99

REVIEW OF THE DRAFT PACKAGE INSERT OF NDA 50-678

Date Submitted: July 20, 1994

Date Review Initiated: July 25, 1994

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

DYNABAC®
(dirithromycin tablets)

DESCRIPTION

Dirithromycin is a semi-synthetic macrolide antibiotic for oral administration. It is a prodrug which is converted non-enzymatically during intestinal absorption into the microbiologically active moiety erythromyclamine.

Chemically, dirithromycin is designated (9S)-9-Deoxo-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy)-ethylidene]oxy] erythromycin and has the molecular formula $C_{42}H_{73}N_2O_{14}$. Its molecular weight is 835.09. The structural formula is:

INSERT FORMULA HERE

Chemically, erythromyclamine is designated _____ and has a molecular formula of _____. Its molecular weight is _____. The structural formula is:

INSERT FORMULA HERE

Dirithromycin is a basic compound. The free base is poorly soluble in water and readily soluble in polar organic solvents. Dirithromycin is hydrolysed to erythromyclamine in acidic aqueous solutions; hydrolysis is virtually complete within 2 hours.

DYNABAC tablets are enteric coated to protect the contents from gastric acid and to permit absorption of the antibiotic in the small intestine. Each enteric-coated tablet contains dirithromycin equivalent to 250 mg and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, magnesium carbonate, magnesium stearate, sodium starch glycolate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol, benzyl alcohol, methacrylic acid copolymer, titanium dioxide, triethyl citrate, and talc.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Absorption:

Dirithromycin is rapidly absorbed and converted to the microbiologically active compound erythromyclamine by nonenzymatic hydrolysis. The absolute bioavailability of the oral formulation is approximately 10%. The pharmacokinetic parameters of erythromyclamine in plasma after single- and multiple-dose oral administration of two 250-mg DYNABAC tablets once daily for 10 days in 10 fasting healthy subjects (19 to 50 years of age) were as follows:

Pharmacokinetic Parameters	<u>Mean (1 S.D.)</u>	
	<u>Day 1</u>	<u>Day 10</u>
C_{max} ($\mu\text{g/mL}$)	0.3 (0.2)	0.4 (0.2)
T_{max} (h)	3.9 (0.9)	4.1 (1.3)
AUC_{0-24h} ($\mu\text{g h/mL}$)	0.9 (0.7)	1.8 (1.1)

Distribution: The protein binding of erythromyclamine ranges between 15% to 30%. Erythromyclamine is widely distributed throughout the body with a mean apparent volume of distribution (V_{Dss}) of 800 L (..SD supplied by sponsor). Rapid distribution of erythromyclamine into tissues and high concentrations within cells result in significantly higher concentrations in tissues than in plasma or serum. There are no data available on cerebrospinal fluid penetration.

TABLE 1

Tissue Concentrations of Erythromyclamine Following Two 250-mg tablets (500 mg) Dirithromycin Orally Once Daily

Tissue	Time After Last Dose (h)	Mean Tissue Concentration ($\mu\text{g/g}$ or $\mu\text{g}/10^7$ cells)	Corresponding Mean Plasma or Serum Concentration ($\mu\text{g/mL}$)	Tissue/Plasma Serum Ratio
Tonsil	14	3.47	0.17	20.4
Healthy Lung	12	3.79	0.13	29.2
Pathologic Lung	12	3.85	0.13	29.6
Bronchial mucosa	12	1.70	0.13	13.1
Alveolar macrophages	5	0.37	0.35	1.1

High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. Erythromyclamine is concentrated in cell lysosomes, which have a low organelle pH at which drug activity is reduced.

Metabolism and Excretion:

Erythromyclamine is primarily eliminated in the bile and undergoes little or no hepatic metabolism. Thus, the primary route of elimination is fecal/hepatic with 81% to 97% of the dose eliminated in this manner. Approximately 2% of the administered dose is eliminated through the kidney, mainly within the first 36 hours following drug administration.

The mean plasma half-life of erythromyclamine was estimated to be about 8 h (..SD supplied by sponsor); while a mean urinary terminal elimination half-life of about 44 h (..SD supplied by sponsor) and a mean apparent total body clearance of approximately 23 L/min (..SD supplied by sponsor) were observed in patients with normal renal function.

Food Effect on Absorption:

The effect of food on the bioavailability of dirithromycin was evaluated following oral administration of two-250 mg DYNABAC tablets 1 or 4 hours before food and immediately after a standard breakfast. Results obtained indicated a slight increase in the absorption of erythromyclamine when dirithromycin tablets were administered after food; while a significant decrease in C_{max} (33%) and AUC (31%) occurred when administered 1 hour before food. The effects of high and low fat meals on the bioavailability of dirithromycin were also investigated. The results showed that the amount of dietary fat had little or no effect on the bioavailability of dirithromycin.

Special Populations:

Hepatic Insufficiency: Mean peak serum concentration, AUC, and volume of distribution increased somewhat with multiple-dose administration; however, based on the magnitude of these changes, no dosage adjustment should be

necessary in patients with mildly impaired hepatic function. The pharmacokinetics of dirithromycin in patients with moderate or severe impairment in hepatic function have not been studied.

Renal Insufficiency:

The mean peak plasma concentration (C_{max}) and AUC tended to increase as creatinine clearance decreased; however, no dosage adjustment should be necessary in patients with impaired renal function, including dialysis patients.

Geriatric Patients:

In a multiple-dose study in which 19 healthy elderly subjects (age 65 to 83 years old) were given two 250-mg DYNABAC® tablets every day for 10 days, C_{max} and AUC tended to increase with age; however, neither C_{max} nor AUC were statistically significantly altered with age. Therefore, based on these pharmacokinetic results, no dosage adjustment should be necessary in elderly patients.

Microbiology:

Dirithromycin and its hydrolytic product, erythromyclamine, exert their antibacterial action by binding to the 50S ribosomal subunits of susceptible microorganisms resulting in inhibition of protein synthesis.

Dirithromycin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the

INDICATIONS AND USAGE section:

Gram-positive aerobes:

Staphylococcus aureus (methicillin-sensitive strains only)

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative aerobes:

Moraxella catarrhalis

Other bacteria:

Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown**. Dirithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 2 µ/mL or less against most ($\geq 90\%$) strains of the following microorganisms; **however, the safety and effectiveness of dirithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.**

Gram-positive aerobes:

Listeria monocytogenes

Streptococci, groups C, F, and G

Streptococcus agalactiae

Viridans group streptococci

Gram-negative aerobes:

Bordetella pertussis

Legionella pneumophila

Anaerobic bacteria:

Propionibacterium acnes

NOTE: Many strains of staphylococci and *Haemophilus influenzae* have demonstrated resistance to dirithromycin. Enterococci and most strains of methicillin-resistant staphylococci are resistant to macrolides including dirithromycin. Microorganisms that are resistant to other macrolides are cross-resistant to dirithromycin.

Susceptibility Tests:

Dilution Techniques:

Quantitative methods that are used to determine minimum inhibitory concentrations (MICs) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method¹ (broth, agar, or microdilution) or equivalent with dirithromycin powder. The MIC values obtained should be interpreted according to the following criteria:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤2	(S) Susceptible
4	(I) Intermediate
≥8	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by dirithromycin monotherapy. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable drug concentrations are unlikely to be inhibitory, and that other therapy should be selected.

Measurement of MIC or minimum bactericidal concentration (MBC) and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **CLINICAL PHARMACOLOGY** section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standard susceptibility test procedures require the use of laboratory control microorganisms. Standard dirithromycin powder should provide the following MIC values:

<u>Organism</u>	<u>MIC Range ($\mu\text{g/mL}$)</u>
<i>S. aureus</i> ATCC 29213	1-4

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² which has been recommended for use with disks to test susceptibility of microorganisms to dirithromycin uses the 15- μg dirithromycin disk. Interpretation involves the correlation of the diameter obtained in the disk test with the MIC for dirithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with the 15- μg dirithromycin disk should be interpreted according to the following criteria:

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥ 19	(S) Susceptible
16-18	(I) Intermediate
≤ 15	(R) Resistant

As with standardized dilution techniques, susceptibility test procedures require the use of laboratory control microorganisms. The 15- μ g dirithromycin disk should give the following zone diameters in the laboratory test quality control strain:

<u>Organism</u>	<u>Zone Diameter (mm)</u>
<i>S. aureus</i> ATCC 25923	18-26

INDICATIONS AND USAGE

DYNABAC (dirithromycin tablets) is indicated for the treatment of mild-to-moderate infections (See **WARNINGS**) caused by susceptible strains of the designated microorganisms in the conditions listed below. (Due to the low serum levels, dirithromycin should not be used in patients who are judged to be inappropriate for outpatient oral therapy, such as patients with known or suspected bacteremias.)

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

NOTE: DYNABAC is NOT indicated for the empiric treatment of acute bacterial exacerbations of chronic or secondary bacterial infection of acute bronchitis. Over 70% of clinical isolates of *H. influenzae* isolated in acute bacterial exacerbation of chronic bronchitis clinical trials exhibited *in vitro* resistance to dirithromycin. The safety and efficacy of dirithromycin in the empiric treatment of patients with acute bacterial exacerbation of chronic bronchitis caused by *H. influenzae* have not been demonstrated.

Secondary Bacterial Infection of Acute Bronchitis due to *Moraxella catarrhalis* or *Streptococcus pneumoniae*. (See above **NOTE**.)

Community-Acquired Pneumonia due to *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*.

Pharyngitis/Tonsillitis due to *Streptococcus pyogenes*.

NOTE: The usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the intramuscular or the oral route. Dirithromycin generally is effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of dirithromycin in the subsequent prevention of rheumatic fever are not available at present.

Uncomplicated Skin and Skin Structure Infections due to *Staphylococcus aureus*. (Abscesses usually require surgical drainage.)

NOTE: Dirithromycin is NOT indicated for the empiric therapy of uncomplicated skin and skin structure infections without the aid of a culture as data are insufficient to recommend treatment of skin and skin structure infections due to *S. pyogenes*. Infections known or suspected to be caused by this microorganism should be treated with a known effective antibacterial agent.

CONTRAINDICATIONS

Dirithromycin is contraindicated in patients with known hypersensitivity to dirithromycin, erythromycin, or any of the macrolide antibiotics.

Dirithromycin is contraindicated in patients receiving terfenadine therapy who have preexisting cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischemic heart disease, congestive heart failure, etc.) or electrolyte disturbances.

WARNINGS

Due to the low serum levels, dirithromycin should not be used in patients who are judged to be inappropriate for outpatient oral therapy, such as patients with known or suspected bacteremias.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including dirithromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic

measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

Information to Patients:

DYNABAC tablets may be administered on an empty stomach or coadministered with food. (See **CLINICAL PHARMACOLOGY**, *Food Effect on Absorption*.)

Drug Interactions:

Terfenadine:

See **CONTRAINDICATIONS**.

Theophylline:

Following co-administration of two-250 mg dirithromycin tablets once daily with theophylline tablets 200 mg twice daily for 10 days to 14 healthy subjects, the steady-state plasma concentration of theophylline was not significantly altered. In general, most patients treated with dirithromycin who are receiving concomitant theophylline therapy do not require empiric adjustment of theophylline dosage or monitoring of theophylline plasma concentrations. However, theophylline plasma concentrations should be monitored, with dosage adjustment as appropriate, in patients with severe pulmonary disease who are dependent on maintaining a given plasma theophylline concentration for optimal pulmonary function or for patients with theophylline concentrations at the higher end of the therapeutic range.

Antacids or H₂ receptor antagonists:

When dirithromycin is administered immediately following antacids or H₂-receptor antagonists, the absorption of dirithromycin is slightly enhanced.

The following drug interactions have been reported with erythromycin products. It is presently not known whether these same drug interactions occur with dirithromycin. **Until further data are available regarding the potential interaction of dirithromycin with these compounds, caution should be used during coadministration.**

- Triazolam:* Erythromycin has been reported to decrease the clearance of triazolam and, thus, may increase the pharmacologic effect of triazolam.
- Digoxin:* Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.
- Anticoagulants:* There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to this drug interaction may be more pronounced in the elderly.
- Ergotamine:* Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.
- Other drugs:* Drug interactions have been reported with concomitant administration of erythromycin and other medications, including cyclosporin, hexobarbital, carbamazepine, alfentanil,

disopyramide, phenytoin, bromocriptine, valproate, astemizole, and lovastatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Lifetime studies in animals to evaluate carcinogenic potential have not been performed with dirithromycin. No mutagenic potential was demonstrated for dirithromycin in standard tests of genotoxicity, which included the following bacterial mutation tests *in vitro* and *in vivo* mammalian systems:

Bacterial Reverse-Mutation Test (Ames test)

DNA repair (UDS) in rat hepatocytes

Chinese hamster lung fibroblast (V79) test

Micronucleus test in mice

Sister-chromatid exchange - human lymphocytes

Sister-chromatid exchange - Chinese hamsters

Mouse Lymphoma Assay

In rats, fertility and reproductive performance were not affected by dirithromycin at doses up to 21 times the maximum recommended human dose on a mg/m² basis.

Pregnancy: Teratogenic Effects. Pregnancy Category B.

Teratology studies conducted in rats at doses up to 21 times the maximum recommended human dose on a mg/m² basis and in rabbits at doses up to 4 times the maximum recommended human dose on a mg/m² basis have revealed no evidence of impaired fertility or harm to the fetus due to dirithromycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

Dirithromycin has not been studied for use during labor and delivery.

Treatment should be given only if clearly needed.

Nursing Mothers:

It is not known whether dirithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dirithromycin is administered to a nursing woman. Dirithromycin is excreted in rat milk.

Pediatric Use:

Safety and effectiveness in infants and children less than 12 years of age have not been established.

Geriatric Use:

In a clinical pharmacology study, healthy geriatric volunteers (65 to 83 years of age) with normal renal and hepatic function had no statistically significant differences in AUC or C_{max} when compared with healthy adult volunteers (19 to 50 years of age). In clinical trials in geriatric patients who received the usual recommended adult dose (500 mg QD PO), clinical efficacy and safety were comparable with results in nongeriatric adult patients.

ADVERSE REACTIONS

In Clinical Trials:

In clinical trials using multiple doses of dirithromycin, ___ patients were treated with the recommended dosage of dirithromycin (500 mg QD PO). There were ___ deaths or permanent disabilities thought related to drug toxicity. ___ (___%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. ___ (___%) of the ___ patients who discontinued therapy did so because of (list major reasons for discontinuation).

The following adverse events were thought to be possibly, probably, or almost certainly related to dirithromycin during evaluation in clinical trials conducted in North America (n=___ dirithromycin-treated patients).

TABLE 2

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In addition to the events reported during North American clinical trials with dirithromycin, the following adverse experiences have been reported from foreign sources during worldwide postmarketing experience:

(List any adverse events reported in postmarketing surveillance not covered by the previous clinical trials listing)

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Although not observed in patients treated with dirithromycin in clinical trials, the following adverse reactions and altered laboratory test results have been reported in patients treated with macrolide antibiotics:

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OVERDOSAGE

The toxic symptoms following an overdose of a macrolide antibiotic may include nausea, vomiting, epigastric distress, and diarrhea. Forced diuresis, peritoneal dialysis, hemodialysis, or hemoperfusion have not been established as beneficial for an overdose of dirithromycin. Hemodialysis has been shown to be ineffective in hastening the elimination of dirithromycin from plasma in patients with chronic renal failure.

DOSAGE AND ADMINISTRATION

DYNABAC (dirithromycin tablets) may be administered on an empty stomach or coadministered with food. (See **CLINICAL PHARMACOLOGY**, *Food Effect on Absorption*.)

TABLE 4
Recommended Dosage Schedule for DYNABAC
(13 years of age and older)

Site and Type of Infection (Mild to Moderate Severity)	Dose	Frequency	Duration (days)
Acute Bacterial Exacerbations of Chronic Bronchitis due to <i>Moraxella catarrhalis</i> or <i>Streptococcus pneumoniae</i>. NOT FOR EMPIRIC THERAPY. (See INDICATIONS AND USAGE.)	500 mg	q day	7
Secondary Bacterial Infection of Acute Bronchitis due to <i>M. catarrhalis</i> or <i>S. pneumoniae</i>. NOT FOR EMPIRIC THERAPY. (See INDICATIONS AND USAGE.)	500 mg	q day	7
Community-Acquired Pneumonia due to <i>Mycoplasma pneumoniae</i> or <i>S. pneumoniae</i>.	500 mg	q day	14
Pharyngitis/Tonsillitis due to <i>Streptococcus pyogenes</i>.	500 mg	q day	10

Site and Type of Infection	Dose	Frequency	Duration (days)
Uncomplicated Skin and Skin Structure Infections due to <i>Staphylococcus aureus</i> . NOT FOR EMPIRIC THERAPY. (See INDICATIONS AND USAGE.)	500 mg	q day	7

HOW SUPPLIED

Tablets (enteric-coated) (elliptical-shaped) (white)

250 mg (No. 4215)--(60's) NDC 0002-4215-60

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Lesions in cardiac and skeletal muscle occurred in rats in studies up to three months by the intravenous route, and in six month studies in the rat and the dog by the oral route. These findings were associated with high tissue-to-plasma concentration ratios of antimicrobial activity. The extensive drug uptake by tissues was reversible upon termination of treatment. Lesions in cardiac and skeletal muscle also were reversed upon termination of treatment. Dirithromycin and/or its microbiologically active metabolites appeared to accumulate in tissues with time. Despite the drug uptake in rat tissues at high multiples (approximately 16 times the anticipated clinical dose in mg/m²), there were no lesions in this species until oral treatment was extended beyond four months.

REFERENCES

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Eli Lilly and Company

ADDRESS

DATE

(7/28/94)

Medical Officer's Comments:

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



Nasim Moledina, M.D.

Medical Officer, FDA.

cc: Orig NDA 50-678

HFD-340

HFD-520

HFD-520/MO/NMoledina

HFD-520/Pharm/SJoshi

HFD-520/Micro/KCreedon

HFD-520/Chem/DKatague

HFD-520/PMS/MDParker

nm/7/26/94/rev 7/27/94.

Concurrence Only:

HFD-520/ActingDirDir/LGavrilovich

HFD-520/SMO/MSAlbuerne *MLA 7/27/94*

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NDA 50-678

MEDICAL OFFICER'S REVIEW OF NDA 50-678

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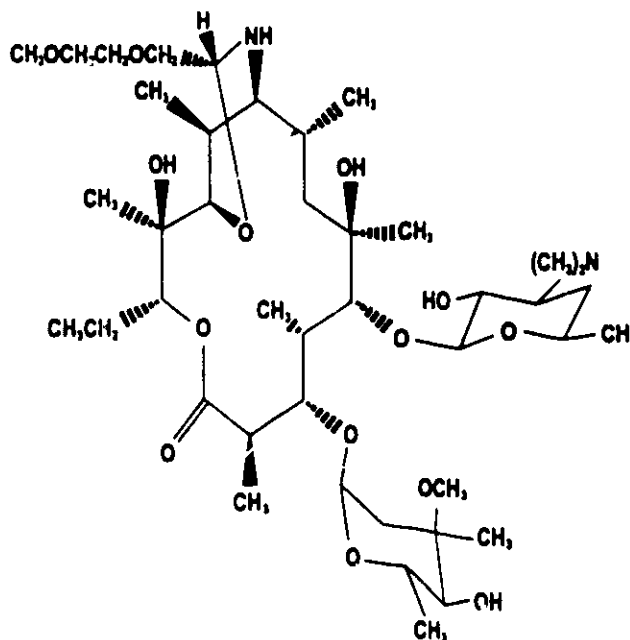
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Date Submitted: April 27, 1993.
 Amendment #1: February 3, 1994.
 MOR Initiated: March 8, 1994.
 MOR Completed: July 22, 1994.

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

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

Chemical Structure:



Molecular Formula: C₄₂H₇₈N₂O₁₄
 Molecular Weight: 835.09

Pharmacologic Category: Macrolide - Antibiotic 3

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-positive 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.

MANUFACTURING CONTROLS:

Refer to the chemistry review by Dr. Katague.

MICROBIOLOGY REVIEW:

Refer to the microbiology review by Dr. Kathy Creedon.

NONCLINICAL PHARMACOLOGY/BIOAVAILABILITY:

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

HUMAN PHARMACOKINETICS/BIOAVAILABILITY:

Please refer to Dr. Aj. yi'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 erythromyclamine formed by the condensation of methoxyacetaldehyde and erythromyclamine. Erythromyclamine is formed by the reductive amination of the C-9 ketone of erythromycin. Upon oral administration, dirithromycin is nonenzymatically hydrolyzed to erythromyclamine, which is microbiologically active.

Microbiology

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The mode of action of dirithromycin and its metabolite, erythromyclamine, 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 erythromyclamine 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 erythromyclamine, which is microbiologically active. Rapid distribution of dirithromycin and erythromyclamine 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 0.48 (0.1-1.97) $\mu\text{g/mL}$ were observed at 4 hours [Sides et al, 1992]. The area under the plasma concentration versus time curve ($\text{AUC}_{0-24\text{h}}$) measured $\mu\text{g}\cdot\text{hr/mL}$. The protein binding of circulating dirithromycin and its metabolite, erythromyclamine, ranged between %. Dirithromycin achieved tissue concentrations of $\mu\text{g/g}$ in nasal mucosa, tonsil, healthy lung, pathologic lung, bronchial mucosa, and prostate tissue, respectively. Tissue/plasma concentration ratios ranged from

Dirithromycin and erythromyclamine 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 erythromyclamine 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								Delta Limits	
		Male				Female				Low	High
Analyte	Age in years:	CAUCASIAN		NON-CAUCASIAN		CAUCASIAN		NON-CAUCASIAN			
		< 50	> 49	< 50	> 49	< 50	> 49	< 50	> 49		
Liver		Units									
ALT	U/L	7-112	5-87	5-121	4-84	5-88	5-77	4-88	4-88	27	27
AST	U/L	10-78	10-78	11-114	7-88	9-68	10-83	9-75	11-71	25	20
GGT	U/L	6-174	5-148	7-320	5-250	5-123	4-183	5-168	5-113	28	28
Alk. Phosphatase	U/L	28-133	24-150	33-144	27-148	28-123	25-154	28-135	22-182	48	39
Bilirubin	umol/L	3-32	3-32	3-29	3-24	3-22	3-21	3-21	2-18	18	18
Muscle											
Creatine Kinase	U/L	15-440	5-383	27-1070	15-840	0-243	0-223	13-345	10-453	278	224
Kidney											
Creatinine	umol/L	62-141	62-168	71-188	71-188	53-115	53-141	53-124	44-141	35	35
BUN	mmol/L	2.5-8.3	2.9-11.1	2.1-8.3	2.1-12.1	1.4-7.8	2.5-10.7	1.8-7.1	2.5-11.1	3.2	3.2
Uric Acid	umol/L	178-571	198-688	190-607	220-630	101-494	137-547	125-629	167-418	125	119
Phosphorus (i)	mmol/L	0.77-1.58	0.71-1.48	0.77-1.81	0.74-1.58	0.74-1.58	0.81-1.58	0.81-1.58	0.81-1.81	0.43	0.38
Calcium	mmol/L	2.12-2.84	2.10-2.82	2.07-2.84	2.10-2.84	2.10-2.82	2.12-2.84	2.05-2.84	2.10-2.88	0.28	0.28
Electrolytes											
Sodium	mmol/L	134-147	133-148	135-150	134-148	132-148	134-150	134-158	134-152	8	8
Potassium	mmol/L	3.4-5.3	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	98-112	95-111	98-110	98-111	98-112	94-112	97-112	93-111	8	8
Bicarbonate	mmol/L	20-28	21-28	21-28	21-28	20-24	21-25	20-28	21-28	7	8
Nutritional											
Glucose	mmol/L	3.7-11.8	3.8-13.5	3.8-9.5	3.8-14.7	3.8-8.8	3.8-15.2	3.8-13.3	3.8-18.1	3.1	3.4
Albumin	g/L	38-52	34-50	34-52	33-49	34-50	34-50	33-49	33-49	7	6
Protein	g/L	62-83	62-82	63-88	62-87	61-80	62-83	64-87	63-88	11	10
Cholesterol	mmol/L	3.08-6.46	3.48-6.98	2.78-6.51	2.92-6.95	3.13-6.12	3.78-6.31	3.34-7.73	3.78-6.72	1.84	1.78
HDL Cholesterol	mmol/L	0.64-2.87	0.44-2.17	0.47-2.34	0.41-2.23	0.54-2.72	0.57-2.58	0.52-2.51	0.52-2.84	0.88	0.88
LDL Cholesterol	mmol/L	1.50-5.88	1.88-6.05	1.22-6.28	1.42-6.43	1.27-5.90	1.81-6.23	1.18-6.82	1.81-6.83	1.98	1.81
Triglycerides	mmol/L	0.54-10.21	0.53-8.74	0.50-9.98	0.51-6.05	0.46-7.23	0.58-8.21	0.41-8.38	0.52-4.41	1.08	2.88
Erythrocytes											
Hemoglobin (Fe)	mmol/L	8.80-11.28	7.51-11.40	6.83-11.23	6.80-10.98	6.80-10.30	7.10-10.33	6.21-10.30	6.27-10.18	1.24	1.24
Erythrocytes	TVL	4.2-8.1	4.0-8.2	3.9-8.4	3.7-8.4	3.8-8.8	3.8-8.7	3.7-8.7	3.5-8.0	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	0.08
MCV	fL	78-108	78-108	72-108	73-104	78-105	78-108	67-102	72-108	8	7
MCH (Fe)	fmol	1.80-2.17	1.81-2.23	1.46-2.17	1.37-2.11	1.50-2.11	1.80-2.17	1.24-2.05	1.43-2.11	0.18	0.20
MCHC (Fe)	mmol/L	18-23	18-23	18-23	18-22	18-23	18-23	18-22	18-22	2	2
Leukocytes											
Leukocytes	GVL	3.5-13.8	3.4-12.8	2.8-13.5	2.8-11.7	3.5-13.5	3.7-12.4	3.2-13.8	3.1-11.4	4.0	3.7
Bands	GVL	0-0.74	0-0.78	0-0.33	0-0.38	0-1.08	0-0.81	0-0.39	0-0.20	0.30	0.28
Neutrophils	GVL	1.82-8.31	1.81-8.83	1.10-8.24	1.25-8.81	1.72-8.80	1.78-8.88	1.18-8.77	1.27-8.80	3.48	3.15
Lymphocytes	GVL	0.88-4.82	0.84-3.37	0.83-4.95	0.84-4.37	1.02-4.34	0.90-4.47	0.88-4.51	0.95-4.54	1.63	1.54
Monocytes	GVL	0-0.88	0-0.83	0-0.81	0-0.78	0-0.82	0-0.88	0-0.80	0-0.71	0.44	0.48
Eosinophils	GVL	0-0.71	0-0.67	0-0.81	0-0.59	0-0.88	0-0.58	0-0.67	0-0.54	0.39	0.39
Basophils	GVL	0-0.18	0-0.18	0-0.15	0-0.14	0-0.18	0-0.17	0-0.16	0-0.15	0.13	0.14
Platelets											
Platelets	GVL	138-410	134-432	142-384	138-437	154-461	148-447	148-455	NA	48	33
Urine											
Specific Gravity	-	1.008-1.036	1.005-1.034	1.007-1.036	1.008-1.036	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
500mg**

**Normal Duration
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 $\geq 133 \mu\text{mol/L}$, $\geq 1.5 \text{ mg/dL}$); 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:

<u>Study Visit</u>	<u>Procedure</u>
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:

<u>Study Visit</u>	<u>Procedure</u>
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

<u>Study Visit</u>	<u>Procedure</u>		
Pretherapy (Within 24 Hours of Receiving the First Dose):	<u>Hematology</u>	<u>Blood Chemistry</u>	<u>Urinalysis</u>
	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	Leukocyte Esterase
	Creatinine	Microscopic -	WBC
	Uric Acid		RBC
	Total Protein		Casts
	Albumin		
	Creatine Kinase*		

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.

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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 $\geq 133 \mu\text{mol/L}$ ($\geq 1.5 \text{ mg/dL}$).

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

Efficacy Procedures:

SYMPTOMATIC RESPONSE DEFINITIONS

<u>Result</u>	<u>Definition of Response</u>
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

<u>Result</u>	<u>Definition of Response</u>
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.

Qualification for Efficacy Analysis:

Cases classified by the sponsor as "qualified" (evaluable) met the following criteria for analysis of symptomatic response: the patient met the inclusion criteria; the patient completed an adequate course of therapy (10 days if categorized "cure" or "improvement"); the pretherapy throat culture obtained within 24 hours prior to start of study-drug medication was positive for group A streptococci; posttherapy clinical and microbiological evaluations were performed; late-posttherapy evaluations were required for patients that were culture-negative and/or symptomatically improved/cured at the posttherapy evaluation; symptomatic response (cure, improvement, relapse, or failure) could be evaluated (symptomatic responses of "Unable to Evaluate" disqualified cases for efficacy analysis).

Cases classified by the sponsor as "qualified" met the following criteria for analysis of bacteriologic response: the patient met the inclusion criteria; the patient completed an adequate course of therapy (10 days); the pretherapy throat culture was positive (≥ 10 colonies per blood agar plate) for group A streptococci; the isolated organism was susceptible to erythromycin; a posttherapy throat culture was obtained, and if negative, a late-posttherapy culture was obtained; pretherapy and late-posttherapy antistreptolysin-O (ASO) titers were obtained (requirement for ASO titers was discontinued after the Phase 2 analysis).

Statistical Methods:

The primary statistical evaluations included all data available from all patients entering the study. The groups of patients, determined by random allocation, were compared by means of chi-square methodology with respect to symptomatic and bacteriologic response rates and with respect to adverse-event frequencies. Appropriate continuous data procedures, such as a two-sample t-test on ranked data, were used for analysis of the laboratory monitoring data. All analyses examined consistency of results among participating clinics. Subgroup analyses (safety and efficacy) were performed for the two formulations of dirithromycin utilized in this study. Since there were only 4 patients who were 65 years of age or older enrolled in the pharyngitis/tonsillitis indication, no subset analysis of safety and efficacy was performed for this group.

Investigators:

A total of 38 investigators enrolled 553 patients.

INVESTIGATOR NAME/LOCATION	NUMBER OF ENROLLED PATIENTS		NUMBER OF EVALUABLE PATIENTS	
	DIR	ERY	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. HASZLBY/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. FENNEL/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. POTSCHAFER/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			ERYTHROMYCIN								
	FEMALE (N=170)		MALE (N=95)	TOTAL (N=265)		FEMALE (N=181)		MALE (N=107)	TOTAL (N=288)			
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)		
12 - <16	13	(7.6%)	16	(16.8%)	29	(10.9%)	15	(8.3%)	9	(8.4%)	24	(8.3%)
≥ 16 - <25	62	(36.5%)	41	(43.2%)	103	(38.9%)	48	(26.5%)	33	(30.8%)	81	(28.1%)
≥ 25 - <45	82	(48.2%)	37	(38.9%)	119	(44.9%)	102	(56.4%)	59	(55.1%)	161	(55.9%)
≥ 45 - <65	12	(7.1%)	1	(1.1%)	13	(4.9%)	13	(7.2%)	6	(5.6%)	19	(6.6%)
≥ 65	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			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	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	12.10	12.16	12.10	12.13	12.04	12.04
MAXIMUM AGE	65.01	56.27	65.01	71.80	58.41	71.80

RACIAL ORIGIN BY TREATMENT GROUP--ALL PATIENTS

	DIRITHROMYCIN		ERYTHROMYCIN	
	N=265		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

THERAPY	HEIGHT IN CM					WEIGHT IN KG						
	NO.	UNK	MEAN	STD DEV	MIN	MAX	NO.	UNK	MEAN	STD DEV	MIN	MAX
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

Evaluable Patients:

Age Ranges by Sex-Evaluable Patients

AGE RANGES	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE (N = 113)		MALE (N = 56)		TOTAL (N = 169)		FEMALE (N = 111)		MALE (N = 56)		TOTAL (N = 167)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
12-<16	7	(6.2%)	9	(16.1%)	16	(9.5%)	11	(9.9%)	5	(8.9%)	16	(9.6%)
16-<25	44	(38.9%)	26	(46.4%)	70	(41.4%)	25	(22.5%)	14	(25.0%)	39	(23.4%)
25-<45	55	(48.7%)	20	(35.7%)	75	(44.4%)	66	(59.5%)	35	(62.5%)	101	(60.5%)
45-<65	7	(6.2%)	1	(1.8%)	8	(4.7%)	8	(7.2%)	2	(3.6%)	10	(6.0%)
65+	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	28.62	28.88
MINIMUM AGE	12.71	12.16	12.16	12.13	12.04	12.04
MAXIMUM AGE	62.52	56.27	62.52	71.80	53.92	71.80

Origin By Therapy Group-Evaluable Patients

ORIGIN	DIRITHROMYCIN N = 169		ERYTHROMYCIN N = 167		TOTAL N = 336	
	n	(%)	n	(%)	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						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	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	1	1
MAXIMUM EXPOSURE DAYS	18	18
PATIENTS WITH INCOMPLETE DATA	7	8

SUMMARY OF EXPOSURE TO STUDY DRUGS--ALL PATIENTS

DAYS OF THERAPY	DIRITHROMYCIN		ERYTHROMYCIN	
	N = 265		N = 288	
	n	(%)	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

	<u>DIRITHROMYCIN</u> N = 169 DAYS	<u>ERYTHROMYCIN</u> N = 167 DAYS
NUMBER OF PATIENTS	169	167
MEAN DURATION EXPOSURE	10.9	10.9
MINIMUM EXPOSURE DAYS	3	2
MAXIMUM EXPOSURE DAYS	18	16
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs-Evaluable Patients

DAYS OF THERAPY	<u>DIRITHROMYCIN</u> N = 169		<u>ERYTHROMYCIN</u> N = 167	
	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 following 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	ERYTHROMYCIN
	N = 265 n (%)	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		ERYTHROMYCIN N = 167	
	n	(%)	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		ERYTHROMYCIN N = 151	
	n	(%)	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.

Bacteriologic Response

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

RESPONSE	DIRITHROMYCIN	ERYTHROMYCIN
	N = 167	N = 165
	n (%)	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	ERYTHROMYCIN
	N = 151	N = 150
	n (%)	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

PATHOGEN	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
	SUSCEPTIBLE (ZONE $\geq$ 17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE $\leq$ 15) N	TOTAL N	SUSCEPTIBLE (ZONE $\geq$ 18) N	INTERMEDIATE (17 $\geq$ ZONE $\geq$ 14) N	RESISTANT (ZONE $\leq$ 13) N	TOTAL N
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

PATHOGEN	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
	SUSCEPTIBLE (ZONE $\geq$ 17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE $\leq$ 15) N	TOTAL N	SUSCEPTIBLE (ZONE $\geq$ 18) N	INTERMEDIATE (17 $\geq$ ZONE $\geq$ 14) N	RESISTANT (ZONE $\leq$ 13) N	TOTAL N
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		ERYTHROMYCIN		P VALUE
	N	(%)	N	(%)	
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%)	0.498
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		ERYTHROMYCIN		P VALUE
	N	(%)	N	(%)	
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		ERYTHROMYCIN		P VALUE
	N	(%)	N	(%)	
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	(5.0%)	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	ERYTHROMYCIN	P VALUE
	N = 265 N (%)	N = 288 N (%)	
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

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	CONCOMITAN. 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	DIARRHEAL 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

IRV	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/PSEUDOPHRINE 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	2	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 BENZYL PENICILLIN 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.

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: 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 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.

NDA 50-678
 AQAS Pharyngitis/Tonsillitis

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	2	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 HASELSY/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 RUGFF/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

AGE RANGES (YRI)	DIRITHROMYCIN						ERYTHROMYCIN	
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL		
	(N=104)	(N=54)	(N=158)	(N=108)	(N=51)	(N=159)	N	(%)
N	(%) N	(%) N	(%) N	(%) N	(%)	N	(%)	
12-<16	9 (8.7%)	11 (20.4%)	20 (12.7%)	8 (7.4%)	3 (5.9%)	11 (6.9%)		
16-<25	33 (31.7%)	22 (40.7%)	55 (34.8%)	37 (34.3%)	21 (41.2%)	58 (36.5%)		
25-<45	55 (52.9%)	19 (35.2%)	74* (46.8%)	52 (48.1%)	26 (51.0%)	78 (49.1%)		
45-<65	6 (5.8%)	1 (1.9%)	7 (4.4%)	9 (8.3%)	1 (2.0%)	10 (6.3%)		
65+	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	100	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		ERYTHROMYCIN	
	N=158		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		N	UNK	MEAN	STD	
				DEV	MIN MAX				DEV	MIN MAX
DIRITHROMYCIN	157	1	167.77	10	143 193	156	2	70.84	17	39 127
ERYTHROMYCIN	159	0	167.57	10	136 192	159	0	70.28	17	38 143

Evaluable Patients:

Age Ranges by Sex
 Evaluable Patients

AGE RANGES	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE		MALE		TOTAL		FEMALE		MALE		TOTAL	
	(N = 78)	(%)	(N = 33)	(%)	(N = 111)	(%)	(N = 80)	(%)	(N = 37)	(%)	(N = 117)	(%)
12-16	7	(9.0%)	7	(21.2%)	14	(12.6%)	7	(8.8%)	2	(5.4%)	9	(7.7%)
17-25	27	(34.6%)	14	(42.4%)	41	(36.9%)	28	(35.0%)	14	(37.8%)	42	(35.9%)
25-45	39	(50.0%)	11	(33.3%)	50	(45.0%)	37	(46.3%)	20	(54.1%)	57	(48.7%)
45-65	4	(5.1%)	1	(3.0%)	5	(4.5%)	7	(8.8%)	1	(2.7%)	8	(6.8%)
65+	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	13.95	12.05	12.05	12.48	13.84	12.48
MAXIMUM AGE	74.17	46.91	74.17	67.68	61.23	67.68

Origin By Therapy Group
 Evaluable Patients

ORIGIN	DIRITHROMYCIN		ERYTHROMYCIN		TOTAL	
	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						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	111	0	165.73	19	143	193	111	0	71.55	17	39	127
ERYTHROMYCIN	117	0	167.49	10	136	190	117	0	70.93	18	38	143

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	1	2
MAXIMUM EXPOSURE DAYS	16	18
PATIENTS WITH INCOMPLETE DATA	1	3

Summary of Exposure To Study Drugs--All Patients

DAYS OF THERAPY	DIRITHROMYCIN		ERYTHROMYCIN		TOTAL	
	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

	<u>DIRITHROMYCIN</u>	<u>ERYTHROMYCIN</u>
	N = 111	N = 117
	DAYS	DAYS
NUMBER OF PATIENTS	111	117
MEAN DURATION EXPOSURE	11.0	10.8
MINIMUM EXPOSURE DAYS	4	2
MAXIMUM EXPOSURE DAYS	16	18
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drug
 Evaluable Patients

DAYS OF THERAPY	DIRITHROMYCIN		ERYTHROMYCIN	
	n	(%)	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	DIRLITHROMYCIN		ERYTHROMYCIN	
	N = 158		N = 159	
	N	(%)	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

RESPONSE	DIRITHROMYCIN		ERYTHROMYCIN	
	N	(%)	N	(%)
CURE	72	(64.9%)	84	(71.8%)
IMPROVEMENT	34	(30.6%)	29	(24.8%)
RELAPSE	4	(3.5%)	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

RESPONSE	DIRITHROMYCIN		ERYTHROMYCIN	
	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.

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	<u>DIRETHROMYCIN</u>		<u>ERYTHROMYCIN</u>	
	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

RESPONSE	<u>DIRETHROMYCIN</u>		<u>ERYTHROMYCIN</u>	
	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					N
	TERMINATION					TERMINATION					
	FAVOR		UNFAVO		FAVOR		UNFAVO				
	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.

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

PATHOGEN	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
	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
CTR 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: Erythromycin

PATHOGEN	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
STR 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 49.3% 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 [redacted] 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 [redacted] 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

EVENT CLASSIFICATION TERM	DIRITROMYCIN		ERYTHROMYCIN		P-VALUE
	N	(%)	N	(%)	
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
ARSCSS	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

EVENT CLASSIFICATION TERM	<u>DIRITHROMYCIN</u>		<u>ERYTHROMYCIN</u>		P-VALUE
	N	(%)	N	(%)	
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%)	10	(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

EVENT CLASSIFICATION TERM	<u>DIRITHROMYCIN</u>		<u>ERYTHROMYCIN</u>		P-VALUE
	N	(%)	N	(%)	
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

EVENT CLASSIFICATION TERM	DIRITHROMYCIN		ERYTHROMYCIN		P-VALUE
	N	(%)	N	(%)	
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

EVENT CLASSIFICATION TERM	DIRITHROMYCIN		ERYTHROMYCIN		P-VALUE
	N	(%)	N	(%)	
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: Test Product
Dirithromycin: 500 mg/dav (two 250-mg tablets q.d.)
CT01003, CT00634: dirithromycin tablets, 250 mg
CT01006, CT00637: placebo capsules
NOTE: Placebo was used to maintain blinding.

Reference Therapy
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. ROTSCHAFFER 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:

	<u>Dirithromycin</u>	<u>Penicillin</u>	<u>Total</u>
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		MALE		TOTAL		FEMALE		MALE		TOTAL	
	(N = 108)		(N = 62)		(N = 170)		(N = 112)		(N = 63)		(N = 175)	
AGE RANGES (YR)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
12-<16	13	(12.0%)	5	(8.1%)	18	(10.6%)	9	(8.0%)	5	(7.9%)	14	(8.0%)
16-<25	28	(25.9%)	23	(37.1%)	51	(30.0%)	24	(21.4%)	20	(31.7%)	44	(25.1%)
25-<45	65	(60.2%)	30	(48.4%)	95	(55.9%)	71	(63.4%)	35	(55.6%)	106	(60.6%)
45-<65	2	(1.9%)	3	(4.8%)	5	(2.9%)	8	(7.1%)	2	(3.2%)	10	(5.7%)
65+	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	12.53	12.44	12.44	12.56	12.14	12.14
MAXIMUM AGE	53.76	65.19	65.19	54.10	65.31	65.31

Racial Origin By Treatment Group
All Patients

ORIGIN	DIRITHROMYCIN N = 170		PENICILLIN N = 175		TOTAL N = 345	
	n	(%)	n	(%)	n	(%)
CAUCASIAN	141	(82.9%)	146	(83.4%)	287	(83.2%)
BLACK	13	(7.6%)	0	(0.0%)	13	(3.8%)
HISPANIC	13	(7.6%)	16	(9.1%)	29	(8.4%)
ASIAN	3	(1.8%)	2	(1.1%)	5	(1.4%)
OTHER	0	(0.0%)	1	(0.6%)	1	(0.3%)

Height and Weight At Admission
 All Patients

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	STD				N	UNK	STD			
			MEAN	DEV	MIN	MAX			MEAN	DEV	MIN	MAX
DIRITHROMYCIN	169	1	168.03	12	71	193	168	2	71.85	10	37	133
PENICILLIN	175	0	168.56	10	145	201	175	0	72.31	10	40	136

Evaluable Patients:

Age Ranges by Sex
 Evaluable Patients

AGE RANGES (YR)	DIRITHROMYCIN			PENICILLIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
	(N = 81)	(N = 40)	(N = 121)	(N = 90)	(N = 46)	(N = 136)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
12-<16	10 (12.34)	3 (7.50)	13 (10.78)	8 (8.90)	4 (8.70)	12 (8.80)
16-<25	22 (27.26)	14 (35.00)	36 (29.88)	19 (21.11)	14 (30.43)	33 (24.30)
25-<45	48 (59.34)	22 (55.00)	70 (57.98)	58 (64.44)	27 (58.70)	85 (63.50)
45-<65	1 (1.24)	0	1 (0.83)	5 (5.56)	1 (2.17)	6 (4.41)
65+	0	1 (2.50)	1 (0.83)	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	26.61	27.66	29.06	27.83	28.65
STD DEV	8.92	4.51	9.08	8.83	8.48	8.70
MEDIAN AGE	27.85	26.51	27.44	28.74	29.62	28.84
MINIMUM AGE	12.53	12.44	12.44	12.56	12.14	12.14
MAXIMUM AGE	46.88	65.19	65.19	54.05	51.48	54.05

Origin by Therapy Group
 Evaluable Patients

ORIGIN	DIRITHROMYCIN N = 121		PENICILLIN N = 136	
	n	(%)	n	(%)
CAUCASIAN	102	(84.30)	114	(83.89)
BLACK	7	(5.80)	5	(3.74)
HISPANIC	10	(8.30)	14	(10.30)
ASIAN	2	(1.70)	1	(0.70)
OTHER	0		2	(1.50)

Height and Weight at Admission
 Evaluable Patients

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	STD				N	UNK	STD			
			MEAN	DEV	MIN	MAX			MEAN	DEV	MIN	MAX
DIRITHROMYCIN	120	1	167.91	13	71	193	120	1	71.19	18	37	130
PENICILLIN	136	0	168.65	10	145	201	136	0	73.32	19	43	136

Drug Administration:

All Patients

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

	<u>DIRITHROMYCIN</u>	<u>PENICILLIN</u>
	<u>N = 170</u>	<u>N = 175</u>
	DAYS	DAYS
NUMBER OF PATIENTS	167	174
MEAN DURATION EXPOSURE	10.3	10.4
MINIMUM EXPOSURE DAYS	1	1
MAXIMUM EXPOSURE DAYS	16	15
PATIENTS WITH INCOMPLETE DATA	3	1

Summary of Exposure to Study Drugs
 All Patients

DAYS OF THERAPY	DIRITHROMYCIN		PENICILLIN	
	N = 170		N = 175	
	n	(%)	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		PENICILLIN	
	N = 121		N = 136	
	n	(%)	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	PENICILLIN
	N = 121	N = 136
	DAYS	DAYS
NUMBER OF PATIENTS	121	136
MEAN DURATION EXPOSURE	11.1	11.0
MINIMUM EXPOSURE DAYS	2	4
MAXIMUM EXPOSURE DAYS	16	15
PATIENTS WITH INCOMPLETE DATA	0	0

Unevaluable Patients

Reason Unevaluable Summary
 All Patients

REASON UNEVALUABLE	<u>DIRETHROMYCIN</u>		<u>PENICILLIN</u>	
	<u>N = 170</u>		<u>N = 175</u>	
	n	(%)	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

RESPONSE	DIRITHROMYCIN		PENICILLIN	
	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

RESPONSE	DIRITHROMYCIN		PENICILLIN	
	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		UNFAVOR			FAVOR		UNFAVOR			N
	N	%	N	%	N	%	N	%	N		
PROJECT											
AQAV	103	85.1	18	14.9	121	108	79.4	28	20.6	136	

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

RESPONSE	DIPHTHEROMYCIN		PENICILLIN	
	N = 120		N = 115	
	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

RESPONSE	DIPHTHEROMYCIN		PENICILLIN	
	N = 115		N = 125	
	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

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

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

Indication: Pharyngitis/Tonsillitis

PATHOGEN STR GRP A	ANTIMICROBIAL DIRITHROMYCIN			PENICILLIN G		
	SUSCEPTIBLE (ZONE >= 17)	RESISTANT (ZONE <= 15)	TOTAL N	SUSCEPTIBLE (ZONE >= 18)	INTERMEDIATE (17 >= ZONE >= 14)	TOTAL N
	N	N	N	N	N	N
	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 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 [redacted] had negative or resistant pre-therapy cultures, and were treated with an unspecified antibiotic, penicillin, trimethoprim/sulfamethoxazole, amoxicillin, and penicillin. Patient [redacted] was not qualified due to a low pretherapy colony count, and was treated with penicillin. Patients [redacted] 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

[redacted] 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 [redacted] 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 cephalixin. 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		PENICILLIN		PVALUE
	N = 170		N = 175		
	n	(%)	n	(%)	
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
LR 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		PENICILLIN		PVALUE
	N = 170		N = 175		
	n	(%)	n	(%)	
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		PENICILLIN		PVALUE
	N = 170		N = 175		
	n	(%)	n	(%)	
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	DIRITHRONACIN		PENICILLIN		PVALUE
	N = 170		N = 175		
	n	(%)	n	(%)	
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		PENICILLIN		PVALUE
	N = 170		N = 175		
	n	(%)	n	(%)	
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	5	(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		PENICILLIN		PVALUE
	N = 177		N = 175		
	n	(%)	n	(%)	
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
METRRORRHAGIA	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	DAYS OF		CAUSE OF	CONCOMITANT MEDICATION
					ORIGIN	THERAPY		
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	GUAIPENESIN 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

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**

PROJECT	THERAPY GROUP														
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN				
	POST THERAPY					POST THERAPY					POST THERAPY				
	FAVORA		UNFAV		N	FAVORA		UNFAV		N	FAVORA		UNFAV		N
	N	%	N	%		N	%	N	%		N	%	N	%	
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**

PROJECT	THERAPY GROUP																	
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN							
	LATEPOST THERAPY					LATEPOST THERAPY					LATEPOST THERAPY							
	FAVORA		UNFAV			N	FAVORA		UNFAV			N	FAVORA		UNFAV			N
	N	%	N	%	N		N	%	N	%	N		N	%	N	%	N	
AQAB	134	79.2	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**

PROJECT	THERAPY GROUP																
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN						
	TERMINATION					TERMINATION					TERMINATION						
	FAVOR		UNFAV			N	FAVOR		UNFAV			N	FAVOR		UNFAV		N
	N	%	N	%	N		N	%	N	%	N		N	%	N	%	
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**

PROJECT	THERAPY GROUP																
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN						
	POST THERAPY					POST THERAPY					POST THERAPY						
	FAVOR		UNFAV			N	FAVOR		UNFAV			N	FAVOR		UNFAV		N
	N	%	N	%	N		%	N	%	N	%		N	%	N	%	
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**

PROJECT	THERAPY GROUP																	
	DIRITHROMYCIN				ERYTHROMYCIN				PENICILLIN									
	LATEPOST THERAPY				LATEPOST THERAPY				LATEPOST THERAPY									
	FAVOR		UNFAV		FAVOR		UNFAV		FAVOR		UNFAV		FAVOR		UNFAV			
	N	%	N	%	N	N	%	N	%	N	N	%	N	%	N	%	N	
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			

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**Bacteriologic Response
 Termination**

PROJECT	THERAPY GROUP														
	DIRITHROMYCIN					ERYTHROMYCIN					PENICILLIN				
	TERMINATION					TERMINATION					TERMINATION				
	FAVOR		UNFAVO			FAVOR		UNFAVO			FAVOR		UNFAVO		
	%	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%** (101/136) 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: Test Product
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.

Reference Therapy
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 duration 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.		NUMBER OF EVALUABLE PTS.	
	DIRITH	ERYTH	DIRITH	ERYTH
D. G. WOOD/BANGOR, WALES	1	1	1	0
M. G. SCOTT/GLASGOW, SCOTLAND	1	2	1	0
M. J. DONNACIE/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/PORRENTROY, 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. K. 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. COTTEP/BANTRY, IRELAND	3	4	0	3
C. MCNAMARA/DUBLIN, IRELAND	6	6	4	2
SULLIVAN/CLOMEL, IRELAND	6	5	4	3
S. KIERNAN/NAVAN, IRELAND	2	2	2	2
M. F. RYAN/CORK, IRELAND	10	9	4	4
F. BRADBRY/KILKENNY, IRELAND	9	9	3	4
P. MCGARRY/LONGFORD, IRELAND	6	6	3	5
E. HARTMANN/CAVAN, IRELAND	3	4	2	2
L. MCKENTEE/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:

All Patients

AGE BY SEX - RANGES
ALL PATIENTS

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE (N=117)	MALE (N=76)	TOTAL (N=193)	FEMALE (N=112)	MALE (N=84)	TOTAL (N=196)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<u>AGE RANGES (YR)</u>						
16-<25	33 (28.2%)	31 (40.8%)	64 (33.2%)	25 (22.3%)	31 (36.9%)	56 (28.6%)
25-<45	72 (61.5%)	38 (50.0%)	110 (57.0%)	71 (63.4%)	45 (53.6%)	116 (59.2%)
45-<65	12 (10.3%)	6 (7.9%)	18 (9.3%)	14 (12.5%)	8 (9.5%)	22 (11.2%)
65+	0	1 (1.3%)	1 (0.5%)	2 (1.8%)	0	2 (1.0%)

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	16.00	16.00	16.00	16.00	16.00	16.00
MAXIMUM AGE	64.00	68.00	68.00	73.00	64.00	73.00

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	197	0	167.66	9	149	192	193	0	67.99	13	45	130	
ERYTHROMYCIN	196	0	168.57	11	125	225	195	1	69.40	14	43	115	

EVALUABLE PATIENTS:

Age Ranges by Sex
Evaluable Patients

AGE RANGES	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE (N = 64)		MALE (N = 33)		TOTAL (N = 97)		FEMALE (N = 67)		MALE (N = 32)		TOTAL (N = 99)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
16 < 25	18	(28.1%)	16	(48.5%)	34	(35.1%)	13	(19.4%)	16	(50.0%)	29	(29.3%)
25 < 45	37	(57.8%)	12	(36.4%)	49	(50.5%)	43	(64.2%)	13	(40.6%)	56	(56.6%)
45 < 65	9	(14.1%)	5	(15.2%)	14	(14.4%)	10	(14.9%)	3	(9.4%)	13	(13.1%)
65+	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	16.00	18.00	16.00	16.00	16.00	16.00
MAXIMUM AGE	64.00	64.00	64.00	65.00	55.00	65.00

Origin By Therapy Group
Evaluable Patients

ORIGIN	DIRITHROMYCIN		ERYTHROMYCIN		TOTAL	
	N = 97		N = 99		N = 196	
	n	(%)	n	(%)	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						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	97	0	168.52	9	150	192	97	0	67.93	12	45	97
ERYTHROMYCIN	99	0	167.55	8	150	188	99	0	67.32	12	43	96

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	2	2
MAXIMUM EXPOSURE, DAYS	16	16
PATIENTS WITH INCOMPLETE DATA	4	6

SUMMARY OF EXPOSURE TO STUDY DRUGS
ALL PATIENTS

DAYS OF THERAPY	DIRITHROMYCIN		ERYTHROMYCIN	
	n	(%)	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%)	87	(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

	<u>DIRITHROMYCIN</u>	<u>ERYTHROMYCIN</u>
	N = 97	N = 99
	DAYS	DAYS
NUMBER OF PATIENTS	97	99
MEAN DURATION EXPOSURE	10.3	10.4
MINIMUM EXPOSURE DAYS	3	2
MAXIMUM EXPOSURE DAYS	14	12
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients

DAYS OF THERAPY	DIRITHROMYCIN		ERYTHROMYCIN	
	n	(%)	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		ERYTHROMYCIN N = 195		TOTAL N = 389	
	n	(%)	n	(%)	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		ERYTHROMYCIN N = 99	
	n	(%)	n	(%)
CURE	76	(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		ERYTHROMYCIN N = 93	
	n	(%)	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

Project	Termination							
	Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable	
N	%	N	%	N	%	N	%	
<i>E001</i>	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		ERYTHROMYCIN N = 98	
	n	(%)	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

RESPONSE	DIRITHROMYCIN		ERYTHROMYCIN	
	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

Project	Termination							
	Dirithromycin				Erythromycin			
	Favorable		Unfavorable		Favorable		Unfavorable	
N	%	N	%	N	%	N	%	
<i>E001</i>	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

PATHOGEN	ANTIMICROBIAL						
	DIRITHROMYCIN				ERYTHROMYCIN		
	SUSCEPTIBLE (ZONE ≥ 17) N	INTERMEDIATE (ZONE = 16) N	RESISTANT (ZONE ≤ 15) N	TOTAL N	SUSCEPTIBLE (ZONE ≥ 18) N	RESISTANT (ZONE ≤ 13) N	TOTAL N
STR GRP A	149	1	9	159	153	6	159

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

PATHOGEN	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
STR 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		ERYTHROMYCIN N = 196		P-VALUE
	n	(%)	n	(%)	
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		ERYTHROMYCIN n = 196		P-VALUE
	N	(%)	N	(%)	
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%)	0.222
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		ERYTHROMYCIN N = 196		P-VALUE
	n	(%)	n	(%)	
PATIENTS WITH AT LEAST ONE EVENT	19	(9.8%)	29	(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%)	0.902
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		ERYTHROMYCIN N = 196		P-VALUE
	n	(%)	n	(%)	
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 CONCOMITANT	PAT MEDICATION	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT
402	BETAMETHASONE/ DEXCHLORPHENIRAMINE	1	18	MALE	CAUCASIAN	6	GENERALISED ALLERGIC EXANTHEMA
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 CONCOMITANT	PAT MEDICATION	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT
402	CISAPRIDE	1	30	MALE	CAUCASIAN	4	NAUSEA
801	PARACETAMOL	1	31	MALE	CAUCASIAN	4	GENERAL MALAISE
804		1	23	MALE	CAUCASIAN	5	DIARRHOEA
805	LOFEPRAMINE	1	34	FEMALE	CAUCASIAN	3	NAUSEA
862	TEMAZEPAM	1	19	FEMALE	CAUCASIAN	6	SICKNESS
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 erythromycin 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 European 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 bacteriologic (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: Test Product
Dirithromycin: 500 mg, given once daily
CT9367,CT9964: dirithromycin tablets,250 mg
CT9368,CT9965: placebo tablets
Note: placebo was used to maintain blinding
Reference Therapy
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 $\mu\text{mol/L}$, 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 $\mu\text{g/mL}$ 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 $\geq 133 \mu\text{mol/L}$ (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. STOLTZ/EVANSVILLE, IN	17	11	5	4
J. WRIGHT/AUSTIN, TX	0	1	0	0
J. 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	14	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. FENNEL/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	1	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. YANCO/TAMPA, FL	4	5	0	0
R. 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. ROTSCHAER/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/BISMARCK, 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'HEMOCOURT/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:

	<u>Dirithromycin</u>	<u>Erythromycin</u>
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

	<u>DIRITHROMYCIN</u>			<u>ERYTHROMYCIN</u>		
	<u>FEMALE</u>	<u>MALE</u>	<u>TOTAL</u>	<u>FEMALE</u>	<u>MALE</u>	<u>TOTAL</u>
	<u>N = 214</u>	<u>N = 179</u>	<u>N = 393</u>	<u>N = 226</u>	<u>N = 183</u>	<u>N = 409</u>
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

AGE RANGES (YR)

12-<16	0	1 (0.6%)	1 (0.3%)	0	1 (0.5%)	1 (0.2%)
16-<25	12 (5.6%)	6 (3.4%)	18 (4.6%)	10 (4.4%)	2 (1.1%)	12 (2.9%)
25-<45	81 (37.9%)	38 (21.2%)	119 (30.3%)	63 (27.9%)	45 (24.6%)	108 (26.4%)
45-<65	87 (40.7%)	65 (36.3%)	152 (38.7%)	94 (41.6%)	67 (36.6%)	161 (39.4%)
65+	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

	<u>DIRITHROMYCIN</u>			<u>ERYTHROMYCIN</u>		
	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	18.78	12.89	12.89	18.33	13.28	13.28
MAXIMUM AGE	87.41	93.76	93.76	83.30	89.62	89.62

Origin by Therapy Group
 All Patients

	<u>DIRITHROMYCIN</u>		<u>ERYTHROMYCIN</u>	
	<u>N = 393</u>		<u>N = 409</u>	
	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						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	392	3	168.67	10	132	198	391	2	76.57	20	35	150
ERYTHROMYCIN	406	3	168.01	10	140	193	409	0	75.33	19	39	163

Evaluable Patients:

Age Ranges by Sex
 Evaluable Patients

AGE RANGES	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE		MALE		TOTAL		FEMALE		MALE		TOTAL	
	N = 56		N = 45		N = 101		N = 48		N = 33		N = 81	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
12-<16	0		1	(2.2%)	1	(1.0%)	0		0		0	
16-<25	5	(8.9%)	2	(4.4%)	7	(6.9%)	1	(2.1%)	1	(3.0%)	2	(2.5%)
25-<45	17	(30.4%)	11	(24.4%)	28	(27.7%)	11	(22.9%)	8	(24.2%)	19	(23.5%)
45-<65	27	(48.2%)	20	(44.4%)	47	(46.5%)	27	(56.3%)	7	(21.2%)	34	(42.0%)
65+	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	20.50	12.89	12.89	19.49	17.35	17.55
MAXIMUM AGE	79.34	76.04	79.34	75.79	78.58	78.58

Origin By Therapy Group
 Evaluable Patients

ORIGIN	DIRITHROMYCIN N = 101		ERYTHROMYCIN N = 81	
	n	(%)	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

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	101	0	167.82	10	147	198	100	1	77.38	23	40	150
ERYTHROMYCIN	81	0	167.25	10	140	188	81	0	76.55	24	39	163

Drug Administration:

All Patients

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

	<u>DIRITHROMYCIN</u>	<u>ERYTHROMYCIN</u>
	<u>N = 191</u>	<u>N = 409</u>
NUMBER OF PATIENTS	385	403
MEAN DURATION EXPOSURE DAYS	6.9	6.9
MINIMUM EXPOSURE DAYS	1	1
MAXIMUM EXPOSURE DAYS	18	17
PATIENTS WITH INCOMPLETE DATA	8	6

Summary of Exposure to Study Drugs
All Patients

DAYS OF THERAPY	DIRITHROMYCIN		ERYTHROMYCIN	
	n	(%)	n	(%)
	N = 397		N = 409	
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

	<u>DIRITHROMYCIN</u> N = 101 DAYS	<u>ERYTHROMYCIN</u> N = 81 DAYS
NUMBER OF PATIENTS	101	81
MEAN DURATION EXPOSURE	7.9	8.6
MINIMUM EXPOSURE DAYS	3	6
MAXIMUM EXPOSURE DAYS	15	15
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
 Evaluable Patients

DAYS OF THERAPY	<u>DIRITHROMYCIN</u> N = 101		<u>ERYTHROMYCIN</u> N = 81	
	n	(%)	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		ERYTHROMYCIN N = 409	
	n	(%)	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 POSTHER. 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

RESPONSE	DIRITHROMYCIN		ERYTHROMYCIN	
	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		IMPROVEMENT		RELAPSE		FAILURE		TOTAL N
	n	(%)	n	(%)	n	(%)	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	0		2
E COLI	0		1	(100.0%)	0	0	0		1
K PNEUMONIAE	0		1	(100.0%)	0	0	0		1

* - These patients had multiple pathog 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		IMPROVEMENT		RELAPSE		FAILURE		TOTAL N
	n	(%)	n	(%)	n	(%)	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 M Catarrhalis	NA NA	Improvement
	Strep Sp M Catarrhalis	NA NA	Cure
	S Aureus - Grp A Strep	NA NA	Cure
	H Influenzae M Catarrhalis	NA NA	Cure
	H Influenzae H Parainfluenzae	UTE UTE	Failure
	H Influenzae S Aureus	FEP FEP	Improvement
	S Pneumoniae Strep Sp	NA NA	Cure
	Strep Sp M Catarrhalis	NA NA	Cure
	Strep Sp M Catarrhalis	NA NA	Cure

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		ERYTHROMYCIN	
	n	(%)	n	(%)
CURE	58	(72.5%)	49	(73.1%)
IMPROVEMENT	13	(16.3%)	12	(17.9%)
RELAPSE	6	(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

PATHOGENS	CURE		IMPROVEMENT		RELAPSE		FAILURE		TOTAL 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 Dornithromycin-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		IMPROVEMENT		RELAPSE		TOTAL N
	n	(%)	n	(%)	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 CATARRHALIS	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 M Catarrhalis	PE PE	Relapse
	Strep Sp M Catarrhalis	NA NA	Cure
	M Catarrhalis H Influenzae	NA NA	Cure
	H Influenzae S Pneumoniae	PE PE	Improvement
	S Pneumoniae Strep Sp	NA NA	Cure
	Strep Sp M Catarrhalis	NA NA	Cure
	Strep Sp M Catarrhalis	NA NA	Cure

NA = No cultures performed 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

RESPONSE	DIRITHROMYCIN		ERYTHROMYCIN	
	N = 93		N = 79	
	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

PATHOGENS	PATHOGEN ELIMINATED		PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
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	PATHOGEN ELIMINATED		PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	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 A REUS	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

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

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

RESPONSE	DIRITHROMYCIN		ERYTHROMYCIN	
	N = 76		N = 66	
	n	(%)	n	(%)
PATHOGEN ELIMINATED	10	(13.2%)	6	(9.0%)
PRESUMED ELIMINATED	60	(79.0%)	54	(81.8%)
RECURRENCE SAME	2	(2.5%)	1	(1.5%)
RECURRENCE SAME, RESISTANCE	1	(1.3%)	0	
RECURRENCE NEW	3	(3.9%)	3	(4.5%)
FAILED TO ELIMINATE	0		2	(3.0%)

Medical Officer's Comments:

There was a favorable bacteriologic response (pathogen eliminated or presumed eliminated) in 70 of 76 (92%) of patients treated with dirithromycin and 60 of 66 (91.0%) of patients treated with erythromycin. Five patients that were clinically evaluable (4 in dirithromycin group and 1 in the erythromycin group) were not bacteriological evaluable.

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

BACTERIOLOGIC RESPONSE SUMMARY/PATHOGEN
 ALL EVALUABLE PATIENTS

THERAPY: DIRITHROMYCIN

PATHOGEN	PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE SAME, RESISTANCE		RECURRENCE NEW		TOTAL n	
	n	(%)	n	(%)	n	(%)	n	(%)		
PATHOGENS										
S PNEUMONIAE	4	(23.5%)	12	(70.5%)	0		0	1	(5.9%)	17
H INFLUENZAE	2	(14.3%)	10	(71.4%)	1	(7.1%)	1	(7.1%)	0	14
STREP SP	1	(7.6%)	13	(76.9%)	1	(7.6%)	0	1	(7.6%)	16
M CATARRHALIS	2	(14.3%)	12	(85.7%)	0		0	0		14
S AUREUS	1	(10%)	8	(80.0%)	0		0	1	(10.0%)	10
H PARAINFLUENZAE	1	(20.0%)	4	(80.0%)	0		0	0		5
GRP A STREP	0		3	(100.0%)	0		0	0		3
E COLI	0		1	(100.0%)	0		0	0		1
K PNEUMONIAE	0		2	(100.0%)	0		0	0		2

BACTERIOLOGIC RESPONSE SUMMARY/PATHOGEN
ALL EVALUABLE PATIENTS

LATE-POSTTHERAPY

THERAPY: ERYTHROMYCIN

PATHOGENS	PATHOGEN	PRESUMED	RECURRENCE	RECURRENCE	FAILED TO	TOTAL
	ELIMINATED	ELIMINATED	SAME	NEW	ELIMINATE	n
H INFLUENZAE	3 (20.0%)	13 (73.3%)	1 (6.6%)	0	0	17
S PNEUMONIAE	1 (10.0%)	10 (80.0%)	0	1 (10.0%)	0	12
GRP A STREP	0	1	0	1 (100.0%)	0	2
S VIRIDANS	0	0	0	0	1 (100.0%)	1
S AUREUS	0	12 (100.0%)	0	0	0	12
STREP SP	0	14 (100.0%)	0	0	0	14
M CATARRHALIS	0	11 (100.0%)	0	0	0	11
GRP G STREP	0	2 (100.0%)	0	0	0	2
NO CULTURE TAKEN	0	0	0	0	0	1

Medical Officer's Comments:

The Medical Officer concurs with the applicant's analysis.

SUSCEPTIBILITY RESULTS

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

PATHOGEN	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
ACINETOBACTER LWOFF			2	2	1		1	2
B CATARRHALIS	15	1	3	19	19			19
C ALBICANS			1	1			1	1
CITROBACTER SP	1		1	2			2	2
E AEROGENES			3	3			3	3
E CLOACAE			6	6			6	6
E COLI	3		3	6	1		5	6
H INFLUENZAE	14		36	50	29	16	0	50
H PARAINFLUENZAE	9		6	15	12	1	2	15
K OXYTOCA			1	1			1	1
K PNEUMONIAE	2	1	5	8	1		7	8
N MENINGITIDIS	1			1	1			1
NEISSERIA SP	1			1	1			1

Medical Officer's Comments:

It is disturbing that 36/50 (72%) of *H. influenzae* isolated are resistant to dirithromycin.

(continued)

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

	ANTIMICROBIAL							
	DIRITHROMYCIN			ERYTHROMYCIN				
	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
STREPTOCOCCUS HOGEN								
PS MIRABILIS			2	2			2	2
PS AERUGINOSA			9	9			9	9
PS MALTOPHILIA	1		1	2			2	2
PSEUDOMONAS SP	1		2	3		1	2	3
S MARCESCENS			3	3			3	3
ST AUREUS	21		3	24	21		3	24
ST SAPROPHYTICUS	1			1	1			1
STAPH COAG-NEG	1		1	2	1		1	2
STR GRP A	3		2	5	5			5
STR PNEUMONIAE	26		4	30	29	1		30
STR VIRIDANS	1		3	4	2	1	1	4
STREPTOCOCCUS MITI	1			1	1			1
STREPTOCOCCUS SP	19		6	25	23	2		25

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

PATHOGEN	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
	SUSCEPTIBLE (ZONE>=17) N	INTERMEDIATE (ZONE=16) N	RESISTANT (ZONE<=15) N	TOTAL N	SUSCEPTIBLE (ZONE>=18) N	INTERMEDIATE (17>=ZONE>=14) N	RESISTANT (ZONE<=13) N	TOTAL N
ACINETOBACTER LWOFF			2	2		1	1	2
B CATARRHALIS	10	1	5	16	15	1		16
CITROBACTER SP	1		1	2	1		1	2
E AEROGENES	1		2	3			3	3
E CLOACAE			1	1			1	1
E COLI	3		5	8	1		7	8
H INFLUENZAE	14	2	35	51	27	16	8	51
H PARAINFLUENZAE	2	1	1	4	3	1		4
HAEMOPHILUS SP	1			1	1			1
K PNEUMONIAE	1		5	6		2	4	6
KLEBSIELLA SP			1	1			1	1
N MENINGITIDIS	1		1	2	1		1	2
PASTURELLA MULTOCII			1	1			1	1
PR MIRABILIS			3	3			3	3
PROTEUS			1	1			1	1
PS AERUGINOSA		1	11	12		1	11	12
PS FLUORESCENS			2	2			2	2
PS MALTOPHILIA			1	1			1	1

(continued)

Medical Officer's Comments:

Sixty-nine percent (35/51) of *H. influenzae* isolated were resistant to dirithromycin.

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

PATHOGEN	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
	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
PS PUTIDA			1	1			1	1
PS STUTZERI			1	1			1	1
PSEUDOMONAS SP	1		1	2	1		1	2
S MARCESCENS			1	1			1	1
S TYPHIMURIUM	1			1			1	1
ST AUREUS	14	2	4	20	18	1	1	20
STAPH COAG-NEG	2		2	4	1		3	4
STAPHYLOCOCCUS SP			1	1			1	1
STR GRP A	2			2	2			2
STR GRP B	2			2	2			2
STR GRP C	1			1	1			1
STR GRP G	2			2	2			2
STR PNEUMONIAE	17		5	22	21	1		22
STR VIRIDANS	3		3	6	3	1	2	6
STREPTOCOCCUS MITI	1		1	2	1	1		2
STREPTOCOCCUS SP	20		9	29	25	1	3	29

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		ERYTHROMYCIN		P-VALUE
	N = 393		N = 407		
	n	(%)	n	(%)	
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

	<u>DIRITHROMYCIN</u>		<u>ERYTHROMYCIN</u>		P-VALUE
	<u>N = 391</u>		<u>N = 409</u>		
	N	(%)	N	(%)	
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%)	0.556
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

	<u>DIBITHROMYCIN</u>		<u>ERYTHROMYCIN</u>		P-VALUE
	<u>N = 393</u>		<u>N = 409</u>		
	N	(%)	N	(%)	
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%)	0.49
SINUSITIS	5	(1.3%)	3	(0.7%)	0.143
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		ERYTHROMYCIN		P-VALUE
	N = 191		N = 409		
	N	(%)	N	(%)	
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 CLASSIFICATION 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	Respiratory Failure

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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	9.770
		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		7.357	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	5.740	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	12.570	8.050
		E	6.540		12.290
		E	7.740	13.390	15.090
	E	4.290		8.080	
	E	8.810		13.700	
	E	3.950		13.740	
	E	7.720		11.190	
	E	7.100		10.530	
Lymphocyte Count		E	2.730		5.210
		E	3.330		5.740
		E	3.290	3.740	1.090
		E	3.960		5.630

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	0.660	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		500,000
		D	437,000		548,000
		E	381,000	561,000	700,000
	E	178,000	555,000	658,000	

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	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

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Distribution of Extreme Laboratory Values (cont)

ANALYTE	Patient #	Drug Therapy	Pretreatment	During Therapy	Posttreatment
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 Aminotransferase		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 Aminotransferase		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	50.000		174.000
Gamma-Glutamyl Transpeptidase		D	110.000		146.000
		D	168.000	168.000	201.000
		E	671.000		692.000
		E	225.000	238.000	176.000
		E	72.000	78.000	76.000
		E	193.000		988.000
		E	119.000		247.000
		E	22.000	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	251.000	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
		E	478.000		636.000
		E	446.000	494.000	601.000
Cholesterol		E	4.170	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	1.018		1.036

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		E	1.015		1.042
Urine PH					
		E	5.000	6.000	8.000

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Distribution of Extreme Laboratory Values (cont)

ANALYTE	Patient #	Drug Therapy	Pretreatment	During Therapy	Posttreatment
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	659.000		762.000
		E	476.000		595.000
		E	311.000		473.000
	E	426.000		584.000	
	E	371.000	481.000		
	E	464.000		946.000	
	E	249.000	504.000		

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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

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Distribution of Extreme Laboratory Values (cont)

Placoelet Count (cont)	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
		E	197.000		680.000
		E	254.000		409.000
		E	244.000		525.000
Gamma-Glutamy Transpeptidase					
		D	122.000		323.000
		D	93.000		121.000
		D	162.000		283.000
		D	150.000		179.000
ALANINE AMINOTRANSFERASE					
		D	43.000		101.000
		D	61.000		167.000
		D	146.000		210.000
		E	98.000		135.000
ASPARTATE AMINOTRANSFERASE					
		D	61.000		167.000
		D	146.000		210.000
		e	98.000		135.000
ALKALINE PHOSPHATASE					
		D	137.000		176.000
		D	53.000		176.000
		D	122.000		172.000
BILIRUBIN					
		E	40.700		81.000
HEMATOCRIT					
		D	0.410		0.330
HEMOGLOBIN					
		E	4.750		6.770
		E	4.500		7.270
		E	4.750	4.010	6.460
		E	7.820		6.460
EOSINOPHYL COUNT					

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	D	0.288		1.715
	E	0.510		1.190
	E	(NO PRE)	0.620	1.610
	E	0.000		1.104
LEUKOCYTE COUNT				
	D	7.650		3.310
URIC ACID				
	D	434.000		595.000
	E	399.000	636.000	595.000
	E	345.000		660.000
	E	150.000		0.250
UREA NITROGEN				
	D	21.100		25.700
CALCIUM				
	D	3.700		4.600
PHOSPHORUS				
	D	0.970		1.260
	E	1.000		2.160
GLUCOSE				
	D	9.200		13.100
	E	6.400	1.600	NO POST
CREATINE PHOSPHOKINASE				
	D	310.000		798.000
	D	281.000		1437.000
	E	119.000		800.000
	E	74.000		2890.000
	E	83.000		3380.000
LEUKOCYTES				
	D	4.99		18.25
	E	8.72	13.07	
BANDS				
	D	0		1.03
	D	0.600		1.460
	D	0		1.100
NEUTROPHILS				
	D	7.46		10.78
	D	0.29		11.32
	E	7.03	10.82	
LYMPHOCYTES				
	D	1.83		5.39
	E	4.84	7.27	
	E	0.76		5.98

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

ECG

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

Medical Officer's Overall Comments:**Efficacy:**

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

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

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

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

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

Medical Officer's Conclusions:

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

REVIEW OF PIVOTAL STUDIES:

II. Study B9Z-EW-E002 Synopsis:

Title: Dirithromycin (LY237216) Versus Erythromycin Base in Bronchitis

Study Centers: There were 110 study centers (all in Europe).

Dates of Study: January 1989 through September 1990.

Clinical Phase: Phase 3.

Objectives: To compare the efficacy and safety of dirithromycin (LY237216), 500 mg daily, with erythromycin, 1000 mg daily, for the treatment of secondary bacterial infection of acute bronchitis and acute bacterial exacerbation of chronic bronchitis.

Methodology: Double-blind, randomized, parallel study.

Number of Patients: Secondary Bacterial Infection of Acute Bronchitis:
Dirithromycin: Male 139, Female 128, Total 267;
Erythromycin: Male 133, Female 129, Total 262.
Acute Bacterial Exacerbation of Chronic Bronchitis:
Dirithromycin: Male 194, Female 153 Total 347;
Erythromycin: Male 186, Female 160, Total 346.

Diagnosis and Inclusion Criteria: Diagnosis of secondary bacterial infection of acute bronchitis or acute bacterial exacerbation of chronic bronchitis with cough, productive of purulent sputum, and a chest radiograph free from acute pulmonary infiltrates.

Dosage and Administration: Test Product
Dirithromycin: 500 mg/day, given once daily
CT9198-7A, CT9549-9A, CT0009-9A:
dirithromycin tablets, 250 mg
CT9199-7A, CT9550-9A, CT0010-9A: placebo tablets
Note: Placebo was used to maintain blinding.

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Reference Therapy

Erythromycin: 1000 mg/day, given 4 times daily
CT9200-7A, CT9200-7A/8B, CT9200-8B, CT9200-
9C: erythromycin tablets, 250 mg
CT9201-7A, CT9201-7A/8B, CT9201-8B, CT9201-
9C: placebo tablets.

Duration of Treatment: Dirithromycin: 7 days
Erythromycin: 7 days

Criteria for Evaluation: Efficacy--A complete efficacy analysis was to be performed on patients completing at least 5 days of therapy who had positive pretherapy sputum culture, returned for posttherapy evaluation, and who had a clinical response that could be evaluated.
Safety--All patients were to be evaluated for safety.

Statistical Methods: Chi-squared methodology and appropriate continuous data procedures such as two-sample t-test on ranked data were to be used for analysis of laboratory tests.

Study Design:

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

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

Inclusion Criteria

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

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

Exclusion Criteria

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

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

Dosing Schedule:

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

Evaluation/Procedures:

PROCEDURES FOR EVALUATION OF CLINICAL RESPONSE

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

PROCEDURES FOR EVALUATION OF BACTERIOLOGICAL RESPONSE

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

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

Safety Procedures:

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

LABORATORY PROCEDURES TO EVALUATE SAFETY

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

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

Late-Posttherapy (10-14 Days After Completion of Therapy): Laboratory tests were to be repeated as clinically indicated.

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

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

Terminations:

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

- Pathogen isolated from initial culture was resistant to erythromycin.
- Obvious clinical failure of the study antibiotic at any time during treatment. There was no minimum treatment period. The duration of therapy was left to the clinical judgment of the investigator.
- If, in the investigator's opinion, significant adverse event(s) or significant alteration(s) in a laboratory parameter occurred, the study antibiotic was discontinued.
- If the patient or attending physician requested, or the investigator so decided, the patient was withdrawn from the study and the reason stated on the clinical report form. In addition, Lilly could decide to terminate the study.
- Study-drug identity was unblinded for safety reasons.

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

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

Efficacy Procedures:

CLINICAL RESPONSE DEFINITIONS

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

BACTERIOLOGICAL RESPONSE DEFINITIONS

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

Medical Officer's Comments:

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

Qualification for Efficacy Analysis:

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

Medical Officer's Comments:

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

Statistical Methods:

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

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Investigators:

Study Population

All Patients Consented and/or Randomized

Indication: Secondary Bacterial Infection of Acute Bronchitis

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIBITHROMYCIN	ERYTHROMYCIN	DIBITHROMYCIN	ERYTHROMYCIN
F. R. CRANFIELD/GWENT, WALES	1	0	0	0
R. DASGUPTA/LANCASHIRE, ENGLAND	0	1	0	1
A. W. DAVIES/GWENT, WALES	0	1	0	0
J. HOSIE/GLASGOW, SCOTLAND	0	1	0	0
R. J. CHESWORTH/LANCASHIRE, ENGLAND	1	0	0	0
C. E. LANGAN/GLASGOW, SCOTLAND	8	13	2	4
D. G. WOOD/BANGOR, WALES	3	3	2	1
M. W. NUTCH/REDFREWSHIRE, SCOTLAND	2	2	0	0
M. G. SCOTT/GLASGOW, SCOTLAND	3	0	1	0
H. J. DOWNACHIE/GLASGOW, SCOTLAND	9	3	2	1
A. W. HARRIS/WEST MIDLANDS, ENGLAND	16	25	4	6
D. WALTON/LANCASHIRE, ENGLAND	3	3	0	0
A. LIENER/SCHMAZ/TIROL, AUSTRIA	2	1	0	0
I. THOMULLER/DRAZ, AUSTRIA	8	8	0	1
K. H. MAYER/WELS, AUSTRIA	0	1	0	0
H. DEUNNEKERS/ROTTERDAM, THE NETHERLANDS	2	1	1	0
P. W. FURRING/ROTTERDAM, THE NETHERLANDS	1	0	0	2
C. M. LIMBURG/ROTTERDAM, THE NETHERLANDS	3	2	0	0
L. VAN HOOKY/ROTTERDAM, THE NETHERLANDS	1	1	1	0
R. C. HENDRIKS/ROTTERDAM, THE NETHERLANDS	0	1	0	0
G. T. VAN DE POEL/ROTTERDAM, THE NETHERLANDS	3	3	0	3
J. D. VAN MECHELEN/ROTTERDAM, THE NETHERLANDS	1	1	0	0
J. COOPEN/ROTTERDAM, THE NETHERLANDS	2	1	2	1
D. H. SMETS ROTTERDAM, THE NETHERLANDS	1	0	0	0
H. FERGUSON ROTTERDAM, THE NETHERLANDS	1	5	1	1

(continued)

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

Indication: Secondary Bacterial Infection of Acute Bronchitis

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

(continued)

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

Indication: Secondary Bacterial Infection of Acute Bronchitis

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

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Study Population
All Patients Consented and/or Randomized

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIBITHROMYCIN	ERYTHROMYCIN	DIBITHROMYCIN	ERYTHROMYCIN
J. K. AGARWALA/LANCASHIRE, ENGLAND	2	2	1	0
Z. AHMAD/MANCHESTER, ENGLAND	5	5	0	1
D. ATKINSON/PRESTON, ENGLAND	2	3	0	1
C. BARAN/DACHAU, GERMANY	4	4	2	4
H. BEUMER/UTRECHT, THE NETHERLANDS	16	16	4	4
M. BRENNAN/CUMBRIA, ENGLAND	2	0	0	0
I. CALDWELL/LANCASHIRE, ENGLAND	6	6	2	2
F. R. CRANFIELD/GWENT, WALES	29	30	9	10
R. DASGUPTA/LANCASHIRE, ENGLAND	9	7	2	1
A. W. DAVIES/GWENT, WALES	10	8	3	2
P. H. DEVICHAND/DYFED, WALES	28	28	6	8
P. M. DEVICHAND/WEST GLAMORGAN, WALES	2	1	2	0
K. K. GARG/LANCASHIRE, ENGLAND	12	12	3	8
J. J. HAMIL/LEICESTER, ENGLAND	2	4	1	3
I. HAQUE/MANCHESTER, ENGLAND	2	4	0	1
D. C. HARGREAVES/SUSSEX, ENGLAND	6	6	2	2
P. R. INGLIS/LANCASHIRE, ENGLAND	12	11	5	3
R. KHANCHANDANI/LUTON BEDS, ENGLAND	2	2	0	0
K. KORLIPARA/LANCASHIRE, ENGLAND	1	0	0	0
F. LUSTMAN NEWCASTLE-UPON-TYNE, ENGLAND	3	4	1	1
P. MAKSYMZYK/SOMERSET, U.K.	5	6	2	0
G. MECHIE/LANCASHIRE, ENGLAND	12	10	8	2
T. O'CONNOR/LANCASHIRE, ENGLAND	2	4	0	0
N. PINHEIRO/LANCASHIRE, ENGLAND	16	18	1	7
R. M. RAJAPAKSA/MILTON KEYNES, ENGLAND	6	7	1	3
J. REPPER/ABERDEEN, SCOTLAND	0	2	0	0
C. L. SAIT SWANSEA, WALES	1	0	0	0
F. SAUL LANCASHIRE, ENGLAND	2	2	0	1
R. SHORTEN DACHAU, GERMANY	3	1	1	2
K. WHITING MANCHESTER, ENGLAND	4	4	1	0
L. ZACHARIAH BUCKS, ENGLAND	17	30	10	11
J. HESSE GLASGOW, SCOTLAND	4	5	1	4

Continued

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

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

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

continued

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

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

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

Medical Officer's Comments:

The Medical Officer concurs with the applicant's evaluability.

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

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

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

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

Medical Officer's Comments:

The Medical Officer concurs with the applicant's analysis.

Patient Demographics:

All Patients-Secondary Bacterial Infection of Acute Bronchitis

Age Ranges by Sex
All Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

AGE RANGES	DIRITHRAMYCIN			ERYTHRAMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
	N = 128 n (%)	N = 133 n (%)	N = 267 n (%)	N = 129 n (%)	N = 133 n (%)	N = 262 n (%)
16-<25	9 (7.06)	18 (12.98)	27 (10.18)	11 (8.53)	15 (11.38)	26 (9.90)
25-<45	58 (45.31)	58 (42.79)	116 (43.43)	55 (42.68)	66 (49.68)	121 (46.20)
45-<65	59 (46.18)	54 (38.89)	113 (42.38)	57 (44.28)	46 (34.68)	103 (39.18)
65+	2 (1.60)	9 (6.59)	11 (4.18)	6 (4.70)	6 (4.58)	12 (4.63)

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

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHRAMYCIN			ERYTHRAMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	128	139	267	129	133	262
MEAN AGE	44.48	42.48	43.44	44.65	42.61	43.61
STD DEV	13.32	14.74	14.09	13.99	14.21	14.11
MEDIAN AGE	43.00	42.00	43.00	44.00	42.00	43.00
MINIMUM AGE	19.00	17.00	17.00	18.00	18.00	18.00
MAXIMUM AGE	75.00	71.00	75.00	86.00	72.00	86.00

Origin by Therapy Group
All Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN		ERYTHROMYCIN	
	n	(%)	n	(%)
ORIGIN				
CAUCASIAN	261	(97.88)	256	(97.78)
BLACK	0		4	(1.58)
ASIAN	2	(0.78)	2	(0.86)
OTHER	4	(1.58)	0	

Height and Weight at Admission
All Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	267	0	168.57	10	124	211	267	0	71.23	14	42	123
ERYTHROMYCIN	267	1	168.35	9	138	190	260	2	71.09	14	45	127

Evaluable Patients - Secondary Bacterial Infection of Acute Bronchitis

Age Ranges by Sex
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

AGE RANGES	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
	N = 33	N = 39	N = 72	N = 26	N = 37	N = 63
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
16-425	3 (9.1%)	3 (7.7%)	6 (8.3%)	2 (7.7%)	2 (5.4%)	4 (6.3%)
25-445	11 (33.3%)	16 (41.0%)	27 (37.5%)	13 (50.0%)	18 (48.6%)	31 (49.2%)
45-465	19 (57.6%)	18 (46.2%)	37 (51.4%)	10 (38.5%)	15 (40.5%)	25 (39.7%)
65+	0	2 (5.1%)	2 (2.8%)	1 (3.8%)	2 (5.4%)	3 (4.8%)

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

Indication: Secondary Bacterial Infection of Acute Bronchitis

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	33	39	72	26	37	63
MEAN AGE	45.24	43.56	44.33	42.88	45.00	44.13
STD DEV	14.12	13.97	13.96	13.37	13.16	13.18
MEDIAN AGE	49.00	46.00	46.00	43.50	44.00	44.00
MINIMUM AGE	18.00	19.00	18.00	23.00	18.00	18.00
MAXIMUM AGE	63.00	65.00	65.00	65.00	65.00	65.00

Origin By Therapy Group
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

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

Height and Weight at Admission
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	72	0	168.70	12	124	211	72	0	70.37	15	42	120
ERYTHROMYCIN	63	0	168.66	10	138	190	63	0	71.60	17	45	127

All Patients-Acute Bacterial Exacerbation of Chronic Bronchitis

Age Ranges by Sex
All Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

AGE RANGES	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
	<u>N = 153</u> n (%)	<u>N = 194</u> n (%)	<u>N = 347</u> n (%)	<u>N = 160</u> n (%)	<u>N = 186</u> n (%)	<u>N = 346</u> n (%)
16-25	2 (1.3%)	6 (3.1%)	8 (2.3%)	8 (5.0%)	5 (2.7%)	13 (3.8%)
25-45	35 (22.9%)	41 (21.1%)	76 (21.9%)	32 (20.0%)	41 (22.0%)	73 (21.1%)
45-65	104 (68.0%)	135 (69.6%)	239 (68.9%)	112 (70.0%)	135 (72.6%)	247 (71.4%)
65+	12 (7.8%)	12 (6.2%)	24 (6.9%)	8 (5.0%)	5 (2.7%)	13 (3.8%)

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

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	153	194	347	160	186	346
MEAN AGE	51.54	52.01	51.80	50.27	51.55	50.96
STD DEV	11.22	11.73	11.49	12.92	11.33	12.09
MEDIAN AGE	54.00	55.00	55.00	52.50	54.00	54.00
MINIMUM AGE	18.00	20.00	18.00	18.00	16.00	16.00
MAXIMUM AGE	74.00	75.00	75.00	77.00	67.00	77.00

Origin by Therapy Group
All Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	DIRITHROMYCIN		ERYTHROMYCIN	
	N = 347		N = 345	
	n	(%)	n	(%)
ORIGIN				
CAUCASIAN	340	(98.00)	333	(96.23)
BLACK	3	(0.87)	5	(1.45)
ASIAN	4	(1.13)	6	(1.72)

Height and Weight at Admission
All Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	347	0	167.26	9	143	189	347	0	70.74	13	37	132
ERYTHROMYCIN	345	1	167.32	11	108	203	345	1	69.61	14	38	127

Origin By Therapy Group
Evaluable Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

ORIGIN	DIRITHROMYCIN N = 89		ERYTHROMYCIN N = 113	
	n	(%)	n	(%)
CAUCASIAN	66	(96.6%)	110	(97.3%)
BLACK	3	(3.4%)	2	(1.8%)
ASIAN	0		2	(1.8%)

Height and Weight at Admission
Evaluable Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

THERAPY	HEIGHT IN CM						HEIGHT IN IN							
	N	UNK	MEAN	STD	DEV	MIN	MAX	N	UNK	MEAN	STD	DEV	MIN	MAX
DIRITHROMYCIN	89	0	168.50	10	150	189	89	0	72.66	14	47	131		
ERYTHROMYCIN	113	0	167.95	10	150	203	113	0	71.85	15	40	127		

Drug Administration:

All Patients

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

	<u>DIBITHROMYCIN</u> N = 614 DAYS	<u>ERYTHROMYCIN</u> N = 608 DAYS
NUMBER OF PATIENTS	607	599
MEAN DURATION EXPOSURE	7.4	7.4
MINIMUM EXPOSURE DAYS	1	1
MAXIMUM EXPOSURE DAYS	11	12
PATIENTS WITH INCOMPLETE DATA	7	9

Summary of Exposure to Study-Drugs
All Patients

	<u>DIBITHROMYCIN</u> N = 614 n		<u>ERYTHROMYCIN</u> N = 608 n	
DAYS OF THERAPY				
PATIENTS WITH				
INCOMPLETE DATA	7	1.1%	9	1.5%
1	1	0.16%	1	0.16%
2	2	0.33%	4	0.66%
3	0		7	1.16%
4	10	1.63%	4	0.66%
5	4	0.65%	7	1.16%
6	8	1.3%	3	0.5%
7	283	46.1%	255	42.1%
8	197	32.1%	219	35.9%
9	14	2.3%	1	0.16%
10	4	0.65%	1	0.16%
11	1	0.16%	0	0%
12	0	0%	1	0.16%

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**Evaluable Patients-Secondary Bacterial Infection of Acute
Bronchitis:**

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

Indication: Secondary Bacterial Infection of Acute Bronchitis

	<u>DIRITHROMYCIN</u> <u>N = 72</u> DAYS	<u>ERYTHROMYCIN</u> <u>N = 63</u> DAYS
NUMBER OF PATIENTS	72	63
MEAN DURATION EXPOSURE	7.5	7.4
MINIMUM EXPOSURE DAYS	6	7
MAXIMUM EXPOSURE DAYS	9	9
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

DAYS OF THERAPY	<u>DIRITHROMYCIN</u> <u>N = 72</u>		<u>ERYTHROMYCIN</u> <u>N = 63</u>	
	n	%	n	%
6	1	1.4%	0	
7	37	51.4%	19	30.2%
8	33	45.8%	23	36.5%
9	1	1.4%	1	1.6%

Medical Officer's Comments:

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

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**Evaluable Patients-Acute Bacterial Exacerbation of Chronic
Bronchitis:**

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

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

	<u>DIRLITHROMYCIN</u>	<u>ERYTHROMYCIN</u>
	<u>N = 89</u>	<u>N = 113</u>
	<u>DAYS</u>	<u>DAYS</u>
NUMBER OF PATIENTS	89	113
MEAN DURATION EXPOSURE	7.5	7.5
MINIMUM EXPOSURE DAYS	4	2
MAXIMUM EXPOSURE DAYS	9	10
PATIENTS WITH INCOMPLETE DATA	0	0

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Summary of Exposure to Study Drugs
Evaluable Patients

Indication: Acute Bacterial, Exacerbation of Chronic Bronchitis

DAYS OF THERAPY	DIRITHROMYCIN		ERYTHROMYCIN	
	N = 82		N = 111	
	n	(%)	n	(%)
2	0		1	(0.9%)
4	1	(1.2%)	0	
5	3		1	(0.9%)
7	42	(47.2%)	48	(42.5%)
8	45	(50.6%)	59	(52.2%)
9	1	(1.1%)	3	(2.7%)
10	0		1	(0.9%)

Medical Officer's Comments:

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

Unevaluable Patients

Reasons Unevaluable Summary
All Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis

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

Medical Officer's Comments

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

Reasons Unevaluable
All Patients

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

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

Medical Officer's Comments

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

**Efficacy Evaluation-Secondary Bacterial Infection of Acute
Bronchitis:**

Clinical Response-Secondary Bacterial Infection of Acute Bronchitis

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

**Clinical Response
All Evaluable Patients Posttherapy**

Indication: Secondary Bacterial Infection of Acute Bronchitis

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

Medical Officer's Comments:

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

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

Clinical Response by Pathogen
All Evaluable Dirithromycin-Treated Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis
Posttherapy

PATHOGENS	CURE		IMPROVEMENT		RELAPSE		FAILURE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n
STR PNEUMONIAE	11	(39.2%)	15	(53.5%)	0	0	2	(7.1%)	28
H INFLUENZAE	11	(44.0%)	11	(44.0%)	2	(8.0%)	1	(4.0%)	25
H PARAINFLUENZAE	3	(42.9%)	4	(57.1%)	0	0	0	0	7
MULTIPLE ORGANISMS*	3	(50.0%)	3	(50.0%)	0	0	0	0	6
M CATARRHALIS	2	(66.7%)	1	(33.3%)	0	0	0	0	3
ST AUREUS	1	(50.0%)	1	(50.0%)	0	0	0	0	2
STR GRP A	1	(100.0%)	0	0	0	0	0	0	1

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

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

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

N/A - Presumed Eliminated

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

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

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

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

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

N/A - Presumed Eliminated

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

Clinical Response
All Evaluable Patients Late-Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

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

Medical Officer's Comments:

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

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

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

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

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

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

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

N/A - Presumed Eliminated

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

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

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

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

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

N/A - Presumed Eliminated

Bacteriologic Response-Secondary Bacterial Infection of Acute Bronchitis

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

Bacteriological Response
All Evaluable Patients Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

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

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

Bacteriologic Response by Pathogen
All Evaluable Dirithromycin-Treated Patients Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

PATHOGEN ELIMINATED	PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE SAME, RESISTANCE		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL n
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	

TABLE 1

S. PNEUMONIAE	10	(12.1%)	10	(56.1%)	0	0	2	(16.5%)	1	(3.2%)	31
H. INFLUENZAE	8	(27.6%)	16	(55.2%)	0	1	(3.4%)	0	4	(13.8%)	29
H. PARAINFLUENZAE	3	(37.5%)	3	(37.5%)	1	(12.5%)	0	1	(12.5%)	0	8
M. CATARRHALIS	1	(16.7%)	5	(83.3%)	0	0	0	0	0	0	6
S. PNEUMONIAE	0	0	1	(100.0%)	0	0	0	0	0	0	1
S. PNEUMONIAE	0	0	1	(100.0%)	0	0	0	0	0	0	1

Bacteriologic Response by Pathogen
All Evaluable Erythromycin-Treated Patients Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

PATHOGEN	PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL n
	n	(%)	n	(%)	n	(%)	n	(%)	
H. INFLUENZAE	7	(24.1%)	18	(62.1%)	2	(6.9%)	1	(3.4%)	29
S. PNEUMONIAE	6	(25.0%)	11	(47.8%)	2	(8.7%)	2	(8.7%)	23
H. PARAINFLUENZAE	4	(57.1%)	3	(60.0%)	0	0	0	0	7
ST. AUREUS	1	(20.0%)	4	(80.0%)	0	0	0	0	5
M. CATARRHALIS	2	(40.0%)	3	(60.0%)	0	0	0	0	5

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

Bacteriological Response
All Evaluable Patients Late-Posttherapy

Indication: Secondary Bacterial Infection of Acute Bronchitis

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

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

Bacteriological Response by Pathogen
All Evaluable Dirithromycin-Treated Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis
Late-Posttherapy

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

Bacteriological Response by Pathogen
All Evaluable Erythromycin-Treated Patients

Indication: Secondary Bacterial Infection of Acute Bronchitis
Late-Posttherapy

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

Efficacy Evaluation- Acute Bacterial Exacerbation of Chronic Bronchitis

Clinical Response- Acute Exacerbation of Chronic Bronchitis

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

Clinical Response
All Evaluable Patients Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

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

Medical Officer's Comments:

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

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

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

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

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

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

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

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

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

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

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

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

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

Clinical Response
All Evaluable Patients Late-Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

RESPONSE	<u>DIRITHROMYCIN</u>		<u>ERYTHROMYCIN</u>	
	<u>N = 76</u>		<u>N = 100</u>	
	n	(%)	n	(%)
CURE	64	(84.2%)	80	(80.0%)
IMPROVEMENT	12	(14.5%)	15	(15.0%)
RELAPSE	1	(1.3%)	5	(5.0%)

Medical Officer's Comments:

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

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

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

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

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

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

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

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

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

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

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

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

Bacteriologic Response-Acute Bacterial Exacerbation of Chronic Bronchitis

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

Bacteriologic Response
All Evaluable Patients Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

RESPONSE	DIRITHROMYCIN		ERYTHROMYCIN	
	n	(%)	n	(%)
PATHOGEN ELIMINATED	24	(27.3%)	36	(42.7%)
PRESUMED ERADICATED	43	(48.9%)	49	(58.5%)
RECURRENCE SAME	4	(4.5%)	12	(14.3%)
RECURRENCE SAME, RESISTANCE	0		2	(2.4%)
RECURRENCE NEW	9	(10.2%)	5	(5.9%)
FAILED TO ELIMINATE	8	(9.1%)	6	(7.1%)

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

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

PATHOGEN	PRESUMED ERADICATION		RECURRENCE SAME		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL n
	n	(%)	n	(%)	n	(%)	n	(%)	
PATIENT									
H INFLUENZAE	11	(25.6%)	22	(51.2%)	3	(7.0%)	1	(2.3%)	43
STR PNEUMONIAE	13	(38.2%)	13	(26.7%)	2	(3.3%)	4	(6.7%)	34
M CATARRHALIS	5	(31.3%)	9	(56.3%)	1	(6.3%)	1	(8.3%)	16
ST AUREUS	2	(28.6%)	3	(42.9%)	0	0	2	(28.6%)	7
STR GRP F	1	(33.3%)	2	(66.7%)	0	0	0	0	3
STR GRP A	1	(50.0%)	1	(50.0%)	0	0	0	0	2

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Bacteriologic Response by Pathogen
All Evaluable Erythromycin-Treated Patients Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

PATHOGEN	PRESUMED ELIMINATED		RECURRENCE SAME		RECURRENCE SAME, RESISTANCE		RECURRENCE NEW		FAILED TO ELIMINATE		TOTAL n	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)		
H. INFLUENZAE	14	(30.4%)	16	(34.8%)	6	(15.7%)	2	(4.3%)	0	6	(13.0%)	46
STR. PNEUMONIAE	12	(37.5%)	13	(40.6%)	3	(12.5%)	0		3	(9.4%)	0	32
M. CATARRHALIS	10	(42.7%)	14	(58.3%)	0		0		0		0	24
ST. AUREUS	1	(12.5%)	7	(87.5%)	0		0		0		0	8
H. PARAINFLUENZAE	1	(14.3%)	4	(57.1%)	1	(16.6%)	0		1	(14.3%)	0	7
STREPTOCOCCUS SP	2	(100.0%)	0	0	0		0		0		0	2
STR. GRP. A	1	(33.3%)	1	(33.3%)	0		0		1	(33.3%)	0	3

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

Bacteriological Response
All Evaluable Patients Late-Posttherapy

Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

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

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

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

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

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

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

SUSCEPTIBILITY RESULTS

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

Bronchitis

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

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

Bronchitis

PATHOGEN	ANTIMICROBIAL							
	DIRITHROMYCIN			TOTAL N	ERYTHROMYCIN			TOTAL N
	SUSCEPTIBLE (ZONE >= 17) N	INTERMEDIATE (ZONE = 16) N	RESISTANT (ZONE <= 15) N		SUSCEPTIBLE (ZONE >= 18) N	INTERMEDIATE (17 >= ZONE >= 14) N	RESISTANT (ZONE <= 13) N	
ACINETOBACTER SP	1		1	2	1		1	2
B. ATARRHALIS	31			31	31			31
CITROBACTER SP			1	1			1	1
F. AERUOMERANS			1	1		1		1
E. COLI			2	2			2	2
H. INFLUENZAE	75	17	30	122	86	30	6	122
H. PARAINFLUENZAE	19	2	1	22	20	2		22
K. OXYTOXA			1	1			1	1
M. MORGANII			1	1			1	1
MR. VULGARIS			1	1			1	1
PROTEUS SP			9	9			9	9
PS. ALRUGINOSA			3	3			3	3
PS. PUTIDA			1	1			1	1
PSEUDOMONAS SP			2	2			2	2
SERRATIA LIQUEFACI			1	1			1	1
ST. AUREUS	17		1	18	17		1	18
STR. GRP A	4			4	4			4
STR. GRP B	1			1	1			1
STR. PNEUMONIAE	71		1	72	71	1		72
STREPTOCOCCUS SP	1			1	1			1

Medical Officer's Comments:

About 25.5% (66/259) of the *H. influenzae* isolates were resistant to dirithromycin.

CONCOMITANT MEDICATIONS:

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

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

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

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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

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

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

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

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

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

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

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

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

	DIBITHROMYCIN		ERYTHROMYCIN		P VALUE
	N = 514		N = 508		
	n	(%)	n	(%)	
PATIENTS WITH					
AT LEAST ONE EVENT	37	(6.0%)	42	(6.9%)	0.531
PATIENTS WITH NO EVENT	577	(94.0%)	566	(93.1%)	0.531
EVENT CLASSIFICATION TERM					
LUNG DISORDER	15	(2.4%)	12	(2.0%)	0.577
DYSPNEA	12	(2.0%)	7	(1.2%)	0.257
ASTHMA	7	(1.1%)	17	(2.8%)	0.037
HYPERVENTILATION	6	(1.0%)	11	(1.8%)	0.224
PHARYNGITIS	3	(0.5%)	3	(0.5%)	0.99
CARCINOMA OF LUNG	1	(0.2%)	1	(0.2%)	0.994
BRONCHITIS	0		1	(0.2%)	0.315
COUGH INCREASED	0		1	(0.2%)	0.315
LARYNGITIS	0		1	(0.2%)	0.315
RHINITIS	0		1	(0.2%)	0.315

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

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

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Patients Who Died or Discontinued Therapy Due to Adverse Events:

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

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

Therapy: Dirithromycin

INV	PATIENT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT
012		1	59	FEMALE	CAUCASIAN	4	DIARRHOEA
012		1	50	MALE	CAUCASIAN	6	NAUSEA
034		1	60	FEMALE	CAUCASIAN	4	NAUSEA
050		1	44	MALE	CAUCASIAN	4	LOOSE AND FREQUENT BOWEL MOTIONS
601		1	62	MALE	CAUCASIAN	5	DYSPEPSIA
801		1	55	FEMALE	CAUCASIAN	4	VOMITING
901		1	39	FEMALE	CAUCASIAN	6	DIZZINESS
801		1	21	FEMALE	CAUCASIAN	1	DIARRHOEA
881		1	56	FEMALE	CAUCASIAN	5	ABDOMINAL PAIN

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Therapy: Erythromycin

INV	PATIENT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT
016		1	51	FEMALE	CAUCASIAN	7	HOSPITALISED BY B BLOCKER EYE-DROPS
035		1	48	FEMALE	CAUCASIAN	5	DIARRHOEA
037		1	64	FEMALE	CAUCASIAN	2	DIARRHOEA
050		1	64	FEMALE	CAUCASIAN	4	WIND VOMITING AND UPPER ABD PAIN
050		1	57	FEMALE	CAUCASIAN	2	FEELS DREADFUL POUNING HEAD
050		1	57	FEMALE	CAUCASIAN	4	SEVERE DYSPEPSIA
050		1	60	FEMALE	CAUCASIAN	3	SICK EMPTY FEELING IN STOMACH
053		1	39	FEMALE	CAUCASIAN	2	NAUSEA, VOMITING
055		1	60	FEMALE	CAUCASIAN	4	PATIENT FELT NAUSEA & GEN. UNWELL
104		1	52	MALE	CAUCASIAN	5	KIDNEY PAIN
802		1	26	FEMALE	CAUCASIAN	3	NAUSEA AND VOMITING
805		1	26	FEMALE	CAUCASIAN	3	ABDOMINAL PAIN
850		1	37	FEMALE	CAUCASIAN	6	ABDOMINAL PAIN
875		1	63	MALE	CAUCASIAN	7	DEBILITATION OF CONDITION BRONCHITIS

Clinical Laboratory Evaluations:

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

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

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

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

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E002 Bronchitis

Distribution of Extreme Laboratory Values

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

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

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

Overall Summary of Pivotal Studies

Clinical Response:

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

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

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

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

Overall Summary

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

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

Clinical Response Summary
E002
Secondary Bacterial Infection

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

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

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

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

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

Bacteriologic Response Summary
E002 Secondary Bacterial Infection

Pathogen	Posttherapy								Late-Posttherapy							
	Doxithromycin				Erythromycin				Doxithromycin				Erythromycin			
	Favorable N	Unfavorable N	Favorable %	Unfavorable %	Favorable N	Unfavorable N	Favorable %	Unfavorable %	Favorable N	Unfavorable N	Favorable %	Unfavorable %	Favorable N	Unfavorable N	Favorable %	Unfavorable %
<i>M. catarrhalis</i>	6	0	100	0	5	0	100	0	6	0	100	0	5	0	100	0
<i>H. influenzae</i>	24	5	82.8	17.2	25	4	86.2	13.8	26	0	100	0	23	2	88.5	11.5
<i>Str. pneumoniae</i>	28	3	90.3	9.7	17	6	73.9	26.1	27	1	96.4	3.6	19	3	86.3	13.7

MEDICAL OFFICER'S CONCLUSIONS:

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

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

MEDICAL OFFICER'S RECOMMENDATIONS:

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

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

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

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

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

REVIEW OF PIVOTAL STUDIES:

I. Study B9Z-MC-AQAB Synopsis:

Title: Dirithromycin versus Erythromycin Base in Bacterial Pneumonia.

Study Centers: There were 93 active study centers.

Dates of Study: October 7, 1988 - May 31, 1991

Clinical Phase: Phase 2-3

Objectives: To compare dirithromycin with erythromycin base for effectiveness and safety in the treatment of bacterial pneumonia.

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

Number of Subjects: Dirithromycin: Male 130, Female 130, Total 260.
Erythromycin: Male 137, Female 120, Total 257.

Diagnosis and Inclusion Criteria: Pneumonia with confirmed susceptible bacterial etiology or appropriate serology for mycoplasma or legionella.

Dosage and Administration:

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, CT9966: erythromycin base tablets, 250 mg
CT9370, CT9967: placebo tablets
NOTE: Placebo was used to maintain blinding.

Duration of Treatment: Dirithromycin: 10-14 days
Erythromycin Base: 10-14 days

Criteria for Evaluation: Efficacy--A complete efficacy evaluation was to be performed on patients completing at least 10 days of therapy who had positive chest x-ray and sputum culture or serology, returned for the during-therapy, posttherapy and the late-posttherapy clinical evaluation (late-posttherapy was required if chest x-ray had not resolved at posttherapy evaluation), and for whom the symptomatic response could be evaluated.

Safety--All patients were to be evaluated for safety.

Statistical Methods: Chi-square tests were to be used for response rates and adverse events. Appropriate continuous data procedures were to be used for analysis of laboratory data. The Type I error was set at 0.05.

Study Design:

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

Inclusion Criteria

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

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

Exclusion Criteria

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

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

Dosing Schedule:

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

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

Evaluation/Procedures:

PROCEDURES FOR EVALUATION OF CLINICAL RESPONSE

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

PROCEDURES FOR EVALUATION OF BACTERIOLOGIC RESPONSE

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

*Erythromycin susceptibility defined as ≥ 18 mm zone size; ≤ 0.5 $\mu\text{g/mL}$ MIC.

**Diagnosis was supported by results showing ≥ 25 pmn's/hpf and ≤ 10 epithelial cells/hpf.

Safety Procedures:

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

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

LABORATORY TESTS TO EVALUATE SAFETY

<u>Study Visit</u>	<u>Procedure</u>																																																
Pretherapy (Within 24 Hours of Receiving the First Dose):	<table border="0"> <tr> <td><u>Hematology</u></td> <td><u>Blood Chemistry</u></td> <td><u>Urinalysis</u></td> </tr> <tr> <td>Hemoglobin</td> <td>Phosphorus</td> <td>Appearance</td> </tr> <tr> <td>Hematocrit</td> <td>Calcium</td> <td>Specific Gravity</td> </tr> <tr> <td>RBC Count</td> <td>Glucose</td> <td>pH</td> </tr> <tr> <td>MCV</td> <td>Cholesterol</td> <td>Protein</td> </tr> <tr> <td>MCH</td> <td>Total Bilirubin</td> <td>Glucose</td> </tr> <tr> <td>MCHC</td> <td>Alkaline Phos.</td> <td>Ketones</td> </tr> <tr> <td>WBC Count</td> <td>GGT</td> <td>Bilirubin</td> </tr> <tr> <td>Differential Count</td> <td>ALT (SGPT)</td> <td>Urobilinogen</td> </tr> <tr> <td>Platelet Count</td> <td>AST (SGOT)</td> <td>Blood</td> </tr> <tr> <td>Morphology</td> <td>Urea Nitrogen</td> <td>Nitrite</td> </tr> <tr> <td></td> <td>-Creatinine</td> <td>Leukocyte Esterase</td> </tr> <tr> <td></td> <td>Uric Acid</td> <td>Microscopic - WBC</td> </tr> <tr> <td></td> <td>Total Protein</td> <td>RBC</td> </tr> <tr> <td></td> <td>Albumin</td> <td>Casts</td> </tr> <tr> <td></td> <td>Creatine Kinase*</td> <td></td> </tr> </table>	<u>Hematology</u>	<u>Blood Chemistry</u>	<u>Urinalysis</u>	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*	
<u>Hematology</u>	<u>Blood Chemistry</u>	<u>Urinalysis</u>																																															
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	Albumin	Casts																																															
	Creatine Kinase*																																																
During Therapy	Laboratory tests were to be repeated as clinically indicated.																																																
Urine samples (Days 3-5):	were to be assayed for presence of antimicrobial activity.																																																
Posttherapy (3-5 Days After Completion of Therapy):	Pretherapy tests were to be repeated. If any abnormal values were found, the tests were to be repeated until values returned to normal or were explained.																																																
Late-posttherapy (2-3 Weeks After Completion of Therapy):	Laboratory tests were to be repeated during Phase 2. Laboratory tests were to be repeated during Phase 3, if clinically indicated.																																																

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

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

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

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

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

Terminations:

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

Pathogen isolated from initial culture was resistant to erythromycin.

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

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

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

Study drug identity was unblinded for safety reasons.

Pretherapy serum creatinine $\geq 133 \mu\text{mol/L}$ (1.5 mg/dL).

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

Efficacy Procedures:

SYMPTOMATIC RESPONSE DEFINITIONS

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

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

BACTERIOLOGIC RESPONSE DEFINITIONS
INDICATION: PNEUMONIA

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

Medical Officer's Comments:

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

Qualification for Efficacy Analysis:

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

TITERS

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

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

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

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

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

LEGIONELLA FLUORESCENT ANTIBODY TEST (IFA* TEST BY ZEUS)

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

Statistical Methods:

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

Investigators:

Study Population
 All Patients Consented and/or Randomized
 Indication Pneumonia

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

(continued)

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DYNABAC

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

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

(continued)

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

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

Medical Officer's Comments:

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

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

Patient disposition was as follows:

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

Patient Demographics:

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

All Patients

Age by Sex - Ranges
 All Patients
 Indication: Pneumonia

AGE RANGES	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
	(N = 130)	(N = 130)	(N = 260)	(N = 120)	(N = 137)	(N = 257)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
12-16	4 (3.1%)	1 (0.8%)	5 (1.9%)	1 (0.8%)	3 (2.2%)	4 (1.6%)
16-25	10 (7.7%)	20 (15.4%)	30 (11.5%)	14 (11.7%)	27 (19.7%)	41 (16.0%)
25-45	59 (45.4%)	68 (52.3%)	127 (48.8%)	52 (43.3%)	54 (39.4%)	106 (41.2%)
45-65	37 (28.5%)	22 (16.9%)	59 (22.7%)	32 (26.7%)	36 (26.3%)	68 (26.5%)
≥65	20 (15.4%)	19 (14.6%)	39 (15.0%)	21 (17.5%)	17 (12.4%)	38 (14.8%)

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

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	130	130	260	120	137	257
MEAN AGE	45.23	42.70	43.97	45.32	42.51	43.82
STD DEV	17.87	18.61	18.25	17.92	18.85	18.44
MEDIAN A	40.92	38.33	39.76	42.85	38.60	41.37
MINIMUM AGE	13.89	13.30	13.30	14.89	12.83	12.83
MAXIMUM AGE	84.51	92.90	92.90	89.24	92.97	92.97

Origin by Therapy Group
 All Patients
 Indication: Pneumonia

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

Height and Weight at Admission
All Patients
Indication: Pneumonia

THERAPY	N	UNK	HEIGHT IN CM				N	UNK	WEIGHT IN KG			
			MEAN	STD	MIN	MAX			MEAN	STD	MIN	MAX
DIRITHROMYCIN	259	1	169.26	11	140	196	258	2	73.10	19	37	168
ERYTHROMYCIN	253	4	169.28	11	122	193	252	5	74.53	19	38	149

EVALUABLE PATIENTS:

Age Ranges by Sex
Evaluable Patients
Indication: Pneumonia

AGE RANGES	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE (N = 21)	MALE (N = 121)	TOTAL (N = 90)	FEMALE (N = 31)	MALE (N = 49)	TOTAL (N = 80)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
12-16	1 (2.0%)	0	1 (1.1%)	1 (2.9%)	1 (2.0%)	2 (2.4%)
16-25	5 (9.8%)	7 (17.9%)	12 (13.3%)	5 (14.7%)	15 (20.6%)	20 (24.1%)
25-45	23 (45.1%)	21 (53.8%)	44 (48.9%)	15 (44.1%)	19 (38.8%)	34 (41.0%)
45-65	16 (31.4%)	5 (12.8%)	21 (23.3%)	7 (20.6%)	10 (20.4%)	17 (20.5%)
65+	6 (11.8%)	6 (15.4%)	12 (13.3%)	6 (17.5%)	4 (8.2%)	10 (12.0%)

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

	<u>DIRITHROMYCIN</u>			<u>ERYTHROMYCIN</u>		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	51	39	90	34	49	83
MEAN AGE	44.40	42.32	43.50	44.91	38.48	41.11
STD DEV	16.91	19.15	17.84	12.01	19.44	19.41
MEDIAN AGE	40.44	39.11	39.56	43.65	35.25	39.07
MINIMUM AGE	14.99	19.88	14.99	14.89	12.83	12.83
MAXIMUM AGE	84.51	92.90	92.90	89.24	92.97	92.97

Origin By Therapy Group
 Evaluable Patients
 Indication: Pneumonia

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

Height and Weight at Admission
 Evaluable Patients
 Indication: Pneumonia

THERAPY	N	HEIGHT IN CM					WEIGHT IN KG					
		UNK	MEAN	STD DEV	MIN	MAX	N	UNK	MEAN	STD DEV	MIN	MAX
DIRITHROMYCIN	90	0	168.89	10	146	196	90	0	70.97	18	48	168
ERYTHROMYCIN	81	0	170.10	10	152	193	82	1	73.32	18	39	132

Drug Administration:

All Patients

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

	DIRITHROMYCIN N = 260	ERYTHROMYCIN N = 257
	DAYS	DAYS
NUMBER OF PATIENTS	248	249
MEAN DURATION EXPOSURE	12.8	12.5
MINIMUM EXPOSURE DAYS	1	1
MAXIMUM EXPOSURE DAYS	21	30
PATIENTS WITH INCOMPLETE DATA	12	8

Summary of Exposure to Study Drugs
 All Patients

Indication Pneumonia

DIRITHROMYCIN		ERYTHROMYCIN	
N = 260		N = 252	
n	(%)	n	(%)

DAYS OF THERAPY

DAYS OF THERAPY	DIRITHROMYCIN		ERYTHROMYCIN	
	n	(%)	n	(%)
PATIENTS WITH INCOMPLETE DATA				
1	12	(4.6%)	8	(3.1%)
2	1	(0.4%)	3	(1.2%)
3	9	(3.5%)	8	(3.1%)
4	6	(2.3%)	4	(1.6%)
5	6	(2.3%)	12	(4.7%)
6	4	(1.5%)	6	(2.3%)
7	7	(2.7%)	5	(1.9%)
8	4	(1.5%)	4	(1.6%)
9	2	(0.8%)	1	(0.4%)
10	0		5	(2.0%)
11	17	(6.5%)	18	(7.0%)
12	11	(4.2%)	10	(3.9%)
13	7	(2.7%)	4	(1.6%)
14	7	(2.7%)	3	(1.2%)
15	52	(20.0%)	53	(20.6%)
16	88	(33.9%)	81	(31.5%)
17	19	(7.3%)	21	(8.2%)
18	3	(1.2%)	2	(0.8%)
19	2	(0.8%)	1	(0.4%)
20	1	(0.4%)	3	(1.2%)
21	1	(0.4%)	3	(1.2%)
22	1	(0.4%)	0	
23	0		1	(0.4%)
24	0		1	(0.4%)

Evaluable Patients

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

	<u>DIRITHROMYCIN</u>	<u>ERYTHROMYCIN</u>
	<i>N</i> = 90	<i>N</i> = 83
	DAYS	DAYS
NUMBER OF PATIENTS	90	83
MEAN DURATION EXPOSURE	14.3	14.5
MINIMUM EXPOSURE DAYS	7	10
MAXIMUM EXPOSURE DAYS	21	20
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
 Evaluable Patients
 Indication Pneumonia

DAYS OF THERAPY	DIRITHROMYCIN		ERYTHROMYCIN	
	<u>N = 90</u>		<u>N = 81</u>	
	n	(%)	n	(%)
7	1	(1.1%)	0	
10	7	(7.8%)	5	(6.0%)
11	2	(2.2%)	3	(3.6%)
12	2	(2.2%)	2	(2.4%)
13	3	(3.3%)	1	(1.2%)
14	23	(25.6%)	25	(30.1%)
15	40	(44.4%)	30	(36.1%)
16	8	(8.9%)	12	(14.5%)
17	1	(1.1%)	1	(1.2%)
18	1	(1.1%)	1	(1.2%)
19	0		2	(2.4%)
20	1	(1.1%)	1	(1.2%)
21	1	(1.1%)	0	

Medical Officer's Comments;

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

Unevaluable Patients

Reason Unevaluable Summary
 All Patients
 Indication: Pneumonia

REASON UNEVALUABLE	DIRITHROMYCIN		ERYTHROMYCIN	
	n	(%)	n	(%)
ALL UNEVALUABLE PATIENTS	170	(65.48)	174	(67.78)
CAUS. ORG. UNIDENT	116		119	
INSUFFICIENT THERAPY	26		41	
NO FOLLOW UP X RAY	27		20	
UNEVAL. BY INVEST	11		19	
CAUS. ORG. RESISTANT	18		12	
NO POST THER. CULTURE	11		14	
UNACCEPT. PATHOGEN	12		9	
NO PRIOR P.O.S. X RAY	5		10	
SENSITIVITY NOT DONE	5		6	
PROTOCOL VIOLATED	3		5	
SEQUENTIAL THERAPY	1		5	
CLINICAL DIAG. ONLY	1		4	
TIMING OF X RAY	1		2	
CONCOMITANT ANTIBIOT	2		3	
INCOMPLETE DATA	1		3	
BACTERIOL. INCOMPLETE	0		3	
NO FOLLOW-UP CULTURE	1		2	
WRONG DIAGNOSIS	1		1	
CONCOMIT. MEDICATION	1		1	
NO INFEC. DEMONSTRATED	1		0	
NO THERAPY	1		0	
INITIAL CULT. EARLY	0		1	

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

Medical Officer's Comments:

Some patients had more than one reason to be unevaluable.

Efficacy Evaluation:

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

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

RESPONSE	DIRITHROMYCIN		ERYTHROMYCIN	
	N = 90		N = 83	
	n	(%)	n	(%)
CURE	50	(55.6%)	56	(67.5%)
IMPROVEMENT	35	(38.9%)	27	(32.5%)
RELAPSE	2	(2.2%)	0	
FAILURE	1	(1.1%)	0	

Medical Officer's Comments:

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

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

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

PATHOGENS	CURE		IMPROVEMENT		RELAPSE		FAILURE		TOTAL n
	n	(%)	n	(%)	n	(%)	n	(%)	
MYCOPLASMA	23	(56.0%)	15	(36.5%)	2	(4.8%)	1	(2.4%)	41
L. PNEUMOPHILA	12	(65.7%)	2	(14.2%)	0		0		14
STR. PNEUMONIAE	5	(38.4%)	8	(62.5%)	0		0		13
H. INFLUENZAE	1	(14.2%)	5	(71.4%)	0		1	(14.2%)	7
ST. AUREUS	4	(80.0%)	1	(20.0%)	0		0		5
H. PARAINFLUENZAE	4	(100.0%)	0		0		0		4
MULTIPLE ORGANISMS*	1	(100.0%)	0		0		0		1
STREPTOCOCCUS SP	0		1	(50.0%)	0		1	(50.0%)	2
M. CATARRHALIS	0		2	(100.0%)	0		0		2
S. MARCESCENS	0		1	(100.0%)	0		0		1

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

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QAAB Pneumonia Indication

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

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

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

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

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

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

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

NA Presumed Eradicated
 FTE FAILURE TO ELIMINATE

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

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

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

Medical Officer's Comments:

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

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

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

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

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

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

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

NA - PRESUMED ERADICATION

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

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

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

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

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

NA - Presumed Eradicated
FTE - FAILURE TO ELIMINATE

Bacteriologic Response

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

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

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

Medical Officer's Comments:

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

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

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

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

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

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

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

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

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

Medical Officer's Comments:

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

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

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

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

NDA 50-678
 AQAB Pneumonia Indication

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

PATHOGENS	PRESUMED ERADICATION		FAILED TO ELIMINATE		TOTAL n
	n	(%)	n	(%)	
H INFLUENZAE	7	(87.5%)	1	(12.5%)	8
STR PNEUMONIAE	15	(93.8%)	1	(6.2%)	16
H PARAINFLUENZAE	5	(100.0%)	0		5
S AUREUS	2	(100.0%)	0		2
HAEMOPHILUS SP	1	(100.0%)	0		1
STR GRP A	1	(50.0%)	1	(50.0%)	2
STREPTOCOCCUS SP	1	(100.0%)	0		1
STR GRP G	1	(100.0%)	0		1

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

Patients with Favorable Clinical Response Posttherapy

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

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

^b Serologic testing for *Chlamydia pneumoniae* was not performed in AQAB.

Patients with Favorable Clinical Response Late Posttherapy

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

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

^b Serologic testing for *Chlamydia pneumoniae* was not performed in AQAB.

NDA 50-678
 AQAB Pneumonia Indication

X-Ray Summary for AQAB Evaluable Patients

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

SUSCEPTIBILITY RESULTS

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

	ANTIMICROBIAL							
	DIRITHROMYCIN				ERYTHROMYCIN			
	SUSCEPTIBLE (ZONE <= 17)	INTERMEDIATE (ZONE = 16)	RESISTANT (ZONE <= 15)	TOTAL N	SUSCEPTIBLE (ZONE >= 18)	INTERMEDIATE (17 >= ZONE >= 14)	RESISTANT (ZONE = 13)	TOTAL N
ENTERICEN	N	N	N	N	N	N	N	N
B. CATARRHALIS	3		2	5	4		1	5
C. JEJUNI SP			1	1			1	1
C. DIFFICILE			1	1			1	1
E. COLI	1			1	1			1
H. INFLUENZAE	7	1	8	16	10	4	2	16
H. PARAINFLUENZAE	4	1	2	7	5	2		7
HAEEMPHILUS SP	3		1	4	3	1		4
K. PNEUMONIAE			3	3			3	3
KS AERUGINOSA			1	1			1	1
S. MARCESCENS			1	1			1	1
ST. AUREUS	6			6	6			6
STAPH COAG NEG	1			1	1			1
STAPH COAG POS	1			1	1			1
STR GRP A	1			1	1			1
STR GRP B	2			2	1	1		2
STR PNEUMONIAE	18		2	20	19	1		20
STR VIRIDANS	1		1	2	2			2
STREPTOCOCCUS SP	3			3	3			3

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

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

PATHOGEN	ANTIMICROBIAL						
	DIRITHROMYCLIN			ERYTHROMYCIN			
	SUSCEPTIBLE (ZONE >= 17) N	RESISTANT (ZONE <= 15) N	TOTAL N	SUSCEPTIBLE (ZONE >= 18) N	INTERMEDIATE (17 >= ZONE >= 14) N	RESISTANT (ZONE <= 13) N	TOTAL N
B. CATAARRHALIS	4	1	5	5			5
BACILLUS CEREUS	1		1	1			1
E. COLI/AE	1	2	3			3	3
H. INFLUENZAE	8	13	21	14	6	1	21
H. PARAHAEMLYTICUS	1		1	1			1
H. PARAINFLUENZAE	5	1	6	5	1		6
HAEMOPHILUS SP	1		1	1			1
K. PNEUMONIAE		1	1			1	1
N. SIETCA		1	1		1		1
PS. AERUGINOSA		2	2			2	2
PSEUDOMONAS SP		1	1			1	1
ST. AUREUS	4		4	4			4
STAPH COAG NEG		1	1	1			1
STAPH COAG POS	1		1	1			1
STR GRP A	1		1	1			1
STR GRP I	1		1	1			1
STR GRP G	1		1	1			1
STR PNEUMONIAE	26	2	28	28			28
TREPTOCOCCUS SP	4		4	4			4

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

CONCOMITANT MEDICATIONS:

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

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

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

Seventeen patients had concomitant antibiotics listed in the database. All but 5 of these patients were not qualified for efficacy analysis. Of the 12 patients who did not qualify for efficacy analysis, 3 discontinued the study because of protocol violations (Patients _____), 2 patients discontinued because of entry exclusions (Patients _____ because of adverse events (Patients _____) and 1 patient _____ was protocol complete but unevaluable because of negative baseline culture. The 5 patients _____ who qualified for efficacy analysis all started their concomitant antibiotics after completing the protocol requirements. One of the 3 _____ was a clinical failure and was placed on erythromycin therapy after discontinuing the study.

SAFETY RESULTS:

Summary of Adverse Event By Body System Table

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

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

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

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

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

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

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

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 266		ERYTHROMYCIN N = 257		P-VALUE
	n	(%)	n	(%)	
PATIENTS WITH AT LEAST ONE EVENT	64	(24.5%)	65	(25.3%)	0.859
PATIENTS WITH NO EVENT	196	(75.4%)	192	(74.7%)	0.859
LUNG DISORDER	17	(6.5%)	16	(6.2%)	0.884
PHARYNGITIS	12	(4.6%)	9	(3.5%)	0.521
DYSPNEA	8	(3.1%)	10	(3.9%)	0.614
RHINITIS	7	(2.7%)	14	(5.4%)	0.113
ASTHMA	5	(1.9%)	11	(4.3%)	0.122
SINUSITIS	5	(1.9%)	10	(3.9%)	0.183
SPUTUM INCREASED	4	(1.5%)	8	(3.1%)	0.235
HYPERVENTILATION	3	(1.2%)	2	(0.8%)	0.663
PLEURAL EFFUSION	3	(1.2%)	0		0.084
COUGH INCREASED	2	(0.8%)	2	(0.8%)	0.991
HEMOPTYSIS	2	(0.8%)	2	(0.8%)	0.991
PNEUMONIA	2	(0.8%)	1	(0.4%)	0.569
RESPIRATORY DISORDER	2	(0.8%)	1	(0.4%)	0.569
BRONCHITIS	1	(0.4%)	3	(1.2%)	0.31
CARCINOMA OF LUNG	1	(0.4%)	4	(1.6%)	0.173
PLEURAL DISORDER	1	(0.4%)	0		0.32
LARYNGITIS	0		1	(0.4%)	0.314
PULMONARY TUBERCULOSIS AGGRAVATED	0		1	(0.4%)	0.314
STRIDOR	0		1	(0.4%)	0.314

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

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 260		ERYTHROMYCIN N = 257		P-VALUE
	n	(%)	n	(%)	
PATIENTS WITH AT LEAST ONE EVENT	13	(5.0%)	14	(5.4%)	0.819
PATIENTS WITH NO EVENT	247	(95.0%)	243	(94.6%)	0.819
RASH	4	(1.5%)	6	(2.3%)	0.235
SWEATING	3	(1.2%)	2	(0.8%)	0.663
MACULOPAPULAR RASH	2	(0.8%)	1	(0.4%)	0.569
PRURITUS	2	(0.8%)	0		0.159
HERPES SIMPLEX	1	(0.4%)	1	(0.4%)	0.993
HERPES ZOSTER	1	(0.4%)	0		0.32
URTICARIA	1	(0.4%)	0		0.32
ACNE	0		1	(0.4%)	0.314
SUBCUTANEOUS NODULE	0		1	(0.4%)	0.314

Patients Who Died or Discontinued Therapy Due to Adverse Events:

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

Summary of Patient Deaths

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

^aDay of death relative to date of study-drug therapy completion. Last day of study-drug therapy = relative day 0

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

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

THERAPY: DIRITHROMYCIN

INT	PAT	VISIT	AGE	SEX	ORIGIN	DAYS OF THERAPY	ADVERSE EVENT
004		1	65	FEMALE	NATIVE AMERICAN	7	INCREASED DYSPNEA
016		1	33	MALE	CAUCASIAN	2	ABDOMINAL CRAMPS
029		1	34	MALE	CAUCASIAN	7	NAUSEA
032		1	30	MALE	BLACK	14	EMPHYEMA
041		1	57	FEMALE	CAUCASIAN	10	EXACERBATION OF COPD
047		1	39	MALE	CAUCASIAN	2	SKIN ERUPTION
101		1	62	FEMALE	CAUCASIAN	1	PNEUMONIA WORSENER
116		1	28	FEMALE	CAUCASIAN	2	NAUSEA
116		1	32	MALE	CAUCASIAN	3	NAUSEA
122		2	28	FEMALE	CAUCASIAN	12	NAUSEA AND VOMITTING
150		1	79	FEMALE	CAUCASIAN	4	DIARRHEA
175		1	37	MALE	CAUCASIAN	2	VOMITING
176		1	63	MALE	HISPANIC	2	NAUSEA AND VOMITING
202		1	40	MALE	BLACK	15	EXTENSION OF PNEUMONIA & ABSCESS DEVELOPMENT

THERAPY: ERYTHROMYCIN

011		2	28	FEMALE	CAUCASIAN	14	PHARYNGITIS
063		1	64	FEMALE	CAUCASIAN	4	SUPRAPUBIC RASH
073		1	36	FEMALE	HISPANIC	2	DIARRHEA
073		1	62	FEMALE	HISPANIC	4	EPIGASTRIC DISTRESS
086		1	21	FEMALE	CAUCASIAN	3	NAUSEA AND VOMITING
096		1	22	MALE	CAUCASIAN	16	SPUTUM, YELLOW
090		1	38	FEMALE	CAUCASIAN	6	RASH
092		1	35	FEMALE	CAUCASIAN	15	COLD SYMPTOMS
101		1	55	FEMALE	BLACK	4	NAUSEA
113		1	59	FEMALE	CAUCASIAN	10	HOMOGENEOUS MASS LEFT LUNG
120		1	25	MALE	CAUCASIAN	7	INSPIRATORY WHEEZING
120		1	71	MALE	CAUCASIAN	6	BLADDER CARCINOMA
123		1	60	FEMALE	CAUCASIAN	2	INCREASED ABDOMINAL PAIN
131		1	54	MALE	CAUCASIAN	4	EXACERBATION OF PNEUMONIA

CLINICAL LABORATORY EVALUATIONS:

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

Distribution of Extreme Laboratory Values

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

ANALYTE	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Platelet Count		D	692.000		867.000
		D	333.000		502.000
		D	514.000		658.000
		D	547.000		754.000
		D	359.000		470.000
		D	370.000		494.000
		D	243.000		464.000
		D	219.000		483.000
		D	356.000		567.000
		D	280.000		509.000
		D	368.000		613.000
		D	239.000		440.000
		D	382.000		561.000
		D	356.000		491.000
		D	376.000		604.000
		D	98.000		466.000
		D	378.000		481.000
		D	384.000		890.000
		D	204.000		481.000
		D	204.000		510.000
		D	308.000		802.000
		D	253.000		501.000
		D	415.000		520.000
		D	269.000		467.000
		D	246.000		437.000
		E	404.000		549.000
		E	314.000	447.000	573.000
		E	297.000		488.000
	E	359.000		607.000	
	E	366.000		563.000	
	E	299.000		497.000	
	E	188.000	336.000	499.000	
	E	372.000		654.000	
	E	276.000		988.000	

Platelet Count (cont)	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
		E	270.000		539.000
		E	420.000		556.000
		E	272.000		439.000
		E	655.000		762.000
		E	476.000		595.000
		E	311.000		473.000
		E	416.000		584.000
		E	371.000	481.000	
		E	464.000		946.000
		E	249.000	504.000	
		E	342.000		447.000
		E	392.000		488.000
		E	276.000		467.000
		E	521.000		928.000
		E	304.000		490.000
		E	273.000		546.000
		E	197.000		580.000
		E	254.000		415.000
		E	244.000		515.000
Gamma-Glutamyl Transpeptidase					
		D	122.000		323.000
		D	99.000		121.000
		D	162.000		283.000
		D	150.000		179.000
ALANINE AMINOTRANSFERASE					
		D	43.000		101.000
		D	61.000		167.000
		D	146.000		210.000
		E	98.000		135.000
ASPARTATE AMINOTRANSFERASE					
		D	61.000		167.000
		D	146.000		210.000
		e	98.000		135.000

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

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

Medical Officer's Overall Comments:

Efficacy:

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

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

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

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

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

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

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

Medical Officer's Conclusions:

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

REVIEW OF PIVOTAL STUDIES:

II. Study B9Z-EW-E003 Synopsis:

Title: Dirithromycin versus Erythromycin Base in Bacterial Pneumonia.

Study Centers: There were 76 active study centers.

Dates of Study: October 25, 1988 - November 12, 1991

Clinical Phase: Phase 2-3

Objectives: To compare dirithromycin with erythromycin base for effectiveness and safety in the treatment of bacterial pneumonia.

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

Number of Patients: Dirithromycin: Male 190, Female 105, Total 295.
Erythromycin: Male 177, Female 119, Total 296.

Diagnosis and Inclusion Criteria: Pneumonia with confirmed susceptible bacterial etiology or appropriate serology for mycoplasma, legionella or chlamydia.

Dosage and Administration: Test Product
Dirithromycin: 500 mg/day (two 250-mg tablets q.d.)
CT9198, CT9549, CT0009, CT00047,
CT00564: dirithromycin tablets, 250 mg
CT9199, CT9550, CT0010, CT00042,
CT00565: placebo tablets
NOTE: Placebo was used to maintain blinding.

Reference Therapy:
Erythromycin Base: 1000 mg/day (one 250-mg tablet q.i.d.)
CT9200, CT9220, CT00040,
CT00566: erythromycin base tablets, 250 mg
CT9201, CT00041
CT00567: placebo tablets
NOTE: Placebo was used to maintain blinding.

Duration of Treatment: Dirithromycin: 10-14 days
Erythromycin Base: 10-14 days

Criteria for Evaluation: Efficacy--A complete efficacy evaluation was to be performed on patients completing at least 10 days of therapy who had positive chest x-ray and sputum culture or serology, returned for the during-therapy, posttherapy and the late-posttherapy clinical evaluation (late-posttherapy was required if chest x-ray had not resolved at posttherapy evaluation), and for whom the symptomatic response could be evaluated.

Safety--All patients were evaluated for safety.

Statistical Methods: Chi-square tests were used for response rates and adverse events. Appropriate continuous data procedures were used for analysis of laboratory data. The Type I error was set at 0.05.

Study Design:

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

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

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

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

Investigators:

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

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

(continued)

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

INVESTIGATOR NAME/LOCATION	NUMBER OF PATIENTS ENROLLED		NUMBER OF EVALUABLE PATIENTS	
	DIRITHROMYCIN	ERYTHROMYCIN	DIRITHROMYCIN	ERYTHROMYCIN
E. TALA/PREITILA, FINLAND	22	22	8	9
P. SAARELAINEN/HELSINKI, FINLAND	7	8	4	4
S. ELLE/ELVERUM, NORWAY	0	2	0	0
L. HENRIKSEN/HALDEN, NORWAY	1	1	0	0
O. STARHEIM/ARENDAL, NORWAY	2	1	0	0
O. F. LEHN/HALDEN, NORWAY	9	7	0	1
E. G. ROGAN/DUBLIN, IRELAND	1	1	1	0
P. LAPPIN/CO. MEATH, IRELAND	3	1	0	0
K. K. GARG/LANCASHIRE, ENGLAND	3	5	1	3
J. J. HAMILL/LEICESTER, ENGLAND	1*	1	0	1
J. ZACHARIAH/BUCKS, ENGLAND	4	5	4	2
M. KANSAGRA/MILTON KEYNES, U.K.	6	6	4	5
LONERGAN/CO. KILKENNY, IRELAND	3	2	0	1
G. C. HALDAR/MILTON KEYNES, U.K.	1	0	1	0
J. HOSIE/GLASGOW, SCOTLAND	6	5	4	2
S. P. WADERA/SUFFOLK, ENGLAND	1	0	1	0
D. COTTER/CO CORK, IRELAND	0	1	0	0
KIERNAN S/CO. MEATH, IRELAND	1	0	1	0
M. F. RYAN/BALLINCOLLIG, IRELAND	3	0	2	0
F. BRADBURY/KILKENNY, IRELAND	2	4	1	3
P. MCGARRY/LONGFORD, IRELAND	4	6	1	1
J. E. MOLLOY/LIMERICK, IRELAND	2	3	1	2
R. AVILA/LISBON, PORTUGAL	16	16	9	7
D. J. WEICH/BLOEMFONTEIN, SOUTH AFRICA	8	5	5	1
C. D. MORRIS/EAST LONDON, SOUTH AFRICA	3	3	3	3
E. L. MURRAY/EAST LONDON, SOUTH AFRICA	1	2	0	0
T. D. WILTON/GERMISTON, SOUTH AFRICA	2	2	0	0
A. R. VAN DER WATT/BENONI, SOUTH AFRICA	1	0	0	0
R. SPAMMER/PAROW, SOUTH AFRICA	1	2	1	0
G. PROMINITZ/ANSFERE, SOUTH AFRICA	4	3	1	1
T. UYS/LIBANON, SOUTH AFRICA	9	9	0	0
J. C. KALLMEYER/NATAL, SOUTH AFRICA	3	3	0	0
W. L. SIELING/TYGERBERG, SOUTH AFRICA	2	1	2	0
U. G. LALLOO/NATAL, SOUTH AFRICA	6	5	3	2
M. V. VAN VUOREN/BLOEMFONTEIN, SOUTH AFRICA	6	4	5	4
BRUDERMAN I TEL AVIV, ISRAEL	6	8	2	3
M. TOPILSKY RAMAT AVIV, ISRAEL	8	8	6	6
TOTAL	235	236	127	118

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

Sponsor's Analysis:

Patient disposition was as follows:

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

Medical Officer's Comments:

The Medical Officer concurs with the sponsor's analysis.

Patient Demographics:

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

All Patients

Age by Sex - Ranges
All Patients
Indication: Pneumonia

AGE RANGES	DIRITHEOMYCIN			ERYTHROMYCIN		
	FEMALE N = 105	MALE N = 190	TOTAL N = 295	FEMALE N = 119	MALE N = 177	TOTAL N = 296
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
0 - 12	0	0	0	1 (0.8%)	0	1 (0.3%)
16 - 25	13 (12.4%)	20 (10.5%)	33 (11.2%)	15 (12.6%)	18 (10.2%)	33 (11.1%)
25 - 45	44 (41.9%)	70 (36.8%)	114 (38.6%)	37 (31.1%)	72 (40.7%)	109 (36.8%)
45 - 65	37 (35.2%)	78 (41.1%)	115 (39.0%)	51 (42.9%)	64 (36.2%)	115 (38.9%)
65+	11 (10.5%)	22 (11.6%)	33 (11.2%)	15 (12.6%)	23 (13.0%)	38 (12.8%)

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

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	105	190	295	119	177	296
MEAN AGE	43.92	45.88	45.19	45.61	46.27	46.00
STD DEV	15.78	15.99	15.92	16.38	16.09	16.18
MEDIAN AGE	43.00	46.50	45.00	48.00	44.00	46.00
MINIMUM AGE	16.00	16.00	16.00	11.00	16.00	11.00
MAXIMUM AGE	78.00	87.00	86.00	75.00	83.00	83.00

Origin by Therapy Group
All Patients
Indication: Pneumonia

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

Height and Weight at Admission
All Patients
Indication: Pneumonia

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	MEAN	STD			N	UNK	MEAN	STD		
				DEV	MIN	MAX				DEV	MIN	MAX
DIRITHROMYCIN	295	0	168.87	7	147	193	295	0	68.94	15	33	125
ERYTHROMYCIN	296	0	169.99	7	149	194	296	1	69.13	15	36	128

EVALUABLE PATIENTS:

**Age By Sex - Ranges
Evaluable Patients
Indication: Pneumonia**

AGE RANGES	DIRITHROMYCIN						ERYTHROMYCIN					
	FEMALE		MALE		TOTAL		FEMALE		MALE		TOTAL	
	(N = 44)		(N = 81)		(N = 127)		(N = 47)		(N = 71)		(N = 118)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
18-24	6	(13.6%)	11	(13.3%)	17	(13.4%)	6	(12.8%)	11	(15.5%)	17	(14.4%)
25-34	19	(43.2%)	35	(42.2%)	54	(42.5%)	18	(38.3%)	32	(45.1%)	50	(42.4%)
35-44	13	(29.5%)	29	(34.9%)	42	(33.1%)	21	(44.7%)	25	(35.2%)	46	(39.0%)
45+	6	(13.6%)	8	(9.6%)	14	(11.0%)	2	(4.3%)	3	(4.2%)	5	(4.2%)

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

	DIRITHROMYCIN			ERYTHROMYCIN		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
NUMBER OF PATIENTS	44	83	127	47	71	118
MEAN AGE	43.05	42.82	42.90	43.19	42.85	42.98
STD DEV	16.69	16.06	16.22	14.69	14.61	14.58
MEDIAN AGE	42.50	39.00	42.00	44.00	41.00	41.00
MINIMUM AGE	16.00	16.00	16.00	16.00	16.00	16.00
MAXIMUM AGE	75.00	74.00	75.00	74.00	75.00	75.00

Origin By Therapy Group
Evaluable Patients
Indication: Pneumonia

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

Height and Weight at Admission
Evaluable Patients
Indication: Pneumonia

THERAPY	HEIGHT IN CM						WEIGHT IN KG					
	N	UNK	STD				N	UNK	STD			
			MEAN	DEV	MIN	MAX			MEAN	DEV	MIN	MAX
DIRITHROMYCIN	127	0	168.87	13	137	182	127	0	68.54	15	40	110
ERYTHROMYCIN	118	0	171.44	10	162	194	118	0	69.93	15	36	128

Drug Administration:

All Patients

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

	DIRITHROMYCIN N = 295 DAYS	ERYTHROMYCIN N = 296 DAYS
PATIENTS WITH COMPLETE DATA	290	294
MEAN DURATION EXPOSURE	12.3	12.5
MINIMUM EXPOSURE DAYS	1	1
MAXIMUM EXPOSURE DAYS	18	18
PATIENTS WITH INCOMPLETE DATA	5	2

Summary of Exposure to Study Drugs
All Patients
Indication: Pneumonia

DAYS OF THERAPY	DIRITHROMYCIN N = 295		ERYTHROMYCIN N = 296		TOTAL N = 591	
	n	(%)	n	(%)	n	(%)
PATIENTS WITH INCOMPLETE DATA	5	(1.7%)	2	(0.7%)	7	(1.2%)
1	3	(1.0%)	2	(0.7%)	5	(0.8%)
2	4	(1.4%)	7	(2.4%)	11	(1.9%)
3	5	(1.7%)	7	(2.4%)	12	(2.0%)
4	5	(1.7%)	4	(1.4%)	9	(1.5%)
5	7	(2.4%)	0		7	(1.2%)
6	4	(1.4%)	4	(1.4%)	8	(1.4%)
7	4	(1.4%)	5	(1.7%)	9	(1.5%)
8	4	(1.4%)	1	(0.3%)	5	(0.8%)
9	6	(2.0%)	4	(1.4%)	10	(1.7%)
10	22	(7.5%)	18	(6.1%)	40	(6.8%)
11	28	(9.5%)	32	(10.8%)	60	(10.2%)
12	27	(9.2%)	25	(8.4%)	52	(8.8%)
13	15	(5.1%)	9	(3.0%)	24	(4.1%)
14	68	(23.1%)	68	(23.0%)	136	(23.0%)
15	91	(30.8%)	98	(33.1%)	189	(32.0%)
16	4	(1.4%)	9	(3.0%)	13	(2.2%)
17	1	(0.3%)	0		1	(0.2%)
18	2	(0.7%)	1	(0.3%)	3	(0.5%)

Evaluable Patients

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

	<u>DIRITHROMYCIN</u> N = 127 DAYS	<u>ERYTHROMYCIN</u> N = 118 DAYS
NUMBER OF PATIENTS	127	118
MEAN DURATION EXPOSURE	13.1	13.6
MINIMUM EXPOSURE DAYS	3	3
MAXIMUM EXPOSURE DAYS	18	18
PATIENTS WITH INCOMPLETE DATA	0	0

Summary of Exposure to Study Drugs
Evaluable Patients
Indication: Pneumonia

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

Unevaluable Patients

Reason Unevaluable Summary
All Patients
Indication: Pneumonia

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

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

Efficacy Evaluation:

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

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

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

Medical Officer's Comments:

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

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

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

PATHOGENS	CURE		IMPROVEMENT		RELAPSE		FAILURE		TOTAL
	n	(%)	n	(%)	n	(%)	n	(%)	n
S PNEUMONIAE	23	(57.5%)	16	(40.0%)	1	(2.5%)	0		40
H INFLUENZAE	14	(66.6%)	4	(19.0%)	0		3	(14.2%)	21
MULTIPLE ORGANISMS	13	(65.0%)	5	(25.0%)	0		2	(10.0%)	20
M PNEUMONIAE	10	(50.0%)	7	(35.0%)	0		2	(10.0%)	19
C PNEUMONIAE SP	5	(33.3%)	4	(80.0%)	0		1	(6.6%)	15
S AUREUS	3	(100.0%)	0		0		0		3
H PARAINFLUENZAE	1	(50.0%)	1	(50.0%)	0		0		2
GRP A STREP	1	(50.0%)	1	(50.0%)	0		0		2
M CATARRHALIS	0		2	(66.6%)	1	(33.3%)	0		3
L PNEUMOPHILA	0		2	(100.0%)	0		0		2

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

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

(cont)

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

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

Abbreviation:

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

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

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

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

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

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

Abbreviation:

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

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

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

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

Medical Officer's Comments:

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

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

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

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

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

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

Abbreviations:

NA = not applicable

UTE = unable to evaluate

PE = pathogen eliminated

IMP = improved

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

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

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

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

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

Abbreviations

NA = not applicable

PE = pathogen eliminated

UTE = unable to evaluate

IMP = improved

Bacteriologic Response

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

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

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

Medical Officer's Comments:

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

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

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

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

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

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

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

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

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

Medical Officer's Comments:

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

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

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

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

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

PATHOGENS	PATHOGEN <u>ELIMINATED</u>		PRESUMED <u>ERADICATION</u>		RECURRENCE SAME, <u>RESISTANCE</u>		FAILED TO <u>ELIMINATE</u>		<u>TOTAL</u> n
	n	(%)	n	(%)	n	(%)	n	(%)	
S. TR. PNEUMONIAE	2	(6.9%)	26	(89.7%)	1	(3.4%)	0		29
H. INFLUENZAE	1	(4.5%)	20	(90.0%)	0		1	(4.5%)	22
M. CATARRHALIS	0		8	(100.0%)	0		0		8
S. PNEUM.	0		6	(100.0%)	0		0		6
H. PARAINFLUENZAE	0		2	(100.0%)	0		0		2
S. TR. GRP. A	0		2	(100.0%)	0		0		2
S. TR. GRP. F	0		1	(100.0%)	0		0		1

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

Patients with Favorable Clinical Response Posttherapy

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

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

- **NOTE: 8 patients in the dirithromycin group and 15 patients in the erythromycin group were enrolled by investigators in the US.**

7/8 patients in the dirithromycin group and 13/15 in the erythromycin group had a favorable outcome.

Patients with Favorable Clinical Response Late-Posttherapy

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

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

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

X-Ray Summary for E003 Evaluable Patients

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

SUSCEPTIBILITY RESULTS

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

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

Medical Officer's Comments:

Forty-three percent (18/42) of the *H. influenzae* isolated were resistant to dirithromycin.

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

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

(continued)

Medical Officer's Comments:

46% (18/39) of the *H. influenzae* isolated were resistant to dirithromycin.

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

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

CONCOMITANT MEDICATIONS:

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

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

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

SAFETY RESULTS:

Summary of Adverse Event By Body System Table

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

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

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

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

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

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

Patients Who Died or Discontinued Therapy Due to Adverse Events:

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

THERAPY: DIRITHROMYCIN

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

THERAPY. ERYTHROMYCIN

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

CLINICAL LABORATORY EVALUATIONS:

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

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

Analyte	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
Platelet Count	452-5646	D	134.000		534.000
		D	175.000		468.000
		D	175.000		472.000
		D	203.000		399.000
		D	205.000		514.000
		D	208.000		625.000
		D	184.000		457.000
		D	207.000		553.000
		D	266.000		411.000
		D	239.000		524.000
		D	133.000		395.000
		D	219.000		486.000
		E	294.000		522.000
		E	246.000		669.000
		E	175.000		504.000
		E	320.000		451.000
		E	195.000		679.000
		E	240.000		409.000
		E	260.000		812.000
		E	232.000		457.000
E	467.000		1080.000		
E	150.000		478.000		
E	133.000		400.000		
E	216.000		412.000		
E	192.000		490.000		
E	210.000		554.000		
TBILI		D	21.000		42.000
GGT		D	440.000		796.000
ALKPH		D	196.000		449.000
		D	141.000		339.000
AST		D	31.000		145.000
ALT		D	91.000		362.000
HCT		D	0.396		0.287
		D	0.425		0.248
		D	0.440		0.730
		E	0.430		0.310

Analyte	Patient #	Drug Therapy	Pretherapy	During Therapy	Posttherapy
HGB		D	6.378		5.585
		D	9.185		4.903
		D	8.502		14.150
		E	8.502		6.144
EOSN		E	0.400		1.500
UR AC		E	221.00		618.00
CREAT		E	82.00		148.00
		E	100.00		156.00
PHOS		D	1.100		2.700
		D	2.920		8.090
		D	2.350		0.610
		D	1.100	1.000	1.860
		D	1.310		3.880
		D	0.940		2.600*
		D	1.000		2.200
		D	0.800		3.000
		E	1.300		3.900
		E	0.960		1.690
		E		1.120	1.610
		E	1.300		2.670
		E	1.450		1.910
CHOL		D	4.600		2.600
CALC		E	2.330		0.590
CPK		D	7.400		2166.000

**Late-post

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

Medical Officer's Overall Comments:

Efficacy:

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

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

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

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

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

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

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

Medical Officer's Conclusions:

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

Overall Summary of Pivotal Studies

Clinical Response:

Clinical Response Summary
Post-therapy
AQAB/E003
Pneumonia

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

Clinical Response Summary
Late Post-therapy
AQAB/E003
Pneumonia

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

Clinical Response Summary by Target Pathogens
AQAB/ E003 Pneumonia

Pathogen	Posttherapy								Late-Posttherapy							
	Dirithromycin				Erythromycin				Dirithromycin				Erythromycin			
	Favorable N	%	Unfavorable N	%	Favorable N	%	Unfavorable N	%	Favorable N	%	Unfavorable N	%	Favorable N	%	Unfavorable N	%
<i>M catarrhalis</i>	4	100	0	0	7	100	-	-	3	100	0	0	5	83.3	1	16.7
<i>C. pneumoniae</i>	14	93.3	1	6.7	18	94.7	1	5.3	15	93.8	1	6.2	13	92.9	1	7.7
<i>L Pneumophila</i>	16	100	-	-	11	100	-	-	15	100	-	-	9	100	-	-
<i>M.pneumoniae</i>	55	91.7	5	8.3	48	96.0	2	4.0	52	100	-	-	45	97.8	1	2.2
<i>H influenzae</i>	24	85.7	4	14.3	22	91.7	2	8.3	19	95	1	5	20	95.2	1	4.8
<i>Str pneumonia</i>	52	98.1	1	1.9	39	97.4	1	2.6	48	96	2	4	35	94.6	2	5.4
Multiple Pathogens	19	90.5	2	9.5	25	92.6	2	7.4	17	100	-	-	20	83.3	4	16.7

Bacteriologic Response

Bacteriologic Response Summary of Target Pathogens
AQAB/E003
Pneumonia

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

Serologic Response

**Patients with Favorable Clinical Response Posttherapy
AQAB/E003**

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

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

**Patients with Favorable Clinical Response Late-Posttherapy
AQAB/E003**

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

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

MEDICAL OFFICER'S CONCLUSIONS:

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

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

In patients who were diagnosed only by serology for the atypical microorganisms, the clinical success rate at late post-therapy was 56/56 (100%) for *M. pneumoniae*, 16/17 (94.1%) for *C. pneumoniae* (7/7 in the US) and 16/16 (100%) for *L. pneumophila* in the dirithromycin group, and 48/50 (96.0%) for *M. pneumoniae*, 17/19 (89.5%) for *C. pneumoniae* (10/12 in the US) and 9/9 (100%) for *L. pneumophila* in the erythromycin group.

MEDICAL OFFICER'S RECOMMENDATIONS:

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

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

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

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

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

OVERALL SAFETY

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

Frequency of All Adverse Events
 Integrated Safety Database Population

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

Medical Officer's Comments:

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

Medical Officer's Recommendations:

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

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

CNS: Headache 5.2%; dizziness 1.2%.

Body as a Whole: Asthenia 1.2%.

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

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

Nasim Moledina

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

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

Concurrence Only:

HFD-520/ActingDirDir/LGavrilovich
HFD-520/SMO/MSAlbuerne

mda 7/28/94
lb 7/28/94

Clin. Study Report
Protocol BQZ-EW-E009
Skin + Skin Structure
Infections

NDA 50678
DYNABAC

6 OF 8

CLINICAL STUDY REPORT
PROTOCOL B92-EW-E004, SKIN AND SKIN STRUCTURE INFECTIONS

1. INTRODUCTION

This study was designed to assess the efficacy and safety of dirithromycin in the treatment of bacterial skin and skin structure infections. Dirithromycin was compared to erythromycin base. This drug, erythromycin, was chosen because it is the prototypical macrolide antibiotic with an extensive safety and efficacy database.

To assess efficacy, dirithromycin-treated patients were evaluated for symptomatic and bacteriologic responses, and their results were compared with those of erythromycin-treated patients. The safety of dirithromycin therapy was evaluated by analyzing adverse clinical events and the results of blood chemistry, hematology, electrocardiograms, and urine tests. These were also compared to the values found in the erythromycin-treated patients.

2. OBJECTIVE

The objective of this study was to compare dirithromycin administered once daily (500 mg/day) with erythromycin administered four times daily (1000 mg/day) for effectiveness and safety in the treatment of bacterial skin and skin structure infections.

3. INVESTIGATIONAL PLAN

a. SUMMARY OF STUDY DESIGN

This was a double-blind, double-dummy, randomized, parallel study. Patients who met the entry criteria and signed a patient consent form were to be assigned by randomization to one of the 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, which were to be done prior to therapy, during therapy and then after completion of therapy. There was no minimum treatment period for patients who did not respond to therapy, but for those who did, the duration of therapy was to be 7 days.

b. INVESTIGATORS

Investigators were from 31 different study centers throughout Europe and were practitioners involved in the diagnosis and treatment of infectious diseases. This clinical trial was conducted according to Ethical Committee guidelines, including the Declaration of Helsinki (1983 Venice Amendment). The protocol was approved by the European Ethical Review Committee (8 June 1988) and independent local ethical committees.

c. DOSAGE AND ADMINISTRATION

Patients randomly assigned to the dirithromycin treatment group were to receive two 250-mg dirithromycin tablets in the morning (total dose of 500 mg) and one tablet of placebo four times daily for 7 days. The placebo tablet was identical in appearance to the erythromycin tablet.

Patients randomly assigned to the erythromycin treatment group were to receive one 250-mg erythromycin tablet four times daily (total of 1000 mg daily) and two tablets of placebo in the morning for 7 days. The placebo tablet was identical in appearance to the dirithromycin tablet.

Formulations used in study: In the early stages of the study, the original formulation (referred to as the "Thomae" formulation) was used. However, a new

formulation was developed (referred to as the "Lilly" formulation) and was used in patients in the latter stages of the study. The switch in formulations was done for the following reasons:

1. The Lilly formulation had an improved enteric coating with better long-term stability (an coating replaced a coating).
2. The new manufacturing process did not induce dirithromycin epimer formation.
3. The new manufacturing process was environmentally desirable because it used aqueous solvents in place of hydrocarbon solvents.

Medical Officer's Comments: The sponsor has submitted data in the NDA application showing that the two formulations have similar biopharmaceutical profiles and antimicrobial activity. Thus, the medical officer treated all patients in the dirithromycin-treated group as a whole and did not separate them into two subgroups.

d. CONCOMITANT MEDICATION

Concomitant medications needed for treatment of underlying diseases or conditions were acceptable with the exception of systemic antibiotics. If a systemic antibiotic was required, the study antibiotic was to be discontinued and appropriate cultures and laboratory tests performed. The case was to be classified as a symptomatic failure and possibly a bacteriologic failure. Patients requiring topical antimicrobial or topical or systemic steroids were not to be enrolled.

e. DISEASE DIAGNOSTIC CRITERIA

Patients with the following bacterial skin and skin-structure infections were included:

1. infected burns,
2. impetigo,
3. pyoderma,
4. infected skin ulcer,
5. post-surgical wound infection,
6. traumatic wound infection,
7. cellulitis.

If patients had an acute infection superimposed on an area of chronic skin disease, and thus rendering it difficult to evaluate clinical response, they were to be excluded from the study. Patients requiring a topical antimicrobial or topical or systemic steroids were not to be enrolled.

All patients were to have a culture obtained at the pretherapy visit. Patients with cellulitis were to have a needle-aspirate culture of the cellulosic area obtained.

f. EFFICACY CRITERIA

Patients were to be evaluated from two points of view, clinical or symptomatic response and bacteriologic response. Responses were assessed by the investigators.

Clinical response could be classified in one of five ways:

Cure:	Elimination of signs and symptoms of infection with no recurrence in the follow-up period.
Improvement:	Significant, but incomplete, resolution of signs or symptoms of infection.
Relapse:	Worsening of signs and symptoms of infection following initial improvement.
Failure:	Signs and symptoms did not subside or improve during

therapy. A case requiring the addition of another antibiotic for the treatment of the skin infection was to be classified as a symptomatic failure.

Unable to
Evaluate:

Unable to evaluate a symptomatic response due to extenuating circumstances. This response disqualified a case for efficacy analysis only.

NOTE: The use of "failure" for cases requiring the addition of another antibiotic was to be reserved for those cases where a different antibiotic was given due to worsening or lack of improvement of the patient's clinical condition. Thus, in patients who had a favorable clinical response ("cure" or "improved"), but an unfavorable bacteriologic response (relapse or failure) and thus treated with a new antibiotic, the patient's clinical response remained as "cure" or "improvement".

Bacteriologic response could be classified in one of seven ways:

Pathogen Eliminated:	Eradication of the pathogen.
Recurrence Same Pathogen:	Original pathogen eliminated during treatment but recurred during the follow-up period.
Recurrence Same Pathogen, Resistance Developed:	Original pathogen susceptible to erythromycin was eliminated during treatment but recurred in the follow-up period and tested as resistant to erythromycin.
Recurrence New Pathogen:	Original pathogen susceptible to erythromycin was eliminated during treatment, but a new pathogen was isolated in the follow-up period.
Failure:	Original pathogen was not eradicated.
Not Applicable:	Patient obtained either a cure or improvement clinically, and the follow-up culture was not clinically indicated or the culture source was eliminated.
Unable to Evaluate:	Term used when cultures were not obtained or when a systemic or topical (nonstudy) antimicrobial agent with activity against cutaneous bacterial pathogens or a systemic or topical corticosteroid agent was used.

NOTE: Superimposed infections, that is, the presence of a new pathogen (bacterial, viral, fungal) resistant to study medication, and with signs and/or symptoms of infection present, were regarded as adverse events and listed as such.

Medical Officer's Comments: As done by the sponsor, patients were evaluated in two ways: clinical response and bacteriologic response. Clinical response was divided into only three categories, compared to the five used by the sponsor. These categories were:

Cure:	Elimination of signs and symptoms of infection with no recurrence in the follow-up period.
Not Cured:	This included patients with: incomplete resolution of signs and symptoms of infection, worsening of signs

and symptoms after initial improvement on therapy, or no improvement of signs and symptoms during therapy. All patients requiring the addition of another antibiotic (be it systemic or topical) were considered as "not cured". Thus, even patients who had clinical resolution of signs and symptoms but who required another antibiotic because of relapse or failure bacteriologically, were classified as "not cured".

Unable to
Evaluate:

Unable to evaluate a symptomatic response due to extenuating circumstances. This response disqualified a case for efficacy analysis only. Included in this category were ALL patients who received either topical or systemic steroids since this treatment can mask the clinical picture.

In regards to the bacteriological response category, the medical officer used the same 7 possible groups as the sponsor, but renamed the "not applicable" as "presumed eradicated". However, if a systemic or topical antimicrobial agent other than the study drug, with activity against cutaneous bacterial pathogens was used, the bacteriologic response was classified as a "failure" and not as "unable to evaluate" as the sponsor may have done.

g. PATIENT DISPOSITION CRITERIA

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

- If a pathogen isolated from initial culture was resistant to erythromycin.
- If obvious clinical and/or unfavourable bacteriologic outcome of the study antibiotic occurred 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 medication was discontinued.
- 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 stated on the CRF.
- Study drug identity was unblinded for safety reasons.
- If the sponsor terminated the study.

Note that all patients discontinued from the study were to have laboratory tests repeated at time of discontinuation.

SAFETY

All patients who gave consent to participate in this study and were randomized to a treatment group were to be included in the safety evaluation, even if they were not treated with a study medication (i.e., an intent-to-treat analysis).

EFFICACY

Cases were classified by the sponsor as "qualified" if they met the following criteria for analysis of efficacy:

- the patient met the inclusion/exclusion criteria (will be discussed in the next section),
- the pretherapy culture, obtained within 24 hours prior to start of study drug medication, was positive for a cutaneous pathogen susceptible to erythromycin,
- the patient completed an adequate course of therapy (5 to 7 days),
- posttherapy clinical and microbiological evaluations were performed,
- the symptomatic response could be evaluated.

NOTE: A late posttherapy visit was not explicitly required for evaluability.

Medical Officer's Comments:

To be qualified for efficacy evaluation, the medical officer required that the subject have a late posttherapy visit, not just an early posttherapy visit as was required by the sponsor. Timing of visits will be described in detail in Section #4 "Procedures and Methods".

b. INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

Patients included males and females and were required to be at least 16 years of age and not older than 65. Women with child-bearing potential were to have a negative pregnancy test prior to therapy and be on effective birth control during the course of therapy. Patients were to be included if they had a clinical diagnosis of a bacterial skin or soft tissue infection.

The investigators attempted to select those patients and/or parents or guardians who had a history of complying with instructions.

EXCLUSION CRITERIA

Patients were to be excluded for any of the following reasons:

- History of renal impairment (serum creatinine ≥ 170 $\mu\text{mol/L}$, 2.0 mg/dL).
- Significant underlying disease or concomitant infection which, in the opinion of the investigator, could have precluded evaluation of response.
- An anticipated requirement of systemic antibiotics other than the study antibiotic during therapy.
- Use of any antimicrobial therapy within 1 week preceding the pretherapy evaluation.
- Use of other investigational agents within 3 months prior to entry into the study.
- Would not be able to come back routinely for follow-up.
- History of hypersensitivity to macrolides.
- Pregnancy, and postpartum/lactating females who were nursing.
- Patients with diabetic ulcers.
- Patients taking ergotamine.

4. PROCEDURES AND METHODS

In general, there were to be 4 patient visits during the course of therapy. They were:

1. Pretherapy Visit:	Within 24 hours preceding the first dose
2. During Therapy Visit:	Between days 3-5 of therapy
3. Posttherapy Visit:	3-5 days after completion of therapy
4. Late-Posttherapy Visit:	10-14 days after therapy was completed.

a. EFFICACY EVALUATION

Procedures that were to be done at each visit so as to evaluate clinical response were as follows:

Pretherapy:	A complete history and physical examination were to be done.
During Therapy:	Evaluate symptomatic response to therapy and assess patient compliance with instructions for taking medication.
Posttherapy:	Physical examination was to be performed to evaluate symptomatic response to therapy.
Late-Posttherapy:	Physical examination was to be performed to evaluate symptomatic response to therapy.

Procedures that were to be done at each visit for evaluation of bacteriologic response were:

Pretherapy:

Culture of cutaneous infection. Patients with cellulitis required a biopsy for culture purposes. Susceptibility of the microorganism(s) isolated to both dirithromycin and erythromycin was to be determined by the NCCLS standardized disk method and/or MIC determination. The pathogen(s) had to be susceptible to erythromycin for the patient to remain in the study. Susceptibility was defined as ≥ 18 mm zone size or ≤ 0.5 $\mu\text{g/mL}$ MIC.

During Therapy:

Culture of cutaneous infection, if source available.

Posttherapy:

Culture of cutaneous infection, if source available.

Late-Posttherapy:

Culture of cutaneous infection, if source available.

b. SAFETY EVALUATION

Safety assessments were to include clinical evaluations (both by examination and by specifically asking about adverse events) and laboratory tests. In terms of adverse events, all patients (or parents or guardians, if the patient was a minor) were to be instructed to contact the investigator or clinical personnel by phone if they experienced an adverse event. Additionally, at each visit adverse events were to be specifically asked about. All adverse events were to be recorded in the clinical report form using the patient's words or the investigator's terms. These were then to be classified by the sponsor based on COSTART definitions in a database referred to as ELECT (Eli Lilly and Company Classification Terms). Adverse events were to be categorized by body system using the algorithm found in the ELECT dictionary.

Selected laboratories were used to determine values for the selected laboratory tests. The following laboratory tests were to be obtained at each visit:

Pretherapy (within 24 hours of receiving the first dose):	<u>Hematology</u>	<u>Blood Chemistry</u>	<u>Urinalysis</u>
	Haemoglobin	Phosphorus	Appearance
	Hematocrit	Calcium	Specific Gravity
	RBC Count	Cholesterol	pH
	MCV	Total Bilirubin	Protein
	MCH	Alkaline Phos.	Glucose
	MCHC	GGT	Ketones
	WBC Count	ALT (SGPT)	Bilirubin
	Differential Count	AST (SGOT)	Urobilinogen
	Platelet Count	Urea	
		Creatinine	Microscopic
		Uric Acid	WBC
		Total Protein	RBC
		Albumin	Casts
		Creatine Kinase*	

During Therapy (days 3-5):

Laboratory tests were to be repeated as clinically indicated. Urine samples were to be assayed for presence of antimicrobial activity.

Posttherapy:

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:

Laboratory tests were to be repeated during Phase II. Laboratory tests were to be repeated during Phase III, if clinically indicated.

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

c. DATA ANALYSIS METHODS

All data obtained from each patient entering the study were to be included in the primary statistical evaluations. Symptomatic and bacteriologic response rates and adverse event frequency rates in the two groups (dirithromycin treated and erythromycin treated) were to be compared by means of chi-square methodology. Laboratory monitoring data were to be analyzed using appropriate continuous data procedures, such as a two-sample t-test on ranked data. Additionally, all analyses were to examine consistency of results among participating clinics. The two formulations of dirithromycin used and "Lilly" formulations) were to be compared also.

Medical Officer's Comments:

As noted before, for the medical officer the two formulations were seen as being identical forms of therapy. Thus, there is no comparison made between the "Thomae" and "Lilly" formulations in the "Results" section.

d. COMPLIANCE

Investigators were to attempt to select those patients and parents or guardians who had a history of complying with instructions. Urine samples were to be obtained from all patients at the during-therapy visit to look for the presence of antimicrobial activity. Additionally, the number of tablets remaining was to be recorded at the posttherapy visit.

5. EVALUABILITY

Based on the above information concerning protocol, efficacy evaluations, and safety evaluations, we can now chronologically look at the actual breakdown of patient evaluability. The easiest and most logical way to do this is to actually look at what occurred at each visit.

a. PRE-THERAPY VISIT: The purpose of this visit was to qualify patients for the study, randomize them into the two treatment groups, determine presenting diagnoses, obtain adequate cultures, obtain routine laboratory tests, perform an initial examination, and obtain signed informed consent forms. Patients qualified if they met the following criteria:

- Had a skin or skin-tissue infection which was acute in nature, appeared to be treatable by the study antimicrobials and was culturable,
- Had a culture of the affected area obtained (either by swab or aspirate, and two blood cultures obtained simultaneously in patients with cellulitis),
- Met inclusion/exclusion criteria,
- Had a history of being reliable and thought to be capable of follow-up visits,
- Signed a consent form approved by a local IRB.

If all these were met, the patient was then randomly (by a randomization scheme devised by the sponsor) assigned to either the dirithromycin or

erythromycin group.

Medical Officer's Comments:

The sponsor did not state explicitly how cultures were to be obtained. For the medical officer, swabs sent for culture were adequate for patients with open or draining lesions. However, for patients with cellulitis or other deep and not open infections, either leading edge or actual area needle aspirate cultures were required. Also, of note, the sponsor did not include patients with infected burns because of the usual severe nature of such infections.

b. DURING THERAPY VISIT: The purpose of this visit was to disqualify patients based on culture or routine laboratory abnormalities, to check the progress of the subjects while on study drug, to follow-up on any abnormal entry laboratory values, and to ask and look for any adverse clinical events. The investigators could disqualify a subject from efficacy evaluation if any of the following were noted:

- Microbiologic disqualification occurred. This included all patients who had one or more of the following:
 1. no growth on culture,
 2. organism(s) grown were resistant to erythromycin,
 3. organism(s) grown were not recognized skin pathogen(s),
 4. culture obtained too late,
 5. culture improperly obtained.
- Disqualification secondary to use of other antimicrobials, be it systemic or topical. If the patient was started on another antimicrobial because of failure of the study drug, then this patient was classified as a "treatment failure".
- Development of adverse event(s) or reporting of an abnormal laboratory measurement requiring termination from the study.
- A violation of inclusion/exclusion criteria was found during therapy.
- Blinding of either the patient or investigator was broken.

Patients discontinued at this time were not eligible for efficacy evaluability, but were included in evaluation for adverse events. Additionally, all patients disqualified at this time had a repeat of their entry laboratory work done.

Medical Officer's Comments:

The sponsor did not specifically list which organisms were classified as recognized skin pathogens. For the medical officer, any culture obtained properly that grew either *Staphylococcus aureus* or *Streptococcus pyogenes* (Group A *Streptococcus*) was seen as evaluable. The majority of cases where *Staphylococcus epidermidis*, or other coagulase negative strains of *Staphylococcus*, was isolated from culture were NOT seen as evaluable by the medical officer. *Staphylococcus epidermidis* is a well recognized "contaminant" or "colonizer" of skin and skin structures, and is usually ONLY seen as a true pathogen in the following patients:

- a. patients who are immunodeficient or who have some compromise of their immune response secondary to chronic disease (such as in diabetics),
- b. patients with central venous or arterial access,
- c. patients with permanent foreign bodies, such as prostheses, heart valves, etc.

Additionally, unless the patient's clinical condition or history revealed a reason to be predisposed, most other organisms were also not accepted as true pathogens. In patients with insulin-dependent diabetes mellitus or with some other chronic disorder predisposing to immunologic difficulties, or with a skin infection known to have flora not *Streptococcal* or *Staphylococcus aureus* in origin (such as infected ulcers or burns), other organisms were accepted.

c. POST-THERAPY VISIT: The purpose of this visit was to evaluate patients for efficacy (both clinical and microbiologic), check for any adverse clinical events, repeat laboratory tests to look for any development of abnormal laboratory values during the clinical trial, and to disqualify those patients from efficacy evaluation that met one of the following criteria:

- Disqualification secondary to use of other antimicrobials, be it systemic or topical. If the patient was started on another antimicrobial because of failure of the study drug, then this patient was classified as a "treatment failure".
- Lost to follow-up, or the patient or investigator terminated the patient from the study secondary to personal reasons.
- Development of adverse event(s) or reporting of an abnormal laboratory measurement requiring termination from the study.
- A late finding that the patient had a violation of initial entry inclusion/exclusion criteria.
- Blinding of either patient or investigator was broken.

Those not disqualified were evaluated for both clinical and microbiologic efficacy, using the criteria noted before in section #3, subsection f. All patients that returned for a post therapy visit were evaluated for safety and laboratory value analysis, regardless if found to be evaluable or not.

At the post-therapy visit, any patient with clinical failure was classified as such and repeat cultures were obtained prior to starting another antimicrobial agent. Patients who were not failures were recultured if applicable or if a source still existed. They were then asked to return for the late post-therapy visit.

Medical Officer's Comments:

There are two points of difference between the sponsor and medical officer at this point. For one, the sponsor evaluated patients only at the post-therapy visit. The results obtained at the late post-therapy visit were recorded but not used as a final endpoint. The medical officer only used the results from the late post-therapy visit for efficacy evaluation. Of note, all patients deemed as failures in visits prior to the late post-therapy visit were carried through to this visit for purposes of statistical evaluation. This is as per the recent recommendations of both the Division of Anti-Infectives at the FDA and the Infectious Disease Society of America (as published in Supplement #1 of the Clinical Infectious Diseases in 1992) to evaluate patients 10-14 days after completion of therapy to look for late recurrences.

The other point of difference is the clinical efficacy criteria used. The sponsor used 5 possible criteria (cured/improved/relapsed/failed/unable to evaluate) while the medical officer used only three (cure/not cured/unable to evaluate). For both the medical officer and sponsor, a patient classified clinically as being "unable to be evaluated" was not included into the final efficacy evaluation.

6. RESULTS

The study population consisted of 391 patients who gave informed consent and were randomized to treatment groups. Of these, 193 (49%) were randomized to the dirithromycin treatment group and 198 (51%) were randomized to the erythromycin treatment group.

The two groups were well matched for weight, height, racial origin, and age but the gender distribution was significantly different. The values obtained by the sponsor were:

- a. Age: the mean age in the dirithromycin treatment group was 40.95 years with the erythromycin group having a mean age of 40.71.
- b. Weight: average weights were 70.42 kg and 71.76 kg for the dirithromycin and erythromycin treatment groups, respectively.
- c. Height: average heights were 168.02 cm and 169.42 cm for the dirithromycin and erythromycin treatment groups, respectively.
- d. Racial origin: 99% of subjects in each treatment group were of caucasian origin.
- e. Gender: in the dirithromycin treatment group, 49.2% of the subjects were female, while only 35.9% of the erythromycin group were female.

a. EVALUABILITY:

The following table shows the number of patients found evaluable for each of the 31 study centers. The table shows both the values obtained by the medical officer and by the sponsor.

CENTER# /INVESTIGATOR	LOCALE	NO. PTS. ENROLLED		NUMBER OF EVALUABLE PATIENTS (%)			
		DIRITHR	ERYTHR	DIRITHROMYCIN		ERYTHROMYCIN	
				SPONSOR	M.O.	SPONSOR	M.O.
301/ Escande	Paris, France	16	16	7 (44%)	7 (44%)	6 (38%)	5 (31%)
702/ Horsman	Kuopio, Finland	11	10	7 (64%)	6 (55%)	7 (70%)	4 (40%)
736/ Kopp	???	1	0	1(100%)	0 (0%)	-----	-----
801/ Cowie	Wilt- shire, U.K.	3	3	2 (67%)	1 (33%)	2 (67%)	1 (33%)
803/ McVey	Dublin, Ireland	13	12	5 (39%)	4 (31%)	8 (67%)	7 (58%)
805/ Khong	Leice- ster, U.K.	3	4	3(100%)	3(100%)	3 (75%)	3 (75%)
806/ Boch- sler	London, U.K.	9	9	6 (67%)	6 (67%)	6 (67%)	6 (67%)
807/ Stone	Bristol , U.K.	6	6	1 (17%)	1 (17%)	2 (33%)	3 (50%)
808/ Walsh	Long- ford, Ireland	1	3	0 (0%)	1(100%)	1 (33%)	1 (33%)
814/ Rosser	Exeter, U.K.	4	3	3 (75%)	2 (50%)	3(100%)	3(100%)

815/ Hughes	Liver- pool, U.K.	3	2	1 (33%)	1 (33%)	2 (100%)	2 (100%)
817/ Munot	Ply- mouth, U.K.	2	3	0 (0%)	0 (0%)	1 (33%)	0 (0%)
818/ Wilson	Staf- ford, U.K.	2	2	1 (50%)	1 (50%)	1 (50%)	1 (50%)
819/ Rodger	Lanark- shire, U.K.	5	6	2 (40%)	2 (40%)	4 (67%)	2 (33%)
820/ Laurie	Renfre- wshire, Scotla.	2	3	0 (0%)	0 (0%)	1 (33%)	1 (33%)
821/ Browne	Wilt- shire, U.K.	4	6	0 (0%)	0 (0%)	3 (50%)	3 (50%)
825/ Marval	Andover Hants, U.K.	5	5	2 (40%)	2 (40%)	4 (80%)	4 (80%)
826/ Qual- trough	Black- pool, U.K.	1	2	0 (0%)	0 (0%)	1 (50%)	1 (50%)
830/ Haworth	Lancs, U.K.	3	3	0 (0%)	0 (0%)	1 (33%)	1 (33%)
855/ Tippins	Birmin- gham, U.K.	2	1	1 (50%)	1 (50%)	0 (0%)	0 (0%)
862/ Shah	Black- wood, U.K.	2	2	2 (100%)	1 (50%)	1 (50%)	1 (50%)
866/ Clarke	Mona- ghan, Ireland	0	1	- - - -	- - - -	1 (100%)	1 (100%)
881/ McNa- mara	Dublin, Ireland	19	18	14 (74%)	14 (74%)	9 (50%)	9 (50%)
882/ Sull- ivan	Tippe- rary, Ireland	12	9	8 (67%)	8 (67%)	3 (33%)	3 (33%)

887/ Harris	Dublin, Ireland	3	2	1 (33%)	1 (33%)	0 (0%)	0 (0%)
888/ Kelly	Kildare Ireland	4	4	3 (75%)	3 (75%)	1 (25%)	1 (25%)
889/ O'Brien	Offaly, Ireland	13	17	8 (62%)	8 (62%)	11 (65%)	12 (71%)
890/ Lyons	Tippe- rary, Ireland	40	41	21 (53%)	24 (60%)	17 (42%)	14 (34%)
897/ O'Con- nell	Cork, Ireland	2	2	0 (0%)	0 (0%)	0 (0%)	1 (50%)
898/ Molloy	Lime- rick, Ireland	0	1	-----	-----	0 (0%)	0 (0%)
899/ Swaine	Dublin, Ireland	2	2	1 (50%)	1 (50%)	0 (0%)	0 (0%)
TOTALS		193	198	100 (52%)	98 (51%)	99 (50%)	90 (45%)

In terms of reasons why subjects were classified as unevaluable, there was a discrepancy in the way the medical officer and sponsor performed this evaluation. The sponsor listed every reason why a subject was found to be unevaluable, and, thus, approximately 20% of unevaluable subjects had more than one reason listed. The medical officer only listed the major reason why a subject was found to be unevaluable, and, thus, each subject had only one reason listed. The following two tables present the sponsor's and medical officer's summaries of why patients were found unevaluable:

TABLE E004 6 1
REASON UNEVALUABLE SUMMARY - ALL PATIENTS

REASON UNEVALUABLE	DIRITHROMYCIN		ERYTHROMYCIN		TOTAL	
	N = 102	%	N = 108	%	N = 210	%
PATS. WITH P. I. REASON	91	88.7%	99	91.7%	190	90.2%
PATS. WITH P. I. RANDOM	71	69.6%	71	65.7%	142	67.1%
PRE-CULTURE NEGATIVE	65	63.7%	74	68.5%	139	66.1%
PAUS. ORG. RESISTANT	22	21.6%	24	22.2%	46	21.9%
UNACCEPT. PATHOGEN	3	2.9%	8	7.4%	11	5.2%
NO POST FOLLOW-UP	3	2.9%	3	2.8%	6	2.9%
UNEVAL. BY INVEST.	3	2.9%	4	3.7%	7	3.3%
INSUFFICIENT THERAPY	1	0.9%	1	0.9%	2	0.9%
NO POST THER. CULTURE	4	3.9%	4	3.7%	8	3.8%
VISIT MISSING	5	4.9%	7	6.5%	12	5.7%
NO INITIAL CULTURE	1	0.9%	1	0.9%	2	0.9%
NO DURING CULTURE	1	0.9%	1	0.9%	2	0.9%
PROTOCOL VIOLATED	2	1.9%	2	1.8%	4	1.9%
WRONG AGE	2	1.9%	2	1.8%	4	1.9%
INCOMPLETE DATA	2	1.9%	2	1.8%	4	1.9%
POSITIVE NOT ONLY	1	0.9%	1	0.9%	2	0.9%
INITIAL CULT. LATE	1	0.9%	1	0.9%	2	0.9%
DURING CULTURE LATE	2	1.9%	2	1.8%	4	1.9%
UNDERLYING INFECTION	2	1.9%	2	1.8%	4	1.9%
POOR COMPLIANCE	1	0.9%	1	0.9%	2	0.9%
CONFLICTING DATA	1	0.9%	1	0.9%	2	0.9%
BEHIND ORDER	1	0.9%	1	0.9%	2	0.9%
POST THER. CULT. EARLY	1	0.9%	1	0.9%	2	0.9%
POST THER. CULT. LATE	1	0.9%	1	0.9%	2	0.9%
INITIAL CULT. LATE	1	0.9%	1	0.9%	2	0.9%
EARLY CLIN. ASSESSMENT	1	0.9%	1	0.9%	2	0.9%

MEDICAL OFFICER'S REASON UNEVALUABLE SUMMARY

	Dirithromycin	Erythromycin
1. MICROBIOLOGIC		
A. no culture	1 (1%)	4 (4%)
B. no growth	9 (9%)	13 (12%)
C. resistant org.	31 (33%)	26 (24%)
D. unacceptable org.	38 (40%)	49 (45%)
E. miscellaneous	1 (1%)	2 (2%)
2. CONCOMITANT MEDICATIONS	1 (1%)	1 (1%)
3. POOR FOLLOW-UP	9 (9%)	12 (11%)
4. ADVERSE EVENTS	2 (2%)	1 (1%)
5. OTHERS	3 (3%)	0 (0%)
A. poor compliance	1	0
B. conflicting data	1	0
C. mistake made by microbiology lab	1	0
TOTALS	95	108

Notes: In this chart the % given is the % of unevaluable patients, not for the entire patient population. Also, the sponsor tested all pathogens for susceptibility to both erythromycin and dirithromycin, but officially reported organisms as being either sensitive or resistant based on the zones obtained with erythromycin. This was done because erythromycin and dirithromycin had similar susceptibility patterns with typical skin infection pathogens (such as *Staphylococcus aureus* and *Streptococcus pyogenes*) so the class antibiotic was chosen (that is, erythromycin).

Medical Officer Comments

The number of patients found evaluable by the medical officer and the sponsor are comparable, unlike the large discrepancy noted in the AQAB skin study. The major reasons that a subject was deemed unevaluable by both the sponsor and the medical officer were microbiologic in nature with between 80-85% of unevaluable patients falling into this category.

Of note, the number of subjects that had erythromycin resistant Staphylococcus aureus as the pathogen was 11 or 6% of all patients with cultures growing this organism. This is significantly less than the 17% resistance rate noted in the AQAB skin study for Staphylococcus aureus. The sponsor submitted data which evaluates the susceptibility patterns based on dirithromycin disk diffusion tests. The resistance rate with dirithromycin is 5%.

As a final note, this study was to be an European study, with the 31 study centers theoretically spread out among the various countries of Europe. However, the VAST majority of study centers in this study were either in Ireland or in the United Kingdom. This may affect the microbiologic picture seen.

b. DEMOGRAPHICS:

The following section deals with the demographics of the evaluable patients as per the medical officer. The sponsor presented demographics dealing with all enrolled patients (this was presented before) but did not give specific demographics for only the evaluable patients.

1. Gender: 53% of the dirithromycin evaluable group was female while only 34% of the erythromycin evaluable group was female.

2. Age: For dirithromycin, the following age distribution was obtained:

YRS	#	%
15-24	23	23%
25-34	23	23%
35-44	20	20%
45-54	9	9%
55-64	20	20%
>=65	3	3%

For erythromycin, the following distribution was obtained:

YRS	#	%
15-24	20	22%
25-34	19	21%
35-44	14	16%
45-54	10	11%
55-64	24	27%
>=65	3	3%

3. Weights: For dirithromycin, the following weight distribution was found:

wt. (kg)	#	%
<40	0	0%
40-49	2	2%
50-59	19	19%
60-69	38	39%
70-79	22	22%
>=80	17	17%

For erythromycin, the following weight distribution was obtained:

<u>wt. (kg)</u>	<u>#</u>	<u>%</u>
<40	0	0%
40-49	1	1%
50-59	15	17%
60-69	28	31%
70-79	27	30%
>=80	19	21%

4. Concomitant medications and illnesses: All patients on other systemic or topical antimicrobials, or using steroid preparations, were seen as unevaluable (unless the other antimicrobial was started due to failure of the study drug, at which time the patient was seen as a failure). In the evaluable population, the most commonly used concomitant medication was paracetamol, and this was used evenly among the two treatment groups. Other commonly used concomitant medications were oral contraceptives and medications specifically for therapy of underlying conditions (such as anti-hypertensives). There was no significant difference between the two treatment groups in regards to % of subjects with underlying illnesses, with regards to % with a specific illness, or with regards to use of a specific medication.

5. Duration of therapy: Subjects with insufficient therapy or with overly prolonged therapy were seen as unevaluable unless a subject discontinued the study drug because of poor response and then was seen as a failure. The duration of therapy that the sponsor was interested in was 7 days. The following distribution of duration of therapy was obtained for dirithromycin:

<u>duration (days)</u>	<u>#</u>	<u>%</u>
<=4	2	2%
5-6	1	1%
7-8	94	96%
9-10	1	1%
>10	0	0%

The following distribution was seen in the erythromycin group:

<u>duration (days)</u>	<u>#</u>	<u>%</u>
<=4	0	0
5-6	3	3%
7-8	85	94%
9-10	2	2%
>10	0	0%

6. Diabetes Mellitus: In each treatment group there was one patient with diabetes mellitus, accounting for 1% of each treatment group evaluable population.

Medical Officer Comments:

Except for the issue of gender, the evaluable portions of each treatment group were similar in their demographics. In regards to the gender, however, there should not have been a physiologic reason to expect different results in males and females in regard to response to therapy for skin and skin structure infections.

c. DISEASE TYPES:

There were 6 different disease types represented by the 188 evaluable patients (as per the medical officer) with the following distribution:

DIAGNOSIS	DIRITHROMYCIN	ERYTHROMYCIN	TOTAL
INFECTED BURNS	3 (3%)	2 (2%)	5
INFECTED ULCERS	4 (4%)	9 (10%)	13
IMPETIGO	25 (26%)	22 (24%)	47
POST-SURGICAL WOUND INFECTIONS	7 (7%)	5 (6%)	12
POST-TRAUMA WOUND INFECTIONS	27 (28%)	23 (26%)	50
PYODERMA	32 (33%)	29 (32%)	61
TOTALS	98	90	188

The sponsor did not divide the evaluable patients into disease entities but did look at this in regards to all enrolled patients. The following table shows the sponsor's data.

DIAGNOSIS	DIRITHROMYCIN (N=193)		ERYTHROMYCIN (N=198)		TOTAL (N=391)	
	N	(%)	N	(%)	N	(%)
INFECTED BURNS	5	(2.6%)	3	(1.5%)	8	(2.0%)
CELLULITIS	1	(0.5%)	2	(1.0%)	3	(0.8%)
IMPETIGO	37	(19.2%)	39	(19.7%)	76	(19.4%)
POST-SURGICAL WOUND INFECTION	15	(7.8%)	9	(4.5%)	24	(6.1%)
TRAUMATIC WOUND INFECTION	43	(22.3%)	51	(25.8%)	94	(24.0%)
PYODERMA	72	(37.3%)	72	(36.4%)	144	(36.9%)
INFECTED SKIN ULCER	20	(10.4%)	22	(11.1%)	42	(10.7%)

Medical Officer's Comments:

In regards to the disease type, there are no statistically significant differences between the two treatment groups in the patients found evaluable by the medical officer.

d. EFFICACY:

This section will present the results obtained by the medical officer. It is essentially divided into two tables. The first table is a combination table where the disease types are matched with specific organisms and then a total efficacy rate for the disease type is presented. The second table presents efficacy rates for each individual organism, irregardless of the disease they caused.

Several points of clarification are necessary prior to the presentation of the tables. All evaluations are done based on the data from the late post-therapy visit. As noted previously, the clinical results were classified as either "Cured" or "Not Cured". The term "Improved" was not used by the medical officer. Patients with a very major improvement were classified as "Cured" while all other "Improved" patients were seen as "Not Cured". In regards to the microbiologic response, the categories presented before were combined into three major categories which were:

1. Assumed eradicated: All subjects in which a repeat culture showed elimination of the initial pathogen and all subjects in which a repeat culture was not obtained due to lack of a site (the "Not Applicable" group) were included here.
2. Not eradicated: This includes all patients in which the repeat culture showed either persistence of the initial organism, growth of a new pathogen, or regrowth of the initial organism but now with a resistance to the study drugs.
3. Unable to Evaluate: This group includes all patients in which the investigator did not state what was done microbiologically with the subject at the late post-therapy visit.

The percent rate of microbiologic cure is thus based on the ratio of "Assumed eradicated" patients divided by the sum of the "Not eradicated" and "Assumed eradicated" patients. The group labelled "Unable to Evaluate" was not included in the ratio.

The criteria for accepting an organism as a true pathogen were presented previously. The accepted pathogens obtained were divided into 5 groups:

1. *Staphylococcus aureus*: all subjects where this was the only pathogen isolated.
2. *Streptococcus pyogenes*: all subjects where this was the only pathogen isolated.
3. Other streptococcal species: all subjects with *Streptococcus* species other than *pyogenes* isolated as the only pathogen.
4. Mixed flora: all subjects where an accepted combination of pathogens were obtained on initial culture. An example is a subject with impetigo having both *Streptococcus pyogenes* and *Staphylococcus aureus* growing on initial culture.
5. Other organisms: subjects, especially diabetics, where more unusual organisms (as far as skin infections are concerned) were accepted as being true pathogens. An example would be a diabetic patient with *Escherichia coli* growing in a culture from an infected ulcer.

For the two tables that follow, "A.E." stands for "Assumed Eradicated" and "UTE" for "Unable to Evaluate".

DIRITHROMYCIN			ERYTHROMYCIN		
INFECTED BURNS					
Organism (# pts.)	Clinical Response	Micro Response	Organism (# pts.)	Clinical Response	Micro Response
<i>S. aureus</i> (3)	3 CURED (100%)	3 A.E. (100%)	<i>S. aureus</i> (2)	2 CURED (100%)	2 A.E. (100%)
TOTALS (3)	3 CURED (100%)	3 A.E. (100%)	TOTALS (2)	2 CURED (100%)	2 A.E. (100%)
INFECTED ULCERS					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (4)	1 CURED (25%)	3 A.E. 1 UTE (100%)	<i>S. aureus</i> (9)	7 CURED (78%)	8 A.E. (89%)
TOTALS (4)	1 CURED (25%)	3 A.E. 1 UTE (100%)	TOTALS (9)	7 CURED (78%)	8 A.E. (89%)
IMPETIGO					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (20)	19 CURED (95%)	18 A.E. (90%)	<i>S. aureus</i> (20)	19 CURED (95%)	20 A.E. (83%)
<i>Strep pyogenes</i> (1)	1 CURED (100%)	1 A.E. (100%)			
Other <i>strep</i> (1)	1 CURED (100%)	1 A.E. (100%)			
Mixed flora (3)	2 CURED (67%)	2 A.E. (67%)	Mixed flora (2)	2 CURED (100%)	2 A.E. (100%)
TOTALS (25)	23 CURED (92%)	20 A.E. (88%)	TOTALS (22)	21 CURED (95%)	22 A.E. (100%)

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POST-SURGICAL WOUND INFECTIONS					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (7)	6 CURED (86%)	6 A.E. (86%)	<i>S. aureus</i> (5)	4 CURED (80%)	4 A.E. (80%)
TOTALS (7)	6 CURED (86%)	6 A.E. (86%)	TOTALS (5)	4 CURED (80%)	4 A.E. (80%)
POST-TRAUMA WOUND INFECTIONS					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (20)	19 CURED (95%)	18 A.E. 2 UTE (100%)	<i>S. aureus</i> (18)	18 CURED (100%)	18 A.E. (100%)
<i>Strep pyogenes</i> (3)	3 CURED (100%)	3 A.E. (100%)	<i>Strep pyogenes</i> (3)	3 CURED (100%)	3 A.E. (100%)
Other strep (2)	2 CURED (100%)	2 A.E. (100%)	Other strep (1)	1 CURED (100%)	1 A.E. (100%)
Other organisms (1)	1 CURED (100%)	1 UTE			
Mixed flora (1)	1 CURED (100%)	1 A.E. (100%)	Mixed flora (1)	1 CURED (100%)	1 A.E. (100%)
TOTALS (27)	26 CURED (96%)	24 A.E. 3 UTE (100%)	TOTALS (23)	23 CURED (100%)	23 A.E. (100%)
PYODERMA					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (28)	26 CURED (93%)	26 A.E. 1 UTE (96%)	<i>S. aureus</i> (24)	19 CURED (79%)	19 A.E. 2 UTE (86%)
<i>Strep pyogenes</i> (3)	3 CURED (100%)	3 A.E. (100%)			
			Other strep (3)	3 CURED (100%)	2 A.E. 1 UTE (100%)
			Mixed flora (1)	1 CURED (100%)	1 A.E. (100%)

DIR			ERY		
Other organisms (1)	1 CURED (100%)	1 A.E. (100%)	Other organisms (1)	0 CURED (0%)	0 A.E. (0%)
TOTALS (32)	30 CURED (94%)	30 A.E. 1 UTE (97%)	TOTALS (29)	23 CURED (79%)	22 A.E. 3 UTE (85%)
TOTALS (98)	89 CURED (91%)	88 A.E. 5 UTE (95%)	TOTALS (90)	80 CURED (89%)	81 A.E. 3 UTE (93%)

The following table looks at the results obtained in regards to specific organisms:

DIRITHORMYCIN			ERYTHROMYCIN		
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (#pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (82)	74 CURED (90%)	74 A.E. 4 UTE (95%)	<i>S. aureus</i> (78)	69 CURED (88%)	71 A.E. 2 UTE (93%)
<i>Strep pyogenes</i> (7)	7 CURED (100%)	7 A.E. (100%)	<i>Strep pyogenes</i> (3)	3 CURED (100%)	3 A.E. (100%)
Other strep (3)	3 CURED (100%)	3 A.E. (100%)	Other strep (4)	4 CURED (100%)	3 A.E. 1 UTE (100%)
Mixed flora (4)	3 CURED (75%)	3 A.E. (75%)	Mixed flora (4)	4 CURED (100%)	4 A.E. (100%)
Other organisms (2)	2 CURED (100%)	1 A.E. 1 UTE (100%)	Other organisms (1)	0 CURED (0%)	0 A.E. (0%)
TOTALS (98)	89 CURED (91%)	88 A.E. 5 UTE (95%)	TOTALS (90)	80 CURED (89%)	81 A.E. 3 UTE (93%)

The following pathogens were found in the mixed flora group:

1. Dirithromycin treatment group: 4 patients with "mixed flora" in their initial culture. All 4 had *Staphylococcus aureus*. The other pathogen found was *Streptococcus pyogenes* in all 4 patients. In regard to response to therapy, 3 patients had both a clinical cure and assumed bacterial eradication, and the 4th subject had both clinical and bacteriologic failure.

2. Erythromycin treatment group: 4 patients with "mixed flora" in their initial culture. All 4 had *Staphylococcus aureus*. The other pathogen found was *Streptococcus pyogenes* in 3 patients and *Streptococcus* species in 1 subject. In regard to response to therapy, the following was found:

- a. *Staphylococcus aureus* & *Streptococcus pyogenes* combination: 3 patients, all of whom were both clinically and microbiologic cures.
 b. *Staphylococcus aureus* & *Streptococcus* species: 1 patient, with a clinical and microbiologic cure.

If the organisms found in the "mixed flora" are considered individually, the results found were:

DIRITHROMYCIN			ERYTHROMYCIN		
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (#pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (86)	77 CURED (90%)	77 A.E. 4 UTE (94%)	<i>S. aureus</i> (82)	73 CURED (89%)	75 A.E. 2 UTE (94%)
<i>Strep pyogenes</i> (11)	10 CURED (91%)	10 A.E. (91%)	<i>Strep pyogenes</i> (6)	6 CURED (100%)	6 A.E. (100%)
Other <i>strep</i> (3)	3 CURED (100%)	3 A.E. (100%)	Other <i>strep</i> (5)	5 CURED (100%)	4 A.E. 1 UTE (100%)

Medical Officer's Comments:

Based on the microbiologic breakdown, *Staphylococcus aureus* was the only pathogen found in enough patients (greater than 10 in each of the two treatment groups) to be able to comment on the efficacy of dirithromycin in clearing skin and skin structure infections caused by this organism. The number of patients found to have infections caused by any of the other organisms was too small to be able to compare with certainty the two antimicrobials.

Using the Chi-square test, the dirithromycin and erythromycin treatment groups' efficacy results were compared for total outcome, patients with *Streptococcus pyogenes*, and patients with *Staphylococcus aureus*. In all three comparisons, there was no statistically significant difference (using a two-sided tail p value of 0.5) among the treatment groups in both the clinical and microbiologic response rates.

e. ADVERSE CLINICAL EVENTS:

The individual investigators listed all clinical adverse events that occurred during the course of the clinical trial. The investigators were also responsible for stating whether the adverse event was probably, possibly, or not related or of unknown relation to the study drug. The sponsor later, when evaluating the data, agreed or disagreed with the investigators' evaluation of the adverse clinical events. The medical officer also went through the investigators' reports and either agreed or disagreed with the investigators' evaluations. The results obtained by the medical officer and by the sponsor were very similar, so only one list of adverse clinical events will be presented in this section will reflect the medical officer's results. The adverse events listed in this section are only those seen as possibly, probably or definitely related to the study drug or of unknown relation. Adverse events not related to the study drugs are not listed.

All adverse events of a mild or moderate degree are listed together. Severe or serious adverse clinical events will be presented individually.

Of the 391 enrolled subjects, a total of 43 experienced one or more adverse clinical events, or a total of 11% of the subjects. Of the 391 enrolled patients, 193 received dirithromycin and 198 received erythromycin. Of the dirithromycin treatment group, 19 subjects experienced an adverse clinical event, or 9.8%. In the erythromycin group, 24 experienced an adverse clinical event, or 12.1%. There were two serious adverse clinical events, one was in the dirithromycin treatment group (pt. #702-7050 with severe tiredness) and the other in the erythromycin treatment group (pt. #898-8117 with severe syncope). The following table shows a breakdown of the adverse clinical events for each antibiotic:

EVENTS	Dirithromycin	Erythromycin
A. GI SYSTEM		
1. Abd. Pain	3 (2%)	5 (3%)
2. Nausea/Dyspepsia	4 (2%)	6 (3%)
3. Diarrhea	2 (1%)	5 (3%)
4. Emesis	0 (0%)	1 (1%)
5. Combination of Nausea/ Vomiting/Diarrhea	0 (0%)	1 (1%)
6. Constipation	0 (0%)	1 (1%)
B. CNS		
1. Headache	4 (2%)	2 (1%)
2. Taste Perversion	1 (1%)	1 (1%)
3. Dry Mouth	0 (0%)	1 (1%)
4. Dizziness	1 (1%)	0 (0%)
5. Auditory Hallucinations	0 (0%)	1 (1%)
C. GENITOURINARY SYSTEM		
1. Vaginitis	2 (1%)	1 (1%)
2. Urinary Tract Infection	1 (1%)	1 (1%)
D. SKIN		
1. Pruritis	0 (0%)	1 (1%)
2. Urticaria	1 (1%)	0 (0%)
3. Pruritic Rash	0 (0%)	1 (1%)

Medical Officer's Comments:

Though there was some variability in the study centers as to the percentage of subjects with adverse clinical events, this did not seem to affect the overall comparison between erythromycin and dirithromycin. Of the adverse events experienced with the dirithromycin, none were unexpected considering the class of antibiotics, macrolides, that dirithromycin is in.

f. LABORATORY VALUES:

Upon evaluating all laboratory results obtained on all of the patients, 29 of the 391 enrolled subjects (or 7.4%) were noted to have significant laboratory value changes possibly or probably associated with study drug use. This was

determined by the medical officer based on the following criteria:

1. There was a clinically significant change in a laboratory test value compared to a baseline value while on the study drug or noted up until the time of the late posttherapy visit.
2. This change in the laboratory value was not secondary to either the disease process that entered the subject into the study, or secondary to a chronic condition. Exceptions to this were made if the study drug caused a change in patients with a chronic condition who were stable until use of the study drug. For example, a patient with a history of high cholesterol levels, but under control, who had a sudden increase in cholesterol levels during the clinical trial would be considered as having had a significant laboratory value change probably related to the study drug.
3. This laboratory change did not stand out on its own, but was consistent with other changes. For example, a patient with a mildly elevated ALT level who had otherwise normal liver function tests would not be considered as having a study drug related laboratory abnormality, but a laboratory value variation.

Of the 29 patients with significant laboratory value changes, 14 were in the dirithromycin treatment group (or 7.3% of those subjects) and 15 in the erythromycin treatment group (or 7.6% of those subjects). Three subjects had severe changes in laboratory values, which were:

1. Pt. #882-4102, erythromycin treatment group, who had a severe decrease in the level of calcium during therapy.
2. Pt. #806-8105, dirithromycin treatment group, who had a severe elevation of BUN and creatinine.
3. Pt. #890-4063, dirithromycin treatment group, who had a severe elevation of BUN, creatinine, and phosphorus.

Of the remaining 26 subjects, the following mild to moderate changes in laboratory values were noted:

<u>LABORATORY VALUE CHANGE</u>	<u>#DIRITHRO</u>	<u>#ERYTHRO</u>
1. decreased platelets	4	1
2. increased eosinophils	1	2
3. decreased calcium	2	0
4. decreased phosphorus	4	8
5. increased phosphorus	0	1
6. increased creatinine	1	2
7. increased alkaline phosphatase	1	0

ADDITIONAL CLINICAL TRIALS IN SKIN AND SOFT TISSUE INFECTIONS

In addition to the 2 major clinical trials described previously (the E004 and AQAB studies), there are 3 other clinical trials involving the use of dirithromycin in treatment of skin and soft tissue infections. A brief summary of each follows.

I. Protocol B9Z-IT-E008: "Dirithromycin Versus Miacamycin in Skin and Soft Tissue Infections"

Study was started in October of 1989, and enrollment was completed in August of 1990. It was a single-blind, randomized, parallel study done at one study center by 5 investigators in Italy.

The objective of the study was to compare dirithromycin and miocamycin for efficacy and safety in the treatment of skin and soft tissue infections caused by susceptible bacterial pathogens.

A total of 70 patients were enrolled in the dirithromycin arm (42 males and 28 females) and 71 in the miocamycin arm (49 males and 22 females). All patients were to receive 7 days of study drug.

As per the investigators, the two groups were well matched with respect to all demographic variables. In order to be qualified for efficacy analysis, patients had to have had a positive pretherapy culture, returned for the posttherapy clinical evaluation, and could be evaluated for a clinical response. Based on this, 80% of the dirithromycin and 87% of the miocamycin group qualified for efficacy analysis, as per the investigators. Reasons why subjects were found as unevaluable were not given.

As per the investigators, a favorable clinical response (cure OR improvement) was noted in 98% of the qualified dirithromycin subjects and 95% of the qualified miocamycin subjects. The bacteriologic response was presumed or proven eradication in 93% of qualified dirithromycin patients and 84% of qualified miocamycin patients. There was no statistically significant difference between the two groups as per the investigator. Of note, no data was provided re:organisms isolated from the initial cultures.

No difference in adverse events were noted by the investigator, and there were 3 patient withdrawals from the study secondary to adverse events, but details were not provided. No deaths or serious adverse events occurred.

II. Study B9Z-MC-AQAU(a): "Dirithromycin 5 Days vs. Erythromycin 7 Days in the Treatment of Skin and Soft Tissue Infections"

Enrollment was started in December of 1991, and at the time of NDA application was still an ongoing study. This is a multi-center (all U.S.), multiple investigator, double-blind, double-dummy, randomized, parallel study.

The objective of the study is to test the hypothesis that 500 mg of dirithromycin taken once daily for 5 days is as safe and effective as 250 mg erythromycin base taken every 6 hours for 7 days in the treatment of skin and soft tissue infections.

As of February 28, 1992, a total of 139 patients were enrolled.

In order to be included in the study, patients had to have one of the following culturable infections of skin and/or soft tissue: subcutaneous abscess (including paronychia, furuncle, or carbuncle); impetigo; pyoderma; infected skin ulcer (excluding ulcers below the knees in diabetic patients); wound infection, post-surgical; wound infection, traumatic; cellulitis or erysipelas; or lymphangitis. In order to be found clinically evaluable, patients had to have completed at least 80% of a 5-day course of study drug, met the above inclusion criteria, and have had pretherapy and posttherapy assessments of signs and symptoms. Bacteriologic evaluability would be based on all of the above, plus a pretherapy culture positive for a pathogen.

At the time of the NDA submission, 139 patients had been enrolled by a total of 28 investigators. Of these subjects, 3 patients discontinued early due to adverse events. Details not provided.

III. Study B92-MC-AQAX(a): "Dirithromycin 5 Days vs Erythromycin 7 Days in the Treatment of Skin and Soft Tissue Infections"

Enrollment started in February of 1992, and at the time of NDA submission one subject had been enrolled. This is a multi-center (all U.S.), multiple investigator, double-blind, double-dummy, randomized, parallel study.

The objective of the study is to test the hypothesis that 500 mg of dirithromycin taken once daily for 5 days is as safe and effective as 250 mg erythromycin base taken every 6 hours for 7 days in the treatment of skin and soft tissue infections.

In order to be included in the study, patients had to have one of the following culturable infections of skin and/or soft tissue: abscess, subcutaneous (including paronychia, furuncle, or carbuncle); impetigo; pyoderma; skin ulcer, infected (excluding ulcers below the knees in diabetic patients); wound infection, post-surgical; wound infection, traumatic; cellulitis or erysipelas; or lymphangitis. In order to be found clinically evaluable, patients had to have completed at least 80% of a 5-day course of study drug, met the above inclusion criteria, and have had pretherapy and posttherapy assessments of signs and symptoms. Bacteriologic evaluability would be based on all of the above, plus a pretherapy culture positive for a pathogen.

As noted previously, one subject had been enrolled at the time of NDA submission. No adverse events were noted in this one subject.

Pharm. memos

Pharm./Tox.

Review

Labeling

MEMO OF RECORD

Date: April 25, 1995

To: Maureen Dillon-Parker, CSO (HFD-520)

From: S.R. Joshi, D.V.M., Ph.D.

Thru: R.E. Osterberg, Ph.D., Supervisory Pharmacologist

RE: DYNABAC^R (dirithromycin) [Lilly] NDA 50-678
Labelling: Response to Dr. Lumpkin dated 4/24/95

A. Pregnancy Category: OK as revised.

B. Nursing Mothers: [present labelling]

"It is not known whether either dirithromycin or erythromyclamine is excreted in human milk, caution should be exercised when dirithromycin is administered to a nursing mother."

Comments:

1. Language for dirithromycin is similar to that for azithromycin.

2. The language for clarithromycin, however, contains an additional sentence:

"It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk."

3. I have not seen any specific study for excretion of dirithromycin in the dam's milk in animals.

4. A rat reproduction study* showed that exposure of neonates to the antibiotic, via maternal milk, occurred but the exposure was minimal.

*Preliminary Fertility and General Development in Rats After Treatment With AS-E 136 BS (dirithromycin). Toxicology Report No.24 (see my pharm./tox review: study "J")

5. Erythromycin is excreted in breast milk, -therefore, caution should be exercised when erythromycin is administered to a nursing mother [labelling for PCE; Erythromycin Delayed-Release Capsules (both Abbott Labs.)]

cc:
NDA 50-678
HFD-520
HFD-520/Pharm/Joshi
N-50-678.5

S.R. Joshi 4/25/95
S.R. Joshi D.V.M., Ph.D.

HFD-520/Moledina
HFD /rd init. by REOsterberg

REO 4/25/95

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 3/24/95

To: Lilian Gavrilovich, M.D.
Acting Division Director, DAIDP (HFD-520)

Thru: R.E. Osterberg, Ph.D., *REC'D 3/24/95*
Supervisory Pharmacologist (HFD-520)

From: S.R. Joshi, D.V.M., Ph.D. (HFD-520) *S.R. Joshi 3/24/95*

Subject: NDA 50-678; DYNABAC (dirithromycin);
Item #12.

This memo pertains to Question No. 12 posed by FDA and Lilly's response.

FDA Request: An explanation of whether animals hydrolyze dirithromycin as do humans and whether an assay was used in the animal studies that would allow differentiation between dirithromycin and any microbiologically active other moiety.

Lilly's Response:

- ... subsequent to dirithromycin dosing of both animals and humans that dirithromycin hydrolyses to erythromyclamine.
- Assays of plasma and/or tissue extracts were conducted by high performance liquid chromatography (HPLC) with electrochemical detection. Copies of:
 - (a) one of the ADME studies (Report No.18) (see Appendix 5)
 - (b) An international Registration Document entitled "Hydrolysis of Dirithromycin to Erythromyclamine" dated May 14, 1991 (see Appendix 6)
 - (c) "Expert Report on Toxicological and Pharmacological Documentation" dated June 1992 (see Appendix 7)

Appendix 5: Plasma and Tissue Concentrations of Dirithromycin and Erythromyclamine in Rats Dosed Intraduodenally with 30 mg/kg of Dirithromycin.

- Dirithromycin hydrolyzed to erythromyclamine in the duodenal lumen prior to absorption.

- Erythromyclamine was present in the portal plasma in higher concentrations than dirithromycin although portal concentrations of both compounds were relatively low.
- Systemic plasma concentrations of dirithromycin and erythromyclamine were very low although erythromyclamine concentrations were constantly greater than those of dirithromycin.
- Dirithromycin hydrolyzed to erythromyclamine in rat plasma at C in vitro (rate constant min^{-1}).
- Tissue concentrations of erythromyclamine were appreciably higher than those in systemic plasma indicating sequestration of erythromyclamine in the tissues whereas dirithromycin tissue concentrations were not detectable.

Appendix 6: Hydrolysis of Dirithromycin to Erythromyclamine And its Relevance to the Toxicologic Evaluation of Erythromyclamine.

- The clinical disposition and metabolism data with dirithromycin are consistent with the animal data in that erythromyclamine is also the predominant drug related material in the circulation with little or no dirithromycin detected.
- It therefore follows that in vivo toxicology studies conducted with dirithromycin reflect not only the safety of administered dirithromycin, but also the safety of erythromyclamine by virtue of the hydrolysis of dirithromycin to erythromyclamine in vivo.
- The authors then discuss the rationale for this position....

Conclusion: It is quite clear from the above, that dirithromycin is indeed hydrolysed to erythromyclamine in the animals as well (as do humans).

Lilly's response to the Question 12 posed by FDA has been adequately addressed.

cc: Oleg NDA

HFD-520

HFD-520/CSO/ DILLON PARKER

[Handwritten signature]

13

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520**

Date CDER Received: 6/5/92
Date Assigned: 6/10/92 & 10/8/93
Date Review Started: 8/25/92 & 10/8/93
Date 1st. Draft Completed: 11/15/93
Date Review Accepted by Supervisor: 11/17/93

NDA # 50-678 (Original submission dated 6/4/92)

Number of Volumes: 39

Drug: DYNABAC[®] (dirithromycin) Tablets
Drug Codes: LY237216 (Lilly); AS-E 136 (Karl Thomae GmbH)

Sponsor: Eli Lilly Research Laboratories, Indianapolis, IN
Contact Person: Dr. Larry Day (317) 276-5037

Category: Macrolide antibiotic

**Dosage Form: Enteric coated tablets, 250 mg, b.i.d (500 mg/day)
for 7-14 days**

Indication: Secondary bacterial infections

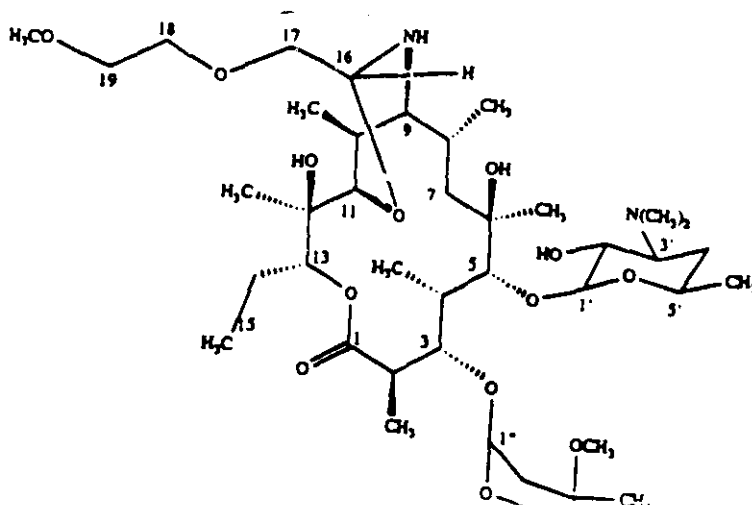
Chemical Name 1) (9s)-9-deoxo-11-deoxy-9,11-[imino(1R)-2-(2-methoxyethoxy)ethylidene]oxy]-erythromycin.
2) erythromycin, 9-deoxo-11-deoxy-9,11-[imino[2-(2-methoxyethoxy)ethylidene]-oxy-, [9s, (R)]-

CAS #: 62013-04-1

Empirical formula: C₄₂H₇₈N₂O₁₄

Molecular weight: 835.09

Structural formula:



Formulation:

<u>Name of Ingredient</u>	<u>Quantity</u>	<u>Reasonable Variations</u>
	<u>(mg/tablet)</u>	<u>(mg/tablet)</u>
<u>Active Ingredient</u>		
Dirithromycin	250.0	(0-3% excess)

Other IngredientsCore Tablet:

- Magnesium Carbonate
- Microcrystalline Cellulose
- Sodium Starch Glycolate
- Hydroxypropyl Cellulose
- Croscarmellose Sodium
- Magnesium Stearate

Core Tablet WeightSubcoating (Theoretical)

- Hydroxypropyl methylcellulose
- Polyethylene Glycol
- Propylene Glycol
- Benzyl Alcohol

Enteric Coating (Theoretical)

- Methacrylic Acid Copolymer
- Triethyl Citrate
- Talc

Related Submissions: INDS' (Macrolide):

Review Objectives: Review preclinical data with regard to safety for the marketing of the drug product.

Reviewer's Notes:

This drug was previously assigned to Dr. Norma Jean Browder, Ph.D., who reviewed the preclinical studies submitted previously in IND Her reviews dated 4/29/88 and 8/4/89 are attached

Index of Studies: see next page

TOXICOLOGY REPORTS (LILLY'S REPORT #; NDA VOLUME #)

<u>Rept #</u>	<u>Study</u>	<u>NDA Vol.</u>	<u>Page</u>
Acute Toxicity:			
1.	Acute Tox (Aug. 1986)	1.9	69
11.	Acute tox in Fischer-344 rats (Dec.1986)	1.9	116
12*.	Acute tox in ICR mouse (Dec. 1986)	1.9	144
Subchronic Toxicity:			
2.	3-mon. oral in rats (Aug. 1986)	1.9,10	169,/2
3.	3-mon. oral in rabbits (Aug. 1986)	1.11	2
13.	3-mon. oral in Beagle dogs (July 1987)	1.11	188
17.	Prelim I.V. in rats (Aug. 1986)	1.14	2
18.	13-week i.v. in Wistar rats(Jan. 1987)	1.14,15	123
19.	4-week, i.v. in rats (Aug. 1986)	1.16,17	
4.	5-Week , i.v. in rabbits (Aug. 1986)	1.18	2
5.	5-Week, i.v. in dogs (Aug. 1986)	1.19	2
Chronic Toxicity:			
28*.	6-month oral tox in Fischer rats 6/91	1.20,1.21	3
29*.	6-month oral Beagle dogs June 1991	1.22, 23	2
34*.	6-month oral in Beagle dogs May 1992	1.24,25	2
Special Toxicity:			
22.	Acute dermal, ocular May 1989	1.27	139
26*.	Mycotoxicity, 4-week, oral, CD rats 6/91	1.26	8,112
27*.	Mycotoxicity, 4-Week, i.v. CD Rats 6/91	1.26,27	240
32*.	Subchronic Inhalation in Beagle dogs 3/92	1.27,28	
23*.	Acute tox. of epidirithromycin, oral, rats. Jan. 1990	1.27	143

Reproduction Studies:

14.	Basic Fertility study of dirithromycin lactobionate, I.V. in male Wistar rats	6/87	1.28	7
21.	Basic Fertility study of dirithromycin lactobionate, I.V. in female Wistar rats	6/87	1.28	50
15.	Segment II in rats	Sept 1986	1.36	2
16.	Terata in rabbits	May 1987	1.36	287
24*.	Preliminary study of Female Fertility and General Development in rats after Oral treatment with AS-E 136 BS [dirithromycin] ("MOD. Segment I")	5/91	1.29	4
25*.	An Oral fertility and General Reproduction Study of Dirithromycin. in the Rat.	5/91	1.31-35	4

Mutagenicity Studies:

6(1).	Ames test	Aug. 1986	1.37	10
8.	Ames test	Sept 1986	1.37	46
7.	DNA repair in rat hepatocytes	July 1986	1.37	73
9.	Forward mutation -mouse	Nov 1986	1.37	97
6(4).	Mutag. in V79 (HGPRT) test	Aug. 1986	1.37	204
10.	Sister-chromatid exchange - Chinese hamsters		1.37	136
6(2).	Micronucleus test in mice	Aug. 1986	1.37	156
6(3)	Sister-chromatid exch.- Human lymphocytes		1.37	178
33*.	Micronuclei in bone maarow	April 1992	1.37	237

Note: Studies marked with asterisk ("*") are reviewed below.

A. Acute Toxicity Study in ICR Swiss Mouse:

An acute oral toxicity study by oral (gavage) route was conducted in male and female ICR Swiss mice given 0., 2821.9, or 4703.1 mg/kg dirithromycin as a suspension in 10% aqueous acacia solution. Two females in the high-dose group died within 5

hours. Clinical signs were leg weakness, hypo-activity, ptosis, lethargy, soft stools and diarrhea.

The median lethal dose was greater than 4703.1 mg/kg.

CHRONIC TOXICITY:

B. Chronic Toxicity Study of dirithromycin (LY237216) Administered Orally to Fischer 344 Rats for 6 Months.

Report No. 28, dated June 1991.

Laboratory Conducting the Study: Lilly Research Labs.,
Greenfield, IN. Study start date: May 8, 1989.

Material Tested: Suspensions of dirithromycin (LY237216)
prepared in 10% neutralized aqueous acacia solution.

Animals: Fischer 344 rats, 6-7 weeks old, males and females.
20/sex/group.

Doses & Duration of Treatment: 0 (vehicle), 100, 400, or 750
mg/kg/day orally, via gavage, for 6 months.

Results:

Mortality: 3/20 male rats of HD (750 mg/kg/day) died of gavage
accidents.

Clinical Signs: Males and females of HD had soft stools for the
first 11 study weeks.

Ophthalmology, Hematology, Urinalysis: No drug-related signs.

Body Weight and Body Weight Gain: Significant dose-related
decreases in males and females at 400- and 750 mg/kg/day from as
early as week 7 at HD and week 11 at MD. Decreases persisted to
termination.

Food Consumption: Slightly increased in males at MD from week 2-
6. Significant decrease at HD from week 18 to termination.

Efficiency of Food Utilization: Significantly decreased in MD
and HD males and females.

Clinical Chemistry: Drug related slight to moderate increases in
serum aspartate and alanine transaminases at the MD and HD.
Decreases in mean concentration of cholesterol, triglyceride,
total protein, albumin and globulin also occurred in males and
females at the MD and HD.

Hepatic Enzyme Activity: "No toxicologically important changes were seen in p-nitroanisole o-demethylase, 7-ethoxyresorufin o-deethylase, or benzphetamine N-demethylase activities or in cytochrome P-450 content."

Tissue Concentration of Phospholipid Phosphorus: "No toxicologically important changes were seen in the concentration of phospholipid phosphorus in the liver and lung of 750 mg/kg/day rats."

Plasma & Tissue Concentration of Dirithromycin: "Plasma antimicrobial activity determined in samples taken 24 hours after dosing were near or below the lower quantifiable limits of detection (i.e. 1 µg/ml). There was a dose related increase in antimicrobial activity in tissues, with the highest lung > kidney > heart > liver > muscle > skin. High tissue-to-plasma concentration ratios indicated extensive uptake of test drug by tissues."

Organ Weights: Statistically significant decrease in absolute weights of kidney, liver, heart, spleen and brain at MD and HD; decreases were due to decreased body weights. Statistically significant increase in adrenal weights (i.e. absolute and relative to body and brain weights) at the MD and HD levels.

Pathology: Grossly, cecal enlargement in 8/20 males at 100 mg/kg, 16/20 males and 18/20 females at 400 mg/kg, and 19/20 males and 20/20 females at 750 mg/kg.

Histopathology:

Heart: Minimal focal degeneration in 3/17 males and 7/20 females at HD (750 mg/kg); slight focal degeneration in 14/17 males and 11/20 females at HD; moderate focal degeneration in 3/20 female at MD.

Skeletal Muscle:

Degeneration: Minimal focal degeneration in 9/20 M and 3/20 F at 400 mg/kg, and in 7/17 M and 18/20 F at 750 mg/kg. Slight focal degeneration in 9/17 M and 2/20 F at 750 mg/kg.

Interstitial Inflammation: Minimal focal interstitial inflammation in 1/20 M and 1/20 F controls. 3/20 M at 100 mg/kg, 3/20 M and 1/20 F at 400 mg/kg, and 8/17 M and 2/20 F at 750 mg/kg.

Focal Necrosis: Minimal focal necrosis in 2/20 F at 400 mg/kg and 1/17 M and 3/20 F at 750 mg/kg.

Focal Regeneration: Minimal focal regeneration in 6/17 M and 3/20 F at 750 mg/kg.

Kidney: Minimal diffuse cytoplasmic tubular swelling in 5/17 M and 1/20 F at 750 mg/kg; slight diffuse cytoplasmic tubular swelling in 8/17 M and 16/20 F at 750 mg/kg; moderate diffuse cytoplasmic tubular swelling in 4/17 M and 3/20 F at 750 mg/kg.

Liver: Cholesterol granuloma in 14/20 F at 400 mg/kg and 1/17 M and 17/20 F at 750 mg/kg. Minimal biliary ductal vacuolation in 12/20 M and 19/20 F at MD, and in 15/17 M and 14/20 F at HD; slight biliary ductal vacuolation in 2/17 M 6/20 F at HD; vacuolation of the smooth muscles of the liver portal vessels (minimally in 10/20 M & 18/20 F at MD, and in 12/17 M and 7/20 F at HD; slight in 1/20 F at MD and 5/17 M & 13/20 F at HD.

Lymph Node: Increased incidence of focal histiocytic infiltration in males and females at the MD and HD.

Esophagus: Minimal focal muscular degeneration in 6/20 M and 5/20 F at HD.

Diaphragm: Moderate to minimal focal degeneration in the HD and slight to minimal focal degeneration at the MD; minimal focal interstitial inflammation and focal necrosis at the MD and HD, and minimal focal regeneration at the MD.

Electron Microscopy: Dose-related increase in the incidence of cytoplasmic lamellar inclusion bodies in parenchyma and interstitial cells of the heart, skeletal muscle, liver and kidney in the MD and HD groups.

Conclusion: No effect dose = 100 mg/kg

C. Chronic Toxicity Study of dirithromycin (LY237216)
Administered Orally to Beagle Dogs for 6 Months.

Report No. 29, dated June 1991.

Laboratory Conducting the Study: Lilly Research Labs.,
Greenfield, IN. Study start date: June 15, 1989.

Material Tested: Enteric coated tablet in gelatin capsules.

Animals: Beagle dogs; 9-13 months old, males and females;
4 dogs/sex/group.

Doses & Duration of Treatment: 0 (gelatin capsules containing placebo tablets), 30, 70, or 150 mg/kg/day for 6 months.

Results:

Mortality: None.

Clinical Signs: Dose-related abnormal stools (soft, soft mucoid, mucoid, or runny), containing apparent compound and/or emesis were seen in all drug-treated groups.

Ophthalmologic Exam., Physical Exam., Electrocardiogram, Body Weight, Food Consumption, Hematology, Urinalysis, Organ Weights: No drug related changes.

Clinical Chemistry: Moderate (3-fold) increase in alanine transaminase (ALT) in HD males and MD and HD females (2-fold). Increase (2-fold) in aspartate transaminase (AST) in the HD males and very slight increase (1 to 1-1/2 fold) in MD females.

Antimicrobial Activity in Plasma and Tissues: "Plasma antimicrobial activity were near or below the lower quantifiable limits of detection at all time points and all doses. Plasma content seldom exceeded a few $\mu\text{g/ml}$ at any dose, the highest recorded value among individual animals not $10.5 \mu\text{g/ml}$. The antimicrobial activity in tissues at 4 and 24 hours was high (i.e. up to 135% relative to the highest value found in the plasma)". There was a dose-related increase in antimicrobial level in tissues, with the highest in liver > kidney > heart > lung > muscle > skin. Comparisons of 4 and 24 hour tissue levels showed slow elimination of antimicrobial activity from tissue with time. Tissue activity at 24 hours declined by no more than 50% of the respective 4% value. In some tissues, 24 hour antibiotic activity was as high or higher than that found at 4 hours (e.g. 24 hour tissue samples in skin and liver at mid dose were 2x that found at 4 hours).

Gross and Histopathology: No drug related changes.

Electron Microscopy: Generalized increase in the incidence of cytoplasmic lamellar inclusion bodies in the heart of dogs at 70 and 150 mg/kg (statistically significant at both doses) and in the skeletal muscle of dogs at 150 mg/kg (statistically significant).

Conclusion: No effect dose = 30 mg/kg

D. **Chronic Toxicity Study of dirithromycin (LY237216)**
Administered Orally to Beagle Dogs for 6 Months.

Report No. 34, dated May 1992

Laboratory Conducting the Study: Lilly Research Labs.,
Greenfield, IN. Study start date: August 15, 1989.

Material Tested: Enteric coated tablet in gelatin capsules.

Animals: Beagle dogs; 11-12 months old, males and females;
4 dogs/sex/group.

Doses & Duration of Treatment: 0 (gelatin capsules containing placebo tablets), 30, 70, or 150 mg/kg/day for 6 months.

Results:

Mortality: None.

Clinical Signs: Treatment and dose-related overt effects (transient) were: apparent compound in the stools, abnormal stools (runny, mucoid, and soft), and emesis.

Ophthalmologic Exam., Electrocardiogram, Food Consumption, Hematology, Urinalysis, Organ Weights: No drug related changes.

Body Weight: Slight decrease in body weight gain in the MD and HD groups compared to body weights of dogs in the control and LD groups.

Clinical Chemistry: Slight increases in serum aspartate transaminase and alanine transaminase activity in MD and HD dogs. There were no toxicologically important changes in serum glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, gamma glutamyltransferase, creatine phosphokinase, calcium, inorganic phosphorus, sodium, potassium, chloride, cholesterol, triglycerides, total protein, albumin, globulin, and albumin/globulin ratio.

Antimicrobial Activity in Plasma and Tissues: Plasma antimicrobial activity were near or below the quantifiable limits throughout the study. Plasma C_{max} and AUC values were similar between days 93 and 184 suggesting that the compound had achieved steady state in plasma. Tissue levels were very high relative to plasma values, and there was slow elimination of antimicrobial activity from tissues.

Histopathology: Changes considered to be treatment-related occurred in skeletal muscle (HD group) and mesenteric lymph node.

- The diaphragm of 2 HD dogs had minimal to slight focal vacuolar myofiber degeneration characterized by multiple vacuoles in the sarcoplasm, without an inflammatory component. The abdominal and pectoral muscles of one HD dog were also affected. There were no remarkable findings in the diaphragm of control dogs. There were no treatment-related skeletal muscle lesions in dogs of the 30- or 70 mg/kg groups.

- Lymph node alterations, characterized by minimal to slight focal histiocytic vacuolar infiltration (foam cells) in the cortex and cortico-medullary borders, occurred with escalating doses of dirithromycin. One dog in the HD group had aggregates of foam cells in germinal centers similar to that reported for erythromycin.

Electron Microscopy: Several myocytes and endothelial cells in the diaphragm of HD dogs contained few to many, variable-sized intracytoplasmic lamellar inclusion bodies. Additionally, myocytes contained vacuolar structures which were sometimes membrane-bound, had electron-lucent contents, and variably contained scant amounts of amorphous electron-dense material. A few myocytes had minimal, segmental disruption of myofibrillar architecture.

Conclusion: No effect level = 30 mg/kg

SPECIAL TOXICITY:

2. Clinicopathologic (Myotoxicity) and Pharmacokinetics Study of CD Rats given Dirithromycin Orally for 4 Weeks With a 4-Week Reversibility Period: Tox. Report # 26. (6/91)

Study Objective: To correlate development of striated muscle lesions, if any, with plasma and tissue antimicrobial activity as related to dose and duration of treatment.

Procedure: Dirithromycin was given to female CD rats (5/group) by gavage at doses of 0, 150, 387, or 1000 mg/kg b.w. Groups of rats were sequentially killed and necropsied on days 1, 7, 14, and 28 of treatment and after 28-day withdrawal (no dosing) period.

Results:

- Dirithromycin was well tolerated at a dose up to 1000 mg/kg.

- There were no physical signs of toxicity or effects on body weight, weight gain, food consumption, efficiency of food utilization or on clinical chemistry parameters.

- Plasma antibacterial activity was near or below level of detection at all doses.

- In general, all tissues had considerably higher levels of antimicrobial activity than that in plasma at each dose level. Concentrations of antimicrobial activity were highest in liver, intermediate in lung, kidney, and heart, and lowest in skeletal muscle. High tissue-to-plasma

concentration ratios indicated that the compound had rapid and extensive penetration into tissues.

- Apparent accumulation in each tissue was evident throughout the 28-day treatment period, dependent upon both the magnitude of the dose and the tissue examined. For the high dose group, antimicrobial levels were 167.4 $\mu\text{g/g}$ in kidney, 314.2 $\mu\text{g/g}$ in the liver, 195.6 $\mu\text{g/g}$ in the lung, 157.8 $\mu\text{g/g}$ in the heart and 22.8 $\mu\text{g/g}$ in the skeletal muscle.

- After the 28-day withdrawal period, tissue levels decreased markedly and were generally near or below the detection level, except for lung tissue from animals of the high dose level which had not returned to base line values.

- There were no gross or light microscopic effects attributed to treatment.

- Electron microscopy of heart and skeletal muscle tissues from rats given the high (1000 mg/kg/day) dose for 28 days revealed a slightly increased incidence of cytoplasmic lamellar inclusion bodies in both myosites and interstitial cells. These changes had completely reversed in the heart and partially reduced in skeletal muscle after treatment was withdrawn for 28 days. EM findings at 150- and 387 mg/kg/day dose levels were similar to those seen in control rats.

F. Clinicopathologic (Myotoxicity) and Pharmacokinetics Study of CD Rats given Dirithromycin Lactobionate Intravenously for 4 Weeks With a 4-Week Reversibility Period:

Tox. Report # 26. (6/91)

Study Objective: To define the morphogenesis of cardiac and skeletal lesions induced by dirithromycin given i.v. and to correlate myopathic effects with and tissue antimicrobial activity and dose and duration of treatment.

Procedure: Groups of 25 female CD rats were given 0, 12.5, 28, or 62.5 mg dirithromycin/kg/day, i.v. as the lactobionate salt daily for up to 28 days followed by a no-treatment period of 28 days for reversibility. Five rats/group were sequentially killed and necropsied on days 1, 7, 14, and 28 of treatment and at 28 days after treatment was withdrawn.

Results:

- There were no deaths. Body weight, weight gain, food consumption, and efficiency of food utilization were not affected by treatment.

- In high dose rats, there was a slight increase in serum aspartate transaminase values on days 7, 14, and 28 of treatment. There was a mild increase in AST values in mid-dose animals on day 28 of treatment. Serum enzyme changes completely reversed after the 28-day no-treatment period.

- Plasma antimicrobial activity was near or below the detection level at all dose levels, while all tissues had considerably higher levels relative to that in plasma at each dose level, indicating that the compound was rapidly and extensively taken up by tissues. The highest antimicrobial levels were found in lung, heart, and kidney. Liver, skin, and skeletal muscle had lower values.

- After the 28-day withdrawal period, tissue antimicrobial levels decreased, but antimicrobial activity was still retained in heart and lung from rats in all dose groups, and in kidney and skeletal muscle from rats in the mid- and high dose groups.

- The high tissue levels attained during i.v. treatment were not associated with toxicity except for changes in cardiac and skeletal muscle. For these tissues, there was a temporal relationship between the development of microscopic (light) lesion, the dose and duration of treatment and antimicrobial activity.

- Rats in the high-dose group had an increased incidence of progressive cardiomyopathy on days 14 and 28 and focal myocardial degeneration on day 28 of treatment. Focal skeletal muscle degeneration was first observed on day 14 and increased in incidence and degree by day 28. At time lesions were first observed on day 14, antimicrobial activity was 799.2 $\mu\text{g/g}$ in the heart and 126.2 $\mu\text{g/g}$ in skeletal muscle. On day 28, respective tissue levels were 1176.8 and 300.6 $\mu\text{g/g}$.

- Rats from the mid-dose group had only minimal heart and skeletal muscle lesions after 28 days of treatment. In these animals, tissue antimicrobial levels were 398.8 and 109.6 $\mu\text{g/g}$ for heart and skeletal muscle, respectively.

- After the 28-day withdrawal period, morphology of striated muscle tissues of rats from the mid- and high dose groups by light microscopy were similar to that of controls. At this time, antimicrobial levels in heart and skeletal muscles were 318.0 and 20.8 $\mu\text{g/g}$ and 495.6 and 78.7 $\mu\text{g/g}$ for the mid- and high dose groups, respectively.

- Electron microscopic evaluation of heart and quadriceps femoris muscle samples revealed a dose-related increase in the incidence of cytoplasmic lamellar inclusion bodies in

various cell types during the treatment phase. After the 28-day withdrawal period, ultrastructural changes in the high dose group were less pronounced.

- There were no treatment-related alterations in the low dose group throughout the study. NOEL was 12.5 mg/kg.

G. Subchronic Inhalation Toxicity in Beagle Dogs.

Toxicology Report No 32 dated 3/92.

Procedure: Beagle dogs, 2/sex/group, were exposed to mean aerosol concentrations of 0 (air control), 6, 24, or 105 mg total suspended particulate (TSP) per cubic meter of air (m^3) which was equivalent to 0, 6, 23, or 100 mg dirithromycin/ m^3 for 4 hours/day for 12 days over a 16-day period (excluding weekends). The mass median equivalent aerodynamic diameters (MMEAD) of aerosols were 2.2, 3.5, or 4.5 μM for groups exposed to 6, 23, or 100 mg dirithromycin/ m^3 , respectively.

Results:

- There were no treatment-related effects on body weight, food consumption, hematology, clinical chemistry, or pathology.
- Heart rates were increased in dogs exposed to mean aerosol concentrations of 100 mg dirithromycin/ m^3 .
- The no-observable-effect concentration was 23 mg dirithromycin/ m^3 .

H. Antimicrobial Activity in Plasma and Tissues of Dogs given Daily Oral Doses of Dirithromycin for Five Days.

Toxicology Report No. 20 dated 12/87.

Procedure: Three male Beagle dogs were given oral doses of 30 mg/kg of dirithromycin in enteric-coated capsules for five days. Blood samples were collected at 0, 0.25, 0.5, 1, 2, 4, 8, and 24 hours after the first and last doses. The dogs were necropsied 24 hours after the last dose. Tissue samples were collected to determine antimicrobial activity in heart, kidney, liver, and lung. Antimicrobial activity in the plasma and tissues were determined in a microbiological agar diffusion assay with Micrococcus luteus ATCC9341.

Results:

- There were no clinical signs of toxicity, no effects on body weight or food consumption, and no abnormal gross pathologic findings.

- High tissue-to-plasma concentration ratios of antimicrobial activity were found in the heart, kidney, liver, and lung. Mean antimicrobial activity in plasma was less than 0.3 µg/ml. Mean antimicrobial activity in heart, kidney, liver, and lung was 2.4, 3.2, 2.7, and 2.7 µg/g, respectively.

I. Acute Toxicity of Epidirithromycin (LY262036) Administered Orally to Fischer 344 Rats. Toxicology Report No. 23.

- Epidirithromycin (a metabolite of dirithromycin) was administered as a single dose of dirithromycin @ 1881.3, 2586.7, 3433.3, or 4703.1 mg/kg b.w., orally (gavage).

- Mortality occurred within 3-5 days post-dosing. Clinical signs were: hypoactivity, soft stools, diarrhea, poor grooming, posterior soiling, hunched posture, piloerection, ptosis, and ocular and nasal discharge.

- The median lethal dose (MLD) of epidirithromycin in males and females was 3034 and 2567 mg/kg, respectively.

Note: An acute oral study was conducted with identical oral doses of dirithromycin. (Toxicology Report # 11). The findings were similar; the MLD with dirithromycin in males and females was 1881-4703 and 3400.9 mg/kg, respectively.

REPRODUCTION STUDIES:

J. Preliminary Fertility and General Development in Rats After Treatment With AS-E 136 BS (dirithromycin).

Toxicology Report No.24

Laboratory Conducting the Study:

The study was initiated on May 9, 1988 and rats necropsied in June/July 1988. Histopathology was conducted by Lilly's Research Laboratories, Greenfield, IN.

This was a preliminary study [purpose not stated] and was limited to the female rats only; males were not treated. A definitive Segment I study in rats is reviewed below.

Procedure: Female CD rats (12/group) were given 0, 150, 500, 750, or 1000 mg/kg dirithromycin orally as a suspension in 0.5% "tylose" 2 weeks prior to mating with untreated males. Treatment

continued through gestation and 21 days postpartum during which time standard measurements of reproductive performance were made.

Results:

- The conception rate decreased at the high dose but the difference relative to controls was not statistically significant.

- No animals died during the study. There was transient reduction in food consumption and increased salivation. Maternal animals from the 750- and 1000 mg/kg dose groups had diarrhea and the high dose rats showed somnolence. At the top dose, serum levels of aldose and aspartate transaminase were slightly increased while alkaline phosphatase was decreased.

- Antimicrobial activity levels in the heart muscle of maternal animals were 5 to 10 fold higher than skeletal muscle. Only marginal concentrations were detected in the hearts of 4-day old offspring and no remarkable amounts were found in either the heart or the skeletal muscles from the 21-day old offspring. These data indicate that:

-the fetus was exposed in utero to the drug;

-exposure of neonates to the antibiotic via maternal milk also occurred but the exposure was minimal.

Histopathology: [see Tables 13a-13d NDA vol. 1.29, pp 53-55]

A few control and treatment dams had very minute degenerative and/or inflammatory changes in the heart and skeletal muscles. The lesions were not severe enough to be functionally significant. The incidence and severity of these alterations were not dose or compound related. No significant tissue alterations were observed in any of the F-1 offspring.

K. An Oral Fertility and General Reproduction Study of LY237216 (dirithromycin) in the Rat.

Toxicology Report No. 25 dated June 1991.

This study was conducted by _____
in compliance with the FDA GLP requirements. The final report was dated June 21, 1991.

Study Dates: Began on 10/31/88 (first day of treatment for males) and was completed on 7/6/89 (last day of necropsy).

Material Tested: Dirithromycin; Lot No. DPD12546; initial potency was 96.2%. The test article was suspended in 10% aqueous acacia (pH 7-8). Suspensions were prepared fresh daily.

Procedure:

- Groups of 20 male and 40 female CD (Sprague-Dawley) rats, forming the F-0 generation, were treated orally by gavage with dirithromycin at levels of 0, 150, 387, or 1000 mg/kg/day.
- The males were treated for 84 days prior to placement for the first mating period and throughout the mating periods until necropsy.
- The females were separated into two phases and those in each phase were treated for 14 days prior to placement for mating and throughout their mating and gestation periods. The littering phase was also treated during the lactation period.
- Females in the teratology phase were subjected to cesarian section on day 20 of gestation.
- The females in the littering phase were allowed to litter to provide the F-1 generation.
- The F-1 generation was weaned on day 21 postpartum, and, following behavioral assessments, 1 male and 1 female per litter were selected for the reproductive phase. These F-1 animals were subsequently bred, the females were allowed to litter, and the viability of the F-2 generation was examined.

Results:

F-0 Generation (Dams):

- There were no deaths attributable to treatment; several rats died of misgavage.
- There was a dose-related increase in postdosing salivation and also nasal/muzzle staining among males.
- Male body weight at the 1000 mg/kg/day level were significantly lower than corresponding control values ($P < 0.01$) from week 6.
- For females of the dirithromycin-treated groups of the littering phase, body weights were significantly ($P < 0.05$, $P < 0.05$ and $P < 0.01$) lower in the 150, 387 and 1000 mg/kg/day groups, respectively on day 21 of gestation

although these differences did not show a dose-relationship. Body weights of females in the teratology phase were unaffected.

- The food intake of the males in the 1000 mg/kg/day group was decreased either slightly or significantly ($P < 0.01$) from the sixth week of treatment. For females in the teratology phase, there was a significant ($P < 0.01$) reduction in food intake during the first week of treatment for 1000 mg/kg/day group.

- The gross pathology revealed no effects of treatment. However, histologic exam. of the heart and skeletal muscle which known targets of dirithromycin toxicity indicated a trend for increased incidence of minimal focal degeneration and necrosis in skeletal muscle of F-0 male rats given 1000 mg/kg/day.

- Tissue antimicrobial activity in heart and skeletal muscle increased in a dose-related manner. Compared to females, male rats had about 2 to 6-fold the antimicrobial activity in skeletal muscle. The higher tissue levels in males may have been due to the longer duration of treatment for males relative to that for females.

- There were no effects upon estrous cycles or parental performance (mating, fertility indices and conception rate).

-In the teratology phase, ovarian and uterine parameters were unaffected. Fetal observations including weights, incidence of malformations, and minor external and visceral anomalies were unaffected. A significant ($P < 0.05$) increase in the incidence of fetuses with minor skeletal anomalies was observed in the 1000 mg/kg/day group primarily as a result of increased incidences of reduced ossification of bones in the skull (parietal, interparietal and supra-occipital).

- Maternal performance in terms of gestation index, number of live, dead and malformed pups and postimplantation losses were unaffected.

F-1 Generation - Pups:

- Pup viability and lactation indices, and clinical and pathological conditions were unaffected.

- Pup weights and parameters of physical development (incisor eruption and eye opening) were not significantly different from control values. Pupillary response was similarly unaffected.

F-1 Generation - Adults:

- There were no effects upon postweaning survival or clinical or gross pathological condition.
- Body weights for females in the 1000 mg/kg/day group were significantly ($P < 0.05$) lower than control values during the pre-mating phase. These differences did not continue during gestation or lactation. Male body weights and food consumption values for both sexes were unaffected.
- Behavioral assessments (motor activity, startle habituation and water maze) were unaffected.
- Parental and maternal performances were not affected.

F-2 Generation - Pups:

- Survival (viability and lactation indices) and clinical and pathological status were unaffected.
- Pup body weights for the control and treated groups were similar.

Conclusion:

- F-0 parental toxicity was exhibited at the 1000 mg/kg/day level of dirithromycin by decreases in male and female body weights and food consumption and occurrence of skeletal myopathy in male rats.
- There was no treatment-related developmental toxicity at doses up to 387 mg/kg/day. At a dose of 1000 mg/kg/day there was reduced ossification in some fetuses of the teratology phase.
- No adverse effects were seen in the reproductive performance of the F-0 animals, in the growth of their F-1 offspring, or survival of the F-2 generation pups.

Histopathology of Cardiac and Skeletal Muscle Lesions: Quoted verbatim from Pathologist's Summary (NDA vol. I.35, pp G3-G4)

"Cardiac and skeletal muscle lesions were found in both controls and LY237216 [dirithromycin]-treated rats. The changes in the heart were consistent with those of an age-related condition in rats commonly referred to as focal myocardial degeneration (Coleman *et al*, 1977*) and diagnosed as progressive cardiomyopathy. The incidence and severity of this spontaneous condition was not increased by drug treatment. Similarly, the focal lesions of

degeneration, necrosis, and/or regeneration of a few muscle fibers in the quadriceps femoris were minimal and functionally insignificant. However, these minimal lesions appeared to increase in F-0 male rats of the 1000 mg/kg dose group. This was probably a consequence of the longer period of dosing and the 18-fold higher antibiotic levels in skeletal muscles from male rats as compared to females at this high dose. The incidence of these lesions in male rats given 387 or 150 mg/kg was equal to or less than controls. The high, middle, and low doses of LY237216 in this study were 142-, 55-, and 21-fold multiples of the human clinical dose.

Other microscopic changes noted in this study were typical of sporadic, naturally occurring lesions in laboratory rats and were not considered to be related to the oral administration of LY237216.

In summary, a trend for increased incidence of minimal focal degeneration and necrosis of skeletal muscle occurred in F-0 male rats administered 1000 mg/kg body weight LY237216 orally. There were no other treatment-related findings in either the males and females of F-0 generation or the F-1 progeny examined."

[* Coleman, G.L. et al. Pathological changes during aging in barrier-reared Fischer 344 male rats. *J. Gerontol.* 32: 258-278].

MUTAGEN CITY:

L. The Effect of Dirithromycin Given by Gavage for 2 Consecutive Days on the Induction of Micronuclei in Bone Marrow of ICR Mice.

Toxicology Report No. 33 dated 4/92.
Study No. 920113MNT2790

This study was conducted by Lilly's Labs. in compliance with the FDA GLP requirements.

The potential of dirithromycin to induce micronuclei in vivo was investigated

Material Tested: Dirithromycin; Lot No. DPD13820

Procedure: ICR Swiss mice were treated orally for 2 consecutive days with either 0, 332.5, 665, or 1330 mg/kg of dirithromycin or 31.25 mg/kg of the promutagen, cyclophosphamide (positive control). Approximately 24 hours after the second treatment, bone marrow was collected and the frequency of micronucleated

polychromatic erythrocytes (PCE) was determined microscopically.

Result: The incidence of micronucleated PCEs' in mice treated with dirithromycin was not different from that of animals receiving the vehicle control. The response to positive control showed that the test system was sensitive to a chemical clastogen.

Conclusion: Dirithromycin did not induce micronuclei in vivo bone marrow of ICR mice.

P H A R M A C O L O G Y

Pharmacology Report No. 1: Summary of the general pharmacology of dirithromycin from

Pharmacology Report No. 2: In vitro studies of dirithromycin in smooth and cardiac muscle from Lilly Research Labs. October 1987.

Pharmacology Report No. 3: A study of the immune response in CD-1 mice treated orally with dirithromycin from Lilly Research Labs. October 1987.

All the above listed reports have been reviewed previously [Please see Addendum-1 (Dr. Browder's review)].

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME)

Studies with regard to nonclinical ADME are listed and summarized in the NDA (see Appendix Tables 10 to 12).

-The elimination half-life of plasma antibiotic activity subsequent to a single 91 mg/kg oral dose of dirithromycin to mice, rats, dogs, and rhesus monkey is tabulated below:

Species	T _{1/2} (hour)	C _{max} (µg/ml)	T _{max} (hour)
Mouse	15.7	2.04	0.5
Rat	33.8	1.32	0.5
Dog	28.5	7.30	2.0
Monkey	56.4	2.05	4.0

The pharmacokinetic parameters are summarized in the Table below:

Table 9
Summary of Dirithromycin Nonclinical Pharmacokinetic Parameters

Species	Strain	Sex	Dose Route	Dose ^a (mg/kg)	C _{max} (µg/ml)				T _{max} ^f (hours)	T _{1/2} ^g (hours)	AUC (µg·hr/ml)	AD ^h Rep
					Antibiotic ^b	Dirithro ^c	EMA ^d	RA ^e				
Mouse	NMRI	F	PO	91	2.04	..	..	..	0.5	15.7	8.3	8
Rat	FW49	F	IV	5.8	1.39	..	..	..	1.5	12.5	7.3	8
Rat	CHbb:Thom	M	IV	10	..	..	..	4.4	0.08	140	..	5
Rat	F344	M	IV	9.4 (X)	..	n.d.	0.38	..	..	..	..	..
Rat	CHbb:Thom	M	IV	41 (X)	13.03	..	..	..	0.08	1.1 & 9.7	26.9	1
Rat	FW49	F	ID	91	3.79	..	..	..	0.5	41.7	24.8	..
Rat	FW49	F	PO	91	1.32	..	..	..	0.5	33.8	5.8	..
Rat	FW49	F	PO	181	1.48	..	..	..	0.5	41.5	7.7	..
Rabbit	Himalayan	F	PO	9	1.48	..	..	..	0.5	41.5	7.7	..
Dog	Beagle	M, F	IV	5.8	2.67	..	..	..	0.25	29.4	45.56	..
Dog	Beagle	M, F	IV	58	25.67	..	..	..	0.5	51.4	328.1	..
Dog	Beagle	M, F	IV	58	31.88	..	..	..	0.16	42.1	375.1	..
Dog	Beagle	M, F	IV	58 (X)	26.33	..	..	..	0.16	56.8	228.8	..
Dog	Beagle	M, F	SC	9	1.17	..	..	..	4	37.9	48.7	..
Dog	Houed	F	PO	8.8	..	0.20	..	..	1	..	0.34	..
Dog	Houed	F	PO	8.8	..	..	0.40	..	3	..	1.46	..
Dog	Houed	F	PO	8.8	..	..	..	0.81	3	62	13.70	..
Dog	Houed	F	PO	26	..	1.05	..	..	3	..	0.29	..
Dog	Houed	F	PO	26	..	..	2.66	..	3	2.8	16.54	..
Dog	Beagle	M, F	PO	91	7.30	..	..	..	2	28.5	104	..
Monkey	Rhesus	F	IV	5.8	3.76	..	..	..	0.5	41.7	45.4	..
Monkey	Rhesus	F	PO	91	2.05	..	..	..	4	56.4	28.5	..
Monkey	Rhesus	F	PO	181	1.67	..	..	..	3	27.6	24.6	..

Abbreviations: IV = intravenous; ID = intraduodenal; n.d. = not detected; SC = subcutaneous; PO = oral; (X) = multiple dose.
^a based on potency of the lot of dirithromycin used.
^b of antibiotic activity determined by bioassay.
^c C_{max} of dirithromycin determined by HPLC.
^d C_{max} of erythromycin determined by HPLC.
^e C_{max} of radioactivity determined by liquid scintillation counting.
^f T_{max} of the assayed entity shown in the C_{max} column. T_{max} or first time point obtained.
^g Half-life of the assayed entity shown in the C_{max} column.

S U M M A R Y**GENERAL:**

1. Dirithromycin is a 14-membered lactone ring macrolide and is derived from erythromycin. Dirithromycin is the C-9 oxazine derivative of erythromyclamine (ECA) formed by the condensation of methoxyacetaldehyde and ECA. ECA is formed by the reductive amination of the C-9 ketone of erythromycin. Upon oral administration, dirithromycin is nonenzymatically hydrolyzed to ECA, which is microbiologically active.
2. The mode of action of dirithromycin and its metabolite, ECA, 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. Macrolide antibiotics reversibly bind to the 50S ribosomal subunit and block the P-site, resulting in impaired transpeptidation and/or translocation.
3. According to the applicant, dirithromycin offers advantages over existing therapies when several of its attributes are considered:
 - The antimicrobial spectrum of dirithromycin provides excellent coverage for pathogens commonly isolated from respiratory and skin infections.
 - improved patient compliance with a once-daily dosing schedule.
 - Dirithromycin pharmacokinetics are not significantly altered in the elderly, renally impaired, or mildly hepatically impaired patients.
 - Unlike erythromycin, dirithromycin may be given without regard to meals.
 - The limited potential of dirithromycin to interact with drugs metabolized by the cytochrome P-450 system will be of benefit to patients prescribed those drugs.
 - Dirithromycin achieves much higher tissue concentrations than erythromycin.

PHARMACOLOGY:

4. Studies designed and performed to determine whether dirithromycin had significant CNS, renal, local tolerance, anti-ulcerative, hemostatic, anti-exudative, broncholytic

food consumption, heart or circulatory, smooth and cardiac muscle or immunotoxic effects have been reviewed. (see Addendum-1, pages 11-16)

Dirithromycin had no CNS or ulcerogenic effects. Oral doses of the base salt, however, @ 50 mg/kg bw, did not produce a decrease in urine volume and the excretion of Na^+ , K^+ and Cl^- . A 50 mg/kg bw oral dose also produced a 27.8% inhibition of stomach ulcers in severely stressed rats.

With respect to in vitro drug effect on hemostasis, dirithromycin produced a reduction in the velocity and potency of collagen-induced platelet aggregation with EC_{50} s of 9.7×10^{-6} and 8.4×10^{-6} Mol/L, respectively. A 200 mg/kg oral dose of the drug produced a marginal 7.47% reduction in swelling in the rat kaolin-induced edema model. In an in vivo model developed to assess drug-induced broncholytic activity in guinea pigs, intraduodenal doses of 5 and 50 mg/kg inhibited broncho-constriction by 11.2%.

In studies to determine dirithromycin drug effects on the heart and circulation, the following was observed: at a concentration of _____ Mol/L, a slight increase in contractility and decrease in rate of contraction of isolated spontaneous beating rat atria, a slight decrease in arterial blood pressure and a slight increase in heart rate and respiratory rate at 3 mg/kg, i.v. in anesthetized cats. The dirithromycin lactobionate at 10 mg/kg, i.v. produced increased blood pressure and heart rate and 3 and 10 mg/kg produced a dose related increase in left ventricular contractility.

In in vitro studies geared to determine the acute effect of dirithromycin on smooth (uterus and vas deferens) and cardiac muscle, dirithromycin had no effect directly or through antagonism of the receptor systems examined at concentrations from 10^{-5} to 10^{-7} M.

With regard to in vivo drug effect on the immune response (i.e. effect on the primary antibody response in CD-1 mice determined by quantitation of serum antibody titers utilizing a hemagglutination procedure), doses of 7.2, 36, and 72 mg/kg dirithromycin for 10 days showed no effect on primary antibody production.

TOXICOLOGY:

5. **Acute Toxicity:** It was studied by the oral and i.v. routes in rats, mice, rabbits and dog.

Oral: Dirithromycin had a low order of toxicity when administered to rodents with median lethal dose(LD) >4000 mg/kg in all but one study. Signs of toxicity were similar in rats and mice and included cyanosis, sedation, ptosis, hypoactivity, and lethargy. Rabbits appeared more sensitive to the acute effects of dirithromycin. The estimated median LD was 1100 mg/kg. In dogs, repeated vomiting precluded determination of an oral median LD. Vomiting occurred at doses from 250 to 1000 mg/kg.

Intravenous: There were no differences in i.v. median LD among the four species tested; however, rabbits, again appeared to be the most sensitive species. Clinical signs were: gasping, emission of cries, convulsion, tremors, ataxia, cyanosis, and recumbency in rodents and rabbits; and vomiting, rapid breathing, tonic-clonic spasms or somnolence, ataxia, and recumbency in dogs.

6. **Subchronic Toxicity:** Several multi-dose toxicity studies in rats, rabbit, and dogs with the treatment ranging from 2 to 13 weeks were reported.

The most notable findings in studies of less than 3-months' duration in rats, rabbits and dogs have been effect on cardiac and skeletal muscle, limited to rats given dirithromycin lactobionate, i.v. In studies conducted by the oral route for up to 3 months, there were no histopathologic findings in striated muscle and other tissues and no systemic toxicity at doses of 150, 15, or 70 mg/kg in rats, rabbits, and dogs, respectively.

In i.v. studies conducted in rats, muscle lesions were not observed when daily doses of 4, 10, 25, or 62.5 mg/kg dirithromycin were administered to the Wistar HAN strain for 3 months. However, dose-related cardiomyopathy was observed in a 4-week study when doses of 50, 100, or 120 mg/kg of lactobionate salt (33.5, 67.0, or 80.4 mg dirithromycin/kg, respectively) were administered to Chbb:THOM strain of rat. Cardiomyopathy, together with degenerative and/or regenerative skeletal muscle lesions, was also observed when this same strain of rat was 12.5, 25, 50, or 100 mg/kg of lactobionate salt (7.3, 14.6, 29.3, and 58.5 mg dirithromycin/kg, respectively). Tissue levels of antimicrobial activity were markedly higher following i.v. dosing than oral dosing in rats and were considered the key element in the development of muscle toxicity in this species. No lesions occurred in the heart and skeletal muscle of rabbits and dogs given dirithromycin lactobionate i.v. Adjusted to the base, the doses of dirithromycin were 0, 5.8, 11.5, or 17.3 mg/kg in the rabbit study and 0, 5.8, 28.8, or 57.5 mg/kg in the dog study.

7. **Chronic (6-month) Toxicity:** Rats were dosed orally (gavage) with dirithromycin @ 100, 400, or 750 mg/kg, and dogs (enteric-coated tablet in gelatin capsule) @ 30, 70, or 150 mg/kg; once daily for 6 months.

Rats: [dirithromycin @ 100, 400, or 750 mg/kg/day] Significant toxic effects occurred in rats given 400 and 750 mg/kg/day by gavage for 6 months. These toxic effects were decreased body weight, weight gain, food consumption and efficiency of food utilization (EFU) values, increased alanine transaminase (ALT) and aspartate transaminase (AST), and morphologic changes including cardiac and skeletal muscle myopathy, swelling and vacuolation of smooth muscle, bile duct and renal tubular epithelial cells, and focal lymphoid histiocytosis. By electron microscopy, cytoplasmic and lamellar inclusion bodies were found in parenchymal and interstitial cells of heart, skeletal muscle, liver and kidney.

No effect level was 100 mg/kg/day.

Dogs: Two dog studies, both dog studies at the same dose levels [dirithromycin (enteric-coated tablet in gelatin capsule) @ 30, 70, or 150 mg/kg/day].

Dogs given 30 mg/kg/day by capsule for 6 months in two studies had no toxicologically important findings. In the first study, clinical signs of emesis and abnormal stools with apparent compound in the vomitus and stools occurred sporadically throughout the study and generally increased in a dose-related manner.

Dogs given 70 or 150 mg/kg had slight to moderate increases in serum levels of aspartate and ALT and increase of cytoplasmic lamellar inclusion bodies in heart and skeletal muscle by electron microscopy. Additional findings in the second dog study were a dose-related increase in mild focal lymphoid histiocytosis and mild focal vacuolar degenerative skeletal myopathy in the 150 mg/kg group. Cardiovascular parameters were not affected in both dog studies.

In all three chronic studies, high tissue-to-plasma ratios of total antimicrobial activity indicated extensive uptake of the test compound during long-term administration of dirithromycin.

1. **Special Studies:** In two rat studies, the morphogenesis of cardiac and skeletal muscle lesions induced by dirithromycin was correlated with plasma and tissue levels of antimicrobial activity and dose duration of treatment by the oral or i.v. route. There was rapid and extensive penetration of dirithromycin into tissues which was greater

in the i.v. compared to the oral study. Rats given 28 or 62.5 mg/kg dirithromycin i.v. had light- and electron microscopy alterations in cardiac and skeletal muscle associated with increased serum levels of aspartate transaminase. These effects were reversible. In the i.v. study in rats, there was a temporal relationship between the development of striated muscle lesions and high tissue levels of antimicrobial activity. In contrast, rats given up to 1000 mg/kg/day orally for one month had no adverse effects.

After dirithromycin was found to epimerize, the acute toxicity of epidirithromycin, the C-16 epimer of dirithromycin, was evaluated in rats and was found not to be significantly more toxic than dirithromycin.

Acute dermal and ocular studies in rabbits and a subacute inhalation study in dogs were conducted. There were no adverse effects in dogs given daily oral doses of 30 mg/kg dirithromycin for five days. High tissue-to-plasma concentration ratios of antimicrobial activity were found in the heart, kidney, liver, and lung.

9. **Reproduction Studies:** Effects of dirithromycin on fertility and general reproduction, including perinatal and postnatal effects, were evaluated in rats given up to 1000 mg/kg orally and up to 62.5 mg/kg i.v. All males that had been treated for 12 weeks prior to mating and through mating period, mated successfully; there were no effects on fertility, various reproduction parameters or the fetuses. Female rats given up to 62.5 mg/kg/day i.v. from 2 weeks before mating to the end of lactation showed no effects on mating, fertility, or progeny survival. Litter size was reduced in all dose groups, and progeny weight was reduced at the high dose. The no effect dose was 387 mg/kg in this study.

Dirithromycin administered orally to females up to 1000 mg/kg/day for 2 weeks prior to mating to the end of lactation or gestation day 20 had no effect on reproductive performance or fertility and no significant effects on offspring. [This study was not conducted according to our guidelines for Segment 1 reproduction study; treated females were mated with untreated males.] This study did show that exposure of neonates to the antibiotic via maternal milk occurred but the exposure was minimal.

Teratology studies were conducted in rats and rabbits (Tox. Report # 15 & 16) Rats were administered up to 1000 mg/kg dirithromycin by oral gavage on gestation days 7 through 16, while rabbits received up to 100 mg/kg on gestation

days 6 through 18. In both species, there was no evidence of a teratogenic effect.

[Reviewer's Note: Several other reproduction studies were reported in the NDA, but were not included in this summary, because these studies did not follow our basic reproduction guidelines, and therefore, their interpretation is difficult. The significant findings were that the antibiotic crossed the placenta, but cardiac and skeletal muscle lesions although noted in the treated dams were not reported in the fetuses; I am unsure whether these lesions were looked for in the fetuses.]

10. **Mutagenicity studies.** A total of nine tests were conducted which included bacterial mutation tests and in vitro and in vivo mammalian systems. All of the studies were negative, indicating that dirithromycin was unlikely to be genotoxic in man.

ABSORPTION, DISTRIBUTION, METABOLISM & EXCRETION (ADME):

11. Dirithromycin was characterized by high tissue penetration and accumulation of antibiotic activity in animals as reflected by high volumes of distribution and high tissue/plasma antibiotic activity at pharmacologic and toxicologic doses.

The compound was 5% to 15% orally bioavailable and exhibited 20% plasma protein binding in animals.

Plasma concentrations of antibiotic activity resulted primarily from circulating erythromyclamine, the principal metabolite of dirithromycin, rather than from unchanged dirithromycin in animals.

Prolonged urinary excretion of antibiotic activity after dirithromycin administration reflected high uptake of antibiotic activity into tissues and a relatively slower elimination of antibiotic from tissues.

Comments:

1. Dirithromycin is a 14-membered lactone ring macrolide and is derived from erythromycin. Dirithromycin is the C-9 oxazine derivative of erythromycylamine (ECA) formed by the condensation of methoxyacetaldehyde and ECA. ECA is formed by the reductive amination of the C-9 ketone of erythromycin. Upon oral administration, dirithromycin is nonenzymatically hydrolyzed to ECA, which is microbiologically active.

2. According to the applicant, dirithromycin offers advantages over existing therapies when several of its attributes are considered:
 - The antimicrobial spectrum of dirithromycin provides excellent coverage for pathogens commonly isolated from respiratory and skin infections.
 - improved patient compliance with a once-daily dosing schedule.
 - Dirithromycin pharmacokinetics are not significantly altered in the elderly, renally impaired, or mildly hepatically impaired patients.
 - Unlike erythromycin, dirithromycin may be given without regard to meals.
 - The limited potential of dirithromycin to interact with drugs metabolized by the cytochrome P-450 system will be of benefit to patients prescribed those drugs.
 - Dirithromycin achieves much higher tissue concentrations than erythromycin.

3. The most notable findings in multiple-dose studies were lesions in cardiac and skeletal muscle that occurred in rats in subchronic studies up to 3 months by the intravenous route, and in chronic rat and dog studies by the oral route. These findings were associated with high tissue-to-plasma concentration ratios of antimicrobial activity. The high tissue levels were well above those which result from the oral use of the product in conventional therapy in man. The extensive drug uptake by tissues was reversible upon termination of treatment. Lesions in cardiac and skeletal muscle also were reversed upon termination of treatment. Dirithromycin and/or its microbiologically active metabolites appeared to accumulate

in tissues with time. Despite the drug uptake in rat tissues at very high multiples (approximately 14x) of the anticipated clinical dose, there were no lesions in this species until oral treatment was extended beyond 4 months. This treatment duration is far in excess of that intended of that intended for clinical purposes. According to the applicant, "it is extremely unlikely that muscle lesions or other changes noted in toxicology studies in rats will occur in man with oral therapy. Human safety data collected to date support this conclusion. Despite extensive monitoring, no evidence of skeletal or cardiac muscle damage has been detected in clinical studies."

Recommendation:

I see no objection from the safety standpoint to the approval of this application. Labelling with regard to carcinogenesis, mutagenesis, impairment of fertility, pregnancy and pregnancy category is acceptable.

S.R. Joshi 11/22/93

3-ATTACHMENTS (Orig.NDA only)

S.R. Joshi, D.V.M., Ph.D.

cc:
 Orig. NDA
 HFD-340
 HFD-520
 HFD-520/Pharm/Joshi
 HFD-520/MO/Moledina
 HFD-520/Chem/Katague
 HFD-520/Micro/Creedon
 HFD-520/CSO/Chapman
 HFD-520 /rd init. by REosterberg
 R/D/11/15/93/FT/11/22/93/SRJ
 N-50-678

Concurrence Only:
 HFD-520/DepDir/LGavrilovich
 HFD-520/SPharm/REosterberg

REC 11/22/93
CSO/Chapman

DEC 2 1994

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

Date CDER Received: 10/24/94
Date Assigned: 11/1/94
Date Review Started: 11/17/94
Date 1st. Draft Completed: 11/17/94
Date Review Accepted by Supervisor: 11/18/94

NDA # 50-678 (Original Amendment dated 10/21/94)

Number of Volumes: 1 -

Drug: DYNABAC^R (dirithromycin) Tablets
Drug Codes: LY237216 (Lilly); AS-E 136 (Karl Thomae GmbH)

Sponsor: Eli Lilly Research Laboratories, Indianapolis, IN
Contact Person: Dr. Wayne Millar (317) 276-2084

Category: Macrolide antibiotic

Review Objectives: Review labelling.

Reviewer's Notes/Recommendations:

In response to FDA approvable letter dated 7/28/94, the applicant has submitted a version of labelling in accordance with our letter. I have gone through the parts pertaining to animal toxicity. The labelling needs corrections as follows:

...Pregnancy Category B: Teratology studies conducted in rats at doses up to 21 times the maximum recommended human dose on a _____ [should be mg/m²] basis ...

Animal Pharmacology and Toxicology:

...While target organ toxicity was identified in these 3-month oral studies, _____ (both cardiac and skeletal)... should be taken out; cardiac muscles are not

S.R. Joshi 11/18/94
S.R. Joshi, D.V.M., Ph.D.

cc:

Orig. NDA

HFD-340

HFD-520

HFD-520/Pharm/Joshi

HFD-520/MO/Moledina

HFD-520/Chem/Katague

HFD-520/CSO/Dillon-Parker

HFD-520 /rd init. by REOsterberg

R/D/11/17/94/FT/11/18/94/SRJ

N-50-678.2

Concurrence Only
HFD-520/Dep.Dir/L.Gavrilovich
HFD-520/SPharm/REOsterberg

16 12/2/94

DEO 11/18/94

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

IND (Original Submission, dated 1/27/88)

DATE REC'D FDA: 1/29/88
 DATE ASSIGNED: 3/7/88
 DATE REVIEW COMPLETED: 4/29/88

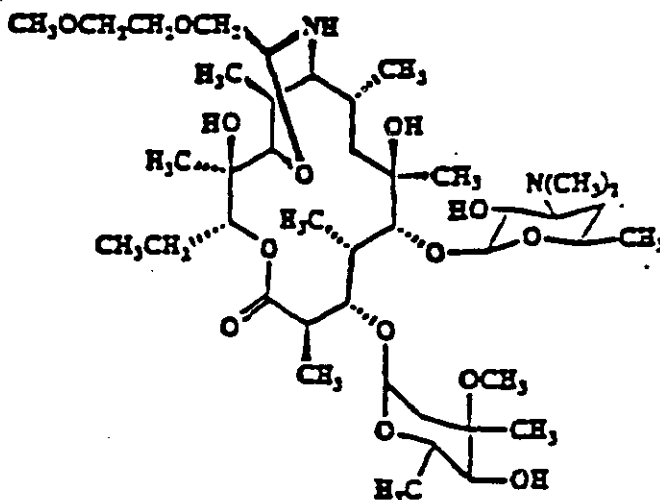
SPONSOR: Eli Lilly & Co., Indianapolis, IN

DRUG: Dirithromycin; LY 237216 (LY)

CATEGORY: Macrolide antibiotic

CHEMICAL NAME: 9-deoxy-11-deoxy-9,11[imino[2-(2-methoxyethoxy)ethylidene]oxy']-(9S)-erythromycin

CHEMICAL STRUCTURE:



DOSAGE FORM & ROUTE OF ADMIN.: Enteric-coated tablets; oral

CLINICAL INDICATION: Treatment of Streptococcal pharyngitis/tonsillitis, bronchitis, lobar pneumonia/bronchopneumonia and bacterial skin/skin structure infections

RELATED SUBMISSIONS: INDS

PROPOSED CLINICAL STUDY

Phase I Protocol [B9Z LC AQAA]

Twenty adult males, aged 21-55, will receive either dirithromycin or erythromycin base for 21 days, according to the following dosing schedule:

<u>Dirithromycin Group A</u>		<u>Erythromycin Group B</u>
	<u>First Dose</u>	
Eryth. placebo		Eryth. tablet (250 mg)
Dirith. tablet (500 mg)		Dirith. placebo
	<u>Second Dose</u>	
Eryth. placebo		Eryth. tablet (250 mg)
	<u>Third Dose</u>	
Eryth. placebo		Eryth. tablet (250 mg)
	<u>Fourth Dose</u>	
Eryth. placebo		Eryth. tablet (25 mg)

Only one dose will be administered on the 21st day of treatment.

Purpose of Study: "To confirm the tolerance profile of dirithromycin compared to erythromycin as described by the European studies, as well as the pharmacologic & pharmacokinetic properties that have been elucidated in the studies to date."

Parameters: Plasma & urine conc. of the 2 antibiotics; 24-hr endogenous creatinine clearance; hematology, liver & kidney function, 24-hr holter monitoring to be performed on 3 days between the 3rd & 19th day of drug treatment and on 3 days during the 5-day period following discontinuation.

Phase II Protocol [B9Z MC AQAB]

Male & female patients, 12 years or older, will be allocated in the following disease indications:

- Streptococcal pharyngitis/tonsillitis, bronchitis & bacterial skin or skin structure infection: 175-225 patients/indication
- Lobar pneumonia/bronchopneumonia: 125-175 patients

Patients will receive kits containing one of the 2 antibiotics (dirith. or eryth.). Those receiving dirith. will receive a total daily dose of 500 mg given in one morning dose of two 250 mg tablets. They will also receive placebo, which looks like eryth. and is given q.i.d. Those receiving eryth. will receive a total daily dose of 1000 mg q.i.d. in 250 mg tablets. They will also receive 2 morning placebo tablets which look like dirith. The maximum duration of treatment for both drugs will be 14 days.

Purpose of Study: "To compare the effectiveness & safety of dirithromycin given once/day, 500 mg/day, with that of erythromycin base given q.i.d., 1000 mg/day, in the treatment of pharyngitis/tonsillitis caused by S. pyogenes (Str. Grp. A), bronchitis, lobar pneumonia/bronchopneumonia and skin & skin structure infections caused by susceptible organisms."

Parameters: Symptomatic response to therapy; bacteriological data to judge response; hematology, blood chemistry & urinalysis; EKG; chest X-rays; assay of urine for antibiotic presence; clinical adverse reactions.

The sponsor indicates that informed consent will be obtained from all subjects. A copy of the forms for both protocols were submitted to the IND for evaluation.

PRECLINICAL STUDIES

PHARMACOLOGY

A. Plasma Levels of LY & Erythromyclamine (EMA) in Dogs

[Lilly Research Labs, Indianapolis, IN; Drug Disposition Rpt #2; 3/14/86]

Material Tested: LY in enteric-coated capsules with & without magnesium carbonate hydrate (MCH)

Animals: F hounds, 19-27kg, 2 groups (with/without MCH), 3/group

Dose Level, Route & Duration: 30 mpk, 2-dose oral dosing; dogs fasted for 16h prior to initial dosing. Seven days after the 1st dose, they were redosed with 30 mpk LY in a crossover design with the alternate formulation (with or without MCH).

Parameters: Determination of LY & EMA in plasma by HPLC with electrochemical detection

Results

Peak plasma levels of LY were low & variable (0.281 ± 0.268 & 0.105 ± 0.105 ug/ml in the presence & absence of MCH, occurring 1.5-3h after dosing), while levels of EMA (hydrolytic metabolite of LY) were higher (2.317 ± 1.267 & 2.663 ± 1.436 ug/ml in the presence & absence of MCH, occurring 2-3h after dosing).

Plasma half-life of LY could not be calculated due to low & variable plasma levels of LY. Plasma half-life of EMA dec'd in a biphasic manner, with an alpha $t_{1/2}$ of 3h measured from 4-10h post-dose (PD) and a beta $t_{1/2}$ of 12.4h measured from 8-24h PD.

MCH had no effect on plasma levels of LY or EMA.

B. Excretion of Radioactivity (RA) & Plasma Levels of RA with LY & EMA in Dogs

[Lilly Res. Labs; Drug Disposition Rpt. #3; 6/23/86]

Material Tested: LY (87.5% pure, lot #853021) and ^{14}C -LY (2.86 uCi/mg, Fo 193/24, 96.1% radiochemical purity). These 2 lots were admixed to make ^{14}C -LY of specific activity of 0.5 uCi/ml. Enteric-coated gelatin capsules were filled with 200 mg of radiolabeled drug.

Animals: 3 F hounds, 19.1-2.05kg

Dose, Route & Duration: 10 mpk, single oral dose; dogs fasted for 16h prior to dosing

Parameters: plasma levels of RA of LY & EMA, as well as urinary & fecal excretion profile of RA.

Results

Whole blood & plasma RA levels of ^{14}C -LY were present at higher concs. in RBC's than in plasma throughout the 120-h PD period, after which there was more uniform distribution of RA between plasma & RBC's.

Peak whole blood & plasma levels of RA occurred 3h PD. Whole blood levels (1.565 ± 0.761 ug equiv. LY/ml) were 2x those of plasma (i.e., 0.805 ± 0.271 ug equiv. LY/ml). The B-phase elimination half-life of whole blood & plasma RA were 64 & 62h, respectively.

Peak plasma level of EMA occurred 3h PD at a value of 0.399 ± 0.201 and dec'd in one dog with a half-life of 1.6h.

LY & EMA plasma RA levels, based on a comparison of the AUC's from 0-168h, were 2 & 11%, respectively of the circulating RA derived from ^{14}C -LY. Plasma levels of LY were lower and more variable than those of EMA.

LY neared complete excretion within 6 days PD, with 99.7 ± 2.3 representing the total cumulative % of dose excreted. Fecal excretion was the primary route of elimination of RA, with $81.3 \pm 4.2\%$ of the dose being excreted 48h after dosing, increasing to $92.2 \pm 3.6\%$ at 144h PD. Urinary excretion accounted for $4.9 \pm 1.1\%$ of the dose 48h PD, increasing to $7.4 \pm 1.5\%$ at 144h PD.

C. Metabolism of LY in Dogs & Rats

[Lilly Res. Labs; Drug Disposition Rpt #4; 8/18/86-2/12/87]

Material Tested: LY (lot # 853021, 87.5% pure) & ^{14}C -LY (2.86 uCi/mg, Fo 193/24, 96.1% radiochemical purity) were admixed to make ^{14}C -LY of specific activity of 7.5 uCi/mg. Enteric-coated gelatin capsules were filled with 200 mg radiolabeled drug.

Methods

Three F hounds (19.1-20.6kg b.w.) were fasted for 16h, followed by single oral dose of 10 mpk. These were the same dogs used in Rpt. #3.

M & F beagle dogs (7.1-8.8kg b.w.), 4/sex/group, were dosed p.o. with capsules at levels of 30, 70 & 150 mpk for 90 days.

Male Fischer rats (# not indicated), weighing $175 \pm 5\text{g}$, were dosed with 10 mpk LY (lot #86303²; 94% pure) by i.v. tail vein injection for 5 days. The drug was given in 90% saline, 10% ethanol vehicle.

Parameters: Plasma & urine levels of parent drug & metabolites

Results

Dogs: Two metabolites were observed in plasma & urine. The sponsor proposed that the first metabolite (#1) was a ring-contracted isomer of EMA. The 2nd metabolite was identified as decadinosyl EMA. In addition to these, the plasma also contained LY & EMA.

Rats: Neither parent LY nor metabolite #1 was observed in plasma samples. Variable plasma levels of EMA were observed.

D. Pharmacokinetics of AS-E 136 & Erythromycin - S.C., P.O. & I.V. in Mice, Rats, Rabbits, Dogs & Rhesus Monkeys

[Dr. Karl Thomae GmbH, Dept. of Biochemistry, Boehringer Ingelheim, Europe]

Materials Tested: [BS = base form; LB = lactobionate; AS-E = AS-E 136]

- Mouse, Rat & Rabbit: For oral & s.c. dosing, AS-E BS & eryth. BS were homogenized in 0.8% Tylose.
- Dog: For s.c. dosing, AS-E BS & eryth. BS were suspended in Tylose.
- Monkey & Dog: For oral dosing, AS-E BS & eryth. BS were given in enteric-coated capsules.
- Rat, Dog & Monkey: For i.v. dosing, eryth. LB & AS-E LB were dissolved in distilled water.
- Rat: For intraduodenal dosing, eryth. BS & AS-E BS were injected as suspensions.

No. Animals: rats & mice - 3/determination time point; dogs & monkeys - 2/species

Dosage Scheme & Drug Level Determinations

Species	Sex	Weight	Dose (mg/kg)	Route	Material Tested	Drug Levels*					
						Serum	Liver	Kidney	Urine	Muscle	Bile
Mouse	F	18-22g	10	S.C.	Eryth. BS	X	X	X	X	X	
					AS-E BS	X	X	X	X	X	
			100	P.O.	Eryth. BS	X	X	X	X	X	
					AS-E BS	X	X	X	X	X	
Rat	F	100-130g	10	S.C.	Eryth. BS	X	X	X	X	X	X
					AS-E BS	X	X	X	X	X	X
					AS-E LB	X	X	X	X		
			10	I.V.	Eryth. BS	X					
					AS-E LB	X					
			50	P.O.	AS-E BS	X	X	X	X	X	X
			100	P.O.	Eryth. BS	X	X	X	X	X	X
					AS-E BS	X	X	X	X	X	X
					AS-E LB	X	X	X	X	X	X
			200	P.O.	AS-E BS	X	X	X	X	X	X
			100	I.D.	Eryth. BS	X	X	X	X	X	X
					AS-E BS	X	X	X	X	X	X
Rabbit (Himalayan)	M&F	2-3kg 8.2-16.4kg	10	S.C.	Eryth. BS	X	X	X	X	X	
					AS-E BS	X	X	X	X	X	
Dog (Chbb Beagle)	M&F		10	S.C.	AS-E BS	X					
			10	i.v.	Eryth. LB	X					
					AS-E LB	X					
			100	I.V.	Eryth. LB	X			X		
					AS-E LB	X			X		
		100	P.O.	Eryth. BS	X			X			
				AS-E BS	X			X			
Monkey	F	5.3-8.5kg	10	I.V.	AS-E LB	X					
			100	P.O.	Eryth. BS	X					
					AS-E BS	X					
			200	P.O.	AS-E BS	X					
					AS-E LB	X					

*Conc. of the 2 antibiotics were determined in serum, urine, bile, liver, kidney & muscle homogenates by a microbiological assay (agar diffusion test).

Results

AS-E (Dirithromycin)

In all species tested, AS-E exhibited a longer terminal elimination half-life than eryth., indicating longer maintained serum levels than eryth. Estimated $t_{1/2}$ s in serum after i.v. dosing of 10 mpk (3-compartment model) were as follows:

<u>Species</u>	<u>($t_{1/2}$) AS-E 136 LB</u>	<u>($t_{1/2}$) Eryth. LB</u>
Rat	12.5 h	2-4 h
Dog	24.0 h	1.6 h
Rhesus Monkey	52.0 h	Not investigated.

The lower, longer-lasting serum levels produced by AS-E was explained as due to its excellent tissue penetration. Liver, kidney & skeletal muscle showed higher antimicrobial concs. than blood. AS-E was eliminated more slowly from tissues than eryth., thus building up longer-lasting drug levels than eryth. Long-lasting urinary excretion of AS-E-136 (7 days duration) occurred, due to slow redistribution of drug from tissue into blood & urine. Half-lives of elimination from tissue ranged from 40-70h after oral dosing.

Erythromycin

Pharmacokinetics after oral dosing were characterized by initially higher, but shorter lasting, serum drug levels than those produced by AS-E.

Urinary excretion following eryth. dosing was complete during the 24-h PD phase, in accordance with the observations that eryth. displayed poor capability to penetrate and remain in tissues, as compared to AS-E.

E. Pharmacokinetics of AS-E BS in Rats [Dr. Kari Thomae]

Materials Tested: ^{14}C -AS-E BS, ^{14}C -eryth. & ^{14}C -EMA

Animals: M albino rats [Chbb:Thom (SPF)] or pigmented F rats (fata-France); 170-190g b.w.; # not indicated. The rats were starved 20h prior to dosing.

Dose, Route & Duration: 10 mpk i.v. single dose

Parameters: Drug blood levels @ 0.08, 0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72, 144, 168 & 216h PD; whole body autoradiography & organ levels; urinary & fecal excretion @ 0-24, 24-48, 48-72 & 72-96h PD; drug elimination in expired air; biliary drug excretion; drug protein binding in vitro; metabolic pattern in biological fluid & tissue (i.e., plasma, bile, urine, liver, lungs, heart, kidney & spleen).

Results: ^{14}C -AS-E BS

Blood Levels: Due to rapid distribution into peripheral compartments, the blood level fell rapidly after dosing. The blood level for total RA had a long half-life of elimination, with a $t_{1/2}$ of 140h and a mean residence time of 150h. Drug elimination from blood occurred so slowly that RA was detected 9 days PD. The sponsor postulated that this was due to redistribution of RA from tissues.

Plasma Protein Binding: Binding did not inc. with increasing concs. of macrolide. In rats, the binding of AS-E & eryth. to plasma protein was low. In man, AS-E & EMA binding was low, whereas eryth. was highly bound to plasma protein.

Drug	% Protein Binding	
	Rat	Human
AS-E	14-17	20-21
EMA		16-18
Eryth.	17-19	68-72

Distribution of RA: Autoradiographs showed excellent drug penetration from blood into most organs & tissues. RA was distributed into the following tissues: liver, skeletal muscle, salivary gland, gastric mucosa, intestinal lumen, heart, lung, spleen, kidney, adrenals, bone marrow, testes, blood & CNS. High, long-lasting concs. of RA were seen in all tissues except the brain. Elimination of RA from tissue was slow, in accordance with the drug's long mean transit time of 150h.

Affinity of RA to Pigmented Tissues: ^{14}C -AS-E displayed no affinity to pigmented rat skin tissue. However, distribution of RA in pigmented areas of the eye was observed. Elimination of RA from pigmented areas of the retina & uvea was slow, as RA was still detected 7 days PD.

Excretion

- Biliary: 20 & 35% of the administered dose was excreted in bile @ 1 & 6h PD, respectively. Excretion was not complete @ 6h.
- ^{14}C -AS-E: 15% of the dose was excreted renally, 60% fecally; 15-20% was detected in the carcass & 7% in expired air, with the bulk of RA (80-85%) being excreted 96h PD.
- ^{14}C -EMA: The bulk of RA was excreted @ 96h PD, with 65% excreted in feces, 15% in urine, 8% in expired air & 12% in the carcass.

Drug Disposition: ^{14}C -Erythromycin: RA was eliminated more rapidly from the body as compared to AS-E BS. RA was distributed into most tissues (liver, bone marrow, intestinal walls, mouth & esophagus mucosa, thymus, hairs), but at lower concs. than seen with AS-E BS.

Metabolic Pattern: ^{14}C -AS-E BS occurred in small amounts in the liver, bile & urine. Higher amounts of parent drug were found in the lung, kidney & spleen. In addition to the AS-E peak, only one metabolite, having the same retention time as ^{14}C -EMA, was found.

F. Blood & Tissue Levels in Rats - I.V. [Dr. Karl Thomae]

Materials Tested: AS-E, EMA & eryth. in soln. as forms of LB

Animals: M rats (Chbb:Thom), 200-220g b.w., 4/group

Dose, Route & Duration: 50 mpk i.v. for 3 days

Parameters: Serum & tissue levels of each antibiotic, determined by microbiological assay (cylinder agar diffusion test)

Results

EMA LB showed 5x higher serum levels than AS-E & eryth. LB

AS-E & eryth. started out at comparably low serum levels, but eryth. was detected only up to 8h PD. After AS-E dosing, serum levels could be detected up to 31h PD.

After AS-E dosing, drug levels in the internal organs @ 10 & 24h PD were twice as high as those after admin. of EMA, whereas eryth. showed only trace amounts of antimicrobial activity in lungs 10h PD.

AS-E, as compared to EMA & E, was characterized as having "a low but long lasting serum level and high & long lasting tissue level."

G. Concentration Determination in Serum & Tissue - I.V. [Dr. Karl Thomae]

Material Tested: AS-E LB in a 10% soln.

Animals: M & F dogs (Chbb Beagle), 11-13 mos. old, 10-15kg b.w.; 6/group; drug serum, tissue & body fluid levels determined by microbiological assay (agar diffusion test).

Groups

<u>Dose (mg/kg)</u>	<u>Autopsy* (days after 1st dose)</u>	<u>Parameters Evaluated</u>
10 x5 wks	37	Daily drug blood levels; drawn before dosing
50 x5 wks	36	" " " " " " "
100 x5 wks	36	" " " " " " "
		and after the 35th dose**
100 (single)	36	Drug blood levels; drawn after single dose**
100 x5 wks	51	Untreated between 35th & 50th day, then autopsied for determination of organ drug levels (recovery dogs)

*At autopsy, samples were collected from brain, lung, liver, bile, spleen, kidney, prostate, skeletal muscle & urine.

**Blood samples drawn @ 0.17, 0.33, 0.66, 1, 2, 3, 4, 6, 8, 24, 47 & 72h after dosing.

Results

Blood levels measured after single & 35-dose repeat i.v. dosing showed comparable serum level curves after the first & last dose, between 5 min. & 7h PD. At 24-72h PD, the repeat-dosed dogs showed higher serum levels, which may have been due to back-diffusion of drug from tissue into blood.

Serum drug levels measured after dosing of 10, 50 & 100 mpk i.v. for 35 days rose only slightly during the 35-day treatment period, indicating no accumulation with repeat dosing. Additionally, increasing the dose did not produce a dose-proportional inc. in the areas under the serum level curves, as the 10 mpk dose yielded higher blood levels than the 50 & 100 mpk doses.

The antimicrobial conc. in organs & urine were orders of magnitude higher than those detected in serum. Antimicrobial activity concs. in tissues after 50 & 100 mpk were disproportionately large when compared to those obtained after 10 mpk. The lung, liver, spleen, kidney & prostate contained higher concs. than skeletal muscle.

Recovery dogs still showed high drug tissue concs. @ 15 days PD. In addition, skeletal muscle & prostate levels @ 15 days PD were considerably inc'd over end of dosing levels.

H. Tissue Distribution of AS-E LB & Eryth. LB in Baboons - I.V.

Materials Tested: AS-E LB or eryth. LB dissolved in distilled water

Animals: M baboons, 7-10kg b.w.; 4 in eryth. gp & 3 in AS-E gp

Doses, Route & Duration: 10 mpk eryth. LB or 11.4 mpk AS-E LB i.v. on 3 occasions at intervals of 24h

Parameters: Plasma & tissue conc. of biologically-active material, 24h after final drug dosing, detected by microbiological assay (agar diffusion test). Organ, tissue & body fluids evaluated consisted of urine, plasma, bile, skeletal muscle, brain, lungs, liver, kidneys, spleen & prostate.

Results

Eryth.: At 24h after the final dose, antimicrobial levels were zero in all tissues except for residual levels of 1 ug/ml detected in bile.

AS-E LB: At 24h after the final dose, high antimicrobial levels were detected in lung, liver, bile, spleen & kidney. Lower levels were observed in prostate, skeletal muscle, urine & plasma. The brain showed the lowest level of activity, with 0.4 ug/ml being detected in 1/3 baboons. Plasma levels were very low compared to tissue levels.

I. Effect on Rat Hepatic Microsomal Cytochrome C Reductase & Cytochrome P-450

[Lilly Research Labs; 6/18/87-7/24/87]

Material Tested: Compound LY 237216 LB dissolved in physiological saline

Animals: M Fischer-344 rats (200 ± 10g b.w.); # not indicated

Doses, Route & Duration: 10 & 30 mpk i.v. for 5 days

Parameters: Drug effect on body wt, liver wt & hepatic microsomal protein content, cytochrome P-450 & cytochrome C reductase activity, hepatic cytochrome P-450 metabolic intermediate (MI) complex formation, as evidenced by a 456nm absorption band in hepatic microsomes.

Results

Body Wt; Liver Wt; Microsomal Protein Content, Cytochrome C Reductase Activity: No drug-related effects

Microsomal Cytochrome P-450 Content: Increased by 30% at both dose levels

Hepatic MI Complex Formation: No drug-related effects

J. Measurement of Fluid & Tissue Conc. of LY in Rodents [Lilly Research Labs]

Methods

<u>Species & No.</u>	<u>Test Material</u>	<u>Dose & Route</u>
ICR Barner Mice 5/group	LY in 10% ETOH q.s. with water	20 mpk S.C. or P.O.
Sprague Dawley Rats 3/group	LY in 20% ETOH q.s. with water	20 mpk S.C. or gavage
Sprague Dawley Rats 15	LY in 1% aqueous tartric acid soln.	20 mpk gavage

Parameters: Plasma, urine, kidney liver & lung concs. of LY detected by microbiological assay (agar diffusion test). Blood levels were obtained until 4h PD in mice dosed s.c. or p.o. until 12h PD in rats dosed s.c. or gavage and until 6h PD in rats gavaged with drug in tartric acid soln.

Results: LY gave prolonged conc. of antibiotic in the serum of rodents when administered s.c. (i.e., still present @ 4h PD in mice & 12h PD in rats) but not when given in soln. by gavage.

Pharmacological Data on AS-E BS Updated & Supplemented by Data on AS-E LB
[Dr. Karl Thomae, GmbH]

K. Central Nervous System Activity

1. Sedative or Excitatory Effect

- a) Influence on Motility: Groups of 9 F SPF mice received 200 mpk p.o. in a 1% methylcellulose (MC) susp. or vehicle, and motility in activity cages was determined by the no. of contacts made between different polarized bars, as compared to veh. controls.

Results: The motility of drug-treated mice was reduced by 8.2%, but considered irrelevant by the investigator, who considers only a 15-20% reduction in activity as relevant.

- b) Influence on Motility: Groups of 9 F SPF rats (Chbb:Thom) received 10, 30 & 100 mpk p.o. in a 2% MC susp. or vehicle. Motility was determined as described above.

Results: 10 & 30 mpk produced no effect on motility; however, 100 mpk produced a 7% decrease.

2. Muscle Relaxing Effect: Groups of 10 F SPF mice received 200 mpk p.o. in a 1% susp. of MC or vehicle. Muscle relaxation was tested according to the method of Young & Evans (Science 105: 368, 1947).

Results: No muscle relaxing effect was seen.

3. Anticonvulsive Effect

- a) Influence on Maximal Electroshock Seizures: Groups of 8 & 10 M SPF mice (Chbb:NMRI) received 200 mpk of AS-E BS p.o. in a 1% MC susp. & the veh. respectively and were tested according to the method of Swinyard, Brown & Goodman (J. Pharmacol. Exp. Ter. 106: 319, 1952).

Results: AS-E BS had no anticonvulsant effect in mice @ 200 mpk p.o.

- b) Influence on Defense Reactions on Application of A Painful Mechanical Stimulus (tail clamp): Groups of 10 M SPF mice (Chbb:NMRI) received 200 mpk of AS-E BS p.o. in a 1% susp. of MC and veh. respectively and were tested according to the method of Haffner (Dtsch. Med. Wschr. 55: 731, 1929).

Results: AS-E BS had no analgesic effect in mice @ 200 mpk p.o.

4. Antidepressive Effect on Reserpine-induced Hypothermia: Groups of 6 M SPF mice (Chbb:NMRI) received 40 mpk AS-E BS p.o. in a 1% susp. of MC or vehicle and were tested according to the method of Askew (Life Sci. 2: 275, 1963).

Results: AS-E BS had no influence on the rise in body temp. after reserpine-induced hypothermia @ 40 mpk p.o.

5. Influence on Hexobarbital-induced Sleep Time: Groups of 10, 20 & 30 M SPF mice (Chbb:NMRI) received 50, 100 & 200 mpk AS-E BS p.o. in 1% MC susp. or vehicle and were tested by placing on a metal plate of 37°C for the time from the disappearance of the righting reflex up to its recovery (i.e., sleep time) after receiving 80 mpk hexobarbital i.p.

Results: AS-E BS had virtually no effect on hexobarbital-induced sleep time in mice @ 50, 100 & 200 mpk p.o.

L. Effect on Diuresis & Electrolyte Excretion

1. AS-E 136 BS: Groups of 6 M SPF rats (Chbb:Thom) received AS-E BS @ 50 mpk p.o. in a 1% MC susp. or vehicle and were given an oral water loading of 4 ml/100g b.w. Urine vol. & conc. of Na^+ , K^+ & Cl^- were determined.

Results: Oral dosing of AS-E BS @ 50 mpk resulted in a reduction of all 4 parameters tested.

2. AS-E LB: Gps of 6 M SPF rats (Chbb:Thom) received 200 mpk AS-E LB p.o. in a 2% MC susp. or veh. and were given an oral loading dose of 0.9% NaCl soln. Urine vol. & concs. of Na^+ , K^+ & Cl^- were determined.

Results: AS-E LB @ 200 mpk p.o. did not influence urinary vol. or excretion of electrolytes.

- M. Stomach Tolerance after Intragastric Admin.: SPF rats (Chbb:Thom), 5/sex, were dosed p.o. once/day x3 days with 100 mpk in a 2% MC susp., sacrificed, and their stomachs inspected for lesions of the mucosal membrane. Lesions were assessed according to the method of Takagi et al. (Chem. Pharm. Bull. 12: 465, 1964).

Results: Oral dosing of AS-E BS @ 100 mpk x3 days produced no ulcerogenic effect in rats.

- N. Influence on the Frequency of Stomach Ulcers in Severely Stressed Rats: SPF (Chbb:Thom) rats, 5 F/group, having stress ulcers induced according to the method of Takagi & Okabe (Japan J. Pharmac. 18: 9, 1968) received 50 mpk in 1% MC susp. or vehicle. At sacrifice, stomachs were examined for erosions in the proventriculus and evaluated according to the method of Marazzi-Uberti & Turba (Med. Exp. 4: 284, 1961).

Results: At 50 mpk p.o. AS-E BS produced a 27.8% inhibition of stomach ulcers in severely stressed rats.

O. Hemostasis

1. Influence on Blood Platelet Aggregation: Platelet aggregation was measured in platelet-rich human plasma according to the method of Born & Cross (J. Physiol. 170: 397, 1964). Before triggering aggregation, AS-E BS dissolved in dimethylformamide was incubated with the plasma for 10 min. @ 37°C at a conc. of 5×10^{-6} & 5×10^{-5} Mol/L. Controls were incubated with dimethylformamide.

Results: AS-E BS reduced the velocity and the potency of collagen-induced platelet aggregation by an EC_{50} of 9.7×10^{-6} & 8.4×10^{-6} Mol/L, respectively.

2. Influence on Bleeding Time: Conscious F SPF mice (Chbb:NMRI), 5 F/group, received 10 mpk AS-E BS in a 1% MC susp. or vehicle. The effect of the drug on bleeding time was determined 1 h PD.

Results: AS-E BS @ 10 mpk p.o. did not influence bleeding time in mice.

- P. Antiexudative Activity: Influence on Kaolin Edema in Rats: According to the method of Hillebrecht [Arzneim-Forsch. (Drug Res.) 4: 607, 1954], Kaolin edema was induced in the hind paws of groups of 10 M SPF rats (Chbb:Thom), after which dosing was initiated with 200 mpk AS-E BS in a 1% MC susp. or vehicle. Five hrs after edema provocation, the sagittal hindpaw diameters of drug-treated rats were measured & compared to those of veh. controls and drug influence calculated as % reduction of swelling.

Results: An oral dose of 200 mpk AS-E BS produced a marginal reduction of 7.47% in swelling (not stat. sig.).

- Q. Broncholytic Effect: According to the method of Konzett & Rossler (Arch. Exp. Path. Pharmac. 195: 71, 1949), artificial respiration was induced in guinea pigs, followed by admin. of acetylcholine as a spasmotic. AS-E BS was given intraduodenally @ 5 & 50 mpk in a susp. of 1% MC to 6 & 5 g-pigs, respectively and its effect on acetylcholine-induced bronchoconstriction measured.

Results: An i.d. dose of 50 mpk AS-E BS inhibited bronchoconstriction by 11.2% (not stat. sig.).

- R. Influence on Food Intake: Rats (Chbb:Thom), 3/sex/group, received 25 mpk AS-E BS p.o. in a 1% susp. of MC or veh. in powdered food.

Results: An oral dose of 25 mpk AS-E BS reduced food intake by 7% (not stat. sig.).

S. Effect on Heart & Circulation

1. Influence on Isolated Rat Atrium: AS-E BS added to an organ bath at a conc. of 1.2×10^{-5} Mol/L slightly inc'd the contractility and dec'd the rate of contraction of isolated spontaneously beating rat atria (% change of contractility = +14.4 for more than 20 min.).

2. Influence on Circulation of Anesthetized Cats

- a) AS-E BS: Three M & F starved anesthetized cats received 1 & 3 mpk AS-E BS i.v. as a soln. of its HCl salt. Arterial BP, HR & RR were measured.

Results: An i.v. dose of 3 mpk produced a weak reduction of arterial BP and a very weak inc. in HR & RR.

- b) AS-E LB: Five starved F anesthetized cats received 0.3, 1, 3 & 10 mpk AS-E LB i.v. Arterial BP, HR & left ventricular contractility were recorded.

Results: An i.v. dose of 10 mpk produced an inc. in BP & HR; 3 & 10 mpk produced dose-related inc's in left ventricular contractility.

3. In Vitro Studies of LY on Smooth & Cardiac Muscle [Toxicology Div., Lilly Research; Proj. No. PM 8703]

Methodology: M & F Sprague Dawley rats & M Hartley guinea pigs were sacrificed and smooth & cardiac muscle tissues were isolated & tested in vitro in organ baths. LY at a dose range of 10^{-5} to 10^{-9} M was evaluated for its ability to contract each preparation from baseline tension or to antagonize the contraction or relaxation produced by field stimulation or other agonists (angiotensin I, oxytocin, norepinephrine, acetylcholine & isoproterenol). Veh. controls were also run. Three tissues per treatment were used.

Results: As shown in the table below, LY did not produce agonist activity in 3 smooth muscles (g-pig ileum and rat uterus & vas deferens) preparations and one cardiac muscle (g-pig atrium) preparation. The drug at a conc. of 10^{-5} did not antagonize the pharmacologic agonists listed above.

<u>Tissue</u>	<u>No.*</u>	<u>Baseline Value**</u>	<u>Concentration of LY 237216</u>		
			<u>10^{-9}M</u>	<u>10^{-7}M</u>	<u>10^{-5}M</u>
G-pig ileum (force, g)	6	1.83 ± 0.28			
G-pig atria (force, g)	5	0.13 ± 0.03			
G-pig atria (rate, BPM)	5	234 ± 9			
Estrogen primed rat uterus (force, g)	9	0.80 ± 0.40			
Rat vas deferens (force, g)	5	0.34 ± 0.02			

*Number of tissues

**Baseline value = the resting tension (ileum, atria, vas deferens) the peak spontaneous contraction (uterus) or rate (atria) of the tissues prior to testing. Shown are mean values $\pm$ standard errors.

T. Immune Response Study [Tox. Div., Lilly Research; Study MO 4186]

Material Tested: LY suspended in 10% aqueous acacia; veh. controls received 10% aqueous acacia.

Animals: C57BL/6J (ICR) BR M mice; 10/group (4 wks of age & 24 ± 0.3 g b.w. at study initiation)

Doses, Route & Duration: 0, 7.2, 36 & 72 mpk, by gavage, for 10 days; on the 4th day, each mouse was injected i.v. with a particulate antigen (0.2 ml sheep RBC susp.).

Species	Sex	Route	LD ₅₀ (mpk)	AS-E Formulation	Observations
Rat (a)	M/F	P.O.	5500 (est.)	BS in 0.5% tylose	Sedation; difficult breathing w/wheezing; soft feces containing white floccules; saltatory cramp; dyspnea; tense abdominal wall; wt loss; hemorrhagic lungs & stomach; cachexia; meteorism & putrescence
Rat (a)	M/F	I.V.	> 150 < 250	LB in unidentified solvent	Accelerated gasping breathing
Mouse (b)	M/F	P.O.	4125	BS in 1% MC susp.	Cyanosis, ptosis; muscle relaxation; sedation; agitation on handling; pilage bristled
Mouse (b)	M/F	S.C.	1875	BS in 1% MC susp.	Excitation; intense grooming behavior; inc'd emission of cries; cyanosis; ptosis; sedation; muscle relaxation; bristling pilage
Mouse (b)	M/F	P.O.	4195	LB in 1% MC susp.	Sedation; cyanotic gasping for breath
Mouse (b)	M/F	S.C.	1645	LB in 1% MC susp.	Excitation & loud vocal emissions; cyanosis; muscle relaxation; bristling pilage; adoption of lateral position; necrosis
Mouse (b)	M/F	I.V.	318	LB in 0.9% NaCl soln.	Cyanosis; clonic convulsions & tremor
Rabbit (c)	M/F	I.V.	433	LB in 0.9% NaCl soln.	Accelerated breathing & staggering movements; extremities move to one side, accomp. by screaming fits & adoption of lateral position; violent excitation; petechial thymus & pulmonary hemorrhage; minor subepicardial hemorrhage
Rabbit (c)	M/F	P.O.	1100 (est.)	BS in 0.5% tylose MH 300	Squatting position; sedation; subsequent anesthetic-like sleep with retarded, shallow breathing; cyanosis; saltatory cramp; passive congestive lung hyperemia; red, thickened g.i. mucosa
Rabbit (c)	M/F	I.V.	135 (est.)	LB in distilled water	Severe convulsions & incipient dyspnea; frontal or lateral recumbency; hot swollen ears; severe saltatory cramps & screaming fits; head tilt & inc'd abdominal breathing; unsteady gait; splayed extremities
Dog (d)	M/F	P.O.	ND (e)	BS formulation	Vomiting; loose fecal discharge
Dog (d)	M/F	I.V.	> 150 < 250	LB in distilled water	Accelerated breathing; ataxia; vomiting; tonic-clonic spasm and/or somnolence; passive hyperemia in liver & kidneys

(a) Chbb:Thom (SPF)

(b) Chbb:NMRI

(c) Chbb:CH

(d) Chbb:Beagle

(e) Not determined. Due to regular vomiting at high doses, unable to induce fatality.

C. Subchronic (3-Mo.) Oral Toxicity in Chbb:Thom Rats [Dr. Karl Thomae]

Material Tested: AS-E BS suspended in 0.5 Tylose; control received veh.

Animals: M & F rats [Chbb: Thom (SPF)]; M, 64 days old; F, 82 days old

Groups: Controls (C), 24/sex; 15 (LD) & 150 (MD) mpk, 12/sex/group; 750 mpk (HD), 24/sex; 12/Sex in C & HD groups were kept for a 6-wk recovery period (RP) after the last dose.

Route & Duration: Oral (gavage) for 3 months

Parameters

- food/water intake & body wt - weekly
- hematology & clin. chem. - predosing & at dose wks 2, 7 & 13 (recovery rats also evaluated during wk 18)
- alpha amylase & urinalysis - dose wks 13 & 18
- organ wt & histopath. (light microscopic) at sacrifice
- bone marrow myelograms on all rats; regularly in 5/sex in C & HD groups

Results

Clin. Chem.: PD salivation at MD & HD levels from 2nd dose wk until end of dosing period.

Mortality: 1/24 C; no LD & MD; 5/24 HD. The sponsor postulated that mortality was due to malnutrition due to reduction in gram-positive intestinal flora.

Food Intake: Decrease in HD M

Water Intake: Sig. inc. in MD & HD M, study wks 1-13 and in HD M thru study wk 19; inc. in HD F, study wks 1-15

Body Wt: Stat. sig. delay in wt inc., study wks 3-19 in HD M

Hematology: Hgb & Hct were inc'd in HD M, wks 7, 13 & 18 and in HD F, wk 13. Erythrocytes were inc'd in HD M, wk 13.

Clin. Chem.: SGOT was inc'd in HD M (dose wks 7 & 13) and in HD F (study wks 2, 7 & 13); these inc's grew as study progressed, but were reversible at wk 18. LD & MD M also showed inc's in SGOT. SGPT was slightly inc'd in HD F (study wks 2, 7 & 13). Alk. phos. dec'd in HD M (wks 2, 7 & 13) and in HD F (study wks 2, 7 & 13). Alpha amylase determination was made only at the 13th & 18th study wks; a slight reversible dec. occurred in LD, MD & HD F. BUN & creatinine inc'd at all treated levels (study wks 2, 7 & 13). Inorganic phosphate dec'd at all treated levels (study wks 2, 7 & 13). Total glycerol dec'd in HD M & F (study wks 2, 7 & 13), but were reversible at wk 18.

Parameters: Survival & clin. observations (daily); body wt (days 1 & 4);
Immunohematology (7 days after sheep RBC antigen injection)

Results

Survival; Clin. Obs.; Body Wt.: No drug-related effects

Immunohematology: No drug-related effect on primary antibody production

TOXICITY STUDIES

A. Preliminary Toxicity in Mice [Dr. Karl Thomae]

Formulation Tested: AS-E BS in 1% MC susp.

Animals: M & F SPF mice (Chbb:NMRI), 5/sex/dose level

Doses, Route & Duration: 1000 & 2000 mpk oral single doses; 500, 1000 & 2000 mpk s.c. single doses

Results

Mortality: 1/5 F @ 2000 mpk p.o.; 1/5 F @ 1000 mpk s.c.; 4/5 F & 1/5 M @ 2000 mpk s.c.

- ▀ Observations:
- 1000 mpk p.o. - sedation, muscle relaxation
 - 2000 mpk p.o. - " " " , aggression
 - 500 mpk s.c. - no drug-related effect
 - 1000 mpk s.c. - excitation, cries, aggression
 - 2000 mpk s.c. - aggression, excitation, sedation, cyanosis

B. Acute Oral & Parenteral Toxicity [Dr. Karl Thomae]



Urinalysis: Decreased average urine vol. & inc'd density in HD M & F (study wk 13). Additionally, there was a reversible deepening in urine color toward dark yellow, golden yellow, light brown & brown.

Organ Wts: End of 3-Month Dosing

	Low Dose		Mid Dose		High Dose	
	M	F	M	F	M	F
<u>Decreased</u>						
Heart				X	X	X
Liver					X	
Kidney					X	
Thymus	X		X	X	X	X
Spleen	X	X	X	X	X	X
Prostate					X	
Ovaries		X		X		X
Adrenals		X		X		X
<u>Increased</u>						
Renals					X	
Pituitary	X	X	X	X	X	X
Thyroid	X	X	X	X	X	X

Organ wt dec's were stat. sig., and according to the sponsor, in accordance with delayed body wt development. At the end of the RP, organ wts were approaching those of C.

Gross Pathology: Enlarged appendices & softer feces in the HD rats

Histopathology: No drug-related findings

Bone Marrow: No drug-related changes

Liver, Kidney, Serum & Urine Levels: These were determined in 1/sex/dose gp after 4, 6, 8, 10 & 12 wks of treatment. Drug concs. were determined via use of microbiological cylinder plate test. Results indicated that urine, liver & kidney did not accumulate drug. Serum levels appeared similar at the LD & MD and higher at the HD.

D. Subchronic (3-Mo.) Oral Toxicity in Rabbits [Dr. Karl Thomae; Proj. Rpt. # 42 F/80]

Material Tested: AS-E BS suspended in 0.5% tylose; controls rec'd vehicle

Animals: Rabbits (Chbb:HM); M & F, 169-197 days old

Dose Groups: Controls (C), 8/sex; 15 (LD) & 150 (MD) mpk, 4/sex; 750 mpk (HD), 8/sex

Route & Duration: Oral (gavage), 7 days/week x3 months

Parameters

- food intake "could not be determined because feeding racks frequently scraped out"
- water intake "could not be determined due to connection to an automatic watering line".
- body wt - cnce/week
- hematology & clin. chem. - prior to drug dosing & at test wks 6 & 12
- urinalysis - test wks 6 & 13
- organ, serum, bile & urinary drug conc., at sacrifice, determined by use of microbiological cylinder plate test)
- organ wts, gross & histopath. - at sacrifice
- bone marrow smears prepared from all rabbits, but only myelograms of C & MD levels regularly analyzed.

Results

Clin. Observ.: Reduced or no defecation at the MD & HD on test day 4. MD rabbits recovered as of wk 6 but were still emaciated due to minimal food ingestion. The HD rabbits died within 15 days, the first death occurring on day 6; some had diarrhea and others had no defecation; severe body wt loss was observed. Microbiological assay showed no bacteria in the intestinal flora of the HD rabbits.

Mortality: None in C or LD gps; 3/8 in the MD gp (after 33rd & 37th dose). At the HD, 14/16 died after the 5th & 14th doses and 2/16 were prematurely sacrificed on days 7 & 15 of dosing.

Food/Water Intake: Not determined for reasons listed above. The sponsor estimated that the MD rabbits showed dec'd food intake, whereas the HD rabbits ingested almost no food.

Body Wt: Sig. dec'd during test wks 3-13 at the MD; sig. dec'd within a few days at the HD.

Hematology: No drug-related findings at the LD & MD. HD data could not be obtained because of the high incidence of mortality during dosing.

Clin. Chem.: Sig. inc. in total bilirubin at the LD; sig. inc. in SGPT, total bilirubin & creatine kinase and slight inc. in cholesterol at the MD; HD data could not be obtained because of the high incidence of mortality during dosing.

Urinalysis; Bone Marrow: No drug-related findings

Organ Wts: Sig. inc. in adrenal & thyroid wts at the MD

Gross Pathology: Cecae at the MD were enlarged, with pasty to watery contents; 1/8 had erosions in the fundic gastric mucosa. Rabbits in the HD gp had hemorrhagic erosions of gastric mucosa or small ulcerations and g.i. contents were liquid.

Histopathology

	<u>Mid Dose</u>	<u>High Dose</u>
<u>Liver</u>		
-fatty degeneration of parenchymal cells	3/8	12/16
-severe hypertrophy of peripheral parench. cells		1/16
-congestive hyperemia	1/8	
-slight interstitial infiltration w/inflamed cells	1/8	
<u>Stomach</u>		
-focal squamous metaplasia	1/8	
-flat ulcer in fundic mucosa	1/8	
-hemorrhagic erosions in fundic & pyloric mucosa		16/16
<u>Intestine</u>		
-severe edema of villous stroma		1/16
-hemorrhagic contents		1/16
-hyperemia & erosion of small intestine mucosa		4/16
-severe epithelial desquam. & necrobiosis of villous stroma & tunica mucosa		9/16
<u>Heart</u>		
-slight macular fine-grained fatty degeneration of myocardial fibers	1/8	5/16
<u>Lymph Nodes</u>		
-absorption hemorrhages in mesenteric lymph nodes	1/8	
-hyperemia, edematous impregnation & absorption hemorrhages in mesenteric lymph nodes		1/16
<u>Lungs</u>		
-congestive hyperemia	1/8	
- " " w/partial serous pulmon. edema		2/16
-partial serous hemorrhagic pulmonary edema		3/16
-congest. hyperemia w/partial serous hemorrhagic pulmonary edema		1/16
-partial serous pulmonary edema		3/16
<u>Aorta</u>		
-subintimal foci of disintegrated elastic fibers w/dystrophic calcification		4/16
<u>Kidney</u>		
-lipid infiltration of tubular epithelia		3/16
<u>Adrenal</u>		
-moderate-slight hypertrophy of adrenal cortex		5/16
<u>Thymus</u>		
-diapedesis hemorrhages from hyperemic vessels		4/16
<u>Pancreas</u>		
-interstitial hemorrhages from hyperemic vessels		1/16

E. Subchronic (5-Wk) I.V. Toxicity in Rabbits [Dr. Karl Thomae; Proj. Rpt. # 37 G/79]

Material Tested: AS-# LB (batch No. EL 416) as a 3% soln. in physiological saline

Animals: Rabbits (Cbb:CH); M (84-112 days old) and F (72-101 days old)

Dose Groups: Controls (C), 4/sex; 10 (LD) & 20 (MD) mpk, 4/sex; 30 mpk (HD), 8/sex

Route & Duration: i.v. for 5 wks

Parameters

- According to the sponsor, food & water intake could not be determined because feeding racks were scraped out frequently and due to connection to an automatic watering line.
- body wts - once/week
- hematology - prior to dosing (wk -3) & test wks 1 & 5
- clin. chem. - prior to dosing (wk -3) & test wks 1, 5 & 7
- urinalysis - test wks -3 to -2, 2, 5 & 7
- organ wts, gross & histopath. - at sacrifice
- bone marrow smears prepared for all rabbits, but myelograms of 8 each from C & HD gps were regularly analyzed.

Results

Clinical Signs: Unrest at the MD & HD during the first 2 wks; slight dyspnea at the MD. Slight convulsions, strained & difficult breathing & apathy lasting 30 min. at the HD. Local injection reactions (auricular erythema & edema) at the MD & HD, resulting in drooping of the ears for 1-2h. Symptoms subsided within the 2nd test week.

Mortality: At the LD, 1/8 rabbits died after the 5th dose, while under anesthesia for blood collecting.

Body Wt; Hematology: No drug-related changes.

Clin. Chem.: No drug-related changes in any parameter evaluated except for a sig. dose-dependent inc. in creatine kinase at the MD & HD in wks 1 & 5. At study wk 7 (RP), values were still significantly elevated but were returning to C levels.

Urinalysis; Gross Pathology: No drug-related changes

<u>Organ Wts:</u>		<u>Low Dose</u>	<u>Mid Dose</u>	<u>High Dose</u>
Increased:	Liver		M & F	M & F
	Thyroid		M	M & F
	Adrenal	F	F	F

Histopathology; Bone Marrow Findings: No drug-related changes

F. Subchronic I.V. Toxicity [Dr. Karl Thomae; Proj. Rpt. # 34 G/80]

Material Tested: AS-E LB in 0.9% NaCl

Animals: M & F Chbb Beagle dogs, 11-13 months old; 3/sex/group

Dose Levels, Route & Duration: Controls (C), 10 (LD), 50 (MD) & 100 (HD) mpk i.v. 7 days/wk x5 weeks

Parameters

- body temp., general condition, visual & auditory function - prior to dosing & test wk 5 in all groups and wk 7 also in HD gp
- macroscopic & electrical ophthalmoscopic exam - prior to drug dosing and in test wk 5
- body wt - prior to drug dosing & weekly
- food intake - daily
- EKG - prior to dosing (wk -1) & test wks 2 & 5 in all groups and during the RP (study wk 7) at the HD. HR, duration of PQ interval, QRS complex & QT intervals, changes in form & rhythm were determined prior to and @ 0.5 & 2h PD.
- hematology - prior to dosing (wk -1) and in test wks 2 & 5 in all gps, and during the RP at the HD
- clinical chemistry - prior to dosing (wk -1) and in test wks 2, 5 & 7
- urinalysis - test wks -1, 2, 5 & 7
- organ wt, gross & histopath. - at sacrifice at end of treatment (all groups) and end of RP (HD)
- bone marrow smears - prepared for all dogs, but only the myelograms of C & HD were analyzed.

Results

Clinical Signs: Emesis at the MD & HD during the first 3-4 wks

Mortality: No drug-related findings

Food Intake: No drug-related findings

Body Wt: Slight dec. in HD dogs

Hematology: No drug-related findings

Clinical Chemistry: SGOT was sig. inc'd in M & F of the MD & HD gps during test wks 2 & 5 (more pronounced at the HD vs MD & in F vs M). At the end of 2 wks RP, HD values were still moderately elevated. SGPT was sig. inc'd in MD & HD M & F during test wks 2 & 5 (more pronounced at study wk 5 vs wk 2 and in F vs M). At the end of the RP, values were still elevated, but less than during treatment. Cholinesterase was slightly inc'd in HD M & F in the test wk 5; this was reversible at the end of the RP. LDH & HBDH were sig. inc'd in HD M & F; this was reversible at the end of the RP. Creatine kinase was sig. inc'd (dose-related) in M & F of the MD & HD gps in test wks 2 & 5; this was partially reversible at the end of the RP.

Urinalysis: No drug-related findings

Ophthalmology: Unspecific follicular conjunctivitis of the 3rd eyelid at the LD, MD & HD, test wk 5. The retina of the HD dogs was pale pink during the 5th test wk; this had disappeared at the end of the RP.

Bone Marrow: No drug-related effect on erythro- or myelopoiesis.

HR: Dose-dependent inc. in LD, MD & HD gps in the 2nd & 5th test wks @ 0.5 & 2h PD; this was reversible in the HD dogs at the end of the RP.

EKG: Slight dec. in QT intervals at the LD, MD & HD due to corresponding inc. in HR reported above. Reduction in duration of PQ interval (LD, MD, HD) in test wks 2 & 5 - still reduced in the HD gp at the end of the RP.

Organ Wts: Drug-related inc's in spleen wts at the MD & HD; 2 wks PD, the RP dogs were comparable to controls. Thyroid wts were inc'd at the MD & HD, even at the end of the RP. Kidney wts were inc'd at the HD.

Gross Pathology: Hemorrhagic infiltration of the skin at the injection site occurred in the HD gp.

Histopathology

Drug-treated & Controls: "Perivascular scarring, hemorrhagic residues in absorption and slight to moderate phlebosclerotic changes in walls of subcutaneous veins at the injection sites, due to drug & placebo administration."

HD Group: Striated muscle showing focal necrosis & absorption of muscle fibers were noted at the injection site. The heart of 1/6 dogs at the end of dosing showed "circumscribed scarring of left ventricular papillary muscle after previous myocardial necrosis. Adjacent to this area, subintimal edema with almost complete vascular stenosis of a small coronary branch." One/6 dogs at the end of the RP showed "minimal focal fine-grained fatty degeneration of myocardial fibers."

G. Acute Oral Toxicity [Lilly Research Labs; Studies R-0-195-86, R-0-196-86, M-0-151-86 & M-0-150-86]

Formulation Tested: LY 237216 (lot H10-KV4-080) in 10% aq. acacia soln.

Route of Admin.: Oral (gavage)

<u>Species</u>	<u>Sex</u>	<u>LD-50 (mpk)</u>	<u>Observations</u>
Adult Fischer 344 Rats	M	1881-4703	Deaths within 4 days PD; leg weakness, poor grooming, hypoactivity, ptosis, lethargy, chromorhinorrhea, soft stools & diarrhea, ataxia, dilated cecum.
	F	3400.9	Deaths within 24h PD & coma, in addition to findings above in M.

<u>Species</u>	<u>Sex</u>	<u>LD-50 (mpk)</u>	<u>Observations</u>
Adult Hsd:(ICP) Mice	M&F	4703.1	Leg weakness, hypoactivity, ptosis, lethargy diarrhea, soft stools; dec'd body wt 14 days PD.

H. Subchronic (3-Mo.) Toxicity - Dog [Lilly Res. Labs; Study # DO 2586]

Formulation Tested: Enteric-coated capsules, each containing starch powder with LY and/or MgCO₃ in gelatin capsules; controls received enteric-coated capsules of starch flowable (also containing 5% silicone) in gelatin capsules.

Animals: M & F Beagle dogs, 7-9 mos. old; 4/sex/group

<u>Dose Levels:</u>	<u>LY 237216 (mpk)</u>	<u>MgCO₃ (mpk)</u>
Group 00	0	0
01	0	30
02	30	30
03	30	0
04	70	0
05	150	0

Route & Duration: p.o. for 3 months (91 days for M; 92 days for F)

Parameters

- Survival, clinical signs & toxicity - daily
- Physical & ophthalmic exams - prior to study & at termination
- EKG - prior to study, 0 & 2h PD at 1 & 6 wks; near termination
- Body Wt - prior to study; at wkly intervals during dosing; termination
- Food intake: estimated visually daily; changes in appetite noted
- Hematology & clin. chem.: prior to study; @ 1 & 2 wks, mos. 1 & 2; termination
- Cytologic eval. of bone marrow, including est. M:E ratio - termination
- Urinalysis: prior to study; week 2, months 1 & 2; termination
- Enzyme induction - at termination
- Plasma conc. of LY & erythromycylamine (EMA) using HPLC with electrochemical detection - 0, 15 & 30 min., 1, 2, 4, 6, 8 & 24h PD on day 1, month 1; termination
- Antimicrobial activity in plasma & tissues (heart, liver, kidney, lung) using microb. agar diffusion assay - during necropsy @ 4 & 24h after last dose
- Organ wts (brain, liver, kidney, heart, thyroid, adrenal, testes or ovaries); organ wts rel. to body & brain wts - at necropsy
- Gross & histopathology - at necropsy

Results

There were no drug-related findings in the following parameters: physical, ophthalmic & EKG exams, body wt, food intake, hematology, urinalysis, bone marrow, organ wts, organ/body wt, organ/brain wt

Mortality: None

Clinical Signs: Abnormal stools (includes soft, soft mucoid, mucoid & runny) and/or emesis intermittently and in low incidence throughout study and in all treatment gps. Both effects appeared to inc. in dose-related manner in LY-dosed gps.

Clinical Chemistry: Stat. sig. inc. in AST & ALT serum levels of M & F @ 150 mpk; inc. in creatinine in M & F @ 150 mpk (stat. sig. in M)

Hepatic Microsomal Metabolism: LY did not produce induction of hepatic p-nitroanisol O-demethylase activity.

Organ Wts: No drug-related changes in abs. wts, organ/body wt ratios or organ/brain wt ratios.

Gross & Histopathology: No drug-related changes.

Plasma Conc. of LY & EMA

Plasma levels of LY were very low & sporadic, exhibiting considerable interanimal variation.

The range of mean peak plasma conc. of LY & erythromycylamine were as follows, with levels of EMA being higher than those of the parent compound:

Dose (mpk)	LY 237216 (ug/ml)		EMA (ug/ml)	
	M	F	M	F
30	0.061	0.131	0.727	1.146
70	0.112	0.436	1.209	2.721
150	0.119	0.293	1.447	2.046

Peak levels of LY occurred @ 1-2h; peak levels of EMA occurred 2-4h PD in all treatment gps except the HD after 90 dosing days, in which a 6-h peak plasma level was seen.

Dose-related inc's in bioavailability parameters (C_{max} or AUC) for LY & EMA were evident when measured on days 30 & 90.

There was no consistent temporal pattern of change in C_{max} or AUC from one dose level to the next to indicate a continual accumulation of either LY or EMA in the plasma compartment during the 90-day dosing period. Both parameters eventually declined with time at the HD, but inc'd with time at the MD.

The mean half-life (alpha phase) for EMA disappearance from plasma between 1 & 8h ranged from 1.8h @ 70 mpk on day 90 to 6.3h @ 150 mpk on day 30.

The dogs dosed with 0 + 30 & 30 + 30 mpk LY + MgCO₃, respectively, showed no consistent or significant effect of MgCO₃ on AUC's & plasma levels of LY or EMA, or on mean plasma half-life (alpha phase) of EMA.

Antimicrobial Activity in Plasma & Tissues

Peak mean plasma antimicrobial activity occurred 2-4h PD and the range of values were as follows:

	<u>Dose (mpk)</u>
30	1.412-1.82
70	1.850-4.90
150	3.990-4.55

The peak mean plasma antimic. activity did not inc. sig. with time except at the MD. The sponsor attributes the higher plasma antibiotic content obtained by microb. assay vs that obtained by HPLC for LY and/or EMA to be due, in part, to the presence of one or more antimicrobially-active metabolites in addition to the parent compound.

Mean plasma antimic. activity did not inc. in direct proportion with dose. The peak mean activities for the 2 lower doses were similar in samples taken on days 1 & 30; the activity for the 2 upper doses were similar in samples taken on day 90.

The mean peak EMA antimicrob. activity values (ug/g) in tissues for M & F combined @ 4 & 24h were as follows:

<u>Dose</u>	<u>Heart</u>	<u>Liver</u>	<u>Kidney</u>	<u>Lungs</u>
30	15.5	49	24.6	18.1
70	32.7	62.1	45.2	43.5
150	91.9	143.4	117.4	132.6

Tissue levels were sig. higher than plasma levels. The liver contained the highest content @ 4h among the tissues examined. Each tissue examined still had sig. persistence of activity @ 24h, with mean activities in tissues taken @ 24h after the last dose being similar to those in tissues taken 4h after the last dose. In some instances, the activity in tissues @ 24h was greater than that seen @ 4h (i.e., at the HD, the %'s of the 4-h antimic. activity remaining in tissues @ 24h were: heart, 118%; liver, 49%; kidneys, 101%; lungs, 66%. There was a tendency for the activity to be slightly higher in tissues from F than those from M.

Co-admin. of 30 mpk MgCO₃ with 30 mpk LY produced no sig. change in plasma levels of parent drug or metabolite (EMA) or in tissue antimic. activity relative to that seen with LY alone.

1. I.V. Dose Range-Finding Study in Chbb:Thom Rats [Dr. Karl Thomae GmbH; study # 98 L]

Material Tested: AS-F LB (batch 3-123) dissolved in saline; controls rec'd saline.

Animals: M & F rats [Chbb:Thom (SPF)]; 10-12 wks old; 5/sex/group

Doses, Route & Duration: 50, 100 & 150 mpk i.v. 7 days/week for 25 days, with the HD being changed from 120 mpk as of the 2nd day of dosing.

Parameters: body wt, prior to dosing & weekly during dosing; food intake, once/week; general behavior, daily during dosing; hematology & clin. chem., wk 4 of study; gross & histopath., 24h after the last dose

Results

General Observations

50 & 100 mpk: circling movements with biting of tails & production of swollen tails on days 23 & 29, respectively.

100 mpk: rattling respiratory sounds between application day 9 & 17, which disappeared after a few seconds.

150 mpk: extremely strong reaction in 4/10 rats, consisting of lying motionless face down or on the side, accelerated respiration & signs of cyanosis. Two of these rats recovered within 30 min. and 2 died within 5 min.

120 mpk: distinct respiratory sounds in most rats, which disappeared as of the 2nd test week.

Food Intake & Body Wt: Dose-related dec. in all drug-treated gps

Hematology: 100 & 120 mpk F had slight inc's in Hgb & Hct; 120 mpk M had slightly inc'd thrombocyte cts; M at all 4 dose levels & 120 mpk F showed dec'd PTT values.

Clin. Chem.: SGOT was stat. sig. inc'd in LD, MD & HD M & F (dose-related in M); aldolase was markedly inc'd (dose-related) in LD, MD & HD M & F (stat. sig. in HD M and MD & HD F); alk. phos. was dec'd (dose-dependent) in M & F of the LD, MD & HD; glutamate dehydrogenase was inc'd in MD & HD F and HD M; total cholesterol inc'd in M & F at all 3 dose levels (stat. sig. in LD & HD M and all F); picrogram showed an inc. in albumin with corresponding dec. in globulin in LD, MD & HD F.

Gross Pathology: Grey-brown myocardial discoloration in HD rats; necrosis affecting parts of tail skin at injection sites at the MD & HD.

Histopathology (Light Microscopy): Heart

50 mpk: All rats of this group showed "disseminated small inflammatory absorption foci in the myocardium, mainly consisting of round-cell elements. Residues of necrotic myocardial fibers were noticeable in isolated areas. These foci usually extended over several myocardial fibers."

100 mpk: 9/10 Rats displayed the following: "Distributed over the whole myocardium, small focal regressive myocardial-fiber changes, partly in the form of large, fat-free vacuoles, partly cellular necrosis associated with loss of myofibrillar structure. These induced a marked phagocytosis activity predominantly round-cell elements."
1/10 Rats showed changes comparable to those seen in the 50 mpk group.

150 or 120 mpk: 9/10 Rats displayed the following: "Myocardial-fiber necroses distributed over the whole myocardium. Usually only isolated cells were affected, less frequently cell units. Damaged muscle fibers showed vacuoles or a loss of myofibrillar structure. Due to their necrosis, they induce a pronounced inc. in mesenchymal cells, apart from marked acute phagocytosis processes." 1/10 Rats showed only slight changes.

J. 13-Week I.V. Toxicity Study in Wistar Rats

Material Tested: AS-E LB (batch 30123) dissolved in 0.9% NaCl soln.; controls rec'd 0.9% NaCl soln.

Animals: M & F rats [Wistar HAN (SPF)] aged 34 days (M) or 35 days (F)

Dosage Groups: Controls, 20/sex/gp; 4, 10 & 25 mpk, 10/sex/gp; 62.5 mpk, 20/sex/gp; 10/sex from the HD & control gps were selected for a recovery period (RP) of 6 wks after discontinuation of drug treatment.

Route & Duration: i.v. 7 days/week for 13 weeks

Parameters: behavior & external appearance, twice daily, 5 min. & 2h PD; feces monitoring & local tolerance, daily; food intake & body wts, weekly; water intake, daily; hematology & clin. chem., prior to first dose, in the 2nd, 6th & 12th test wks and in RP rats at test wk 19 (blood was drawn 24h after dosing in fasting rats); urinalysis, prior to dosing, in the 2nd, 6th & 12th test wks, and in RP rats at test wk 19; histopathology, at sacrifice after 13 or 19 expt. wks; auditory acuity, tooth inspection, organ wts, at sacrifice.

Results

There was no mortality and no drug-related effects on local tolerance, feces, food/water intake, urinalysis.

Mortality: None

Behavior: Excitation for 5-10 min. after dosing in HD rats from test wk 9 on; during wks 10-13, this became more severe, with rats running hectically & uncontrollably for 10-20 min. Squeaking was observed for up to 20 min. after dosing during wks 11-13.

External Appearance: Rough fur in HD rats beginning test wk 10

Body Wts: During treatment, wt gain inhibition occurred in 25 mpk M (5%, test wk 4; 10-11% test wk 12 & 13) and in 62.5 mpk rats (M - 8-14%, test wks 6-13; F - 4-7% from test wk 8 on). During the RP, normalization of body wt gain occurred after discontinuation of HD dosing, but sig. inhibition still seen in M.

Hematology: During treatment, lymphocyte cts were slightly dec'd in test wk 12 in the 25 mpk gp and after 12 wks in the 62.5 mpk gp. Hgb, Hct & erythrocytes were slightly inc'd in the 62.5 mpk gp. In the RP, the 62.5 mpk gp M had a slight but sig. dec. in # of reticulocytes.

Clin. Chem.

Treatment Period: At 25 mpk: inc'd serum aspartate aminotransferase (AST/GOT) during test wk 12 (sig. in M); dec'd (slight but sig.) serum Cl in M & F, test wk 12; inc'd aldolase (not stat. sig.) in M & F, wk 12. LDH inc'd in M @ 10 & 25 mpk and F @ 25 mpk (not. stat. sig. in either sex). At 62.5 mpk: dose-related sig. inc. i. serum AST/GOT in M & F; sig. inc. in LDH; inc. in aldolase in M & F, wk 12 (sig. in F); slight but sig. inc. in serum uric acid in M & F, test wk 12; slight but sig. inc. in blood urea in M, test wk 6.

RP: At 62.5 mpk: sig. inc. in AST/GOT in M & F; inc. in LDH in M & F (sig. in F); sig. inc. in aldolase in F.

Organ Wts: At 62.5 mpk: sig. dec. in abs. testicular & brain wts concluded to be due to inhibited body wt gain as the rel. values for these organs were comparable to controls. At the end of 6 wks recovery, HD F rats had a sig. inc. in heart wt.

Gross & Histopathology (Light Microscopy): No drug-related changes found at the end of dosing.

K. 4-Week I.V. Toxicity Study in Rats [Dr. Karl Thomae, GmbH; Study # 50 N]

Material Tested: AS-E LB dissolved in physiological NaCl soln.

Animals: M & F rats [Chbb:Thom (SPF)], approx. 10 wks old; 10/sex/group

Dosage Groups: 12.5, 25, 50 & 100 mpk; there were 2 control gps - one remained untreated, the other received physiological NaCl soln.

Route & Duration: i.v.; 4 weeks

Parameters: body wt, food & water intake, weekly; general observations, daily; hematology & clin. chem., prior to dosing and study wk 4; urinalysis, prior to dosing & study wk 4; pharmacokinetics, end of study (parts of lung, heart, liver, kidney & plasma taken from 5/sex/gp); cylinder plate test with *Micrococcus luteus* ATCC 9341 used as test microorganism and determinations made 24h after the last of 30 i.v. injections; organ wts & histopathology, at sacrifice.

Results

Mortality: None

General Observations: No drug-related findings.

Body Wt: Marked sig. reduced inc. @ 50 & 100 mpk

Histopathology
(10/sex/group)

	Untreated		12.5 mpk		25 mpk		50 mpk		100 mpk		Saline	
	M	F	M	F	M	F	M	F	M	F	M	F
<u>Liver</u>												
-focal vacuoliz'n: min.	4	4	7	6	4	5	6	7	6	6	4	2
slight	3		1		3	2	3	1	1	1		
mod.									3			
<u>Heart</u>												
-focal myocardial degeneration: min.		1	1		2	3	7	4	6	9	1	2
slight	1				1		1		3		1	
-focal interstitial inflammation: min.	4	2	4	2	4	2	8	7	4	3	5	1
slight									4			
-focal pericarditis: min.					1							
<u>Tongue (muscle)</u>												
-focal degen.: minimal						1	1	3	4	8		
slight									2			
-focal regen.: minimal									3	3		
slight									3			
<u>Esophagus (muscular layer)</u>												
-min. focal degen.									1			
-min. focal interest. inflam.										1		
-min. focal regen.									2			
<u>Testes</u>												
-bilateral severe hypospermatogenesis			1						1			
<u>Injection Site</u>												
-focal musc. degen.: min.			1	2					2	1		1
slight						1			1			
-perivascular fibrosis			1	1	1	7	2	4	1	5		1
-foreign body granuloma subcutis					3	1		2	1	1		
-focal dermal inflammation			2	1	3	1	1		4			
-severe focal epidermal necrosis											1	
-thrombophlebitis			2			2	1	1		4		2
<u>Skeletal Muscle</u>												
-focal degen.: min.					1		7	10	7	7		2
slight									2	3		
-focal regen.: min.						1		4	5	3		
slight									1			
<u>Diaphragm</u>												
-focal degen.: min.					2	2	7	8	5	6		
slight								1	3	2		
-focal regen.: min.					5		5	5		4		
slight							5	2	10	6		
<u>Pituitary</u>												
-cyst			2	1			1	1	1			

Summary Diagnosis

	Untreated		12.5 mpk		25 mpk		50 mpk		100 mpk		Saline	
	M	F	M	F	M	F	M	F	M	F	M	F
<u>Heart</u>												
-progressive cardio-myopathy: min.		1		1	3	3	7	4	6	9	1	2
slight	1						1		3		1	
<u>Whole Animal</u>												
-toxic myopathy: min.					7	2	5	7		2		
slight							5	3	10	8		
<u>Liver</u>												
-focal vacuoliz.: min.	4	4	7	6	4	5	6	7	6	6	4	2
slight	3		1		3	2	3	1	1	1	4	
mod.									3		4	
<u>Injection Site</u>												
-focal musc. degen.: min.			1	2					2	1		1
slight						1			1			
-perivasc. fibrosis			1	1	1	7	2	4	1	5		1
-foreign body granuloma subcutis					3	1		2	1	1		
-focal dermal inflam.			2	1	3	1	1		4			
-thrombophlebitis			2			2	1	1		4		2

Tissue Levels of AS-E LB

Conc. values of antimicrobial activity (ug/g tissue or ug/ml plasma) in tissues were much higher than plasma levels. The highest concs. of antimicrobial activity were found in the lungs, with the heart & kidney showing lower concs. The lowest were seen in the liver. (See table below.)

No dose proportionality was obtained for tissues & plasma by raising the doses of AS-E LB.

Conc. of Antimicrobial Activity (ug/g Tissue & ug/ml Plasma)
24 Hrs after Last of 31 I.V. Injections

Dose (mpk)	Heart		Lung		Kidney		Liver		Plasma	
	M	F	M	F	M	F	M	F	M	F
12.5	105	109	342	280	219	168	34	39	0.147	0.112
25	354	485	1184	1260	544	702	71	104	0.281	0.239
50	910	873	1522	2319	842	833	266	301	0.394	0.326
100	2644	2411	7524	6244	1836	2037	683	957	2.186	1.654

L. Antimicrobial Activity in Plasma & Tissues of Dogs
[Lilly Research Labs; Study # D06187]

Material Tested: LY in enteric-coated capsules

Animals: Three M beagle dogs

Dose Level, Route & Duration: 30 mpk p.o. for 5 days

Methods: Blood samples for determination of antimicrobial activity in plasma were collected at 0, 0.25, 0.5, 1, 2, 4, 8 & 24h after the first & last doses. Dogs were necropsied 24h after the last dose and tissue samples collected to determine antimicrobial activity in heart, liver, kidney & lung. Antimicrobial activity in plasma & tissues was determined by microbiological agar diffusion assay with Micrococcus luteus ATCC 9341.

Results

Body Wt; Food Intake; Gross Pathology: The sponsor states "there were no clinical signs of toxicity."

Plasma & Tissue: Mean antimic. activity in plasma was less than 0.3 ug/ml at all time points. Mean antimic. activity in tissues (heart, kidney, liver & lung) was 2.4, 3.2, 2.7 & 2.7 ug/g, respectively. The sponsor attributed these lower results (compared to those obtained from previous studies) as being due to poor dissolution of the enteric-coated capsules.

MUTAGENICITY STUDIES

[Studies 1-4 performed by Dr. Karl Thomae, GmbH; Studies 5-8 performed by Eli Lilly Research Labs.]

A. Ames Test [Proj. Report #6]

Test System: Ames test using the following indicator organisms: S. typhimurium - TA 1535, 1537, 1538, 98 & 100

Activation System: Drugs were tested in the presence of S-9 fractions (i.e., liver microsomal enzyme preparations) obtained from untreated rats as well as from Aroclor 1254-induced rats.

Materials & Concs. Tested:

	<u>ug/plate</u>
AS-E LB (batch EL 416) dissolved in A. bidest., DMSO	
AS-E BS (batch TK 703) dissolved in acetone, methanol	
Nitroso derivatives of AS-EX 159 BS (batch SL 1511) dissolved in DMSO	
AS-EX 159 reaction soln. (batch SL 1543) diluted in DMSO.	

Positive Controls:

- Benzo(a)pyrene
- 2-Aminoanthracene (2-AA)
- Cyclophosphamide
- 4-Nitroquinoline-N-oxide (4-NQO)
- Dimethylnitrosamine (DMNA)
- Diethylnitrosamine (DENA)
- N-methyl-N-nitro-N-nitrosoguanidine (MNNG)

Results: Test substances AS-E LB & AS-E BS, with & without metabolic activation, induced no base substitutions (S. typhimurium TA 1535, 100) and no frame shift mutations (S. typhimurium TA 1537, 1538, 98) in the Ames test. The nitro derivatives AS-EX 159 & AS-EX 159 BS were also negative for mutagenicity in this assay. The reference substances tested were found to be mutagenic.

B. Mouse Micronucleus Test

Materials Tested: AS-E LB (batch EL 416) dissolved in physiological saline; negative control, phys. saline; positive control, cyclophosphamide

Animals: M & F mice [Chbb:NMRI (SPF)], 6 wks old; 6/sex/group

Dose Levels, Route & Duration: AS-E LB, 200 mpk (MTD); pos. control, 20 mpk; neg. control, 10 ml/kg; i.v. single dose

Parameters: Bone marrow analysis - 24, 48 & 72h PD, consisting of determination of micronucleated polychromatic erythrocytes (PE) per 1000 PE and ratio of poly- to normochromatic forms (NE) in 1000 erythrocytes scored. Drug content in bone marrow homogenate was measured by microbiological assay.

Results

Micronucleated Polychromatic Erythrocytes & Ratio of Poly- to Normochromatic Erythrocytes

AS-E LB: No inc. in micronucleus values; the PE/NE ratio was within control range at all times.

Cyclophosphamide: Sig. inc. in micronucleated PE @ 24 & 48h. After 72h, the no. of induced micronuclei showed a gradual dec. The PE/NE ratio showed a change in favor of the NE.

Drug Content in Bone Marrow Homogenate: Low but sustained drug levels (0.85, 0.36 & 0.28 ug/ml in M & 0.65, 0.47 & 0.27 ug/ml in M & F @ 24, 48 & 72h, respectively).

C. In Vitro Human Lymphocyte Sister Chromatid Exchange (SCE) Assay: [Trial # Gen Tox 07/85]

Activation System: Drugs were tested in the absence & presence of S-9 liver microsomal enzyme preparation from Aroclor-induced rats.

Materials & Concs. Tested: mol/l

AS-E LB (batch EL 416) diss. in dist. water	
Mitomycin C	" " " "
Cyclophosphamide	" " " "
Neg. Control: distilled water	

Parameters: Mitotic index & distribution pattern; incidence of SCE

Results

Mitotic Index & Distribution Pattern

AS-E LB: No cytotoxic or growth-inhibiting effects on the lymphocyte population

Mitomycin C & Cyclophosphamide: The frequency of mitosis was unaffected by exposure. No M3 mitoses were observed after cyclophosphamide.

SCE Induction

AS-E LB: No sig. inc. in either the absence or presence of metabolic activation.

Cyclophosphamide: In the presence of metabolic activation, a conc.-related inc. in SCE to 3-8x the spontaneous value.

Mitomycin C: Test concs. were too low. Latt et al. (1981) report induction of SCE's only at conc. of $3-4.5 \times 10^{-7}$ mol/l.

D. In Vitro Mesenchymal Chinese Hamster Lung Fibroblast (V79) HGPRT Forward Mutation Assay [Proj. Rpt. No. Gen Tox 18/85]

Activation System: Drugs were tested in the absence & presence of S9 liver microsomal enzyme preparations from Aroclor-induced rats

Materials & Concs. Tested: ug/ml

AS-E LB (batch EL 416) diss. in dist. water
 Pos. Controls:
 Ethylmethane sulfonate (EMS) " " "
 7,12-Dimethylbenzanthracene (DMBA) in DMSO
 Neg. Control: distilled water

Parameters: Drug-induced cytotoxicity; incidence of HGPRT mutants with/without metabolic activation

Results: AS-E LB was cytotoxic @ 1000 ug/ml & above. It produced no inc. in HGPRT clones with or without metabolic activation, when tested @ 100-2000 ug/ml.

E. DNA Repair Synthesis: [Study #'s 860506 UDS 2790 & 860513 UDS 279]

Test System: In vitro induction of unscheduled DNA synthesis in primary cultures of adult rat hepatocytes. Unscheduled DNA synthesis was measured by autoradiography. Assay was conducted using 2 independent hepatocyte preparations.

Materials Tested: LY (Lot # DPP 10698) dissolved in DMSO; pos. controls = MNNG and 2-acetylaminofluorene (2-AAF); neg. cont. = 1% DMSO

Concs. Tested: ug/m

LY (Lot # DPP 10698) dissolved in DMSO
 Pos. Controls:
 MNNG
 2-AAF
 Neg. Control: 1% DMSO

Parameters: Net nuclear silver grain count as determined by the difference between the gross nuclear grain count and the mean cytoplasmic background count.

Results: LY was inactive for the induction of UDS. With MNNG & 2-AAF, there was a positive autoradiographic response for UDS.

F. Ames Test: [Study #'s 860708 AMT 2790 & 860818 AMS 2790]

Test System: Ames test using the following indicator organisms: S. typhimurium strains TA 1535, 1537, 98 & 100, and E. coli strain WP2UVrA-.

Activation System: Drugs were tested in the presence of S9 fraction (liver microsomal enzyme preparation) obtained from Aroclor 1254-induced rats.

Materials & Concs. Tested: ug/plate

LY (Thomae lot 853021) in sterile water

Pos. Controls:

MNNG

9-Aminoacridine (9-Am Ac)

2-Nitrofluorene (2-NF)

2-Aminoanthracene (2-AA)

Neg. Control: distilled water

Parameters: Induction of reverse mutations in the appropriate S. typhimurium & E. coli tester strains in nonactivated & activated tests.

Results: LY was not mutagenic in the mammalian microsome test for bacterial mutation. With MNNG, 2-NF, 9-Am Ac & 2-AA, there was dose-related induction of reverse mutations in the S. typhimurium & E. coli tester strains.

G. Mouse Lymphoma [Study #'s 860806 MLT 2790, 860813 MLA 2790 & 860917 MLA 2790]

Test System: L5178Y TK⁺/₋ mouse lymphoma cell assay

Activation System: Drugs were tested in the presence of S9 fraction (liver microsomal enzyme prep.) obtained from Aroclor 1254-induced rats.

Materials & Concs. Tested: ug/ml

LY (lot 853021) in sterile Milli-Q water

Pos. Controls:

EMS dissolved in DMSO

3-methylcholantrene (3-MC) dissolved in DMSO

Neg. Control: distilled water

Parameters: Induction of L5178Y TK⁻/₋ mutants

Results: LY was nonmutagenic at concs. of 500-100 ug/ml in the nonactivated test & 1000-100 ug/ml in the activated test. With EMS & 3-MC, there was induction of L5178 TK⁻/₋ mutants.

H. SCE Exchange [Study # 86117 SCE 2790]

Test System: In vivo SCE in bone marrow of Chinese hamsters.

Animals: Adult F Chinese hamsters; 3/group

Materials & Doses Tested: LY (Thomae lot 853021) susp. in 10% aq. acacia, 125, 250 & 500 mpk; cyclophosphamide in 10% aq. acacia (pos. cont.), 50 mpk; 10% aqueous acacia (neg. cont.)

Route & Duration: p.o. single dose

Parameters: Ability of drug to cause a dose-related inc. in SCE frequency

Results: LY had no effect on SCE frequency compared to controls. With cyclophosphamide, there was a stat. sig. positive response for SCE induction.

REPRODUCTION STUDIES

A. Segment I Fertility Study

Material Tested: AS-E 136 LB (batch 30123) dissolved in 0.9% NaCl soln.; controls rec'd 0.9% NaCl soln.

Dose Levels & Route: 4, 10, 25 & 62.5 mpk i.v.

Methods: M Wistar rats, 10/sex/group (originating from a previous 13-wk subchronic i.v. toxicity study), were treated for 12 wks prior to mating, then copulated 7 days with a corresponding no. of untreated F of the same strain. The F remained untreated, but the M partners were treated constantly until completion of the mating phase, then sacrificed. The dams were sacrificed on day 13 of gest. and examined for fertility results.

Parameters

Parent Rats: behavior & general condition, food & water intake and body wt (daily)

Dams with Laparotomy: No. of corpora lutea & implantations (abs./dam, distribution in ovaries in %), # implantations (abs./dam, distribution in uterus in %); # placentae (abs.), # resorptions (abs./dam - early 2 mm, late 2 mm), resorption rate in % (resorptions/implantations x 100), fertility index in % (preg. rats/rats used x 100) and preimplantation loss in % (corpora lutea-implantation/corpora lutea x 100).

Time of Sacrifice: M - after successful mating (at the earliest after 13 wks treatment); F - on day 13 of pregnancy

Results

There were no drug-related effects on the fertility of untreated F parents. The M parent rats showed the following.

Local Tolerance: No drug-related findings.

Systemic Changes: There were no drug-related findings @ 4 & 10 mpk. At 25 mpk: inhibition of body wt gain occurred in the last 2 dose wks by 10-11%. At 62.5 mpk: increasing excitation for up to 20 min. from wk 9 on; rough fur during last 4 wks; squeaking in wks 11-13 for 20 min. PD, inhibition of body wt gain at the end of dosing by 14%.

B. Segment II Teratology Study [Dr. Karl Thomae GmbH; Trial no. 97H]

Material Tested: AS-E BS (batch TK 703) suspended in 0.5% tylose; controls received 0.5% tylose.

Animals: F Chbb:Thom (SPF) rats, 35/group

Doses, Route & Duration: 15, 150 & 1000 mpk, by gavage, days 7-16 of gestation.

Methods: In each test gp, 23 F were sacrificed on day 21 of gestation, uteri were removed & examined for viable & dead fetuses & resorptions, and 2/3 fetuses were evaluated for skeletal anomalies. The heads of the remaining 1/3 fetuses were removed and underwent free-hand dissection & exam according to the method of Wilson; autopsy was performed and thorax & abdomen were examined to assess viscera. The remaining 12 F/group were allowed to give birth and raise offspring for 3 wks, at which time body wt development, eruption of incisors, development of pelage, opening of the auditory canals & eyes and gait were evaluated. At 4 wks, pupillary & righting reflexes, hearing capacity & mortality of young were evaluated.

Results

Dams: At 150 mpk: inc'd salivation as of day 10 of gestation, chromodacryorrhea & inc'd respiratory sounds. At 1000 mpk: inc'd salivation, diarrhea & soft feces, inc'd defense reactions, inc'd respiratory sounds, chewing of bedding material, chromodacryorrhea, piloerection, poor general condition, slight sedation, dec'd wt gain, premature deaths of 2 rats.

In the litters of the dams sac'd on gest. day 21, the # corpora lutea, implantations, viable & dead fetuses, resorptions, preimplantation loss & sex distribution for drug-treated gps were comparable to controls.

Fetuses: At 150 mpk, 3/224 viable fetuses had skeletal malformations vs 0/227 viable fetuses in control gps, consisting of 2 fetuses with vertebral cleft & 1 with hemivertebra. At 1000 mpk, 2/23 viable fetuses had skeletal malformations vs 0/227 controls, consisting of 2 fetuses with wavy ribs. Also at the HD there was inc'd incidence of delayed ossification of forelimbs, hindlimbs & sternbrae. There was inc'd incidence of cervical ribs at the MD & HD & lumbar ribs in the LD, MD & HD.

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Among fetuses of dams allowed to birth & raise offspring for 3 wks, there was no drug-related effect on duration of gestation, # of young, embryonal loss post-implantation, survival rate, viability, discontinuance, offspring wt, maturation parameters, righting reflex or hearing. Three HD rats showed abnormal pupillary reflexes (i.e., pupils of hexagonal or oval form, enlarged, and not contracting normally upon light stimulus).

C. Segment II Teratology [Dr. Karl Thomae GmbH; Study # 98H]

Material Tested: AS-E BS (batch TK 703) suspended in 0.5% tylose; controls rec'd 0.5% tylose.

Animals: Russian rabbits (Himalayan) Chbb:HM (SPF); 18 F/group

Doses, Route & Duration: 15, 40 & 100 mpk by gavage, days 6-18 of gest.

Parameters: Clinical signs, body wt (prior to dosing and days 1, 21 & 28 of gest.), # corpora lutea, # & site of viable & dead fetuses, early & late resorption, # implantations, fetal malformations, avg. fetal wt, preimplantation loss (corpora lutea-implantations/corpora lutea x 100), resorption rate = resorptions in % of implantations.

Results: Dams

Mortality: 1/18 HD dams died on gest. day 9; autopsy showed intestinal inflation & liquid feces. Death was attributed to diarrhea.

Clinical Signs: In all drug-treated gps, dose-related disturbances of defecation (reduced or lacking, pasty-liquid feces, dry & hard stool).

Abortions: Observed in 2/18 dams in the LD & HD gps.

Body Wt: Delayed gain in LD, MD & HD gps, seen during the first 10 days in the LD, with normalization at day 12. Reduced body wt gain was continuous throughout dosing in the MD & HD gps, with a loss in body wt at the HD during the entire dosing period.

Litter Results

There was no mortality among the fetuses.

There were no sig. drug-related differences, compared to controls, in corpora lutea, implantations or sex ratio.

The # of viable fetuses was comparable among controls, LD & MD gps, but the HD gp had sig. fewer viable fetuses compared to controls.

Resorptions were sig. inc'd (27.3%) in the HD gp compared to controls (13.2%), and a larger # of late resorptions were observed.

Fetal Results

There was no drug-related effect on body wt.

Runts: Fetuses weighing less than 65% normal wt were observed in the control (3), MD (2) & HD (5) gps.

Malformations consisted of 1 control fetus with atresia of the gall bladder, 3 HD fetuses with delayed ossification of the hindlimbs, and 1 HD fetus with umbilical hernia with eventration of the intestine. The gall bladder atresia, umbilical hernia & intestinal eventration were within historical control range for this strain of rabbit.

D. Reproduction Study in Rats: Interim Report [Lilly Research; Study # R 14387]

Material Tested: LY

Animals: Female CD rats; 20/group

Doses, Route & Duration: 0, 12.5, 28 or 62.5 mpk i.v. daily for 2 wks prior to mating, during 2 wks of cohabitation, and throughout gestation & lactation until necropsy at about 3 wks postpartum.

Parameters: drug effect on mating, fertility, body wt, food intake & pathology

Results

Mortality: 2/20 HD rats died after 40 & 44 days of dosing. Gross path. showed pale he. congested & edematous lungs & mottled livers.

Mating & Fertility: No drug-related effect

Body Wt; Food Intake: Dec'd in HD mothers throughout the study. Body wt dec. occurred in all other dose gps during the latter part of pregnancy.

Histopathology
(20 Rats/Group)

	Dose Groups (mpk)			
	Controls	12.5	28	62.5
<u>Heart</u>				2
-mod. focal degen. & slight fibrosis				
-min. to mod. focal myocard. lesions distinguished from age-related progressive cardiomyopathy			2	17
-age-related progressive cardiomyopathy	3	5	13	
<u>Lung</u>				2
-congestion & edema				
<u>Liver</u>				2
-centrilobular congestion & necrosis				
<u>Skeletal Muscle</u>			18	20
-min-mod. focal degen. and/or regen.				
-min. focal degenerative changes	2	2		
-min. focal regeneration		1		
-min. focal interstitial inflammation		2		

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

IND: (Amendments dated November 21, 1988 and May 15, 1989)

DATE REVIEW COMPLETED: August 4, 1989

SPONSOR: Eli Lilly and Co., Indianapolis, IN

DRUG: Dirithromycin (i.e., also known as Compound LY 237216 and as AS-E 136)

CATEGORY: Macrolide antibiotic

COMMENTS:

1. An original review of this IND was performed on 4/29/88.
2. Preclinical data submitted to this IND since the original review consists of the following:
 - a. A ten-week basic fertility study of dirithromycin (LY 237216) lactobionate administered i.v. to female CD rats
 - b. Acute dermal and ocular studies of LY 237216 in rabbits
3. The purpose of this review is to supply an evaluation of the studies cited above.

TOXICOLOGY

Reproduction Studies: Final Report:

A. Segment I Fertility Study (Female Rats):

Lab Performing Study: Lilly Research Laboratories, Greenfield, Indiana

Proj. Rpt. No: R14387; the interim report of this study, dealing only with the adverse maternal effects produced by this drug were reviewed in the original pharmacology review dated 4/29/88.

Material Tested: LY 237216 (the lactobionate salt), lot #87200; potency 58.5% as dirithromycin; 83.6% as lactobionate salt of dirithromycin

Formulation Composition: Solutions of dirithromycin lactobionate at concn.'s of 4.3, 9.6 or 21.4 mg total material/mL in 0.9% sodium chloride for injection; concentrations equate to 2.5, 5.6 and 12.5 mg dirithromycin activity/mL

Dose Levels Tested:

Treatment Group	Dirithromycin Dose (mg/kg)	
	Lactobionate	Base
0 (control)	--	--
1	21.4	12.5
2	47.9	28.0
3	106.8	62.5

Route and Duration: Intravenous; 10 weeks (2 weeks prior to mating and throughout mating, gestation, and lactation until necropsy at about 3 weeks postpartum)

Species, Sex, Age and Weight: Pregnant female Cr1: CD (SD) rats; 10 weeks of age and $201 \pm 8.1g$ in weight at study initiation

No. of Animals Tested: 20/group

Parameters Evaluated:

<u>Dams:</u>	<u>Dose Days</u>
Clinical signs	Daily
Body Weight	Postmating days 0, 7, 14 & 21 & on postpartum days 1, 7, 14, & 21
Food Consumption	Postmating days 0, 7, 14, & 21 & on postpartum days 0, 7, 10 & 14
Precoital period length, gestation length; # live & dead progeny; mating & fertility index; gross histopath.	Day of delivery
<u>Progeny:</u>	
# surviving progeny	Postpartum days 1, 4, 7, 14 & 21
Sex of each pup	Postpartum day 1
Total litter weights	Postpartum days 1, 7 & 14
Clinical signs & anomalies	Throughout postpartum period
Individual pup weights by sex	Postpartum day 21
Overt anomalies	At sacrifice

Results:

Dams:

<u>Mortality & Clinical Observation - Maternal Animals</u>				
<u>Dose (mg/kg/day)</u>	0	21.4	47.9	106.8
Animals/Group	20	20	20	20
Deaths/Group	0	0	0	2
<u>Observation</u>				
Incisor overgrowth, teeth clipped	3	4	10	12
Chromorhinorrhea	0	0	0	1
Thinness	0	0	0	4
Decreased Muscle Tone	0	0	0	1

Body Weight: Statistically significant decrease in mean body wt. gain in HD females throughout the study (i.e., pre mating, gestation and postpartum periods); significant decrease in mean body weight gain in MD & HD females during the third gestation week; decrease in mean body weight gain in MD females throughout postpartum period, statistically significant on postpartum day 21.

Food Consumption: Statistically significant decrease in HD females during the gestation and postpartum periods.

Mating Performance and Fertility: All drug treated females mated and were fertile. There was no drug-related effect on the length of precoital period.

Reproductive Findings:

Gestation Length: No drug related effects produced

Litter Size: Non dose-related, statistically significant decrease in LD, MD & HD drug treated animals

Progeny Findings:

Sex Ratio and Survival Indices: No drug related effects were produced

Mean Body Weight Gain: Statistically significant decrease in HD females throughout lactation; according to the sponsor, this decrease was due to drug-related maternal effects.

# Animals Dosed	20	20	20	20
# Animals Evaluated	20	20	20	20
# Animals Survived	20	20	20	18
<u>Tissue/Observations:</u>				
<u>Liver (# Examined):</u>	1			2
-centrilobular congestion				2
-focal necrosis	1			2
<u>Heart (# Examined):</u>	20	20	20	20
-min. focal myocardial degeneration			1	3
-slight focal myocardial degeneration			1	11
-moderate focal myocardial degeneration				5
-min. focal necrosis				4
-slight focal necrosis				9
-moderate focal necrosis				1
-min. focal progressive cardiomyopathy	3	5	13	1
-thrombosis, right atrium				1
<u>Lung (# Examined):</u>				2
-vascular congestion				2
-focal alveolar edema				2
<u>Skeletal Muscle</u>				
<u>(# Examined):</u>	20	20	20	20
-min. focal degeneration	2	2	16	6
-slight " "			2	12
-mod. " "				2
-minimal focal				

Histopathology* Dams: (Continued)

	Dose (mg/kg)			
	Control	21.4	47.9	106.8
<u>Skeletal Muscle (Cont.)</u>				
interstitial inflammation			1	
-min. focal regeneration	1		11	8
-slight focal regeneration			2	11
<u>Diaphragm (# Examined):</u>	19	20	20	20
-min. focal degeneration			3	9
-slight focal degeneration				9
-min. focal interstitial inflammation	2			1
-min. focal regeneration			3	4
-slight focal regeneration				7

- * Since striated muscles have been identified as target tissues for dirithromycin-induced pathology, only the following tissues were collected for histopathology: heart, diaphragm, rectus abdominis, quadriceps femoris and gastrocnemius

Conclusion: Pregnant female rats dosed i.v. with 0, 21.4, 47.9 or 106.8 mg/kg dirithromycin lactobionate (equivalent to 0, 12.8, 28 & 62.5 mg/kg dirithromycin base) for ten weeks experienced the following: drug related deaths (HD), sig. decrease in mean body wt gain (MD & HD) & food intake (HD), and dose-related focal myocardial and skeletal muscle lesions (MD & HD). Progeny exposed to HD drug demonstrated significant decreases in mean body weight gain which was assumed to be due to treatment-related maternal effects.

B. Acute Dermal and Ocular Studies of LY237216: Rabbits:

Lab. Performing Study: Lilly Research Labs., Greenfield, Indiana

Proj. Rpt. No.'s: B-0-087, B-E-084-87, B-E-107-87

1. Dermal Toxicity and Irritation: Rabbits were evaluated by single dose application of 1.0 g/kg of drug to their backs. After a 24 hour exposure period, drug treated sites were washed and animals observed for 14 days. Results showed slight erythema developing in 1/3 animals within 24 hours. This reaction was reversible and cleared within 48 hours post dosing.
2. Acute Ocular Toxicity: Single dose application of 45mg of LY237216 (0.1cc) into the eyes of three rabbits resulted in moderate corneal opacity, marked to severe iritis and moderate to extreme conjunctivitis developing within one hour of dosing. Corneal vascularization occurred by test day 8 and persisted through test day 27 in 2/3 animals; this was accompanied by corneal dullness in one of these animals at study termination. Washing the eyes for 5 minutes past dosing, reduced the severity and duration of irritation slightly.

Pages taken
directly from
Application

Tables 10, 11 + 12

Table 10
Dirithromycin Plasma Protein Binding, Hepatic Induction, Cytochrome P-450 Binding, and Metabolism Studies

Species	Strain	Sex	Route	Dose ^a (mg/kg)	Study Type	Results	ADME Report
Rat	CHbb:Thom	M			In Vitro Plasma Protein Binding	Determined at 37°C; ultracentrifugation methodology; drug added to a concentration of 0.2 and 2 µg/ml. The extent of binding was 14.2% and 17.2%, respectively.	9
Rat	F344	M	IV	5.8, 17.4 (X)	Hepatic Induction, and P-450 MI-Complex	Dirithromycin was administered once daily for 5 days. No effect was observed on rat liver weight, microsomal protein, or cytochrome c reductase activity at either dose. Cytochrome P-450 was elevated at 17.4 mg/kg/day. No MI-complex was observed after five daily doses of 17.4 mg/kg/day.	5
Rat	SD	M			In Vitro Hepatic P-450 MI-Complex	Dirithromycin (DIR) was incubated with hepatic microsomes from untreated, phenobarbital and dexamethasone pretreated rats. DIR did not induce a type I binding spectrum with any microsomes tested. DIR formed a very small MI-complex only with microsomes from dexamethasone pretreated rats which was only 6% of that observed with triacetyloleandomycin.	6
Rat	CHbb:Thom	M	IV	10	Biotransformation	Five minutes after IV dosing with ¹⁴ C-dirithromycin (DIR), 63% of the plasma radioactivity was DIR and 17% was erythromyclamine (EMA). At the same time, EMA was the predominant form of radioactivity in lung (52%), liver (74%), kidney (55%), and spleen (37%). Only small concentrations of DIR were observed in these tissues. In bile, DIR accounted for 35% of the radioactivity 1 hr after dosing, 14% 2 hr after dosing, 10% 4 hr after dosing and was not observed thereafter. Conversely, EMA accounted for 48% of the radioactivity 1 hour after dosing, 71% 2 hours after dosing, 80% 4 hours after dosing, and 88% 6 hours after dosing. Approximately 75% of the urinary radioactivity collected from 0-4 hours was EMA.	9

(continued)

9.4.51-677
 ATTACHMENT 3

Table 10 (continued)
Dirithromycin Plasma Protein Binding, Hepatic Induction, Cytochrome P-450 Binding, and Metabolism Studies

Species	Strain	Sex	Route ^a	Dose ^a (mg/kg)	Study Type	Results	ADME Report
Rat	F344	M, F	PO	100, 400, 750 (X)	Induction	Rats were dosed daily by gavage for 6 months (Toxicology Protocol R00389). p-Nitroanisole O-demethylase, benzphetamine N-demethylase, and 7-ethoxymisofurin O-demethylase activities and cytochrome P-450 were evaluated. Slight but significant increases in p-nitroanisole O-demethylase and benzphetamine N-demethylase activities were noted. These changes were so slight as to be of no biological significance. Although a 1.5-fold increase in benzphetamine N-demethylase was observed in high dose females, this was not observed in males.	15
Dog	Beagle	M, F	PO	53, 105, 228 (X)	Induction	Dogs were dosed daily with enteric-coated capsules for 2 weeks (Toxicology Protocol D00586). No effect of dirithromycin on p-nitroanisole O-demethylase was observed at any dose level.	16
Dog	Beagle	M, F	PO	26, 61, 131 (X)	Induction	Dogs were dosed daily with enteric-coated capsules for 3 months (Toxicology Protocol D02586). No effect of dirithromycin on p-nitroanisole O-demethylase was observed at any dose level.	17
Dog	Beagle	M, F	PO	8.8, 26, 61, 131 (X)	Metabolism	Plasma levels of dirithromycin after chronic administration of dirithromycin to dogs were very low. Dirithromycin was biotransformed by dogs to three metabolites. Erythromycylamine (EMA) was the primary metabolite in plasma. A 12-membered ring-contracted metabolite of EMA was present in the plasma which had biological activity equivalent to EMA. Decladinosyl-erythromycylamine was present in plasma and urine of dogs.	4

(continued)

5300

5-1

Table 10 (concluded)
 Dirithromycin Plasma Protein Binding, Hepatic Induction, Cytochrome P-450 Binding, and Metabolism Studies

Species	Sex	Sex	Route	Dose ^a (mg/kg)	Study Type	Results	ADME Report
Human					In Vitro Plasma Protein Binding	Determined at 37°C; ultracentrifugation methodology; drug added to a concentration of 0.2 and 2 µg/ml. The extent of binding was 21.0% and 19.5%, respectively.	9
Human					In Vitro Hepatic P-450 MI-Complex	Dirithromycin (DIR) was incubated with hepatic microsomes from untreated patients and patients on recent barbiturate/phenytoin therapy. DIR did not induce a type I binding spectrum or MI-complex with any microsomes tested. Erythromycin base did not form a type I binding spectrum and formed only a very small MI-complex in one patient on phenobarbital/phenytoin. These data are compared with results with triacetyloleandomycin and erythromycin.	7

Abbreviations: IV = intravenous; ID = intraduodenal; SC = subcutaneous; PO = oral; MI = metabolic intermediate; (X) = multiple dose.
^a Dose based on potency of the lot of dirithromycin used.

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Table 11
 Diritramycin Excretion Studies

Species	Strain	Sex	Animals/ Group	Route	Dose ^a (mg/kg)	Collection Period (hr)	Urine	Feces	Bile	Carcass	Total	ADME Report
Row	CHbb:Thom	M	5	IV	10	0-6	--	--	34.9	--	--	9
Row	CHbb:Thom	M	5	IV	10	0-25	10.2	45.6	--	--	55.8	9
						0-96	13.7	69.7	--	16.9	100.3	9
Dog	Hovand	F	3	PO	8.8	0-72	6.0	85.3	--	--	91.3	3
						0-144	7.4	92.2	--	--	99.6	3

^a Dose based on potency of the lot of dicitramycin used.

Table 12
 Tissue Distribution of Dirithromycin

Species	Strain	Sex	Route	Dose ^a (mg/kg)	Assay Type	Results	ADME Report
Mouse	NMRL	F	PO	91	Bioassay	C_{max} was higher in liver (17.1 µg/ml) and kidney (9.5 µg/ml) than in serum (2.0 µg/ml). $T_{1/2}$ was longer in liver (38 hours) and kidney (35 hours) than in plasma (16 hours). Skeletal muscle parameters were similar to serum. Higher and more sustained levels of antibiotic activity were generally observed in tissues compared with plasma.	8
Rat	FW49	F	PO	91	Bioassay	C_{max} was higher in liver (14.0 µg/ml) and kidney (13.3 µg/ml) than in serum (1.3 µg/ml). $T_{1/2}$ was longer in kidney (69 hours) than in liver (34 hours) or serum (34 hours). Higher and more sustained levels of antibiotic activity were consistently observed in soft tissues compared with serum irrespective of dose and route of administration (9 mg/kg SC, 45 mg/kg PO, 91 mg/kg PO). Skeletal muscle kinetic parameters were similar to those observed in plasma.	8
Rat	FW49	F	PO	181	Bioassay	C_{max} was higher in liver (22.5 µg/ml) and kidney (10.3 µg/ml) than in serum (1.5 µg/ml). $T_{1/2}$ was longer in liver (69 hours) and kidney (69 hours) than in serum (42 hours). C_{max} of skeletal muscle (1.1) was similar to serum; however, $T_{1/2}$ of antibiotic activity in skeletal muscle (69 hours) was longer. Higher and more sustained levels of antibiotic activity were generally observed in tissues compared with serum.	8
Rat	Chib:Thom	M	IV	10	Whole Body Radiography	Radioactivity distributed very well from blood into liver and skeletal muscle but not into brain. High concentrations of radioactivity were observed in liver, intestine (bile/ery excretion), salivary gland, kidney, lung, and spleen. Heart muscle showed a higher concentration of radioactivity than skeletal muscle. Radioactivity was also present in bone marrow and adrenal gland. In pigmented rats, the radioactivity did not exhibit affinity for pigmented parts of the skin whereas there was distribution into the pigmented parts of the eye.	9

(continued)

Table 12 (continued)
 Tissue Distribution of Daptomycin

Species	Strain	Sex	Route	Dose ^a (mg/kg)	Assay Type	Results	ADME Report
Rat	CHB:Thom	M	IV	41 (X)	Bioassay	Ten hours after the last of four daily doses, lung, kidney, liver and skeletal muscle concentrations were 494, 370, 227 and 92 times greater than the plasma concentrations (0.89 µg/ml), respectively. Twenty-four hours after the last dose, lung, kidney, liver and skeletal muscle concentrations were 732, 543, 308 and 125 times greater than the plasma concentration (0.58 µg/ml), respectively.	10
Rat	CHB:Thom	M, F	IV	7.3, 15, 29, 59 (X)	Bioassay	Tissue concentrations of antibiotic activity were dose-dependent but not dose-proportional. Concentrations in lungs were 2300-7000 times greater than in plasma. Concentrations in heart were 700-2600 times greater than in plasma. Concentrations in kidney were 800-2900 times greater than in plasma. Concentrations in liver were 200-900 times greater than in plasma. No sex difference in tissue concentrations of antibiotic activity was apparent.	13
Rabbit	Himalayan	F	SC	9	Bioassay	Liver and kidney concentrations of antibiotic activity were higher and more sustained than those in serum. Skeletal muscle concentrations were similar to those in serum.	8
Dog	Beagle	M, F	IV	5.8, 29, 58 (X)	Bioassay	Concentrations of antibiotic activity in brain were 2.3 times higher than in serum, and those in skeletal muscle were 2-6 times higher than in serum after 35 daily doses. Concentrations in soft tissues were appreciably higher. After 35 daily 58 mg/kg doses, concentrations of antibiotic activity in spleen, kidney, lung, prostate, and liver were 288, 181, 180, 112, and 108 times the serum concentration (9.4 µg/ml), respectively. Concentrations of antibiotic activity were dose-dependent but not dose-proportional; tissue concentrations at the low dose were disproportionately lower than those at the two higher doses. Concentrations of antibiotic activity in brain, lung and liver decreased over a 15-day washout period; however, antibiotic activity in skeletal muscle, spleen, kidney and prostate did not.	11

(continued)

Table 12 (concluded)
 Tissue Distribution of Dirithromycin

Species	Strain	Sex	Route	Dose ^a (mg/kg)	Assay Type	Results	ADME Report
Beagle		M	IV	9.4 (X)	Bioassay	Twenty-four hours after the last of three daily 9.4-mg/kg doses, concentrations of antibiotic activity in spleen, kidney, lung, liver, prostate, and leg muscle were 175, 167, 107, 75, 51, and 25 times higher than that observed in plasma (0.592 µg/kg).	12

Abbreviations: IV = intravenous; SC = subcutaneous; PO = oral; (X) = multiple doses.

^a Dose based on potency of the lot of dirithromycin used.

Micro Memo

Micro Reviews



MEMORANDUM

Date: June 13, 1995

From: Kathleen A. Creedon, Ph.D., Reviewing
Microbiologist, DAIDP *KAC/klm*

Through: Albert Sheldon, Ph.D., ^{to 6/16/95} Supervisory Microbiologist
and Maureen Dillon-Parker, Consumer Safety
Officer, DAIDP
Murray Lumpkin, M.D., Deputy Director, CDER

To: The file of HFD-520, for the record of NDA 50-678.

Subject: Non-approval of a claim for
Eli Lilly Company's Dynabac (dirithromycin) under
NDA 50-678.

The following is a summary of information detailed in the microbiology reviews for dirithromycin, concerning the lack of inclusion of _____ in the *in vitro* section of the package insert. This summary, should this claim ever be requested in the future, is for the purpose of understanding the issues upon which the omission of _____ was based, as conveyed to and discussed with the applicant prior to approval of this NDA.

cc
HFD-520/ActgDir/LGavrilovich
HFD-520/SMO/MAlbuerne
HFD-520/MO/NMOledina

This application was originally submitted on April 27, 1993. It was refused to file based in part on a lack of correlation of clinical and bacteriological outcomes. The applicant agreed to submitted the data in a format to address this issue. The application was resubmitted on June 15, 1993.

The first microbiology review of this application (July 11, 1994) indicated that the *in vitro* preclinical studies (not the NDA clinical trials) of the susceptibility of species isolates had been determined by dilution techniques (thus yielding minimal inhibitory concentration [MIC] susceptibility data). The National Committee for Clinical Laboratory Standards (NCCLS) recommends (M2-A3 and M7-A3; 1994) the testing of dirithromycin against species by dilution methods and not by the diffusion method. A summary of the submitted data may be found in Table 1.

However, during the clinical trials the disk diffusion susceptibility test method had been used for all isolates including and *H. parainfluenzae*.

The use of the disk diffusion method created two problems: 1. Lack of an indirect correlation of MIC susceptibility to clinical outcome (the assumption being that there is an association between the blood concentration (ug/mL) of the antibiotic, the concentration (ug/mL) at which an organism is susceptible to the antibiotic *in vitro*, and antibiotic concentration (ug/mL) at which the organism is susceptible *in vivo* at the site of infection; and 2. and the lack of zones produced with this method when testing dirithromycin and species.

The first issue was dealt with by assuming that the results of an *in-vitro* study¹ which correlated (by log-linear regression) MIC (dilution) to zone diameter (diffusion) measurements of susceptibility could be used to determine the clinically relevant susceptible breakpoints for zone diameter and MIC measurements. However, due to the second problem, this type of assumption could not be made for species.

¹ (Barry, A.L., 1991 Lilly report #B020.26, volume 1.62, pages 65-126)

Table 1. In-vitro Activity of Macrolide Antibiotics against *Haemophilus* species

ORGANISM	n	DIRITHRO		ERYMYCL		ERYTHRO		AZITHRO		CLARITHRO	
		MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range
<i>Haemophilus ducreyi</i>	54 ⁷	.01	.002-.03	-	-----	.125	.002-.125	-	-----	.03	.002-.06
<i>H. ducreyi</i>	36 ²	1	.25-4	-	-----	.25	.13-.25	.5	.25-1	.25	.13-.25
<i>H. influenzae</i> Amp ^S	24 ²	8	4-8	-	-----	4	2-8	.5	.13-2	4	1-4
<i>H. influenzae</i> Amp ^R	55 ²	16	8-16	-	-----	4	.5-4	1	.06-2	8	1-8
<i>H. influenzae</i>	22 ¹	>16	8->16	-	-----	8	2-8	1	.12-1	8	.5-16
<i>H. influenzae</i>	22 ³	8	2-8	8	4-8	4	.5-4	.5	.12-.5	8	2-8
<i>H. influenzae</i>	95 ⁵	>16	8->16	-	-----	8	4-16	-	-----	-	-----
<i>H. influenzae</i>	199 ⁴	64	.125-128	-	-----	-	-----	-	-----	-	-----
<i>H. influenzae</i>	34 ⁶	64	2-64	64	1-128	8	.25-16	-	-----	-	-----
<i>H. parainfluenzae</i>	10 ²	16	8-16	-	-----	4	2-4	2	.25-2	8	1-8
<i>H. parainfluenzae</i>	17 ⁴	64	1->128	-	-----	-	-----	-	-----	-	-----

1. Yu, K.W. and H.C. Neu (1990) *J. Antimicrob. Chemother.* 34(9):1839-42.
2. Bauernfeind, A. (1993) (a German study) *J. Antimicrob. Chemother.* 31(C):39-49.
3. Hardy, D.J. et al. (1988) *Antimicrob. Agents Chemother.* 32(11):1710-9.

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4. Duval, J. (1991) (a French study) Lilly report #B9Z-FP-1304, B020.19, 1.62:270-96.
5. Houvineu, P. (1989) (a Finish study) Lilly report #B9Z-HL-0001, B020.03, 1.62:365-71.
6. Acar, J.F. (1985) (a French study) Lilly report #B9Z-EW-P010, B020.17, 1.62:3-8.
7. Miller, S. (1990) Lilly report #B9Z-UA-0002, 1.63:30-36.

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The clinical trial studies were conducted during a time when the NCCLS-recommended method of testing _____ species when the disk diffusion method was used had undergone a minor, yet significant change. Prior to the approved standard (4th edition of April 1990), _____ species were to be tested using Mueller-Hinton agar with 1% hemoglobin (or 5% horse blood) and a factor V and X supplement. Incubation in CO₂ was not required. In comparison, the present method (originally in the approved standard of December 1993; M2-A5, and still in the current sixth edition of December 1994) recommends incubating the plates in 5-7% CO₂; although it does not recommend this method for testing susceptibility to macrolides, since zones are not formed.

As a result, the zone diameters measured for the clinical isolates (Table 2.; taken from Table 5. of microbiology review #1) could not be properly interpreted. Sometimes a zone was measured (presumably using the older method of not incubating with CO₂, but not confirmed) and other times one was immeasurable (less than 6 mm and recorded as 0) making it difficult to correlate zone diameter susceptibility measurements with clinical outcome. Therefore, it was difficult to validate and incorporate the in-vitro _____ zone diameter susceptibilities reported¹ with clinical outcome.

Consequently, a clinically relevant susceptible breakpoint could not be determined for _____ resulting in the omission of this organism from the list of microorganisms susceptible to dirithromycin in-vitro in the approved package insert for Dynabac. (The reader is referred to the medical officer's reviews for the lack of clinical efficacy to include _____ in the clinical indications of the package insert.)

Table 2. Bacteriological eradication and clinical cure/
 improvement rates versus zone diameter (15 µg disk) in oral
 dirithromycin pneumonia and bronchitis studies of

Zone diameter (mm)	Bacteriological (%)	Clinical (%)
0	3/6 (50.0%)	15/18 (83.3%)
7	-/- (---)	1/1 (100 %)
8	-/- (---)	3/3 (100 %)
9	-/- (---)	1/1 (100 %)
10	0/2 (0.0%)	4/4 (100 %)
11	0/1 (0.0%)	1/2 (50.0%)
12	-/- (---)	2/4 (50.0%)
13	2/3 (66.7%)	4/6 (66.7%)
14	2/2 (100 %)	2/3 (66.7%)
15	4/6 (66.7%)	8/11 (72.7%)
16	0/5 (0.0%)	11/13 (84.6%)
17	0/2 (0.0%)	9/9 (100 %)
18	2/4 (50.0%)	13/15 (86.7%)
19	2/2 (100 %)	5/5 (100 %)
20	10/13 (76.9%)	21/21 (100 %)
21	5/6 (83.3%)	6/6 (100 %)
22	2/2 (100 %)	9/10 (90.0%)
23	2/4 (50.0%)	5/6 (83.3%)
24	3/4 (75.0%)	7/9 (77.8%)
25	-/- (---)	-/- (---)
26	1/2 (50.0%)	7/7 (100 %)
27	-/- (---)	-/- (---)
28	3/3 (100 %)	3/4 (75.0 %)
29	-/- (---)	1/1 (100 %)
30	1/3 (33.3%)	13/15 (86.7%)
31	-/- (---)	1/1 (100 %)
32	1/1 (100 %)	2/2 (100 %)

33	-/- (---)	-/- (---)
34	-/- (---)	-/- (---)
35	-/- (---)	1/1 (100 %)

The information required (and remaining as outstanding requests made of the applicant during the review of NDA 50-678) to include _____ in the approved package insert as an organism susceptible to dirithromycin at clinically relevant *in-vitro* concentrations follows:

1. The applicant should submit a full analysis and individual patient line listings of the bacteriological and clinical diagnoses and outcomes. The susceptibilities (actual numerical MIC and zone size results, preferably both) should be submitted for every pathogen isolated per patient, including pre- and post-therapy isolates.

The applicant had submitted a response in appendices 1A and 1B of the August 30, 1994 submission, and has agreed to provide the information electronically.

An electronic submission has not been made to date. The data was requested primarily for looking at the clinical correlation for _____ infections with bacteriological outcome.

Furthermore, data were available (in graph form) for the gram-positive organisms which were granted in the indications. Consequently, a line by line analysis, without the benefit of an electronic submission is not appropriate until an additional indication, with separate susceptibility limits is requested.

2. The applicant should state the exact method (or reference method if followed precisely) used to measure the susceptibility of clinical isolates to either dirithromycin, erythromyclamine and erythromycin. This should also include methods used for fastidious organisms. The citation should include the year, volume and issue of the reference.

The applicant stated that "in all cases, the protocol called for the isolates to be susceptible to erythromycin by either the disk susceptibility test

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(NCCLS standard M2-A3, 1984) or a standardized dilution test (NCCLS standard M7-A, 1985)".

This is not entirely correct, as discussed below for species. However, it is an acceptable response for the organisms being claimed in the draft labeling submitted October 21, 1994.

3. If in a future submission the applicant requests either a clinical or an *in vitro* claim for _____ species, the applicant should submit the following. A description of the methods by which zone diameters were measured for _____ in the clinical trials, since it is clear from the literature that the currently established NCCLS method for agar diffusion does not result in zones of inhibition when testing _____ species. Since dilution methods were not used in the clinical trials, it is not possible to establish MIC susceptibility limits for _____ species based on the clinical trials.

Furthermore, since the NCCLS diffusion method does not result in zones of inhibition with the dirithromycin 15 µg disk, no data is available to correlate MIC and zone diameter measurements to test the *in vitro* activity of dirithromycin against _____ species. Due to the technical difficulties encountered using the diffusion assay for _____ the diffusion assay is NOT recommended for _____ species. Consequently, an adequate *in vitro* test method for testing the susceptibility of _____ species must be established before susceptibility criteria can be determined, if a clinical indication is sought for this genera.

The applicant agreed that the current (requiring CO₂ incubation as tentatively proposed in November 1988 [M2-T4] and approved in April 1990 [M2-A4]) disk diffusion NCCLS method is not appropriate for testing dirithromycin activity against _____ species. [The protocols followed the earlier, 1984 method (M2-A3) which did not require the use of CO₂.] However, the applicant contends that "The usual MIC of dirithromycin against _____ is 2, 4, or 8 µg/mL", and suggests interpretive criteria of susceptible ≤ 8 µg/mL and resistant ≥ 32 µg/mL.

Note: This statement is not consistent with the data submitted in the application and replicated in the summary table (Table 1). Furthermore, the clinical data was not correlated to MIC values.

4. The applicant should also explain why no studies were conducted on quality control strains. Due to the problems associated with the susceptibility testing, and the applicant's request for separate MIC susceptibility limits for this organism, MIC quality control limits for this organism should be established, if a claim for this genera is to be pursued.

The applicant also is not requesting a QC strain for at this time since they are no longer requesting a claim for this organism. However, in the future the NCCLS disk diffusion method as it currently is written will not be acceptable since the inclusion of CO₂ results in a lack of zone formation.

The applicant has made several suggestions for determining in vitro susceptibility of once clinical efficacy can be established with associated breakpoints. The suggestions are as follows:

- a. Establish an exception to the standard method and suggest that tests for dirithromycin be done in an atmosphere without added CO₂. (Note: This was the recommendation by NCCLS prior to November, 1988 and thus is how most of the protocols were written.)
- b. Report dirithromycin susceptibility only on the basis of MICs using the proposed ≤ 8 , 16, ≥ 32 $\mu\text{g/mL}$ breakpoints.
- c. Obtain simultaneous data on susceptibility to dirithromycin, clarithromycin, and azithromycin, using the proposed MIC breakpoints for dirithromycin and the recommended breakpoints for the other two, to illustrate uniform cross susceptibility. Then accept the proposal of Jones, et al [Diagn Microbiol Infect Dis. 1994; 18:243-9] that the azithromycin disk be established as the "class disk" for the advanced (indicated) macrolides.

Note: All three of the above suggestions requires further data to support such conclusions. When the applicant has conducted such studies, with clinical correlates, and

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requests an indication in which is claimed, such suggestions will be considered and the associated data reviewed.

However, since the applicant has chosen not to pursue a claim for species at this time, this information will be requested and reviewed if and when this claim is sought.

These issues were further discussed during a telephone conference on August 12, 1994 and a meeting with Cathy Jones and Eric Stouffer on August 30, 1994.

The applicant suggested the inclusion in the package insert of with susceptibility limits separate from those listed for the approved pathogens (in vivo). **The problem:** The susceptibility limits established for the approved organisms is $MIC \leq 2 \mu g/mL$, the MIC_{90} of does not meet this criteria (MIC_{90} values from the in vitro studies range from $\mu g/mL$). Without the clinical data, we don't know which MIC limit corresponds to eradication of. Furthermore, the applicant has submitted zone sizes, when the diffusion test could not be validated for this organism/drug combination. However, the only reason for doing susceptibility tests is to infer that clinically the drug will eradicate the pathogen.

The validation of the Kirby-Bauer tests used by the individual laboratories during the clinical trials that actually were able to detect measurable zones diameters which were reported in the NDA for. The applicant would need to submit the quality control organisms used by those labs and the actual test methods used. However, even if the "old" NCCLS test method works, how can it be incorporated into the package insert, if it is no longer the method recommended by the NCCLS, and referenced and recognized by FDA?

The final discussion was on the actual data sets obtained, even if all the other information could be gathered. There appears to be an equivalent efficacy (or lack of efficacy) **INDEPENDENT** of the zones obtained when correlated with clinical outcome. So how does one determine exactly how

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this in vitro test predicts clinical outcome, it appears that in this case it simply does not.

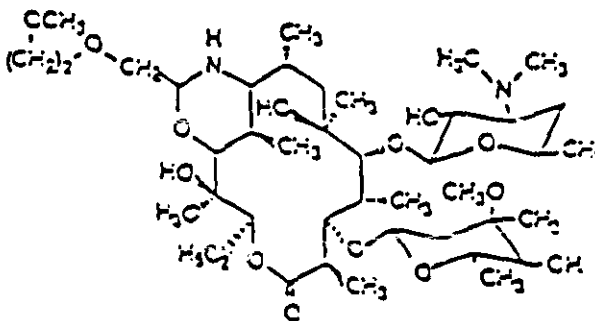
The preceding information will be required of the applicant in any future submissions made in which an *in-vitro* susceptible claim for is requested.

Division of Anti-Infective Drug Products
Microbiology Review Notes of Refuse to File Response

A. 1. NDA 50-678 Date Completed: September 25, 1992

Sponsor: Eli Lilly and Company
Address: Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46825
Contact Person: Maxwell Talbott, Ph.D.
Phone Number: (317) 276-2574

2. Product Names:
- a. Proprietary: Dynabac
 - b. Non-proprietary: Dirithromycin
 - c. Code numbers: LY237216; AS-E 136
3. Dosage Form: 250 mg enteric-coated tablets
Route of Administration: oral
4. Pharmacological Category: Macrolide antibiotic
5. Structural Formula and Chemical Name:



9-deoxy-11-deoxy-9,11-imino(2-(2-methoxy)-ethylidene)-oxy-(9S)-erythromycin

Molecular Formula: $C_{27}H_{46}N_2O_{14}$

Molecular Weight: 875.69

- B. 1. Initial Submission: June 4, 1992
Received by CDR: June 5, 1992
Received by reviewer: June 12, 1992
Review initiated: June 15, 1992
Refused for filing: August 4, 1992
2. Amendments dated: August 27 and September 4, 1992
Review completed: September 25, 1992
3. Supporting INDs, NDAs, DMFs, and Letters of Authorization: INDs:
DMFs:

all authorization
letters submitted.

C. Remarks:

This NDA was not found acceptable for filing by the Agency in part due to lack of correlation and validation of the microbiological and HPLC (chemical) assays used to monitor biological fluids for dirithromycin or erythromyclamine activity. The applicant was notified in a "Refuse to File" letter dated August 4, 1992. The applicant responded with two submissions dated August 27 and September 4, 1992 which are reviewed here.

D. Review Notes:

Dirithromycin is hydrolyzed to erythromyclamine upon gastric absorption. Both compounds have antimicrobial activity. The applicant has monitored the majority of the clinical studies using a microbiological (MIC) assay which would detect activity of either compound when present in biological fluids, and a microbiological (dirithromycin disk) assay when determining the susceptibility of different clinical pathogenic isolates to dirithromycin. The HPLC assay was later used in some of the bioavailability studies. Two different HPLC assays have been developed; one which is capable of differentiating a dirithromycin from an erythromyclamine peak; and one in which dirithromycin is hydrolyzed upon extraction, so that both active components are observed as an erythromyclamine peak.

The applicant had submitted some of the required information in the original NDA, however, it was difficult to locate in the volumes of published literature and in-house reports which were not visibly separable or tabulated. However, some of the data is still omitted.

The applicant needs to submit raw data, including HPLC chromatograms of calibration and patient serum samples indicating the dirithromycin and erythromyclamine peaks, to validate the use of the HPLC assay for the bioavailability or pharmacokinetic studies. The HPLC assay which had been used for the different studies should be clarified and details of the chromatographic conditions should be given. The applicant should state whether the assay used in a given study can differentiate dirithromycin from erythromyclamine. The microbiological assay used for monitoring activity in biological samples should clearly identify which organisms have been used as test organisms, and whether different results are obtained if a different organism is used. 21 CFR Part 436, Subpart D methods should be used.

The applicant has submitted data on the rate of hydrolysis (1.14×10^{-2} /min; assuming a first order reaction) of dirithromycin to erythromyclamine in trypticase soy broth at 37°C, pH 8, as analyzed by HPLC, and has suggested that dirithromycin is hydrolysed in plasma. However, the example given, that of rat plasma, is an inappropriate example, since dirithromycin is unstable in rat plasma and is not unstable in plasma of dog; or humans. The more appropriate information which should be submitted in response to this issue is the rate of hydrolysis in human plasma.

The applicant also has submitted the results of the studies used to correlate the microbiological and HPLC assays used for the bioavailability and pharmacokinetic studies. However, the HPLC assay and the test microorganism of the microbiological assay, which were employed in each instance, should be clearly identified. The results submitted in the September 14, 1992 amendment indicate that the microbiological assay consistently yields a higher level (up to 1.7 times higher) of dirithromycin activity than the HPLC assay (all measured as erythromyclamine) when testing human plasma samples from the bioavailability studies. Furthermore, most of the samples were just at the limit of sensitivity of both assays, so the error looks less, although the data point is less accurate. The microbiological assay is the more appropriate assay to be used and will most likely be the assay of choice if a CFR assay is to be required when this application is accepted for filing.

The applicant has submitted the requested data showing the results of the susceptibility tests when either dirithromycin or erythromyclamine was employed. In general, dirithromycin and erythromyclamine show similar MIC values (within a one-tube dilution). The applicant also has submitted data comparing the susceptibility of various microorganisms to dirithromycin and erythromyclamine when measured using the disk diffusion method. Based on the rate of hydrolysis discussed above, most of the dirithromycin is expected to be converted to erythromyclamine before colonies will be visible on agar plates. The disk zone size, assuming similar rates of diffusion for dirithromycin and erythromyclamine, is expected to be similar independent of the disk content of dirithromycin or erythromyclamine. The data from Dr. Arthur Barry's report using 430 gram-positive and gram-negative organisms indicates a linear correlation ($r=0.9906$) between the zone diameters, when measured with either a 15 mg disk of dirithromycin or erythromyclamine, with a slope of 1.0038. These data will be thoroughly reviewed when the application is accepted for filing by the Agency, when all review disciplines have found the application acceptable for filing.

E. Conclusions and Recommendations:

The applicant needs to submit raw data, including HPLC chromatograms of calibration and patient serum samples indicating the dirithromycin and erythromyclamine peaks, to support the use of the HPLC assay for the bioavailability or pharmacokinetic studies. The HPLC assay which had been used for the different studies should be clarified and details of the chromatographic conditions should be given. The applicant should state whether the assay used in a given study can differentiate dirithromycin from erythromyclamine. The microbiological assay used for monitoring activity in biological samples should clearly identify which organisms have been used as test organisms, and whether different results are obtained if a different organism is used. 21 CFR Part 436, Subpart D methods should be used.

The applicant has submitted data on the rate of hydrolysis (1.14×10^{-2} /min; assuming a first order reaction) of dirithromycin to erythromyclamine in trypticase soy broth at 37°C, pH 8, as analyzed by HPLC, and has suggested that dirithromycin in hydrolysed in plasma. However, the example given, that of rat plasma, is an inappropriate example, since dirithromycin is unstable in rat plasma and is not unstable in plasma of dogs or humans. The more appropriate information which should be submitted in response to this issue is the rate of hydrolysis in human plasma.

The applicant also has submitted the results of the studies used to correlate the microbiological and HPLC assays used for the bioavailability and pharmacokinetic studies. However, the HPLC assay and the test microorganism of the microbiological assay, which were employed in each instance, should be clearly identified.

Kathleen A. Creedon 10/5/92
Kathleen A. Creedon

Microbiologist, HFD-520
 September 25, 1992

cc: Orig NDA 50-678

HFD-473

HFD-235

HFD-502

HFD-520

HFD-520/CSO/KChapman

HFD-520/MO/NMoledina

HFD-520/Pharm/NBrowder

HFD-520/Chem/DKatague

HFD-520/MICRO/KCreedon: 9/25/92; 10/05/92

Concurrence Only:

HFD-520/DepDir/LGavrilovich

HFD-520/SMicro/ASheldon *AS 9/25/92*

BFD in 9/25/92 by AS

10/6/92

JUL 15 1994

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Clinical Microbiological Review

NDA #: 50-678 REVIEW #: 1 REVIEW DATE: 11-JUL-94

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	27-APR-93	29-APR-93	12-MAY-93
AMENDMENTS	03-DEC-93	06-DEC-93	02-FEB-94
	06-JUN-94	10-JUN-94	15-JUN-94

NAME & ADDRESS OF APPLICANT: Eli Lilly and Company
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

CONTACT PERSON: Maxwell Talbott, Ph.D.
Phone Number: (317) 276-2574

DRUG PRODUCT NAME:
Proprietary: Dynabac Tablets
Nonproprietary: Dirithromycin
Code Names: LY237216; AS-E 136
Chemical Type: Macrolide
Antibiotic
Therapeutic Class: 1 C

ANDA Suitability Petition/DESI/Patent Status:

N/A--Patent 4,048,306 Expires 9/13/94; Patent 4,755,385
expires 7/5/05

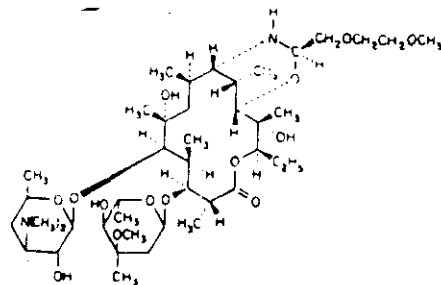
PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: enteric-coated tablets
STRENGTHS: 250 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:

9-deoxy-11-deoxy-9,11-imino[2-(2-methoxy)-ethylidene]-oxy-
(9S)-erythromycin

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



SUPPORTING DOCUMENTS:

INDs:

DMFs:

All authorization letters have been properly submitted.

REMARKS/COMMENTS:

This application was originally submitted on April 27, 1993. It was refused to file based in part on a lack of correlation of clinical and bacteriological outcomes. The applicant agreed to submitted the data in a format to address this issue. The application was resubmitted on June 15, 1993.

CONCLUSIONS & RECOMMENDATIONS:

This application is **NOT APPROVABLE** from a microbiology perspective as submitted under section 507 of the Act, and 21 CFR section 314.125(b)(2) and (4) for insufficient information to correlate test methods applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. The following information was inadequately submitted resulting in an inability to assigned in vitro susceptibility criteria for this drug product in its labeling.

1. The applicant should submit a full analysis and individual patient line listings of the bacteriological and clinical diagnoses and outcomes. The susceptibilities (actual numerical MIC and zone size results, preferably both) should be submitted for every pathogen isolated per patient, including pre- and post-therapy isolates.
2. The applicant should state the exact method (or reference method if followed precisely) used to measure the susceptibility of clinical isolates to either dirithromycin, erythromyclamine and erythromycin. This should also include methods used for fastidious organisms. The citation should include the year, volume and issue of the reference.
3. The applicant should describe the methods by which zone diameters were measured for Haemophilus influenzae and H. parainfluenzae in the clinical trials, since it is clear from the literature that the currently established NCCLS method for agar diffusion does not result in zones of inhibition when testing Haemophilus species. Since dilution methods were not used in the clinical trials, it is not possible to establish MIC susceptibility limits for Haemophilus species based on the clinical trials.

Furthermore, since the NCCLS diffusion method does not result in zones of inhibition with the dirithromycin 15 µg disk, no data is available to correlate MIC and zone diameter measurements to test the in vitro activity of dirithromycin against Haemophilus species. Furthermore, due to the technical difficulties encountered using the diffusion assay for Haemophilus influenzae, the diffusion assay is NOT recommended for Haemophilus species. Consequently, an adequate in vitro test method for testing the susceptibility of Haemophilus species must be established before susceptibility criteria can be determined.

4. The applicant should submit data (as required in NCCLS document M23-T2, section 4.0 July 1994) for the development of in vitro susceptibility testing criteria and quality control parameters, to compare the broth and agar dilution methods, and the broth microdilution and macrodilution methods.

5. The applicant should clarify why each laboratory testing Staphylococcus aureus ATCC 25923 did not report the results from 20 repeated tests. The applicant should state why Staphylococcus aureus ATCC 25923 was not proposed for inclusion in the package insert as a quality control (QC) strain. The applicant should also explain why no studies were conducted on Haemophilus influenzae quality control strains. Due to the problems associated with the susceptibility testing, and the applicant's request for separate MIC susceptibility limits for this organism, MIC quality control limits for this organism should be established.

These deficiencies should be relayed to the applicant.

Kathleen A. Creedon 7/11/94

Kathleen A. Creedon, Ph.D.
Review Microbiologist 7/11/94

cc:Orig. NDA 50-678

HFD-520/Division File
HFD-520/KCreedon/7-11/13-94
HFD-520/MO/NMoledina
HFD-520/Pharm/ROsterberg
HFD-520/Chem/DKatague
HFD-520/CSO/MDillon-Parker

Concurrence Only:

HFD-520/ActgDir/LGavrilovich
HFD-520/SUPERVISOR/ASheldon
R/D Init by: ATS/7-12/14-94
filename: N50-768.rev *TS 7/14/94*

6 7/15/94

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INTRODUCTION

The applicant has submitted this NDA for dirithromycin 500 mg/d (p.o.) for the indications of pharyngitis and tonsillitis, secondary bacterial infection of acute bronchitis, acute bacterial exacerbations of chronic bronchitis, and skin and skin structure infections.

PRECLINICAL STUDIES

In vitro

Mechanism of Action.

The macrolides provide their antimicrobial activity by reversibly binding to the 50S ribosomal subunit, blocking the peptidyltransferase site and hence preventing the transpeptidation and/or translocation of the peptidyl tRNA from the ribosome. In order to demonstrate that this is also the active mechanism by which erythromyclamine, the active (hydrolyzed) derivative of dirithromycin, inhibits of protein elongation, the applicant has submitted as a portion of an in-house report a study conducted by Dr. Werner measuring the inhibition of poly A-dependent poly-lysine synthesis.

The incorporation in ^{14}C from lysine into polylysine peptides was measured using a prokaryotic ribosomes and cytosolic components or eukaryotic ribosomes and cytosolic components in the presence or absence of erythromycin or dirithromycin. (No additional details as to the source of the components was provided.) The results indicate that neither macrolide inhibited the formation of polylysine peptides in the reconstituted eukaryotic system; and that dirithromycin was more effective than erythromycin at $\geq 0.67 \mu\text{M}$, and equally effective at $\leq 0.33 \mu\text{M}$ in decreasing peptide synthesis. Based on this result the applicant concludes that dirithromycin's bacteriostatic activity is based on the same mechanism as erythromycin's bacteriostatic activity. No competitive binding studies were reported.

This reviewer had done a Medline search of the medical literature and requested that the applicant submit copies of reports published between the initial refuse to file and final submission date. Included in the request were two articles concerning the molecular mechanism of action of dirithromycin and three concerning uptake by lymphocytes. The applicant responded by submitting the requested references on June 9, 1994.

Phagocytic cells accumulate macrolides, consequently the accumulated drug may alter the action of the drug or phagocyte on intracellular pathogens, including Staphylococcus, Listeria, Legionella, Mycoplasma, Bordetella and Chlamydia species. Studies of the effects of dirithromycin, erythromycylamine and erythromycin on the oxidative burst and phagocytosis of neutrophils and macrophages expose intersubject variability and different results depending on the method of analysis and the test organism. In general, the results of these studies indicate these macrolides are accumulated in phagocytes by passive transport and slow efflux, probably due to their basic nature.^{2,3} The drugs then diminish the production of superoxide anion (oxidative burst) possibly by diminishing priming of neutrophils and NADPH oxidase assembly. They do not alter intracellular macrophage killing, but may increase intracellular bacteriostasis⁶ and chemotaxis.

An in-house study⁷ was conducted using a mouse model to determine uptake of dirithromycin and chemotaxis by macrophages. Antibiotic was administered (sc) for 3 days and the extracellular (peritoneal cavity) and intracellular (peritoneal macrophage) concentration followed for three days. Extracellular antibiotic activity indicated dirithromycin concentrations of 130-190 ng/mL, while intracellular concentrations ranged from 4-10 times greater. Erythromycin (control) intracellular concentrations were below the level of detection (<20 ng/mL). In the second part of the study, a polyurethane sponge containing susceptible Staphylococcus aureus, was placed in the peritoneal cavity, 4 days after initiation of antibiotic prophylaxis and 3 days after stimulation of peritoneal macrophages. After two days the sponges were removed and bacterial colony counts conducted on the sponges. Dirithromycin decreased the colony counts by 2.5 logs while erythromycin reduced the counts by 0.5 logs. The results do not necessarily indicate that "dirithromycin-loaded macrophages" migrated to the site of infection as the applicant suggests, since the dirithromycin has a longer half-life than erythromycin, and it is implied that the drugs were administered at the site of infection.

The interpretation of this data to the clinical situation is difficult. The concentrations which diminish the oxidative burst are achievable in vivo, however, the resultant modulation on phagocytic activities is difficult to determine based on the wide variability of the in vitro results, the pathogen and site of infection, and the immunological status of the patient.

Antimicrobial Spectrum of Activity.

Dirithromycin and its active metabolite, erythromyclamine, have been compared to erythromycin and other macrolides as summarized in the following tables. Only those organisms which are potential pathogens in one of the four indications being sought for approval are evaluated here.

The in-house study authored by Counter *et. al*⁸ was conducted using microbiological methods as described in the ASM Manual of Clinical Microbiology; other studies were conducted in Europe and are noted as such in the References section. Initial screening of the activity of dirithromycin and erythromyclamine was conducted using the agar dilution method and laboratory strains. The results indicated that dirithromycin was slightly less or equivalent in activity as erythromyclamine, and both compounds had diminished *in vitro* activity compared to erythromycin. However, the typical *in vitro* difference of 1-2 fold tube dilution is compensated by the increase in tissue penetration and half-life of dirithromycin and erythromyclamine, compared to erythromycin. The laboratory strains of the following organisms displaying susceptibility $\leq 2 \mu\text{g/mL}$ to dirithromycin or erythromyclamine were strains of: Staphylococcus aureus, S. epidermidis, Enterococcus faecium, Streptococcus pyogenes, S. pneumoniae, Bordetella bronchiseptica, Haemophilus influenzae, Helicobacter pylori, Bacteroides fragilis, Fusobacterium necrophorum, Peptostreptococcus intermedium, Clostridium perfringens, Mycoplasma pneumoniae and Chlamydia trachomatis. However, distinct strains of some of these same species were also found to be resistant, including: Staphylococcus aureus, S. epidermidis, Enterococcus faecium and Haemophilus influenzae, Bacteroides fragilis, Clostridium perfringens in addition certain strains of Peptostreptococcus anaerobius, Bacteroides thetaiotaomicron, B. melaninogenicus (Prevotella melaninogenica), B. vulgatus, B. corrodens (Eikenella corrodens), Clostridium septicum, Propionibacterium acnes, Peptococcus (Peptostreptococcus) assacharolyticus and P. prevotii were also found to be resistant. The applicant states¹⁰ that 17 strains of P. assacharolyticus was tested but the cited reference does not show this data. The data presented, if valid, indicates that these laboratory isolates were susceptible to dirithromycin ($\text{MIC} \leq 1 \mu\text{g/mL}$). The Enterobacteriaceae were consistently uninhibited by the macrolides. Bacterial strains resistant to erythromycin are cross-resistant to dirithromycin and erythromyclamine. As a result, all patients from whom erythromycin-resistant

clinical isolates were obtained were excluded from the enrollment in the clinical trials.

Note: A statement of this macrolide cross-resistance should be incorporated into the package insert.

The applicant had submitted several small in-house studies (primarily conducted in Europe) and a number of literature reports to support the inclusion of microorganisms in the in vitro section of the label. However, the applicant failed to update the references between the original refused-to-file submission and the resubmission a year later. Consequently, this reviewer did a literature search and requested several articles, some of the original articles were now in final print. These were submitted on June 10, 1994 and are included in this review.

The following tables summarize the comparative in vitro activity of dirithromycin (DIRITHRO), the active metabolite, erythromyclamine (ERYMYCL), and the currently approved macrolides: erythromycin (ERYTHRO), azithromycin (AZITHRO) and clarithromycin (CLARITHRO). The atypical organisms were supported by literature reports and are summarized below.

Note: Based on these results and the need for ≥ 100 strains per species for inclusion in the in vitro section of the package insert (except atypical organisms) with an $MIC_{90} \leq 2 \mu\text{g/mL}$, the following organisms may be included in the package insert: Staphylococcus aureus (penicillin-sensitive only, unless clinically indicated), Streptococcus pneumoniae (penicillin-sensitive only, unless clinically indicated), Streptococcus pyogenes, S. agalactiae, Streptococci group C, F, G, Viridans group streptococci, Listeria monocytogenes, Propionibacterium acnes, Moraxella catarrhalis and Bordetella pertussis. In addition, if clinically approved Legionella pneumophila may be included, and once the clinically relevant susceptibility can be determined for Haemophilus species, it can then be determined if H. influenzae or H. parainfluenzae or H. ducreyi (if clinically relevant) may be included.

The applicant submitted five literature reports,^{12,13,14,15,16} one¹³ which was also submitted as an earlier in-house report¹⁷ on the activity against Helicobacter (Campylobacter) pylori. Minor discrepancies were noted in

Table 1. In-vitro Activity of Macrolide Antibiotics

ORGANISM	n	DIRITHRO		ERYMYCL		ERYTHRO		AZITHRO		CLARITHRO	
		MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range
<u>Staphylococcus aureus</u>	62 ¹²	4	.25-8	-	-----	1	.13-4	4	.25-8	1	.13-4
<u>S. aureus</u> Met ^S	30 ¹¹	>32	.5->32	-	-----	>32	.25->32	>32	.12->32	>32	.06->32
<u>S. aureus</u> Met ^R	30 ¹¹	>32	.25->32	-	-----	>32	.12->32	>32	.12->32	>32	.06->32
<u>S. aureus</u> Met ^S	16 ¹⁸	>128	.12->128	>128	.06->128	>128	.06->128	>128	.06->128	>128	.03->128
<u>S. aureus</u> Met ^R	13 ¹⁸	>128	128->128	>128	128->128	>128	>128	>128	>128	>128	>128
<u>S. aureus</u> Pen ^S	25 ¹⁹	1	.06-2	-	-----	.5	.12-.5	-	-----	.5	.06-.25
<u>S. aureus</u> Met ^S	20 ¹⁹	>64	.06->64	-	-----	>64	.12->64	-	-----	>64	.03->64
<u>S. aureus</u> Met ^R	25 ¹⁹	>64	>64	-	-----	>64	>64	-	-----	>64	>64
<u>S. aureus</u> Pen ^S	24 ²⁰	1	.13->128	-	-----	-	-----	-	-----	-	-----
<u>S. aureus</u> Met ^S	110 ²⁰	8	.06->128	-	-----	-	-----	-	-----	-	-----
<u>S. aureus</u> Met ^R	39 ²⁰	>128	.25->128	-	-----	-	-----	-	-----	-	-----
<u>S. epidermidis</u> Met ^S	30 ¹¹	>32	.5->32	-	-----	>32	.06->32	-	-----	-	-----
<u>S. epidermidis</u> Met ^R	30 ¹¹	>32	.25->32	-	-----	>32	.06->32	-	-----	-	-----
<u>S. epidermidis</u>	36 ¹²	1	.25-4	-	-----	.25	.13-.25	.5	.25-1	.25	.13-.25
<u>S. epidermidis</u>	15 ¹⁸	>128	.06->128	>128	.12->128	>128	.06->128	>128	.06->128	>128	.03->128
<u>S. epidermidis</u>	25 ¹⁹	>64	.5->64	-	-----	>64	.12->64	-	-----	>64	.06->64
<u>S. epidermidis</u>	36 ²⁰	>128	.5->64	-	-----	>64	.12->64	-	-----	>64	.06->64
<u>Streptococcus pyogenes</u>	46 ¹¹	2	.03-4	-	-----	4	.03-8	4	.25-8	.25	.03-1
<u>S. pyogenes</u>	122 ¹²	.25	.13-.5	-	-----	.06	.03-.06	.13	.03-.13	.03	.016-.06
<u>S. pyogenes</u>	15 ¹⁸	.12	.03-.12	.12	.06-.12	.03	.03-.06	.03	.03-.12	.015	.015
<u>S. pyogenes</u>	16 ¹⁹	.12	.03-.12	-	-----	.25	.12-.25	-	-----	.12	.06-.12
<u>S. pyogenes</u>	84 ²¹	.6	.5-16	-	-----	16	.06-16	-	-----	-	-----
<u>S. pyogenes</u>	86 ²⁰	.5	.03-1	-	-----	-	-----	-	-----	-	-----
<u>S. pneumoniae</u> (Pen ^S)	20 ¹²	.25	.25-1	-	-----	.06	.03-.5	.25	.06-.5	.06	.008-.25
<u>S. pneumoniae</u> (Pen ^R)	62 ¹²	8	.25-8	-	-----	2	.013-2	8	.013-8	1	.003-1
<u>S. pneumoniae</u>	28 ¹¹	.12	.03-.25	-	-----	.25	.03-.25	.25	.06-.25	.06	.03-.06
<u>S. pneumoniae</u>	13 ¹⁸	.12	.06-.12	.06	.06-.12	.03	.03	.12	.03-.12	.015	.004-.015
<u>S. pneumoniae</u>	25 ¹⁹	.12	.12-.25	-	-----	.25	.06-.5	-	-----	.12	.06-.5
<u>S. pneumoniae</u>	39 ²¹	1	.5-1	-	-----	.125	.06-.13	-	-----	-	-----
<u>S. pneumoniae</u>	140 ²⁰	>128	.08->128	-	-----	-	-----	-	-----	-	-----
<u>S. pneumoniae</u>	24 ²²	16	.25-64	32	.12-128	4	.016-128	-	-----	-	-----

Table 1. In-vitro Activity of Macrolide Antibiotics (continued)

ORGANISM	n	DIRITHRO		ERYMYCL		ERYTHRO		AZITHRO		CLARITHRO	
		MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range
<u>S. agalactiae</u>	36 ¹¹	.12	.03-.12	-	-----	.25	.06-.25	.5	.12-.5	.06	.06-.12
<u>S. agalactiae</u>	38 ¹²	.25	.13-.25	-	-----	.06	.03-.06	.13	.03-.25	.06	.016-.06
<u>S. agalactiae</u>	15 ¹⁸	.25	.12-.25	.12	.12	.06	.06	.12	.12	.06	.03-.06
<u>S. agalactiae</u>	19 ²⁹	.25	.12-.5	-	-----	.12	.03-.25	-	-----	.25	.06-.25
Streptococci											
group C	19 ¹¹	.12	.06-1	-	-----	.12	.06-.5	-	-----	-	-----
group C	21 ¹²	.25	.13-.5	-	-----	.13	.03-.13	.13	.06-.13	.03	.03-.06
group F	25 ¹²	.5	.13-1	-	-----	.13	.03-.13	.13	.06-.25	.06	.03-.06
group G	26 ¹¹	.12	.06-.25	-	-----	.5	.12-.5	-	-----	-	-----
group G	16 ¹⁹	.06	.03-.12	-	-----	.06	.03-.12	-	-----	.06	.03-.12
Viridans group											
streptococci	62 ¹²	4	.25-8	-	-----	1	.13-4	4	.25-8	1	.13-4
Viridans grp. strep.	10 ¹¹	.25	.06-.25	-	-----	.12	.015-.25	-	-----	-	-----
Viridans grp. strep.	13 ¹⁸	.25	.06-.25	.12	.03-.12	.06	.015-.12	.12	.015-.12	.03	.008-.03
<u>Corynebacterium jeikeium</u>	2 ¹²	>64	>64	-	-----	>64	>64	>64	>64	>64	>64
<u>C. jeikeium</u>	19 ¹⁹	8	.06-16	-	-----	>64	.12->64	-	.12->64	4	.06-8
<u>Listeria monocytogenes</u>	14 ¹⁸	2	1-2	1	1-2	.5	.25-.5	2	1-2	.25	.25-.5
<u>L. monocytogenes</u>	33 ¹¹	4	.5-32	-	-----	2	.25-32	4	.5-16	2	.06-32
<u>L. monocytogenes</u>	13 ¹⁹	1	.5-1	-	-----	.5	.5-1	-	-----	.5	.06-.25
<u>Clostridium difficile</u>	9 ¹²	8	1-8	-	-----	1	.25-1	4	.05-4	1	.13-4
<u>C. perfringens</u>	15 ¹¹	4	1-4	-	-----	1	1-2	.5	.25-.5	.5	.25-.5
<u>C. perfringens</u>	1 ²⁰	8	8	-	-----	-	-----	-	-----	-	-----
<u>Fusobacterium</u>											
<u>necrophorum</u>	2 ¹²	.25	.13-.5	-	-----	.06	.03-.06	.13	.03-.13	.03	.016-.06
<u>Peptostreptococcus</u>											
<u>prevotii</u>	2 ¹²	16	8-16	-	-----	2	1-2	2	.5-2	1	.5-1
<u>Propionibacterium acnes</u>	12 ¹⁸	.5	.25-1	.5	.12->128	.03	.03-128	.03	.004-4	.03	.03-64

Table 1. In-vitro Activity of Macrolide Antibiotics (continued)

ORGANISM	n	DIRITHRO		ERYMYCL		ERYTHRO		AZITHRO		CLARITHRO	
		MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range
<u>Haemophilus ducreyi</u>	54 ²³	.01	.002-.01	-	-----	.125	.002-.125	-	-----	.03	.002-.06
<u>H. ducreyi</u>	36 ¹²	1	.25-4	-	-----	.25	.13-.25	.5	.25-1	.25	.13-.25
<u>H. influenzae Amp^S</u>	24 ¹²	8	4-8	-	-----	4	2-8	.5	.13-2	4	1-4
<u>H. influenzae Amp^R</u>	55 ¹²	16	8-16	-	-----	4	.5-4	1	.06-2	8	1-8
<u>H. influenzae</u>	22 ¹¹	>16	8->16	-	-----	8	2-8	1	.12-1	8	.5-16
<u>H. influenzae</u>	22 ¹⁸	8	2-8	8	4-8	4	.5-4	.5	.12-.5	8	2-8
<u>H. influenzae</u>	95 ²¹	>16	8->16	-	-----	8	4-16	-	-----	-	-----
<u>H. influenzae</u>	199 ²⁰	64	.125-128	-	-----	-	-----	-	-----	-	-----
<u>H. influenzae</u>	34 ²²	64	2-64	64	1-128	8	.25-16	-	-----	-	-----
<u>H. parainfluenzae</u>	10 ¹²	16	8-16	-	-----	4	2-4	2	.25-2	8	1-8
<u>H. parainfluenzae</u>	17 ²⁰	64	1->128	-	-----	-	-----	-	-----	-	-----
<u>Moraxella catarrhalis</u>	22 ¹²	.25	.06-.25	-	-----	.13	.03-.25	.03	.03-.06	.13	.03-.13
<u>M. catarrhalis</u>	17 ¹⁸	.25	.12-.25	.25	.06-.25	.25	.03-.25	.06	.03-.06	.25	.03-.25
<u>M. catarrhalis</u>	65 ²⁰	4	.016-4	-	-----	-	-----	-	-----	-	-----
<u>Legionella pneumophila</u>	14 ¹⁸	16	1-16	8	1-8	2	.5-2	2	.12-2	.25	.12-.25
<u>Bordetella pertussis</u>	7 ¹²	.03	.03-.13	-	-----	.03	.03-.13	.06	.016-.13	.03	.008-.06
<u>B. pertussis</u>	18 ¹⁸	.03	.03-.12	.03	.015-.25	.03	.008-.06	.06	.015-.12	.03	.008-.06
<u>Campylobacter jejuni</u>	12 ¹⁸	.25	.06-.5	1	.12-1	1	.06-1	.12	.03-.12	2	.12-2
<u>Helicobacter pylori</u>	16 ¹²	2	.06-4	-	-----	4	.13-4	1	.25-2	4	.06-4
<u>Neisseria gonorrhoeae</u>	15 ¹⁸	4	.5-4	2	.5-2	.5	.06-1	.06	.03-.06	.5	.06-.5
<u>N. gonorrhoeae</u>	10 ¹¹	4	.5-4	-	-----	.5	.12-2	-	-----	-	-----
<u>N. gonorrhoeae Pen^S</u>	5 ¹²	2	.25-2	-	-----	.25	.03-.25	.03	.008-.03	.25	.003-.25
<u>N. gonorrhoeae Pen^R</u>	9 ¹²	4	.5-4	-	-----	.05	.03-.5	.13	.008-.13	1	.03-1

the results reported in the in-house versus final published report by Elharrif and colleagues; however, the results indicate that dirithromycin, erythromyclamine and erythromycin have similar activity against H. pylori, and oleandomycin is slightly less active than these macrolides. The MIC₉₀ values ranged from 0.25-16 µg/mL for dirithromycin, to 0.5-16 µg/mL for erythromyclamine, to 0.03-16 µg/mL for erythromycin. Similar results were obtained for Campylobacter jejuni and C. coli. An increase in the MIC results was consistently noted and associated with a decrease (especially below 6.8 units) in pH when H. pylori was evaluated.

An in-house report was submitted describing the activity of dirithromycin, erythromyclamine and erythromycin against mycoplasmas (9 Mycoplasma pneumoniae isolates, 92 M. hominis isolates and 96 Ureaplasma urealyticum isolates). Reference strain (one or four per species) results were also included in the summary tables and not separately defined. M. hominis was resistant (MIC₉₀ ≥ 258 µg/mL) to all three macrolides. M. pneumoniae isolates, although limited in number, were the most susceptible mycoplasmas test with MICs ranging from ≤ 0.01 to 0.02 µg/mL for dirithromycin, 0.1-0.2 µg/mL for erythromyclamine, and ≤ 0.01 µg/mL for erythromycin. U. urealyticum were of intermediate susceptibility with MIC values ranging from 0.5 to 16 µg/mL and MIC₉₀ = 4 µg/mL for dirithromycin and erythromyclamine, which were slightly less active than erythromycin (MIC range 0.25 to 4 µg/mL and MIC₉₀ = 2 µg/mL). In an in-house contracted study²⁵ six U. urealyticum isolates were studied and found to be inhibited by dirithromycin at concentrations of ≤ 0.25 µg/mL. Similar results were obtained for clarithromycin and erythromycin.

One²⁶ of the literature reports submitted at the request of this reviewer was to support the requested claim for Legionella pneumophila. In this report the 9 reference type-strains were included in the summation of the results with 94 hospital isolates. Dirithromycin was least active (with the exception of clindamycin) having MICs ranging from 0.25-4 µg/mL and an MIC₉₀ = 4 µg/mL. Clindamycin was the most active (MIC₉₀ = 0.12 µg/mL) macrolide while rifampicin was the most active compound (MIC₉₀ = 0.008 µg/mL) tested. These results are similar to those in the preceding table¹⁸ and in other studies^{18,22,27,28} submitted by the applicant in which dirithromycin was the least effective (next to spiramycin) agent tested with MICs ranging from 0.12-16 µg/mL and MIC_{90s} = 16 µg/mL. In an in-house report²⁹ of 14 L. pneumophila

isolates, dirithromycin was less active than erythromycin (MIC₉₀=1.0 µg/mL and 0.12 µg/mL, respectively). Another microorganism for which the applicant requests an in vitro label claim is Chlamydia trachomatis. **Note: The inclusion of C. trachomatis will depend on the medical officer's acceptance of this organism, as a pathogen in one of the approved indications.** A study²⁵ was submitted in which five C. trachomatis isolates were studied and found to be sensitive to all macrolides studies with MICs ranging from 0.03 to 1 µg/mL. In a second study³⁰ only one isolate was tested which was least sensitive to dirithromycin with an MIC of 1.5 µg/mL based on inclusion body counts. The activity against one strain each of C. pneumoniae (Twar) and C. psittaci was also determined and found to be 0.5 and 2.5 µg/mL, respectively, with dirithromycin the least active compound tested compared with roxithromycin, josamycin and minocycline.

There was a French study²⁹ submitted addressing the in vitro activity of dirithromycin against Pasteurella multocida²⁹ in which there were 14 clinical isolates that showed similar sensitivity to dirithromycin and erythromycin (MICs ranging from 0.53 to 4 µg/mL). A 1993 report³¹ by Garcia-Rodriguez and colleagues describes the activity of macrolides against 62 clinical isolates of Brucella species (43 were B. melitensis but were not separately described) with dirithromycin MICs ranging from 0.5 to 16 µg/mL and an MIC₉₀=16 µg/mL. In an earlier abstract³² from this group it was stated that the MIC of 32 strains of B. melitensis ranged from 4-8 µg/mL, being less effective than erythromycin (1-4 µg/mL).

Based upon the above review of the submitted in vitro reports Chlamydia trachomatis and Haemophilus ducreyi may be included in the in vitro section of the package insert ONLY if found to be potential pathogens in one of the approved indications for an adult population. Furthermore, if the following organisms are not clinically approved, the submitted in vitro data alone is insufficient to allow their inclusion in the in vitro section of the package insert: Chlamydia pneumoniae and Legionella pneumophila.

Mechanism of Resistance Studies.

The applicant has not submitted specific studies to address the mechanism of resistance to dirithromycin (or its active metabolite, erythromycylamine), rather, the assumption was made that the mechanisms which are known to exist for other

macrolides will also apply to dirithromycin. However, which of these mechanisms apply were also not extensively tested.

Macrolide resistance may result from drug inactivation, active efflux of drug³³, decreased permeability of the cell wall (in Enterobacteriaceae), or alteration of the target (23S ribosomal RNA [rRNA]) by point mutation in the 23S rRNA gene (rrn)³⁴, or by N⁶-demethylation of adenine on the 23S rRNA of the 50S subunit of bacterial ribosomes.^{35,36,37} These latter mechanisms have been shown to cause "dissociated" induction by rrn mutations³⁴, and "constitutive" induction of specific methylase genes (eight classes of erythromycin resistance methylase genes identified as erm genes)^{38,39,40,41}. The macrolides may increase transcription by binding to the methylase leader sequences and inhibiting attenuation⁴², or they may increase translation^{38,39,40} by binding to the leader sequences of the erm genes and stalling the ribosomes to allow correct secondary structure formation. Examples of organisms in which erm genes have been found include: Staphylococcus aureus, Streptococcus pneumoniae, Corynebacterium diphtheriae, Bacteroides fragilis, Clostridium perfringens, Lactobacillus casei, Streptomyces erythreus, and Legionella pneumophila.^{35,36,37} The rrn mutation has been seen in a laboratory mutant Escherichia coli strain.³⁴ Resistance is generally plasmid-mediated, and transposable in Staphylococcus species and Streptococcus species.³⁵

The in-house reference, submitted by the applicant is by _____ and simply compares the susceptibility of clinical isolates to a variety of macrolides. Specifically, it address the susceptibility of Staphylococcus aureus isolates to dirithromycin and other macrolides. The 42 strains which were sensitive to erythromycin (MIC ≤ 0.5 $\mu\text{g/mL}$) were also sensitive to the other macrolides, including dirithromycin (MIC ≤ 1 $\mu\text{g/mL}$). Four isolates with intermediate sensitivity to erythromycin (MIC 2 to 4 $\mu\text{g/mL}$) were resistant to dirithromycin (MIC ≥ 8 $\mu\text{g/mL}$). The 26 strains with inducible-resistance (MIC ≥ 8 $\mu\text{g/mL}$) and 20 strains with constitutive-resistance (MIC >128 $\mu\text{g/mL}$) to erythromycin were all resistant (MIC >128 $\mu\text{g/mL}$) to dirithromycin.

In vivo

Pharmacokinetics/Bioavailability

The following is taken from the review by Dr. Ajayi dated March 29, 1994: "Dirithromycin, a prodrug, is rapidly

hydrolyzed to erythromyclamine immediately after administration....A microbiological assay methodology was employed for the estimation of dirithromycin and/or erythromyclamine in plasma, urine, and tissues using Micrococcus luteus as the test organism....The microbiological assay was employed in most of the studies....Although there is some degree of correlation between the HPLC and the microbiological methods ($r^2=0.95$), the former gave lower measurements in some studies....In most cases, the plasma concentrations are near or at the lower limit of detection. Thus, careful interpretation should be given to the following results:

The fecal excretion amounts to 65-95% of the dose with the bulk...occurring during the first 48 h after drug administration. Approximately 2-4% of the dose is recovered in urine mainly within the first 12 hours. Thus giving an indication that about 10% (5.5-13%) of the oral dose is absorbed. The terminal half life...ranged from 16 to 65 hours with a mean of 40 h....The protein binding of dirithromycin and erythromyclamine is approximately 19%....There was no apparent drug accumulation...Tissue concentrations of erythromyclamine were generally 20 to 30-fold higher than those obtained in plasma and persist for longer periods of time...it should be noted that the observed mean peak plasma concentration, C_{max} , of erythromyclamine in the reported PK studies (approximately 0.34 $\mu\text{g/mL}$) is lower than the MIC value for most susceptible organisms."

CLINICAL EFFICACY

Clinical Microbiology

Correlation of Test Results with Outcome Statistics

The applicant states in the clinical summary section that NCCLS methods were used; however, a statement is also made that early NCCLS methods (e.g., testing of Haemophilus influenzae) is "**suspected**" to have been used (which did not require CO_2 incubation) Note, the reader is referred to the section on susceptibility testing, following, for an explanation of the problems with the testing of Haemophilus influenzae by the current NCCLS method. In fact, the ability to measure zone diameters when testing Haemophilus species indicates that the current NCCLS method was probably not used during the clinical trials.

The applicant should state the exact method (or reference method if followed exactly) used to measure the susceptibility of clinical isolates to either dirithromycin, erythromyclamine and erythromycin. This should include methods used for fastidious organisms. The citation should include the year, volume and issue of the reference.

Since the data was not submitted in a format to directly compare a patient's clinical outcome and bacteriological outcome, only the in vitro susceptibility zone diameter test outcome could be associated with the cumulative patient end points. It must be assumed that the same patients that were considered a clinical cure also had a positive bacteriological outcome. Furthermore, these correlations were only presented for five organisms in 4 indications (Tables 2-4). Interestingly, one of these organisms, Haemophilus influenzae, was reported by zone sizes, even though it was known that this method (NCCLS) would give little or no zone of inhibition. Yet, this study makes it clear that zone sizes were measured, as reported. It is not stated in the protocols the method used to determine these zones for the H. influenzae isolates.

Comment:

If the data submitted is valid (i.e., H. influenzae zone sizes) and the assumption that positive clinical and bacteriological outcomes were correlated for most patients, then the zones sizes which correlate with the suggested MIC susceptibility limits (described later in this review) may be acceptable. These limits would be:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Zone diameters (mm)</u>	<u>Interpretation</u>
≤ 2	> 19	Susceptible
4	16-18	Intermediate
≥ 8	≤ 15	Resistant.

The limits for Haemophilus influenzae and H. parainfluenzae will have to be based on the clinical outcomes. Since this was not done using MICs it is impossible to establish a susceptibility limit by comparison to the zone sizes of the clinical H. influenzae isolates which were eradicated, since no such data has been submitted. Furthermore, from the clinical data which has been submitted, zone sizes similar to those suggested above for the other approved pathogens appear most appropriate (see Table 5). However, due to the technical difficulties encountered using the diffusion assay for Haemophilus influenzae, the diffusion assay is NOT recommended for Haemophilus species. Consequently, this

Table 2 Bacteriological eradication and clinical cure/improvement rates versus zone diameter (15 µg disk) in oral dirithromycin pharyngitis studies of Streptococcus pyogenes.

Zone diameter (mm)	Bacteriological (%)	Clinical (%)
0	2/8 (25.0%)	7/8 (87.5%)
10	1/1 (100 %)	1/1 (100 %)
11	0/1 (0.0%)	1/1 (100 %)
12	2/2 (100 %)	1/2 (50.0%)
13	6/6 (100 %)	6/6 (100 %)
14	2/3 (66.7%)	2/2 (100 %)
15	6/7 (85.7%)	7/7 (100 %)
16	9/12 (75.0%)	11/12 (91.7%)
17	12/19 (63.1%)	16/16 (100 %)
18	22/24 (91.7%)	24/24 (100 %)
19	26/31 (83.9%)	33/35 (94.3%)
20	61/66 (92.4%)	63/68 (92.6%)
21	39/47 (83.0%)	44/47 (93.6%)
22	38/51 (74.5%)	48/50 (96.0%)
23	34/41 (82.9%)	41/43 (95.3%)
24	53/65 (81.5%)	64/69 (92.8%)
25	40/44 (90.1%)	42/42 (100 %)
26	25/30 (83.3%)	29/32 (90.6%)
27	17/22 (72.3%)	24/25 (96.0%)
28	23/28 (82.1%)	28/31 (90.3%)
29	9/10 (90.0%)	10/10 (100 %)
30	15/20 (75.0%)	19/20 (95.0%)
31	3/3 (100 %)	2/2 (100 %)
32	10/11 (90.1%)	9/9 (100 %)
33	3/5 (60.0%)	5/5 (100 %)
34	2/2 (100 %)	2/2 (100 %)
35	1/1 (100 %)	1/1 (100 %)
36	2/2 (100 %)	2/3 (66.7%)
37	0/1 (0.0%)	0/1 (0.0%)
38	3/3 (100 %)	3/3 (100 %)
39	-/- (---)	-/- (---)
40	1/1 (100 %)	1/1 (100 %)

Table 3 Bacteriological eradication and clinical cure/improvement rates versus zone diameter (15 µg disk) in oral dirithromycin skin and skin structure studies of Staphylococcus aureus

Zone diameter (mm)	Bacteriological (%)	Clinical (%)
0	6/9 (66.7%)	8/12 (66.7%)
10	-/- (---)	0/1 (0.0%)
11	-/- (---)	0/1 (0.0%)
12	-/- (---)	0/1 (0.0%)
13	-/- (---)	0/1 (0.0%)
14	1/1 (100 %)	1/2 (50.0%)
15	1/1 (100 %)	7/7 (100 %)
16	3/4 (75.0%)	5/5 (100 %)
17	4/4 (100 %)	5/6 (83.3%)
18	8/10 (80.0%)	11/11 (100 %)
19	4/5 (80.0%)	5/5 (100 %)
20	24/27 (88.9%)	27/28 (96.4%)
21	12/14 (85.7%)	20/21 (95.2%)
22	14/19 (73.7%)	21/25 (84.0%)
23	6/7 (85.7%)	12/12 (100 %)
24	11/15 (73.3%)	28/30 (93.3%)
25	4/4 (100 %)	8/8 (100 %)
26	7/8 (87.5%)	16/16 (100 %)
27	1/1 (100 %)	1/2 (50.0%)
28	5/5 (100 %)	9/9 (100 %)
29	2/2 (100 %)	2/3 (66.7%)
30	-/- (---)	5/5 (100 %)
31	-/- (---)	-/- (---)
32	0/1 (0.0%)	2/2 (100 %)
33	-/- (---)	1/1 (100 %)
34	-/- (---)	1/1 (100 %)
35	-/- (---)	-/- (---)
36	-/- (---)	-/- (---)
37	-/- (---)	-/- (---)
38	1/1 (100 %)	1/1 (100 %)
39	-/- (---)	-/- (---)
>40	1/2 (50.0%)	1/2 (50.0%)

Table 4 Bacteriological eradication and clinical cure/improvement rates versus zone diameter (15 µg disk) in oral dirithromycin pneumonia and bronchitis studies of Streptococcus pneumonia

Zone diameter (mm)	Bacteriological (%)	Clinical (%)
0	-/- (---)	-/- (---)
8	1/1 (100 %)	1/1 (100 %)
11	-/- (---)	1/1 (100 %)
12	1/1 (100 %)	1/1 (100 %)
13	-/- (---)	1/1 (100 %)
14	-/- (---)	-/- (---)
15	-/- (---)	-/- (---)
16	1/1 (100 %)	1/1 (100 %)
17	1/1 (100 %)	2/2 (100 %)
18	1/1 (100 %)	8/8 (100 %)
19	2/2 (100 %)	4/4 (100 %)
20	4/4 (100 %)	4/5 (80.0%)
21	3/3 (100 %)	5/5 (100 %)
22	5/6 (83.3%)	11/12 (91.6%)
23	1/1 (82.9%)	4/4 (100 %)
24	3/3 (100 %)	7/7 (100 %)
25	1/2 (50.0%)	5/7 (71.4%)
26	3/3 (100 %)	8/8 (100 %)
27	4/4 (100 %)	8/8 (100 %)
28	6/6 (100 %)	7/7 (100 %)
29	-/- (---)	7/7 (100 %)
30	5/5 (100 %)	16/16 (100 %)
31	2/4 (50.0%)	7/9 (77.8%)
32	6/7 (85.7%)	15/16 (93.8%)
33	2/2 (100 %)	7/7 (100 %)
34	1/1 (100 %)	3/3 (100 %)
35	1/1 (100 %)	3/3 (100 %)
36	-/- (---)	4/4 (100 %)
37	-/- (---)	1/1 (100 %)
38	-/- (---)	5/5 (100 %)
39	-/- (---)	1/1 (100 %)
> 40	1/1 (100 %)	8/8 (100 %)

Table 5 Bacteriological eradication and clinical cure/improvement rates versus zone diameter (15 µg disk) in oral dirithromycin pneumonia and bronchitis studies of Haemophilus influenzae

Zone diameter (mm)	Bacteriological (%)	Clinical (%)
0	3/6 (50.0%)	15/18 (83.3%)
7	-/- (---)	1/1 (100 %)
8	-/- (---)	3/3 (100 %)
9	-/- (---)	1/1 (100 %)
10	0/2 (0.0%)	4/4 (100 %)
11	0/1 (0.0%)	1/2 (50.0%)
12	-/- (---)	2/4 (50.0%)
13	2/3 (66.7%)	4/6 (66.7%)
14	2/2 (100 %)	2/3 (66.7%)
15	4/6 (66.7%)	8/11 (72.7%)
16	0/5 (0.0%)	11/13 (84.6%)
17	0/2 (0.0%)	9/9 (100 %)
18	2/4 (50.0%)	13/15 (86.7%)
19	2/2 (100 %)	5/5 (100 %)
20	10/13 (76.9%)	21/21 (100 %)
21	5/6 (83.3%)	6/6 (100 %)
22	2/2 (100 %)	9/10 (90.0%)
23	2/4 (50.0%)	5/6 (83.3%)
24	3/4 (75.0%)	7/9 (77.8%)
25	-/- (---)	-/- (---)
26	1/2 (50.0%)	7/7 (100 %)
27	-/- (---)	-/- (---)
28	3/3 (100 %)	3/4 (75.0 %)
29	-/- (---)	1/1 (100 %)
30	1/3 (33.3%)	13/15 (86.7%)
31	-/- (---)	1/1 (100 %)
32	1/1 (100 %)	2/2 (100 %)
33	-/- (---)	-/- (---)
34	-/- (---)	-/- (---)
35	-/- (---)	1/1 (100 %)

application is NOT APPROVABLE at this time until an adequate in vitro test method for testing the susceptibility of Haemophilus species has been established.

MIC broth/agar dilution comparisons.

The applicant has not submitted the data as required according to the accepted methodology as defined by the National Committee for Clinical Laboratory standards (NCCLS). According to the NCCLS document M23-T2 (August 1992) for the development of in vitro susceptibility testing criteria and quality control parameters (section 4.0), the applicant should submit data comparing the broth and agar dilution methods, as well as the broth microdilution and macrodilution methods.

Deficiency: The applicant has not submitted data (as required in NCCLS document M23-T2 (section 4.0) July 1994, for the development of in vitro susceptibility testing criteria and quality control parameters, to compare the broth and agar dilution methods, and the broth microdilution and macrodilution methods.

MIC/Disk diffusion correlation studies.

In the contracted French study²⁰, Dr. Duval determined that by regression analysis of 547 strains susceptibilities as measured by zone diameters and MIC values for dirithromycin yielded a regression line conforming to $Y = -2.2194 \log_2 x + 20.19$ with a correlation coefficient of -0.76473 . Using the applicant's proposed MIC limits of 2 and 8 $\mu\text{g/mL}$, the corresponding zone diameters were 14 and 18 mm. However the author suggested using limits of 1 and 4 $\mu\text{g/mL}$, with corresponding zones of 16 and 21 mm, which included results obtained with 195 Haemophilus influenzae strains.

The applicant had submitted a study⁴⁴ by Dr. Barry and colleagues in the original application describing the disk susceptibility tests. However, on June 21, 1994 the applicant submitted notice that the final publication⁴⁵ of this study (submitted in the June 9, 1994 amendment) contained errors which were to be corrected and submitted. The errors have to do with the inclusion of Haemophilus influenzae (150 isolates) in the regression analyses and the calculations of the error rates for these analyses. Since, the applicant is requesting separate susceptibility limits for Haemophilus species, this genus must be segregated for these analyses.

This analysis was conducted by this reviewer from the line listing of the original isolates as submitted as an in-house report⁴⁵ using only the organisms to be approved in the package insert. These included: H. influenzae (55 isolates analyzed separately), Listeria monocytogenes (20), Staphylococcus aureus (35), Streptococcus pyogenes (20),

S. agalactiae (20), S. pneumoniae (30), Streptococcus group C (10) and group G (10) and Corynebacterium jeikeium (10).

The results indicate that for H. influenzae 82% (45/55) of the isolates did not show a zone of inhibition. For the remainder of the 10 strains there was a clear demarcation between susceptible and resistant organisms. In fact, by only including the organisms for which this drug is being approved, there were NO major errors, and only 3.2% (5/155) minor errors (3 organisms with intermediate MIC=4 µg/mL with susceptible zones of 20-22 mm; and 2 organisms with intermediate zones of 16 mm and MICs of 8 and 64 µg/mL) when the susceptibility limits, as proposed by the U.S. study, were used, which are similar to those recommended in the French study²⁰. **A full analysis of these in vitro data and the clinical data (if both MIC and zone sizes are available) should be conducted to confirm these analyses.** These limits are therefore tentatively recommended by this reviewer as:

<u>MIC (µg/mL)</u>	<u>Zone diameters (mm)</u>	<u>Interpretation</u>
≤2	≥19	Susceptible
4	16-18	Intermediate
≥8	≤15	Resistant.

It was noted during these studies, that the carbon dioxide atmosphere (5-7%) used during the incubation of Haemophilus influenzae cultures produced no (or very small) zone sizes. This inability to inhibit growth was media independent, and in fact was also noted with the control strain, Staphylococcus aureus (ATCC 29213), but to a lesser degree.

Quality control studies (MIC and Disk diffusion).

The testing of two quality control strains were reported in the Barry et al. study⁴⁵ and submitted in draft⁴⁶ in the original submission. Five and six laboratories participated in the analysis of broth microdilution plates and the 15 µg dirithromycin disks, respectively, against the quality control strains: Staphylococcus aureus ATCC 25923 (for agar diffusion) and Staphylococcus aureus ATCC 29213 and Enterococcus faecalis ATCC 29212 (for microdilution).

The results of these analyses are summarized in the following tables. It should be noted that each of the laboratories did not always report results from the number of repeat observations (there should be 20 results reported per laboratory for the test lots, there is a total of 6 S. aureus tests for which the results are unaccounted).

Table 6. Quality control organism zone diameter susceptibility ranges for 15 µg dirithromycin disk.

QC organism	Zone diameter (mm)								
	test lots/[common lots]								
	18	19	20	21	22	23	24	25	26
<u>S. aureus</u>	4	27	118	150	208	151	89	29	
ATCC 25923	[3]	[9]	[7]	[17]	[15]	[25]	[14]	[0]	

Table 7. Quality control organism minimum inhibitory concentration susceptibility ranges for dirithromycin.

QC organism	MIC (µg/mL)						
	test lots/[common lots]						
	0.5	1.0	2.0	4.0	8.0	16.0	32.0
<u>S. aureus</u>	18	51	10	15	0		
ATCC 29213	[0]	[0]	[7]	[11]	[7]		
<u>E. faecalis</u>			20	0	33	29	18
ATCC 29212			[0]	[0]	[5]	[16]	[1]

In the testing of E. faecalis there was one laboratory whose results were much lower than the other five laboratories, and which used media from a different supplier. The results of the common lot yielded all of the MIC values at 8 µg/mL, and all of test lot MIC values of ≤2 µg/mL shown in table 7. If this laboratory is omitted the results indicate that the ranges should be 8-32 µg/mL. However, this organism is not being granted in the indications section nor the in vitro section, and therefore, this reviewer does not recommend including it the quality control section of the package insert, unless it is the only reliable QC strain available. Similarly, this same laboratory had the lowest results for the test lot media (1 MIC at 1 µg/mL and 18 at ≤0.5 µg/mL). All other test media were from Difco, this laboratory used media from BBL. If the data from this laboratory is an outlier and discarded the MIC limits for S. aureus 29213 should be set at 1-4 µg/mL (this differs from the applicant's recommendation).

The authors tentatively recommend the following ranges for the proposed quality control strains, however, they state that "Extreme variability between laboratories was observed when different broth media were used. Consequently, it is not possible to define practical control limits with great confidence." when summarizing the results of the QC MIC tests. The proposed zone ranges by the authors for Staphylococcus aureus ATCC 25923 is: 19-25 mm. It may be more appropriate to increase this range from 18-26 mm. The applicant does not state why this QC strain was not proposed for inclusion in the package insert.

The applicant only suggested that the following QC strain MIC ranges be included in the package insert; no QC zone ranges have been proposed:

Staphylococcus aureus ATCC 29213 0.5-2 ($\mu\text{g/mL}$)
Enterococcus faecalis ATCC 29212 8-32 ($\mu\text{g/mL}$).

Based on the data submitted in this application, this reviewer recommends only the inclusion of Staphylococcus aureus ATCC 29213 with limits of 1-4 $\mu\text{g/mL}$. Furthermore, this reviewer recommends the inclusion of Staphylococcus aureus ATCC 25923, as a quality control strain for measuring zone diameters, with limits of 18-26 mm. Finally, this reviewer recommends the inclusion of a quality control strain of Haemophilus influenzae be included for the testing of MIC ranges; no zone diameters will be established for Haemophilus influenzae since the currently approved method is inappropriate for testing the susceptibility of this organism to dirithromycin.

Deficiencies:

The applicant should clarify why each laboratory testing Staphylococcus aureus ATCC 25923 did not report the results from 20 repeated tests. The applicant should state why Staphylococcus aureus ATCC 25923 was not proposed for inclusion in the package insert as a quality control (QC) strain. The applicant should also explain why no studies were conducted on Haemophilus influenzae quality control strains. Due to the problems associated with the susceptibility testing, and the applicant's request for separate MIC susceptibility limits for this organism, a quality control limits for this organism should be established.

Indications/Pathogens.

The reviewing medical officers (see reviews by Drs. Moledina and Rakowsky, have at the time of the writing of this review indicated to this reviewer, that the application will be approvable for the following indications caused by the listed microorganisms:

Pharyngitis due to Streptococcus pyogenes
Secondary bacterial infections of acute bronchitis due to: Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis
Pneumonia due to: Streptococcus pneumoniae, (Haemophilus influenzae and Moraxella catarrhalis), Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pneumophila
Skin and skin structure infections due to: Staphylococcus aureus.

Package Insert.

As stated earlier in this review, a statement of the cross-resistance of organisms to dirithromycin and other macrolides should be incorporated into the package insert.

The package insert may include the following statements as requested by the applicant and revised by the conclusions of this review. However, due to the gross deficiencies in this application, and the resultant inability to interpret susceptibility limits and quality control strain limits. A complete wording of the microbiology section cannot be completed at this time. Upon receipt and review of a response to the deficiencies delineated in this review, a microbiology section will be drafted for this product (if found approvable) that will conform to the labeling that is current at the time of approval.

"MICROBIOLOGY

Dirithromycin acts by binding to the 50S ribosomal subunits of susceptible microorganisms to inhibit protein synthesis. Beta-lactamase production has no effect on dirithromycin activity."

In vivo:

Gram-positive aerobes: Staphylococcus aureus, Streptococcus pneumoniae and S. pyogenes

Gram-negative aerobes: Haemophilus influenzae, H. parainfluenzae, Moraxella catarrhalis and Legionella pneumophila

Other bacteria: Mycoplasma pneumoniae and Chlamydia pneumoniae"

The following statements may be include in the in vitro section of the package insert (*denotes that the inclusion of this organism must be supported by its ability to be pathogenic in one of the approved indications and approved patient populations).

Gram-positive aerobes: Streptococci groups C, F and G, S. agalactiae, Viridans group streptococci and Listeria monocytogenes

Gram-negative aerobes: Bordetella pertussis and Haemophilus ducreyi*

Anaerobic bacteria: Propionibacterium acnes

Other bacteria: C. trachomatis*

Note: Some strains of staphylococci have demonstrated resistance to dirithromycin and erythromycin. Enterococci and most strains of methicillin-resistant staphylococci are resistant to macrolides such as dirithromycin and erythromycin."

The reader is reminded that since only speciated organisms may be included, the applicant's request for the inclusion in the in vitro section of Peptostreptococcus species and Corynebacterium species cannot be granted.

Interpretative Criteria Established.

Based on the data submitted, the following susceptibility limits are recommended by this reviewer as:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Zone diameters (mm)</u>	<u>Interpretation</u>
≤ 2	≥ 19	Susceptible
4	16-18	Intermediate
≥ 8	≤ 15	Resistant.

The limits for Haemophilus influenzae and H. parainfluenzae cannot be determined based on the data submitted. However, the diffusion assay is not recommended for Haemophilus species.

The applicant recommends the following QC strain MIC ranges, no QC zone ranges have been proposed:

Staphylococcus aureus ATCC 29213 1-4 ($\mu\text{g/mL}$).

Due to the gross deficiencies in this application, and the resultant inability to interpret susceptibility limits and quality control strain limits. A complete wording of the microbiology section cannot be completed at this time. Upon receipt and review of a response to the deficiencies delineated in this review, a microbiology section will be drafted for this product (if found approvable) that will conform to the labeling that is current at the time of approval.

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. DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Clinical Microbiological Review

NDA #: 50-678 REVIEW #: 3 REVIEW DATE: 22-JAN-95

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	27-APR-93	29-APR-93	12-MAY-93
AMENDMENTS	30-AUG-94	31-AUG-94	03-OCT-94
	21-OCT-94	24-OCT-94	31-OCT-94

NAME & ADDRESS OF APPLICANT: Eli Lilly and Company
Lilly Research
Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

CONTACT PERSON: Maxwell Talbott, Ph.D.
Phone Number: (317) 276-2574

DRUG PRODUCT NAME: Proprietary: Dynabac Tablets
Nonproprietary: Dirithromycin
Code Names: LY237216; AS-E 136
Chemical Type:
Macrolide Antibiotic
Therapeutic Class:
1 C

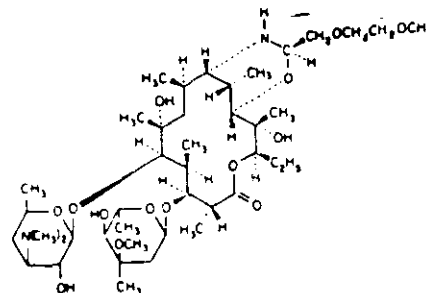
ANDA Suitability Petition/DESI/Patent Status:
N/A--Patent 4,048,306 Expires 9/13/94; Patent 4,755,385
expires 7/5/05

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: enteric-coated tablets
STRENGTHS: 250 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:

9-deoxo-11-deoxy-9,11-imino[2-(2-methoxy)-ethylidene]-oxy-(9S)-erythromycin



Molecular Formula: C₄₂H₇₈N₂O₁₄
Molecular Weight: 835.09

SUPPORTING DOCUMENTS:

INDs:

DMFs:

All authorization letters have been properly submitted.

REMARKS/COMMENTS:

This review is of the applicant's responses to the approvable letter issued July 28, 1994. The October 21, 1994 submission contains revised draft labeling. The following lists the microbiology review comments which were transmitted in the approvable letter. These are followed by the applicant's response and this reviewer's assessment of each response.

1. The applicant should submit a full analysis and individual patient line listings of the bacteriological and clinical diagnoses and outcomes. The susceptibilities (actual numerical MIC and zone size results, preferably both) should be submitted for every pathogen isolated per patient, including pre- and post-therapy isolates.

The applicant has submitted a response in appendices 1A and 1B of the August 30, 1994 submission, and has agreed to provide the information electronically.

An electronic submission has not been made to date. The data was requested primarily for looking at the clinical correlation for *Haemophilus influenzae* infections with bacteriological outcome. This indication is no longer being pursued by the applicant. Furthermore, data were available (in graph form) for the gram-positive organisms which were granted in the indications. Consequently, a line by line analysis, without the benefit of an electronic submission is not appropriate until an additional indication, with separate susceptibility limits is requested.

2. The applicant should state the exact method (or reference method if followed precisely) used to measure the susceptibility of clinical isolates to either dirithromycin, erythromyclamine and erythromycin. This should also include methods used for fastidious organisms. The citation should include the year, volume and issue of the reference.

The applicant states that "in all cases, the protocol called for the isolates to be susceptible to erythromycin by either the disk susceptibility test (NCCLS standard M2-A3, 1984) or a standardized dilution test (NCCLS standard M7-A, 1985)".

This is not entirely correct, as discussed below for *Haemophilus* species. However, it is an acceptable response for the organisms being claimed in the draft labeling submitted October 21, 1994.

3. If in a future submission the applicant requests either a clinical or an *in vitro* claim for *Haemophilus* species, the applicant should submit the following. A description of the methods by which zone diameters were measured for *Haemophilus influenzae* and *H. parainfluenzae* in the clinical trials, since it is clear from the literature that the currently established NCCLS method for agar diffusion does not result in zones of inhibition when testing *Haemophilus* species. Since dilution methods were not used in the clinical trials, it is not possible to establish MIC susceptibility limits for *Haemophilus* species based on the clinical trials.

Furthermore, since the NCCLS diffusion method does not result in zones of inhibition with the dirithromycin 15 μg disk, no data is available to correlate MIC and zone diameter measurements to test the *in vitro* activity of dirithromycin against *Haemophilus* species. Furthermore, due to the technical difficulties encountered using the diffusion assay for *Haemophilus influenzae*, the diffusion assay is NOT recommended for *Haemophilus* species. Consequently, an adequate *in vitro* test method for testing the susceptibility of *Haemophilus* species must be established before susceptibility criteria can be determined, if a clinical indication is sought for this genera.

The applicant agrees that the current (requiring CO_2 incubation as tentatively proposed in November 1988 [M2-T4] and approved in April 1990 [M2-A4]) disk diffusion NCCLS method is not appropriate for testing dirithromycin activity against *Haemophilus* species. [The protocols followed the earlier, 1984 method (M2-A3) which did not require the use of CO_2 .] However, the applicant contends that "The usual MIC of dirithromycin against *H. influenzae* is 2, 4, or 8 $\mu\text{g}/\text{mL}$ ", and suggests interpretive criteria of susceptible $\leq 8 \mu\text{g}/\text{mL}$ and resistant $\geq 32 \mu\text{g}/\text{mL}$.

Note: This statement is not consistent with the data submitted in the application and replicated in the summary table (Table 1) below. Furthermore, the clinical data was not correlated to MIC values.

Table 1. In-vitro Activity of Macrolide Antibiotics against *Haemophilus* species

ORGANISM	n	DIRITHRO		ERYMYCL		ERYTHRO		AZITHRO		CLARITHRO	
		MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range	MIC ₉₀	Range
<i>Haemophilus ducreyi</i>	54 ⁷	.01	.002-.03	-	-----	.125	.002-.125	-	-----	.03	.002-.06
<i>H. ducreyi</i>	36 ²	1	.25-4	-	-----	.25	.13-.25	.5	.25-1	.25	.13-.25
<i>H. influenzae</i> Amp ^S	24 ²	8	4-8	-	-----	4	2-8	.5	.13-2	4	1-4
<i>H. influenzae</i> Amp ^R	55 ²	16	8-16	-	-----	4	.5-4	1	.06-2	8	1-8
<i>H. influenzae</i>	22 ¹	>16	8->16	-	-----	8	2-8	1	.12-1	8	.5-16
<i>H. influenzae</i>	22 ³	8	2-8	8	4-8	4	.5-4	.5	.12-.5	8	2-8
<i>H. influenzae</i>	95 ⁵	>16	8->16	-	-----	8	4-16	-	-----	-	-----
<i>H. influenzae</i>	199 ⁴	64	.125-128	-	-----	-	-----	-	-----	-	-----
<i>H. influenzae</i>	34 ⁶	64	2-64	64	1-128	8	.25-16	-	-----	-	-----
<i>H. parainfluenzae</i>	10 ²	16	8-16	-	-----	4	2-4	2	.25-2	8	1-8
<i>H. parainfluenzae</i>	17 ⁴	64	1->128	-	-----	-	-----	-	-----	-	-----

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3. Hardy, D.J. et al. (1988) *Antimicrob. Agents Chemother.* 32(11):1710-9.
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6. Acar, J.F. (1985) (a French study) Lilly report #B9Z-EW-P010, B020.17, 1.62:3-8.
7. Miller, S. (1990) Lilly report #B9Z-UA-0002, 1.63:30-36.

The applicant has made several suggestions which are a possibility, once clinical efficacy can be established with associated breakpoints. The suggestions are as follows:

a. Establish an exception to the standard method and suggest that *H. influenzae* tests for dirithromycin be done in an atmosphere without added CO₂. (Note: This was the recommendation by NCCLS prior to November 1988 and thus is how most of the protocols were written.)

b. Report dirithromycin susceptibility only on the basis of MICs using the proposed ≤ 8 , 16, ≥ 32 $\mu\text{g/mL}$ breakpoints.

c. Obtain simultaneous data on *H. influenzae* susceptibility to dirithromycin, clarithromycin, and azithromycin, using the proposed MIC breakpoints for dirithromycin and the recommended breakpoints for the other two, to illustrate uniform cross susceptibility. Then accept the proposal of Jones, et al [Diagn Microbiol Infect Dis. 1994; 18:243-9] that the azithromycin disk be established as the "class disk" for the advanced (*Haemophilus*-indicated) macrolides.

Note: All three of the above suggestions requires further data to support such conclusions. When the applicant has conducted such studies, with clinical correlates, and requests an indication in which *Haemophilus influenzae* is claimed, such suggestions will be considered and the associated data reviewed.

However, since the applicant has chosen not to pursue a claim for *Haemophilus* species at this time, this information will be requested and reviewed if and when this claim is sought.

4. The applicant should submit data (as required in NCCLS document M23-T2, section 4.0 July 1994) for the development of *in vitro* susceptibility testing criteria and quality control parameters, to compare the broth and agar dilution methods, and the broth microdilution and macrodilution methods.

The applicant responded by referencing Vol 1.61, p115 and p134 of the original NDA. Page 115 contains (irrelevant) information about growth in different media and page 134 contains a table (Table 2) comparing the various dilution methods using gram-positive cocci. The MIC results differ by up to 4-fold (16 times) between methods with agar dilution typically yielding the largest MIC value. This range brackets the susceptible limit for some strains of *Staphylococcus aureus*, *S. epidermidis* and *Enterococcus faecalis*.

Table 2.
 Comparison of Methodologies for Measurement of MIC Values
 for Dirithromycin at Lilly Research Laboratories (1.61:134)

Organism and Strain	Method and MIC Value (µg/mL)		
	Agar Dilution	Broth Dilution	Microtiter
<i>Staphylococcus aureus</i> 3055	1	0.5	0.125
<i>S. aureus</i> V57	32	16	32
<i>S. aureus</i> V104	1	0.5	0.5
<i>S. aureus</i> 25923	4	1	1
<i>Staphylococcus epidermidis</i> ST-215	4	0.5	2
<i>S. epidermidis</i> ST-216	1	1	0.25
<i>S. epidermidis</i> ST-217	1	0.5	0.5
<i>S. epidermidis</i> ST-222	0.25	0.125	0.06
<i>Streptococcus pyogenes</i> C203	0.125	0.125	0.06
<i>S. pyogenes</i> 10389	0.125	0.125	0.015
<i>Streptococcus pneumoniae</i> Park I	<0.06	0.06	0.008
<i>S. pneumoniae</i> 14	0.25	0.125	NT
<i>Streptococcus sanguis</i> I-910	0.125	0.25	0.125
<i>S. sanguis</i> I-547	0.125	0.25	0.06
<i>Streptococcus salivarius</i> S-262	0.25	0.25	0.06
<i>Enterococcus faecalis</i> 238	4	2	25
<i>E. faecalis</i> Mitis	4	4	
<i>E. faecalis</i> SS992	4		4
<i>E. faecalis</i> Shrigley	48	4	8
<i>Enterococcus faecium</i> 8043	0.5	0.25	1

NT = not tested.

The later two organisms are not being claimed in any approved indications, and the former is the quality control strain, *S. aureus* ATCC 25923 that is used for agar diffusion methods not dilution methods. Consequently, this difference is not a significant factor in obtaining a false test result when using various dilution methods. The applicant's response is acceptable.

5. The applicant should clarify why each laboratory testing *Staphylococcus aureus* ATCC 25923 did not report the results from 20 repeated tests. The applicant should state why *Staphylococcus aureus* ATCC 25923 was not proposed for inclusion in the package insert as a quality control (QC) strain. The applicant should also explain why no studies were conducted on *Haemophilus influenzae* quality control strains. Due to the problems associated with the susceptibility testing, and the applicant's request for separate MIC susceptibility limits for this organism, MIC quality control limits for this organism should be established, if a claim for this genera is to be pursued.

The applicant responded that each of the six laboratories submitted results of 150 tests with unique lots and 15 with a common lot. However, one laboratory only submitted 146 results for *Staphylococcus aureus* ATCC 25923 with the unique lots. The applicant should provide an explanation of the missing data for these four samples.

Note: There was a column missing from the Table 6 of the first review; the corrected table follows:

Table 6. Quality control organism (*S. aureus* ATCC 25923) zone diameter susceptibility ranges for 15 µg dirithromycin disk.

QC organism		Zone diameter (mm)							
		test lots/[common lots]							
18	19	20	21	22	23	24	25	26	
4	27	118	150	208	151	120	89	29	
[3]	[9]	[7]	[17]	[15]	[25]	[14]	[0]	[0]	

Consequently, *Staphylococcus aureus* ATCC 25923 should be included in the package insert as a quality control strain with limits of 18-26 mm for the 15 µg dirithromycin disk, unless the missing data points change the conclusion of these results.

Note that the applicant claims that they requested the inclusion of *Staphylococcus aureus* ATCC 25923 in the original draft package insert. The applicant also is not requesting a QC strain for *Haemophilus influenzae* at this time since they are no longer requesting a claim for this organism. However, in the future the NCCLS disk diffusion method as it currently is written will not be acceptable since the inclusion of CO₂ results in a lack of zone formation.

The quality control strain *Staphylococcus aureus* ATCC 25923 should be included in the package insert with limits of 18-26 mm for the 15 µg dirithromycin disk.

6. The package insert should be revised to incorporate the wording dictated for the microbiology and reference sections.

*MICROBIOLOGY

Erythromycylamine, the microbiologically active product of dirithromycin hydrolysis, exerts its activity by binding to the 50S ribosomal subunits of susceptible microorganisms resulting in inhibition of protein synthesis.

Dirithromycin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Gram-Positive Aerobes:

Staphylococcus aureus (methicillin-sensitive strains only)
Streptococcus pneumoniae
Streptococcus pyogenes

Gram-Negative Aerobes:

Legionella pneumophila
Moraxella catarrhalis

Other Bacteria:

Mycoplasma pneumoniae

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

Dirithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 2 µg/ml or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of dirithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Aerobes:

Listeria monocytogenes
Streptococci groups C, F and G
S. agalactiae
Viridans group streptococci

Gram-Negative Aerobes:

Bordetella pertussis

Anaerobic Bacteria:

Propionibacterium acnes

Note: Microorganisms that are resistant to other macrolides are cross-resistant to dirithromycin. Most strains of methicillin-resistant staphylococci and many strains of methicillin-susceptible staphylococci are resistant to macrolides.

SUSCEPTIBILITY TESTING

Dilution techniques: Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method^{1, 2, 3} (broth, agar, or microdilution) or equivalent with dirithromycin powder. The MIC values obtained should be interpreted according to the following criteria:

<u>MIC ($\mu\text{g/ml}$)</u>	<u>Interpretation</u>
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product).

Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard dirithromycin powder should provide the following MIC values:

<u>Microorganism</u>	<u>MIC ($\mu\text{g/mL}$)</u>
<i>Staphylococcus aureus</i> ATCC 29213	1.0-4.0

Diffusion techniques: Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure^{3,4} that has been recommended for use with disks to test the susceptibility of microorganisms to dirithromycin uses the 15 μg dirithromycin disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for dirithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 μg dirithromycin disk should be interpreted according to the following criteria:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 19	Susceptible (S)
16-18	Intermediate (I)
≤ 15	Resistant (R)

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, diffusion susceptibility test methods require the use of laboratory control microorganisms. The 15 μg dirithromycin disk should provide the following zone diameters in these laboratory test quality control strains:

<u>Microorganism</u>	<u>15 μg dirithromycin Disk Zone Diameter (mm)</u>
<i>Staphylococcus aureus</i> ATCC 25923	18-26

REFERENCES:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically--Third Edition; Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.
2. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria--Third Edition; Approved Standard NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA, December 1993.
3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Fifth Informational Supplement, NCCLS Document M100-S5, Vol. 14, No. 16, NCCLS, Villanova, PA, December 1994.
4. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--Fifth Edition; Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993."

CONCLUSIONS & RECOMMENDATIONS:

The following comments should be relayed to the applicant in the final action letter along with the following revisions to the package insert.

Since the currently established NCCLS method for agar diffusion does not result in zones of inhibition when testing *Haemophilus* species with a dirithromycin disk, the applicant must submit data to support an interpretive susceptibility criteria if a claim for *Haemophilus* species is sought in a future indication. That data may be supportive of the general suggestions made by the applicant in the August 30, 1994 submission, but should be concurred by the division's reviewing microbiologist when requested. All three of the applicant's suggestions require conducting further studies, with clinical correlates.

It has been noted that the applicant contends that "The usual MIC of dirithromycin against *H. influenzae* is 2, 4, or 8 $\mu\text{g/mL}$ ", and suggests interpretive criteria of susceptible $\leq 8 \mu\text{g/mL}$ and resistant $\geq 32 \mu\text{g/mL}$. However, this statement

is not consistent with the data submitted in the application, and is not acceptable for consideration unless clinical trials data are correlated to MIC values.

However, since the applicant has chosen not to pursue a claim for *Haemophilus* species at this time, this information will be requested and reviewed if and when this claim is sought.

In the Quality control study conducted by one laboratory only submitted 146 results for *Staphylococcus aureus* ATCC 25923 with the unique lots. The applicant should provide an explanation of the missing data for these four samples.

The package insert should be revised to incorporate the wording dictated for the microbiology and reference sections.

***MICROBIOLOGY**

Erythromyclamine, the microbiologically active product of dirithromycin hydrolysis, exerts its activity by binding to the 50S ribosomal subunits of susceptible microorganisms resulting in inhibition of protein synthesis.

Dirithromycin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Gram-Positive Aerobes:

Staphylococcus aureus (methicillin-sensitive strains only)
Streptococcus pneumoniae
Streptococcus pyogenes

Gram-Negative Aerobes:

Legionella pneumophila
Moraxella catarrhalis

Other Bacteria:

Mycoplasma pneumoniae

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

Dirithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 2 µg/ml or less against most

(≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of dirithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Aerobes:

Listeria monocytogenes
Streptococci groups C, F and G
S. agalactiae
Viridans group streptococci

Gram-Negative Aerobes:

Bordetella pertussis

Anaerobic Bacteria:

Propionibacterium acnes

Note: Microorganisms that are resistant to other macrolides are cross-resistant to dirithromycin. Most strains of methicillin-resistant staphylococci and many strains of methicillin-susceptible staphylococci are resistant to macrolides.

SUSCEPTIBILITY TESTING

Dilution techniques: Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method^{1,2,3} (broth, agar, or microdilution) or equivalent with dirithromycin powder. The MIC values obtained should be interpreted according to the following criteria:

<u>MIC (µg/ml)</u>	<u>Interpretation</u>
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category also provides a

buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product).

Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard dirithromycin powder should provide the following MIC values:

<u>Microorganism</u>	<u>MIC ($\mu\text{g/mL}$)</u>
<i>Staphylococcus aureus</i> ATCC 29213	1.0-4.0

Diffusion techniques: Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure^{3,4} that has been recommended for use with disks to test the susceptibility of microorganisms to dirithromycin uses the 15 μg dirithromycin disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for dirithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 μg dirithromycin disk should be interpreted according to the following criteria:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 19	Susceptible (S)
16-18	Intermediate (I)
≤ 15	Resistant (R)

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, diffusion susceptibility test methods require the use of laboratory control microorganisms. The 15 μg dirithromycin disk should

NDA 50-678
Eli Lilly
Dynabac

Page 15 of 15.

provide the following zone diameters in these laboratory test quality control strains:

Microorganism 15 µg dirithromycin Disk Zone Diameter (mm)

Staphylococcus aureus ATCC 25923 18-26

REFERENCES:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically--Third Edition; Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.
2. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria--Third Edition; Approved Standard NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA, December 1993.
3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Fifth Informational Supplement, NCCLS Document M100-S5, Vol. 14, No. 16, NCCLS, Villanova, PA, December 1994.
4. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--Fifth Edition; Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993."

Kathleen A. Creedon 3/10/95
Kathleen A. Creedon, Ph.D.
Review Microbiologist 1/26/95

cc: Orig. NDA 50-678
HFD-520/Division File
HFD-520/KCreedon:1/26 & 3/9/95
HFD-520/MO/NMoledina
HFD-520/Pharm/ROsterberg
HFD-520/Chem/DKatague
HFD-520/CSO/MDillon-Parker

Concurrence Only:
HFD-520/ActgDir/LGavrilovich
HFD-520/SUPERVISOR/ASheldon
R/D Init by: ATS:2/15/95 *AS*
filename: N50-678.rev *3/10/95*

100 2/15/95

MAR 1 2

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-678 **CHEM. REVIEW #:** 01 **REVIEW DATE:** 28-Feb-94

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-JUN-92	06-JUN-92	17-JUN-93
REFUSED for Filing	04-AUG-92	Accepted to File	17-JUN-93
AMENDMENT	03-DEC-93	06-DEC-93	13-DEC-93

NAME & ADDRESS OF APPLICANT:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46825
Contact Person: M. Talbott (317)-276-2574

DRUG PRODUCT NAME

<u>Proprietary:</u>	Dynabac
<u>Nonproprietary/USAN:</u>	Dirithromycin
<u>Code Names/#'s:</u>	LY237216; AS-E 136
<u>Chemical Type/</u>	<u>Macrolide Antibiotic</u>
<u>Therapeutic Class:</u>	1 8

ANDA Suitability Petition/DESI/Patent Status:

N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Macrolide Antibiotic

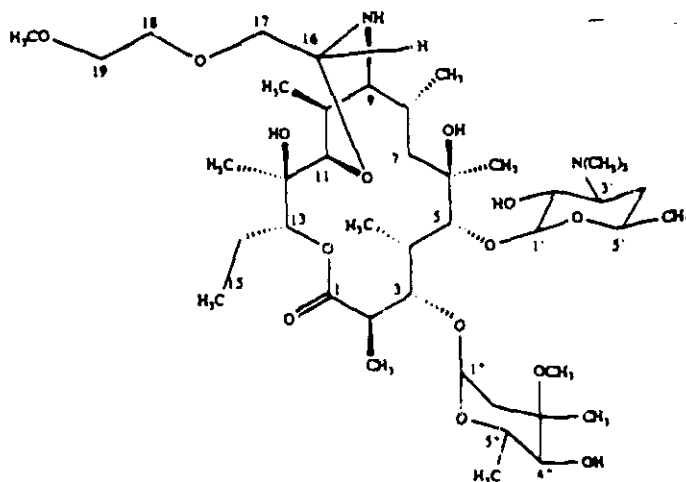
<u>DOSE FORM:</u>	enteric coated tablets
<u>STRENGTHS:</u>	250 mg
<u>ROUTE OF ADMINISTRATION:</u>	oral
<u>DISPENSED:</u>	☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,

MOL. WT:

(9S)-9-deoxy-11-deoxy-9,11-[imino((1R)-2-(2-methoxyethoxy)ethylidene)oxy] erythromycin

- Empirical formula: $C_{42}H_{78}N_2O_{14}$
- Molecular weight: 833.09
- Structural formula:



RELATED DOCUMENTS :

CONSULTS:

Microbiology in Progress
Biopharmaceutics in Progress

REMARKS/COMMENTS:

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. The new drug provides excellent coverage for pathogens commonly isolated from respiratory and skin infections. The proposed once-daily dose regimen will improved patience compliance and unlike erythromycin, Dirithromycin may be given without regards to meals.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 507 of the Act. Specific items which are not approvable or are incomplete are identified under the following headings:

David B. Katague 2/28/94
D.KATAGUE, Review Chemist

cc: Orig. NDA 50-678 HFD-520/Division File
HFD-520/Katague HFD-520/MO/Moledina HFD-520/Pharm
HFD-520/Micro HFD-520/CSO/Dillon Parker
HFD-520/SUPERVISOR/BeCamp HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR

filename:50678-1

Act. Sup. Chem. DL 2/14/94

Chem. Reviews

APR 20 1994

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-678 **CHEM.REVIEW #:** 02 **REVIEW DATE:** 04-APR-94

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-JUN-92	06-JUN-92	17-JUN-93
REFUSED for Filing	04-AUG-92	Accepted to File	17-JUN-93
AMENDMENT	03-DEC-93	06-DEC-93	13-DEC-93

NAME & ADDRESS OF APPLICANT:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46825
Contact Person: M.Talbott (317)-276-2574

DRUG PRODUCT NAME

<u>Proprietary:</u>	Dynabac
<u>Nonproprietary/USAN:</u>	Dirithromycin
<u>Code Names/#'s:</u>	LY237216; AS-E 136
<u>Chemical Type/</u>	<u>Macrolide Antibiotic</u>
<u>Therapeutic Class:</u>	1 8

ANDA Suitability Petition/DESI/Patent Status:

N/A

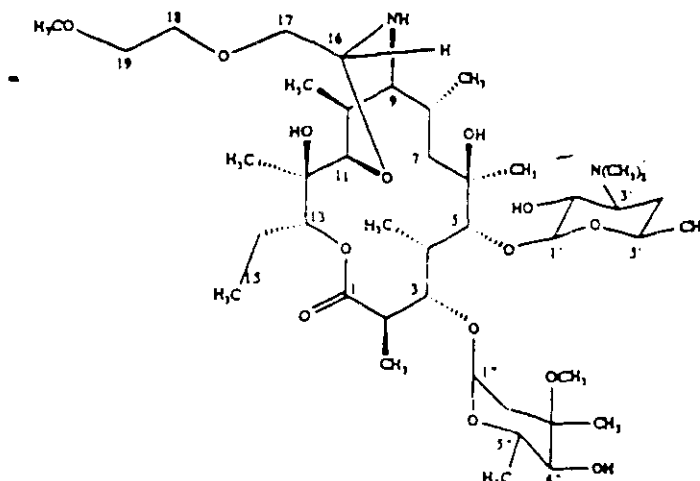
PHARMACOLOGICAL CATEGORY/INDICATION: Macrolide Antibiotic

<u>DOSAGE FORM:</u>	enteric coated tablets
<u>STRENGTHS:</u>	250 mg
<u>ROUTE OF ADMINISTRATION:</u>	oral
<u>DISPENSED:</u>	☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,

MOL.WT:

(9S)-9-deoxy-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy)ethylidene]oxy] erythromycin



RELATED DOCUMENTS :

CONSULTS:

Microbiology in Progress
Biopharmaceutics Completed-3/30/94-Acceptable

REMARKS/COMMENTS:

This review deals primarily with the proposed tolerance range, referred to as "reasonable variation" in the formulation of the drug product. The variation ranges for the ingredients are not acceptable. Unless the applicant provides, bioavailability data for the low and high ranges, the applicant is requested to delete the reasonable variation ranges in the quantitative composition of the drug product as listed

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 507 of the Act. In addition to the deficiencies listed in Chem review #1, dated 2/28/94, the reasonable variation range in the chemical composition of the drug formulation is not acceptable. CSO should communicate the above deficiency to the applicant.

D. A. Katague 4/7/94
D.KATAGUE, Review Chemist

cc: Orig. NDA 50-678 HFD-520/Division File
HFD-520/Katague HFD-520/MO/Moledina HFD-520/Pharm/05-76622
HFD-520/Micro/CKE HFD-520/CSO/Dillon Parker
HFD-520/SUPERVISOR/Roy HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR 4/12/94

filename:50678-2

4/20/94

JUL 11 1994

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-678 CHEM.REVIEW #: 03 REVIEW DATE: 11-JUL-94

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-JUN-92	06-JUN-92	17-JUN-93
REFUSED for Filing	04-AUG-92	Accepted to File	17-JUN-93
AMENDMENT	03-DEC-93	06-DEC-93	13-DEC-93
AMENDMENT	22-JUN-94	23-JUN-94	30-JUN-94

NAME & ADDRESS OF APPLICANT:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46825
Contact Person: M.Talbott (317)-276-2574

DRUG PRODUCT NAME

Proprietary: Dynabac
Nonproprietary/USAN: Dirithromycin
Code Names/#'s: LY237216; AS-E 136
Chemical Type/ Macrolide Antibiotic
Therapeutic Class: 1 S

ANDA Suitability Petition/DESI/Patent Status:

N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Macrolide Antibiotic

DOSAGE FORM: enteric coated tablets
STRENGTHS: 250 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:

(9S)-9-deoxy-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy)ethylidene]oxy] erythromycin

See Chem Review #1 (2/94) and #2 (4/94)

REMARKS/COMMENTS:

This review deals with the amendment dated 6/22/94 which addresses the CMC deficiencies communicated to the applicant on 3/8/94 and 5/23/94. Specifically, the proposed tolerance range, referred to as "reasonable variation" in the formulation of the drug product was discussed. The variation ranges for the ingredients are not acceptable. The amendment also provides for the addition of a 60 count package. This presentation is in the container-closure system of the same material used for the 10 and 100 count bottles. The 60 count package is within the bracket of 10 and 100 count presentations. The sponsor has provided full-shelf life stability data of 24 months for the 10 and 100 count

presentations. The applicant's response to the reviewer's comments are discussed in detail

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable for manufacturing and controls under section 507 of the Act pending satisfactory resolution of deficiencies under Drug Substance: Specifications/Analytical Methods, Drug Product: Components/Composition and Labeling.

D. B. Katague
D.B.KATAGUE, Review Chemist

cc: Orig. NDA 50-678 HFD-520/Division File
HFD-520/Katague HFD-520/MO/Moledina HFD-520/Pharm
HFD-520/Micro HFD-520/CSO/Dillon Parker
HFD-520/SUPERVISOR/SRoy HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR

filename:50678-3

*Act. Sup. Chem
7/11/99*

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
 Review of Chemistry, Manufacturing, and Controls

NDA #: 50-678 **CHEM.REVIEW #:** 04 **REVIEW DATE:** 10-MAR-95

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-JUN-92.	06-JUN-92	17-JUN-93
REFUSED for Filing	04-AUG-92	Accepted to File	17-JUN-93
AMENDMENT	03-DEC-93	06-DEC-93	13-DEC-93
AMENDMENT	22-JUN-94	23-JUN-94	30-JUN-94
AMENDMENT	30-AUG-94	31-AUG-94	06-SEP-94

NAME & ADDRESS OF APPLICANT:

Eli Lilly and Company
 Lilly Corporate Center
 Indianapolis, IN 46825
 Contact Person: M.Talbott (317)-276-2574

DRUG PRODUCT NAME

<u>Proprietary:</u>	Dynabac
<u>Nonproprietary/USAN:</u>	Dirithromycin
<u>Code Names/'s:</u>	LY237216; AS-E 136
<u>Chemical Type/</u>	<u>Macrolide Antibiotic</u>
<u>Therapeutic Class:</u>	1 8

ANDA Suitability Petition/DESI/Patent Status:

N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Macrolide Antibiotic

<u>DOSAGE FORM:</u>	enteric coated tablets
<u>STRENGTHS:</u>	250 mg
<u>ROUTE OF ADMINISTRATION:</u>	oral
<u>DISPENSED:</u>	_____ X Rx _____ OTC
<u>CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,</u>	
<u>MOL.WT:</u>	

(9S)-9-deoxo-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy) ethylidene]oxy] erythromycin

See Chem Review #1 (2/94), #2 (4/94) and #3 (7/94)

REMARKS/COMMENTS:

This review deals with the amendment dated 8/30/94 which addresses the CMC deficiencies communicated to the applicant on the approvable letter dated 7/28/94. Specifically, the proposed tolerance range, referred to as "reasonable variation" in the formulation of the drug product was discussed. The applicant's response to the reviewer's comments are acceptable and discussed in the attached pages. The review also include the final update of all establishments. All other CMC items remain approvable as in Review #1 (2/28/94), Review #2 (4/4/94), and Review #3 (7/11/94). The FONSI dated 12/13/94 has been received from HFD-102.

NDA 50-678
Katague, David

page 2

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable for chemistry,
manufacturing and controls under section 507 of the Act.
Acceptable CGMP for all establishments is valid up to 4/6/95


D.B.KATAGUE, Review Chemist

cc: Orig. NDA 50-678 ~~HFD-520/Division File~~
HFD-520/Katague HFD-520/MO/Moledina HFD-520/Pharm
HFD-520/Micro HFD-520/CSO/Dillon Parker
HFD-520/SUPERVISOR/SBroy R/D Init by: SUPERVISOR

filename: 50678-4

to 3/15/95

3/14/95

Stat. Reviews

Statistical Review and Evaluation
Addendum

NDA #: 50-678/1C

Applicant: Eli Lilly and Company

Name of Drug: Dirithromycin (DYNABAC)

Documents Reviewed: Age, Gender and race analyses submitted by the sponsor on July 18, 1994.

Indications: Pharyngitis and Tonsillitis, Skin and Skin Structure Infections, Acute Bronchitis, Acute Superimposed on Chronic Bronchitis, and Bacterial Pneumonia.

Clinical Input: None at this point.

A. Review by indications

1. Pharyngitis/Tonsillitis

In my original review of this submission for the Pharyngitis/Tonsillitis indications, Study B9Z-MC-AQAB showed that for Late Posttherapy/Overall Study Termination Evaluations, relative to bacteriologic response (pathogen eliminated or not applicable), there is statistically a significant difference between Dirithromycin (69.9%) and Erythromycin (86.0%) treatment groups (pages 2 and 3 of the original review under efficacy analyses section). Studies B9Z-MC-AQAS and B9Z-EW-E001 also showed that, relative to bacteriologic response (pathogen eliminated or not applicable), for Overall Study Termination Evaluation (page 5 of the original review) and Late Posttherapy Evaluation (page 7 of the original review), the 95% CIs do not satisfy the guidelines of DAIDP. This is reflected in the subgroup analyses of all the Pharyngitis/Tonsillitis Protocols combined, relative to sex, origin and age.

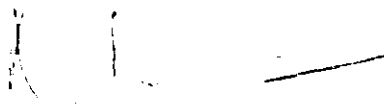
For the bacteriologic response (pathogen eliminated or not applicable), relative to Posttherapy Evaluation, there is a statistically significant difference in favor of Erythromycin, relative to female ($p=0.001$ and the 95% CI on the difference (Dirithromycin - Erythromycin) is $_{255,268}(-0.163,-0.035)_{80.7\%,89.7\%}$) and white ($p=0.01$ and the 95% CI on the difference (Dirithromycin - Erythromycin) is $_{308,304}(-0.131,-0.015)_{82.2\%,89.5\%}$).

For the Late Posttherapy Evaluation, there is a significant difference in favor of Erythromycin, relative female ($p=0.022$ and the 95% CI on the difference between the two treatment groups is, $_{230,241}(-0.143,-0.006)_{81.3\%,88.8\%}$), male ($p=0.016$ and the 95% CI on the difference between the two treatment groups is, $_{111,113}(-0.224,-0.013)_{77.5\%,89.4\%}$), white ($p=0.001$ and the 95% CI on the difference between the two treatment groups is, $_{277,284}(-0.163,-0.037)_{79.4\%,89.4\%}$) and age ≤ 20 years ($p=0.011$ and the 95% CI on the difference between the two treatment groups is, $_{200,199}(-0.169,-0.017)_{79.1\%,86.4\%}$).

2. Skin and Skin Structure Infections

In my original review. Studies B9Z-MC-AQAB and B9Z-E 1-E004 showed that for **Posttherapy Evaluation**, there are no statistically significant differences between Dirithromycin and Erythromycin relative to **bacteriologic outcomes (pathogen eliminated or not applicable)**. The "Age" subgroup analyses show that relative to **age $\leq$ 30 years**, there is significant difference in favor of Erythromycin, $p=0.025$ and the 95% CI on the difference, (Dirithromycin - Erythromycin) is $_{97.85}(-0.206,-0.006)_{83.5\%,84.1\%}$ and that relative to **age $\geq$ 45 years**, there is significant difference in favor of Dirithromycin, $p=0.026$ and the 95% CI on the difference, (Dirithromycin - Erythromycin) is, $_{90.77}(0.001,0.233)_{92.2\%,80.5\%}$. These results are in opposite directions and any clinical significance must be developed by the medical officer.

The results of the subgroup analyses relative to sex, race and age for the other indications (**Acute Bronchitis, Acute Superimposed on Chronic Bronchitis and Pnaumonia**) are similar to that of the overall results in the original submission, i.e., there are no statistically significant differences noted.

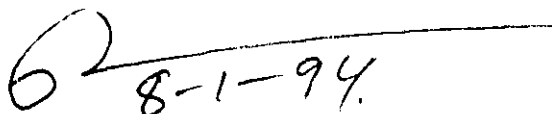


R. Srinivasan, Ph.D.
Mathematical Statistician, Group 7



Concur: Dr. Ralph Harkins

Dr. Satya Dubey



cc:

Orig: NDA 50-678

HFD-520

HFD-520/Dr. Gavrilovich

HFD-520/Dr. Albuerne

HFD-520/Dr. Molidina

HFD-520/Dr. Dubey [File DRU 1.3.2]

HFD-713/Dr. Harkins

HFD-713/Dr. Srinivasan

HFD-520/Ms. DeSantis

HFD-344/Dr. Lisook

Chron.

This **addendum** contains 2 pages.

Srinivasan/07/25/94/X4594/WPTXT/C:\reviews.nda\Dyanabac.add

JUL 14 1992

Statistical Review and Evaluation

NDA #: 50-678/1C
Applicant: Eli Lilly and Company
Name of Drug: Dirithromycin (DYNABAC)
Documents Reviewed: Word Perfect files submitted on June 4, 1992
Indications: Pharyngitis and Tonsillitis (Page 1)
Skin and Skin Structure Infections (Page 8)
Acute Bronchitis (Page 14)
Acute Superimposed on Chronic Bronchitis (Page 16)
Bacterial Pneumonia (Page 19)
Clinical Input: Nasim Molidina, M.D. (HFD-520)

I. Introduction:

The sponsor has submitted 10 controlled studies (U.S. and Foreign) in support of sponsor's claim of safety and efficacy of Dirithromycin (Tablets) in the treatment of Pharyngitis and Tonsillitis, Acute Bronchitis, Acute Superimposed on Chronic Bronchitis, Pneumonia and Skin and Skin Structure Infections. In the following sections, I will present a synopsis of sponsor's results and conclusions followed by my review and conclusions. All confidence intervals are presented as $n_t, n_c (LCL, UCL)_{pt, pc}$, where n_t = Number in the treatment group, n_c = Number in the comparator group, p_t = Proportion of cures in the treatment group and p_c = Proportion of cures in the comparator group.

II. Review of Studies by Indication:

A. Pharyngitis/Tonsillitis

1. Protocol B9Z-MC-AQAB

a. Study design, dosage administration, and efficacy criteria

This was a multicenter, double-blind parallel study. Patients were evaluated for symptomatic and bacteriologic responses to treatment. Safety was measured by clinical assessment and laboratory tests. In patients who responded to treatment, the duration of therapy was 10 days. The design for this study was double-blind, double-dummy, and randomized. Due to the differing dosing frequencies of dirithromycin (2 tablets once daily) and erythromycin base (1 tablet four times daily), a double-dummy design was employed to maintain the double-blind. Each patient received one kit that contained two bottles: one bottle contained 24 tablets of either dirithromycin or dirithromycin placebo and a second bottle contained 56 tablets of either erythromycin placebo. The appearance of the tablets in each kit was the same for both treatment groups. Patients randomly allocated to the dirithromycin treatment group received two 250-mg dirithromycin tablets in the morning (total 500 mg) and one tablet of placebo four times daily. The placebo tablet was identical in appearance to the erythromycin tablet. Patients randomly allocated to the erythromycin treatment group received one 250-mg

erythromycin tablet four times daily (total 1000 mg) and two tablets of placebo in the morning. The placebo tablet was identical in appearance to the dirithromycin tablet.

Evaluation of response to treatment with dirithromycin or erythromycin involved assessment of the clinical or symptomatic response and the bacteriologic response. Symptomatic response was assessed by the investigator. Bacteriologic response was evaluated by the sponsor.

b. Study population and Demographic Characteristics

The study population consisted of 553 randomized patients enrolled by 38 investigators in the United States (US). Two hundred sixty-five (47.9%) patients were randomized to the dirithromycin treatment group and 288 (52.1%) patients were randomized to the erythromycin treatment group. Of the 265 patients treated with dirithromycin 169 (63.8%) patients qualified for efficacy analysis. Bacteriologic reasons for disqualification (e.g., causative organism unidentified, causative organism resistant, no follow-up culture) were cited most frequently in both treatment groups. In the dirithromycin treatment group, 164 of 169 qualified patients had posttherapy evaluations. Of these, 153 (93.3%) were evaluated at the late-posttherapy visit. In the erythromycin group, 164 of 167 qualified patients had posttherapy evaluations. Of these, 151 (92.1%) were evaluated at the late-posttherapy visit.

The groups were well matched with respect to age distribution (84% of the patients in both groups were from 16 to 45 years of age), gender, height, weight, ethnic origin, and presenting clinical condition ($p > 0.05$). The treatment groups were well matched with respect to alcohol use, historical diagnoses, chronic illnesses, admission events, and drug usage before, during, and after administration of the study drug. Although not a statistically significant difference, slightly fewer dirithromycin-treated patients than erythromycin-treated patients were smoker (19.6% vs. 22.9%, $p = 0.345$).

c. Efficacy analyses (by the reviewer)

i. Posttherapy Evaluations - Evaluable Patients

There are no statistically significant differences between the treatment groups in the distribution of symptomatic or bacteriologic responses (95% CIs for the difference (Dirithromycin - Erythromycin) are, respectively, 169,167(-0.061,0.050)_{94.1%,94.6%} and 169,167(-0.156,0.017)_{79.3%,86.2%}) in evaluable patients posttherapy.

ii. Late-Posttherapy Evaluations - Evaluable Patients¹

There is no statistically significant clinical response rate between the treatment groups at the late-posttherapy evaluation (95% CI for the difference (Dirithromycin - Erythromycin) is 153,151(-.091,.068)_{87.5%,88.7%}). There is a statistically significant bacteriologic response rate between the treatment groups at the late-posttherapy evaluation (95% CI for the difference

¹ Late-Posttherapy Evaluation is the Efficacy End Point Measure according to the reviewing medical officer.

between the treatment groups is, $_{153,151}(-.259, -.064)_{89.9\%, 86.0}$.

iii. Overall Study Termination Evaluation²

Patients who were symptomatic relapses or failures at the posttherapy visit, were discontinued from the study at that visit. Consequently, their symptomatic response data were not contained in the late-posttherapy analysis. 11 patients in the dirithromycin group and 13 in the erythromycin group were symptomatic relapses or failures and terminated from the study at the posttherapy visit. To permit a single analysis of all patients who discontinued study participation, symptomatic response data from these patients were combined with symptomatic response data from qualified patients at the late-posttherapy visit. This analysis is termed the "overall study termination evaluation". There is no statistically significant difference between the treatment groups in the distribution of symptomatic responses for all patients qualified for efficacy evaluation at the study termination evaluation (95% CI for the difference between the treatment groups is, $_{189,167}(-.100, .069)_{82.9\%, 84.4\%}$). There is a statistically significant difference in favor of Erythromycin between the treatment groups in the distribution of bacteriologic responses for all patients qualified for efficacy evaluation at the study termination evaluation (95% CI for the difference between the treatment groups is, $_{184,164}(-.235, -.033)_{86.5\%, 79.9\%}$).

d. Safety analyses (by the sponsor and checked by the reviewer)

Analysis of treatment-emergent events showed fewer patients reporting adverse events in the dirithromycin group than in the erythromycin group; one or more events were reported from 117 (44.2%) dirithromycin-treated patients, compared with 157 (54.5%) from erythromycin-treated patients ($p=0.015$). When event terms were analyzed individually, a significant difference between treatment groups was noted for rash ($p=0.026$), with a higher incidence in the erythromycin-treatment group (1/265 vs. 8/288). The greater incidence of adverse events in the erythromycin group was due to greater reporting of adverse events from most body systems. 58% (140/240) of all dirithromycin adverse events and 74% (219/294) of all erythromycin adverse events occurred during the period of study-drug administration. There was a statistically significantly greater incidence of digestive system events ($p=0.016$) and skin events ($p=0.011$) in the erythromycin group with onset during therapy.

Analyses of clinical laboratory data revealed no statistically significant differences between the treatment groups that were considered drug-related. Analysis of ECG data performed at the end of Phase II demonstrated no adverse effects of either study drug on ECGs.

e. Overall conclusions

This study shows that for the Posttherapy Evaluations, the two treatment groups are not statistically different relative to the distribution of symptomatic and bacteriologic responses. For Late-Posttherapy and Overall Study Termination Evaluations, the analyses do not show statistical significance for symptomatic response, but show statistical significance in favor of

² Overall Study Termination Evaluation is also an Efficacy End Point Measure according to the reviewing medical officer.

Erythromycin for the bacteriologic response (see Item c above).

Analysis of treatment-emergent events showed fewer patients reporting adverse events in the dirithromycin group than in erythromycin group.

Analyses of clinical laboratory data revealed no significant differences between the treatment groups that was considered drug related.

2. Protocol B9Z-MC-AQAS

The study design, dosage administration, efficacy criteria are the same in Protocol B9Z-MC-AQAB.

a. Study Population and Demographic Characteristics

The study population consisted of 317 randomized patients enrolled by 15 investigators in the U.S and 2 investigators in South Africa. 158 (49.8%) patients were randomized to the dirithromycin treatment group and 159 (50.2%) patients were randomized to the erythromycin treatment group.

Of the 158 patients treated with dirithromycin, 111 (70.3%) patients qualified for efficacy analysis; 117 of the 159 (73.6%) patients in the erythromycin group qualified for efficacy analysis. Bacteriologic reasons for disqualification (e.g. negative pretherapy culture, low pretherapy colony count) were cited most frequently in both treatment groups.

One hundred nine of 111 qualified patients in the dirithromycin group were seen for posttherapy evaluation. Of these, 99 (90.8%) had a late-posttherapy evaluation. 114 of 117 qualified patients in the erythromycin group were seen for posttherapy evaluation. Of these, 110 (96.5%) had a late-posttherapy evaluation.

The treatment groups were well matched with respect to age distribution (85.5% of the patients in both groups were from 16 to 45 years of age), gender, height, weight, ethnic origin, and presenting clinical condition ($p > 0.05$).

b. Efficacy analyses (by the reviewer)

i. Posttherapy Evaluations - Evaluable Patients

There are no statistically significant differences between the two groups in the distribution of symptomatic and bacteriologic responses (95% CIs for the difference between the treatment groups are, $111,117(-.070,.049)_{95.4\%,96.6\%}$ and $111,117(-.150,.018)_{87.4\%,94.0\%}$, respectively) in evaluable patients posttherapy. However, the 95% CI for the bacteriologic response rates does not satisfy the guidelines of DAIDP. There are no statistically significant treatment-by-investigator interaction for symptomatic response (cure vs other) and for bacteriologic response (pathogen eliminated vs other) in a logistic regression model (chi-square 0.77, 1 d.f., $p = 0.380$ and chi-square 0.54, 1 d.f., $p = 0.463$, respectively). The model included terms for treatment, investigator, and the interaction.

ii. Late-Posttherapy Evaluations - Evaluable Patients³

There are no statistically significant difference between the treatment groups in symptomatic and bacteriologic responses in all evaluable patients returning for the late-posttherapy visit (95% CIs for the difference between the treatment groups are, $99.110(-.100,.095)$ _{87.8%,88.2%} and $99.110(-.107,.069)$ _{89.9%,91.8%}, respectively).

3. Overall Study Termination Evaluation⁴

Patients who relapsed or failed at the posttherapy visit were discontinued from the study at that visit. Consequently, their symptomatic and bacteriologic response data were not included in the late-posttherapy analysis. 12 evaluable patients in the dirithromycin group and 7 evaluable patients in the erythromycin group were terminated from the study at the posttherapy visit for having an unfavorable symptomatic response (relapse or failure) or for having an unfavorable bacteriologic response (recurrence or failure to eliminate the pathogen). To permit a single analysis of all patients who discontinued study participation, symptomatic response data from these patients were combined with symptomatic response data from qualified patients at the late-posttherapy visit. This analysis is termed the "overall study termination evaluation". There are no statistically significant difference between the treatment groups in the distribution of symptomatic and bacteriologic responses for all patients qualified for efficacy evaluation at the study termination evaluation (95% CIs for the difference between the treatment groups are, $111.117(-.109,.093)$ _{84.7%,85.5%} and $111.117(-.175,.035)$ _{80.2%,87.2%}, respectively). However, for the bacteriologic response rates, the 95% CI does not satisfy the guidelines of DAIDP.

c. Safety Analyses (by the sponsor and checked by the reviewer)

When the entire study period was considered, at least one adverse event was reported from 93 (58.9%) of 158 patients treated with dirithromycin compared to 87 (54.7%) of 159 patients treated with erythromycin; this difference was not statistically significant ($p=0.456$). 184 events were reported from the dirithromycin-treated group and 166 events were reported from erythromycin-treated patients. The events most frequently reported in both treatment groups were symptoms associated with the body as a whole, the digestive system, and the respiratory system. When adverse events were classified by body system, there was a similar incidence of adverse events in most body systems. However, a greater incidence of adverse events in dirithromycin arm was observed for the body system "special senses" ($p=0.017$). When event classification terms were analyzed individually, there was a significant difference in the number of patients reporting ear pain; six dirithromycin patients reported ear pain, while this event was not reported from patients randomized to therapy with erythromycin ($p=0.013$). The sponsor is of the opinion that it is unlikely that this statistically significant difference is of any clinical significance.

³ Late-Posttherapy Evaluation is the Efficacy End Point Measure according to the reviewing Medical Officer.

⁴ Overall Study Termination Evaluation is also an Efficacy End Point Measure according to the reviewing Medical Officer.

At least one event was reported to have started during the course of study-drug therapy. At least one event was reported by 84 (53.2%) patients treated with dirithromycin and by 69 (43.4%) patients treated with erythromycin; this difference was not statistically significant ($p=0.082$). With the exception of Otagia, no other treatment-emergent events with onset during the period of study-drug administration occurred at a frequency which was significantly different between the 2 treatment groups. Otagia was reported from 6 (3.8%) dirithromycin-treated patients while no patient in the erythromycin-treated group reported this event ($p=0.013$). The sponsor is of the opinion that due to the nature of this event and the relatively low frequency, it is unlikely that its occurrence is of clinical significance with respect to study drug.

At least one adverse event was reported by 32 (20.3%) of the dirithromycin-treated patients and 38 (23.9%) of the erythromycin treated-patients during the posttherapy period. Rhinitis and headache were the most frequently reported events in both treatment groups. There were no statistically significant differences between the two treatment groups when comparing event classification terms in the posttherapy period.

Statistically significant changes 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 mean cell hemoglobin (MCH), non-fasting blood glucose, and cholesterol. The sponsor is of the opinion that none of the mean changes for any analyte approached a level that would be considered of clinical significance.

The sponsor has also submitted results of an analysis involving categorizing, for each analyte, each patient's pretherapy and posttherapy values as normal, high, or low. Each patient's values are then put into a 3-by-3 matrix, with the baseline status denoted in rows and endpoint values in columns. The hypothesis tested is that there is equivalence between groups with respect to the frequency of the nine possible changes generated by this scheme. When these analytes were analyzed for the frequency with which patients changed status during therapy (i.e., normal, low, high), no statistically significant differences between the treatment groups were noted for any of the analytes tested.

d. Overall Conclusions

This study shows that for the Posttherapy, Late Posttherapy and Overall Study Termination Evaluations, the two treatment groups, Dirithromycin and Erythromycin, are not statistically different, relative to the distribution of symptomatic responses and bacteriologic responses. However, relative to bacteriologic response rates for the Posttherapy and Overall Study Termination Evaluations, the 95% CIs do not satisfy the guidelines of DAIDP. Treatment-emergent events are comparable between the two treatment groups. Analyses of clinical laboratory data revealed no significant differences between the treatment groups that was considered drug related.

3. Protocol B9Z-EW-E001

The study design, dosage administration, efficacy criteria of this multicenter (European) study, are the same as in Protocol B9Z-MC-AQAS.

a. Study Population and Demographic Characteristics

A total of 389 patients consented and were randomized. 193 were treated with dirithromycin and 196 with erythromycin. Of the patients in the dirithromycin group, 97 (50.3%) qualified for efficacy analysis, compared with 99 (50.5%) qualified patients in the erythromycin group. Of the 96 patients disqualified in the dirithromycin group, 43 were disqualified for more than one reasons. 44 of the 97 disqualified patients in the erythromycin group also had multiple reason. Bacteriologic reasons were the most frequently cited: 84 times in the dirithromycin group and 85 times in the erythromycin group. The primary bacteriologic reasons for disqualification were lack of culturing group A streptococci, culturing less than 10 colonies of group A streptococcus per culture plate at pretherapy, culturing of an organism other than group A streptococci, or inappropriate timing or omission of required cultures.

The treatment groups are well-matched with respect to age distribution (88% of the patients in both groups were 16 to 45 years of age), gender, height, weight, tobacco and alcohol habits, chronic illnesses, presenting diagnosis and presenting clinical conditions. The treatment groups were well matched with respect to tobacco and alcohol habits, historical diagnoses, chronic illnesses, admission events, and drug usage before, during, and after the administration of the study drug. The greater majority of patients (99.5%) were caucasian.

b. Efficacy analyses (by the reviewer)

i. Posttherapy Evaluations - Evaluable Patients

There are no statistically significant differences in the clinical and bacteriologic response rates between the two treatment groups (95% CIs for the difference (Dirithromycin - Erythromycin) are, 97.99(-.104,.060)_{91.7%,93.9%} and 97.99(-.167,.058)_{91.4%,96.9%}, respectively. However, the 95% CI for bacteriologic response does not satisfy the guidelines of DAIDP.

ii. Late Posttherapy Evaluations - Evaluable Patients⁵

There are no statistically significant differences between the two treatment groups, relative to clinical and bacteriologic response rates, the 95% CIs are, 99.93(-.124,.031)_{92.2%,96.8%} and 99.93(-.142,.066)_{96.5%,99.3%}, respectively. However, these confidence intervals do not satisfy the guidelines of DAIDP.

The sponsor has not submitted the results of Overall Study Termination Evaluation.

⁵ Late-Posttherapy Evaluation is the Efficacy End Point Measure according to the reviewing Medical Officer.

c. Safety analyses

Analysis of treatment-emergent events showed fewer patients reporting nausea in the dirithromycin group than in the erythromycin group ($p = 0.012$). Analysis of clinical laboratory data revealed no statistically significant differences between the treatment populations that could be ascribed to study-drug therapy.

d. Overall conclusions

This study shows that for Posttherapy and Late Posttherapy evaluations, the two treatment groups are not statistically different, relative to clinical and bacteriologic response rates. However, relative to the comparison of bacteriologic response rates, the 95% CIs do not satisfy the guidelines of DAIDP.

B. Skin and Skin Structure Infections

1. Protocol B9Z-MC-AQAB

a. Study Design, Dosage Administration and Efficacy Criteria

This was a multicenter, double-blind, double-dummy, randomized, parallel study. The objective of this study was to compare dirithromycin administered once daily (500 mg/day) with erythromycin administered four times daily (1000 mg/day) for effectiveness and safety in the treatment of bacterial skin and skin-structure infections. Patients were evaluated for symptomatic and bacteriologic responses to treatment. Safety was measured by clinical assessment and laboratory tests. For patients who responded to treatment, the duration of therapy was 7 days. There was no minimum treatment period for patients who did not respond to therapy. Patients with the following bacterial skin and skin-structure infections were included: subcutaneous abscess, impetigo, pyoderma, infected skin ulcer, post-surgical wound infection, post-traumatic wound infection, or cellulitis.

b. Study Population and Demographic Characteristics

The study population consisted of 578 patients who gave informed consent and were randomized to treatment groups. 304 patients were randomized to the dirithromycin treatment group. A total of 87 (5 qualified, 82 not qualified) dirithromycin patients discontinued therapy early. Of the 5 qualified patients who were discontinued from the study early, 4 patients were discontinued due to lack of efficacy and 1 patient due to an adverse event.

Of the 82 dirithromycin patients who did not qualify for efficacy analysis and were terminated from the study before the posttherapy visit, 57 patients failed to meet the entry criteria for study and/or baseline bacteriologic requirements, 10 patients discontinued study participation early due to adverse events, 9 were lost to further follow-up, 4 patients were protocol violations, 1 patient discontinued due to patient decision, and 1 patient discontinued due to lack of efficacy. The remaining 217 (151 qualified and 66 not qualified) patients were seen at the posttherapy visit. Of the qualified patients, 9 patients were considered treatment failures (symptomatic or bacteriologic) and were terminated from the study. These patients

were not brought back for a late-posttherapy visit, since the purpose of the late-posttherapy visit was to evaluate possible relapse. Two patients were discontinued because of adverse event, 2 patients were protocol violations, 2 patients were discontinued because of physician decision, and 1 patient was lost to follow-up.

The remaining 135 qualified dirithromycin patients completed the late-posttherapy visit; 134 were considered "protocol complete" and 1 patient was discontinued for lack of efficacy.

Of the 66 dirithromycin patients seen at the posttherapy visit who were ultimately considered unqualified, 36 patients were discontinued at the posttherapy visit. Twenty-six of the 36 patients were discontinued due to entry criteria exclusions, 5 patients because of protocol violation, 2 patients because of adverse events, 1 patient because of lack of efficacy, and 2 patients were lost to follow-up between the posttherapy and late-posttherapy visits. The remaining 30 patients completed the late-posttherapy visit. Of the 30 patients, 16 patients were discontinued because of entry criteria exclusions, 10 patients were "protocol complete", and 4 patients discontinued because of protocol violation.

Two hundred seventy-four patients were randomized to the erythromycin treatment group. Two qualified erythromycin patients discontinued study participation prior to the posttherapy evaluation: 1 patient discontinued because of lack of efficacy, and 1 patient discontinued because of an adverse event.

Eighty-two erythromycin patients, who did not qualify for efficacy analysis, terminated study participation early: 57 patients because of entry criteria violations, 11 patients because of adverse event, 6 patients were lost to follow-up, 5 patients because of protocol violation, and 3 by patient's decision.

Of the 190 erythromycin patients (125 qualified and 65 not qualified) seen posttherapy, 11 qualified patients were dropped from the study. 7 of the 11 qualified patients discontinued study participation due to lack of efficacy, 2 by physician decision, 1 by patient decision and 1 patient discontinued due to protocol violation.

33 unqualified erythromycin patients were dropped from the study at posttherapy: 24 patients because of entry criteria exclusions, 5 patients because of protocol violations, 1 patient by physician decision, 1 because of adverse event, 1 because of lack of efficacy, and 1 patient was lost to follow-up. The remaining 146 patients (114 qualified and 32 not qualified) completed the late-posttherapy visit.

The groups are well-matched with respect to age distribution, gender, racial origin, height, weight, tobacco and alcohol habits, historical diagnosis, significant chronic illnesses, admission events, and drug usage before, during, and after administration of the study drug.

c. Efficacy analyses (by the reviewer)

i. Posttherapy Evaluations - Evaluable Patients⁶

There is no statistically significant difference between the treatment groups in the distribution of symptomatic responses in evaluable patients at the posttherapy visit (95% CI for the difference (Dirithromycin - Erythromycin) is $156.127(-0.065,0.063)$ _{93.6%,93.7%}). There is no statistically significant difference between the two treatment groups with respect to the symptomatic response rates (cure + improvement) by infecting pathogen, *Staphylococcus aureus* (95% CI for the difference is $105.79(-0.077,0.095)$ _{93.2%,92.3%}). No statistically significant difference between the treatment groups was noted in the distribution of bacteriologic outcomes (pathogen eliminated or not applicable⁷) in all qualified patients at posttherapy visit (95% CI for the difference between the treatment groups is, $156.137(-0.081,0.092)$ _{97.1%,96.6%}).

There is no statistically significant difference between the treatment groups relative to the bacteriologic response summary by the pathogen, *Staphylococcus aureus* (95% CI for the difference between the treatment groups is $102.76(-0.095,0.116)$ _{99.2%,98.2%}).

ii. Late-Posttherapy Evaluations - Evaluable patients

There is statistically significant difference between the treatment groups in the distribution of symptomatic response rates in evaluable patients in Late-posttherapy visit (95% CI for the difference between the treatment groups is, $135.114(0.000,0.131)$ _{97.8%,91.2%}).

There is statistically significant difference between the two treatment groups with respect to the symptomatic response rates (cure + improvement) by infecting pathogen, *Staphylococcus aureus*, in all qualified patients in the Late-posttherapy visit, (95% CI for the difference is $91.88(0.012,0.209)$ _{97.7%,96.6%}).

No statistically significant difference between the treatment group was noted in the distribution of bacteriologic outcomes (pathogen eliminated or not applicable⁸) in all qualified patients at Late-posttherapy visit (95% CI for the difference between the treatment groups is, $138.114(-0.018,0.148)$ _{93.3%,96.8%}).

There is no statistically significant difference between the treatment groups relative to the bacteriologic response summary by the pathogen, *Staphylococcus aureus* (95% CI for the difference between the treatment groups is $91.68(-0.007,0.235)$ _{92.3%,90.8%}).

⁶ Posttherapy Evaluation is the Efficacy End Point according to the reviewing Medical Officer.

⁷ A bacteriologic response of "not applicable" was assigned when a patient obtained either a cure or improvement clinically and the follow-up culture was not clinically indicated, or the culture source was eliminated.

⁸ A bacteriologic response of "not applicable" was assigned when a patient obtained either a cure or improvement clinically and the follow-up culture was not clinically indicated, or the culture source was eliminated.

d. Safety analyses (by the sponsor and checked by the reviewer)

Analysis of treatment-emergent events showed one or more adverse events were reported from 121 (39.8%) dirithromycin-treated patients compared with 93 (33.9%) erythromycin-treated patients ($p = .145$). In total, 201 adverse events were reported in the dirithromycin group and 143 adverse events were reported in the erythromycin group. When event terms were analyzed individually, a statistically significant difference in reporting incidence was observed only for surgical procedure ($p = .019$). Only 2 of the 6 surgical procedures were for treatment of the underlying infection (incision and drainage, foot ulcer debridement). When adverse event terms were analyzed by body system, statistically significant differences in reporting incidence were seen for events related to the body system "body as a whole" ($p = .034$) and the respiratory system ($p = .05$). When "body as a whole" adverse event terms were analyzed individually, no statistically significant differences were found. There were no deaths reported during this study. Eleven serious adverse events were reported with 5 dirithromycin and 3 erythromycin events not related to study drug administration. The sponsor is of the opinion that the remaining 3 dirithromycin serious events were unlikely to be study-drug related, although a causal relationship to study drug could not be excluded. Fifteen dirithromycin and 13 erythromycin patients discontinued study participation early due to adverse events. Analyses of clinical laboratory data revealed no significant differences between the treatment groups that were considered drug related. Analysis of electrocardiograms performed during phase II showed no study-drug induced effects on electrocardiograms.

e. Conclusions:

This study shows that for the Posttherapy Evaluations, there is no statistically significant difference between the two treatment groups relative to symptomatic responses, bacteriologic outcomes (pathogen eliminated or not applicable) and bacteriologic response summary by the pathogen, *Staphylococcus aureus*, in all qualified patients.

For Late-Posttherapy evaluations, there is a statistically significant difference between the two treatment groups in the distribution of symptomatic response rates and symptomatic response rates (cure + improvement) by infecting pathogen, *Staphylococcus aureus*. But for bacteriologic outcomes and bacteriologic response summary by pathogen, *Staphylococcus aureus*, there are no statistically significant differences in the difference between the two treatment groups.

2. Protocol B9Z-EW-E004

a. Study Design, Dosage Administration and Efficacy Criteria

This was a multicenter (31 centers, European), double-blind, randomized, parallel study. The objective of the study was to compare dirithromycin administered once daily (500 mg/day) with erythromycin administered four times daily (1000 mg/day) for efficacy and safety in the treatment of bacterial skin and soft tissue infections. Evaluation of response to treatment with dirithromycin or erythromycin involved assessment of the symptomatic or clinical response and the bacteriological response. Patients with the following bacterial skin and soft tissue infections were included: impetigo, pyoderma, infected skin ulcer, post-surgical wound infection, traumatic wound infection, cellulitis, or infected burns.

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b. Study Population and Demographic Characteristics

Three hundred and ninety one (391) patients were entered into the study and randomly assigned to study drug. One hundred and ninety three (193) patients were randomized to the dirithromycin-treatment group.

Six patients who were not qualified for efficacy analysis, discontinued therapy early. Three of these patients failed to return for the posttherapy visit and were lost to further follow-up. The remaining three patients discontinued study participation early due to adverse events.

The remaining 187 (100 qualified + 87 not qualified) patients were seen at the posttherapy visit. Of the 100 qualified patients, 3 were considered treatment failures and were terminated from the study. These patients were not brought back for a late posttherapy visit, since the purpose of this visit was to evaluate possible relapse. Five additional qualified patients were lost to follow-up between the posttherapy and late posttherapy period, but remained evaluable due to having had cultures at the posttherapy visit. One additional patient had an adverse event (increasingly painful lesion) at post therapy and was considered a clinical failure. He was not seen at the late post therapy visit. The remaining 91 qualified patients completed the late posttherapy visit.

Of the 87 patients seen at the posttherapy visit who were considered unqualified, 48 were discontinued at the posttherapy visit. Forty five of the 48 were discontinued due to recognition of entry criteria exclusions, two patients were lost to follow-up and the remaining patient discontinued early due to the sponsor's decision (study drug was out of date). The remaining 39 patients completed the late posttherapy visit. Of these, one patient was misclassified as 'protocol complete' and should have been classified as protocol violation because his posttherapy visit occurred before he stopped therapy.

One hundred and ninety eight (198) patients were randomized to the erythromycin treatment group. No qualified patients discontinued study participation prior to the posttherapy evaluation.

Eight of the erythromycin-treated patients, who did not qualify for efficacy analysis, terminated study participation early: 1 due to entry criteria exclusion, 2 due to adverse event 1 due to sponsor decision (study drug was out of date), and 4 failed to return for the posttherapy visit and were lost to follow-up.

Of the 190 erythromycin patients (99 qualified + 91 not qualified) seen at posttherapy, 7 qualified patients were discontinued early from the study (1 due to lack of efficacy, 1 was lost to follow-up, and five had no late posttherapy visits but remained evaluable due to having had a culture at the post therapy visit). Forty eight unqualified patients were discontinued early from the study: 43 due to entry criteria exclusions, 1 due to lack of efficacy, and 2 due to adverse events. Two patients were lost to follow-up between the posttherapy and late posttherapy visits. The remaining 135 patients (92 qualified + 43 not qualified) completed the late posttherapy visit. One unqualified patient was misclassified as 'protocol complete' and should have been classified as 'entry criteria exclusion' due to a resistant organism. A further 2 unqualified patients were misclassified as 'protocol complete' and should have been classified as a 'protocol violation'. A fourth patient was classified as 'entry criteria exclusion'

but was evaluable and should have been classified as 'protocol complete'. Overall, these mis-classifications are minor and do not effect evaluability.

The groups are well-matched for age distribution, but the gender distribution was significantly skewed in the erythromycin-treatment group with a larger number of male patients than female patients ($p=0.008$). The treatment groups are well-matched for racial origin, height, weight, smoking and drinking habits, significant historical diagnosis, significant chronic illnesses, concomitant drug use, and presenting diagnosis ($p>0.05$).

c. Efficacy analyses (by the reviewer)

i. Posttherapy Evaluations - Evaluable Patients⁹

There is no statistically significant difference between the treatment groups in the distribution of clinical responses in evaluable patients at the posttherapy visit (95% CI for the difference (Dirithromycin - Erythromycin) is $100.93(-.083,.023)_{98\%,99\%}$). There is no statistically significant difference between the treatment groups with respect to the symptomatic response rates (cure + improvement) by infecting pathogen, *Staphylococcus aureus* (95% CI for the difference between the treatment groups is $83.77(-.065,.043)_{97.5\%,98.6\%}$).

No statistically significant difference between the treatment groups was noted in the distribution of bacteriologic outcomes (pathogen eliminated or not applicable) in all qualified patients at posttherapy visit (95% CI for the difference between the treatment groups is, $100.83(-.119,.027)_{87\%,89\%}$).

Though there is no statistically significant difference between the treatment groups relative to the bacteriologic response summary by the pathogen, *Staphylococcus aureus*, the 95% CI for the difference between the treatment groups, $83.87(-.165,.058)_{88\%,91\%}$, does not satisfy the DAIDP guidelines.

ii. Late Posttherapy Evaluations - Evaluable Patients

There is no statistically significant difference between the treatment groups in the distribution of symptomatic response rates in evaluable patients in Late-Posttherapy visit (95% CI for the difference is $91.82(-.031,.075)_{98.9\%,99.9\%}$).

There is no statistically significant difference between the treatment groups with respect to the symptomatic response rates (cure + improvement) by infecting pathogen, *Staphylococcus aureus* (95% CI for the difference is $78.72(-.05,.05)_{98.6\%,98.6\%}$).

No statistically significant difference between the treatment groups was noted in the distribution of bacteriologic outcomes (pathogen eliminated or not applicable) in all qualified patients at posttherapy visit (95% CI for the difference between the treatment groups is, $91.87(-.039,.125)_{95.6\%,91.3\%}$).

⁹ Posttherapy Evaluation is the Efficacy End Point Measure according to the reviewing Medical Officer.

There is no statistically significant difference between the treatment groups relative to the bacteriologic response summary by the pathogen, *Staphylococcus aureus* (95% CI for the difference between the treatment groups is, $75.72(-.084,.089)$ _{94.8%,94.3%}).

d. Safety Analyses (by the sponsor and checked by the reviewer)

One or more events were reported from 23 (11.9%) dirithromycin-treated patients compared with 29 (14.6%) erythromycin-treated patients ($p \approx 0.427$). The incidence of adverse events was comparable in the two treatment groups. In total, 30 adverse events were reported in the dirithromycin-treated group; 41 adverse events were reported in the erythromycin-treated group.

"Body as a whole" body system, digestive system, and skin and appendages system events predominated in both groups. 7% of patients in both groups reported events related to the body as a whole. Eight (4%) dirithromycin-treated patients reported events related to the digestive system compared to 14 (7.1%) erythromycin-treated patients ($p = 0.209$). 2% of the dirithromycin-treated patients and 1% of erythromycin-treated patients reported events related to the skin and appendages system ($p = 0.393$).

Each patient's results for each analyte were classified as normal, high, or low. Non-numeric results were classified as normal or abnormal. Each patient was included in a 3 by 3 matrix; rows represented baseline status (normal, high or low) and columns represented endpoint status, allowing statistical (chi-squared) comparison of treatment groups. The hypothesis tested is that there is equivalence between groups with respect to the frequency of the nine possible changes generated by this scheme. There are no statistically significant differences between treatment groups in frequency of patients who changed status between baseline and endpoint examinations for any of the analytes.

e. Conclusions:

This study shows that at the Posttherapy and Late-Posttherapy visits, there are no statistically significant differences between the two treatment groups in the distribution of clinical responses, in the symptomatic response rates (cure + improvement) by infecting pathogen, *Staphylococcus aureus*, in the distribution of bacteriologic outcomes (pathogen eliminated or not applicable) and in the distribution of bacteriologic response summary by pathogen, *Staphylococcus aureus*, in the treatment of patients with skin and skin structure infections.

C. Acute Bronchitis

1. Protocol B9Z-EW-E002

a. Study design, Dosage administration and Efficacy criteria

This was a double-blind, randomized, parallel study. The objective of this study was to demonstrate the equivalence of dirithromycin administered orally once daily (500 mg/day) to erythromycin administered orally four times daily (100 mg/day) in effectiveness and safety for the treatment of acute bronchitis caused by susceptible bacterial pathogen and the treatment of patients with an acute exacerbation of chronic bronchitis.

Evaluation of response to treatment with dirithromycin or erythromycin involved assessment of the clinical (symptomatic) response and the bacteriological response.

b. Study Population and Demographic Characteristics

Of the 529 patients randomized, 267 patients were randomized to the dirithromycin group and 262 patients were randomized to the erythromycin group. The treatment groups were well matched with respect to age distribution, gender, origin, and height and weight ($p > 0.05$). The treatment groups were well matched with respect to alcohol use, historical diagnoses, admission events, and drug usage before, during, and after administration of the study drug. One or more chronic illnesses were reported from 85 (31.8%) patients treated with dirithromycin and 93 (35.5%) patients treated with erythromycin. Asthma, hypertension and allergies were most commonly reported in both treatment groups. Arthritis was reported in 9 (3.4%) patients in the dirithromycin group and 12 (4.6%) patients in the erythromycin group ($p = 0.476$). The groups were evenly matched for those entering in a serious vs. fair condition.

c. Efficacy analyses (by the reviewer)

Of the 267 patients randomized to the dirithromycin group, 72 (27.0%) qualified for efficacy analysis. Sixty-three of 262 (24.0%) patients treated with erythromycin qualified for efficacy analysis. Bacteriologic reasons for disqualification (e.g., negative pretherapy culture, causative organism resistant, causative organism unidentified, and no organism identified) were most frequently cited as disqualifiers for both treatment groups.

i. Posttherapy Evaluations - Evaluable patients¹⁰

There is no statistically significant difference between the treatment groups in the distribution of clinical responses in evaluable patients at the posttherapy visit (95% CI for this difference, (Dirithromycin - Erythromycin) is, $72.67(-0.116, 0.072)_{93\%, 95\%}$). It is to be noted here that this 95% CI does not satisfy the guidelines of DAIDP.

There is no statistically significant difference between the treatment groups in the distribution of bacteriologic responses in evaluable patients at the posttherapy visit (95% CI for the difference (Dirithromycin - Erythromycin) is $72.63(-0.151, 0.087)_{94.4\%, 95.7\%}$).

ii. Late-Posttherapy - Evaluable patients

There are no statistically significant differences between the treatment groups in the distribution of clinical and bacteriologic responses in evaluable patients at the Late-Posttherapy visit (95% CIs for the difference (Dirithromycin - Erythromycin) are, $85.59(-0.089, 0.027)_{98.9\%, 100\%}$ and $85.59(-0.065, 0.142)_{95.4\%, 97.5\%}$, respectively).

There are no statistically significant drug-demographic interactions for age, gender, or race for clinical and bacteriologic responses for all patients and evaluable patients at posttherapy and

¹⁰ Posttherapy Evaluation is the Efficacy End Point Measure according to the reviewing Medical Officer.

late-posttherapy vis.its.

D. Acute superimposed on Chronic Bronchitis

1 Protocol B9Z-EW-E002

a. Study design, Dosage administration and Efficacy criteria

This was a double-blind, randomized, parallel study. The objective of this study was to demonstrate the equivalence of dirithromycin administered orally once daily (500 mg/day) to erythromycin administered orally four times daily (100 mg/day) in effectiveness and safety for the treatment of patients with acute superimposed on chronic bronchitis.

Evaluation of response to treatment with dirithromycin or erythromycin involved assessment of the clinical (symptomatic) response and the bacteriological response.

b. Study population and Demographic characteristics

The study population consisted of 693 randomized patients enrolled by 110 European investigators. 347 (50.1%) patients were randomized to the dirithromycin group and 346 (49.9%) patients were randomized to the erythromycin group. Of the patients in the dirithromycin group, 89 (25.6%) qualified for efficacy analysis, compared with 113 (32.7%) qualified patients in the erythromycin group. Bacteriologic reasons for disqualification (e.g., negative pretherapy culture, sensitivity not done, causative organism resistant, causative organism unidentified, no initial culture) were most frequently cited in both treatment groups.

Eighty-nine qualified patients in the dirithromycin group were seen for posttherapy evaluations, and of these 76 (85.4%) patients had a late-posttherapy evaluation. 113 patients in the erythromycin group qualified for efficacy analysis at the posttherapy evaluation and 100 (88.5%) patients had a late-posttherapy evaluation.

The groups are well matched with respect to age distribution, gender, height, weight, origin and presenting clinical condition. The treatment groups were well matched with respect to tobacco and alcohol habits, exposure to smoking in their family environment, historical diagnoses, chronic illnesses, admission events, and drug usage before, during and after the administration of the study drug.

c. Efficacy analyses (by the reviewer)

i. Posttherapy evaluations - Evaluable patients¹¹

There are no statistically significant differences between the treatment groups in the distribution of clinical and bacteriological responses at the Posttherapy visit, the 95% CIs for the difference (Dirithromycin - Erythromycin) are, $_{89,113}(-0.112,0.069)_{89.9\%,92\%}$ and

¹¹ Posttherapy Evaluation is the Efficacy End Point Measure according to the reviewing Medical Officer.

09.113 (-0.129, 0.131)_{75.3%, 75.3%}, respectively. However, the 95% CI for the clinical response does not satisfy the DAIDP guidelines.

ii. Late Posttherapy Evaluations - Evaluable patients

There are no statistically significant differences between the treatment groups in the distribution of clinical and bacteriological responses at the Late-Posttherapy visit, the 95% CIs for the difference (Dirithromycin - Erythromycin) are, $78,100(-0.025, 0.098)$ _{98.7%, 95%} and $78,100(-0.066, 0.142)$ _{90.8%, 87%}, respectively.

d. Safety analyses (by the sponsor and checked by the reviewer)

Safety data in this section are based on information from all patients through the late-posttherapy visit; no distinction was made for patients treated for acute bronchitis and acute exacerbation of chronic bronchitis.

The extent of exposure of study-drug was comparable between the two study arms. The most frequently reported events from both groups were gastrointestinal symptoms or those associated with respiratory tract infections. Only asthma was reported significantly more frequently, by erythromycin-treated patients ($p = 0.037$).

To examine the potential effects of study-drug therapy on laboratory test results for the two treatment populations, an analysis was performed to examine the changes in mean values for each population for each analyte. Statistically significant within-group changes were seen in both treatment groups for several analytes including a number of hematologic parameters (HCT, Hb, WBC, PMNs, monocytes, platelets), alkaline phosphatase, GGT, total protein, BUN, serum phosphorus, uric acid, and cholesterol. There were no statistically significant changes between groups noted.

2. Protocol B9Z-MC-AQAB

a. Study design, Dosage administration and Efficacy criteria

This was a double-blind, randomized, parallel study. The objective of this study was to compare dirithromycin, administered once daily (500 mg/day), with erythromycin administered four times daily (1000 mg/day), for effectiveness and safety in the treatment of acute superimposed on chronic bronchitis.

Evaluation of response to treatment with dirithromycin or erythromycin involved assessment of the clinical (symptomatic) response and the bacteriological response.

b. Study population and Demographic characteristics

The study population consisted of 802 randomized patients enrolled by 98 investigators in the United States. 393 (49.0 %) patients were randomized to the dirithromycin group and 409 (51.0 %) patients were randomized to the erythromycin group. Of the 393 patients treated with dirithromycin, 101 (25.7 %) qualified for efficacy analysis; 81 of 409 (19.8%) patients treated with erythromycin were qualified. Bacteriologic reasons for disqualification (e.g.,

negative pretherapy culture, causative organism resistant, causative organism unidentified) were most frequently cited in both treatment groups. Of the 101 qualified patients in the dirithromycin group, 80 patients (79.2 %) had a late-posttherapy evaluation. Of the 81 qualified patients in the erythromycin group 67 (82.7 %) had a late-posttherapy evaluation.

The treatment groups are well matched with respect to age distribution, gender, height, weight, origin, and presenting clinical condition ($p > 0.05$). The two arms are also well matched with respect to alcohol use, historical diagnoses, chronic illness, admission event, and drug usage before, during, and after administration of the study drug.

c. Efficacy analyses (by the reviewer)

i. Posttherapy evaluations - Evaluable patients¹²

There are no statistically significant differences between the treatment groups in the distribution of clinical and bacteriologic responses at the posttherapy visit, the 95 % CIs for the difference between (Dirithromycin - Erythromycin) are, $101.81(-0.135,0.08)_{86.2\%,88.9\%}$ and $101.81(-0.094,0.148)_{84.1,81.5\%}$.

ii. Late-Posttherapy Evaluations - Evaluable patients

There are no statistically significant differences between the treatment groups in the distribution of clinical and bacteriologic responses at the posttherapy visit, the 95 % CI for the difference (Dirithromycin - Erythromycin) are, $10.07(-0.277,-0.019)_{88.8\%,91\%}$ and $80.67(-0.137,0.096)_{87.5\%,89.8\%}$, respectively. It is to be noted that the 95% CI for the clinical response fails to satisfy the guidelines of DAIDP.

d. Safety analyses (by the sponsor and checked by the reviewer)

Safety data in this section are based on information from all patients through the late-posttherapy visit; no distinction was made for patients treated for acute bronchitis and acute exacerbation of chronic bronchitis.

The extent of exposure of study-drug was comparable between the two study arms. One or more events were reported from 180 (45.8%) dirithromycin-treated patients compared with 182 (44.5%) erythromycin-treated patients ($p = 0.711$). Lung disorder occurred in 23 (5.9%) of dirithromycin-treated patients versus 12 (2.9%) in the erythromycin-treated group ($p = 0.043$). Increased cough was more common in the erythromycin groups with 5 patients (1.2%) compared to none in the dirithromycin group ($p = 0.028$). Given the population enrolled in this study, these types of adverse events are expected. There was also a statistically significant difference ($p = 0.003$) in the number of patients reporting diarrhea [16 (4.1%) in the dirithromycin group and 38 (9.3%) in the erythromycin group]. The incidence of adverse events was otherwise comparable in the two treatment groups. In total, 344 adverse events were reported in the dirithromycin group; 351 adverse events were reported

¹² Posttherapy Evaluation is the Efficacy End Point Measure according to the reviewing Medical Officer.

in the erythromycin group.

Analysis of clinical laboratory data revealed statistically significant but clinically unimportant differences between the treatment groups for several hematologic values (hematocrit, hemoglobin, red blood cell count, and lymphocyte count) as well as albumin and creatine kinase.

d. Conclusions:

Study E002 shows that there are no statistically significant differences between the treatment groups in the distribution of clinical and bacteriologic responses in patients with Acute Bronchitis at Posttherapy and Late Posttherapy visits.

Study E002 shows that there are no statistically significant differences in the distribution of clinical and bacteriological responses in patients with Acute superimposed on Chronic Bronchitis at the Post and Late-Posttherapy visits. However, the 95% CI for the clinical response at the Posttherapy visit does not satisfy the guidelines of DAIDP (see Page 16, c(1)).

Study AQAB shows that there are no statistically significant differences in the distribution of clinical and bacteriological responses in patients with Acute superimposed on Chronic Bronchitis for Post and Late-posttherapy visits. However, the 95% CI for the clinical response at the Late-posttherapy visit fails to satisfy the guidelines of DAIDP.

E. Bacterial Pneumonia

1. Protocol B9Z-MC-AQAB

a. Study design, Dosage administration and efficacy criteria

This was a multicenter (93 centers) double-blind, randomized, parallel study. The objective of this study was to compare dirithromycin administered once daily (500 mg/day) with erythromycin administered four times daily (1000 mg/day) for effectiveness and safety in the treatment of bacterial pneumonia. Patients were evaluated for symptomatic and bacteriologic responses to treatment. Safety was measured by clinical assessment and laboratory tests.

b. Study population and demographic characteristics.

The study population consisted of 517 randomized patients enrolled by 93 investigators in North America. Two-hundred sixty (50.3%) patients were randomized to the dirithromycin group and 257 (49.7%) patients were randomized to the erythromycin group. Of the 260 patients randomized to the dirithromycin group, 90 (34.6%) qualified for efficacy analysis. Eighty-three of 257 (32.3%) patients treated with erythromycin qualified for efficacy analysis. Bacteriologic reasons for disqualification (e.g., negative pretherapy culture, causative organism resistant, causative organism unidentified, and no organism identified) were cited most frequently in both treatment groups.

The treatment groups were well matched with respect to age distribution (the mean age of the patients in each group was approximately 43.9 years), gender, height, weight, origin, and

presenting clinical condition ($p > 0.05$). The treatment groups were well matched with respect to alcohol use, historical diagnoses, chronic illnesses, admission events, and drug usage before, during, and after administration of the study drug.

Of the 90 qualified patients in the dirithromycin group for posttherapy evaluations, 79 patients had a late-posttherapy evaluation and of the 83 qualified patients in the erythromycin group for the posttherapy, 77 patients had a late-posttherapy evaluation.

c. Efficacy analyses (by the reviewer)

i. Posttherapy evaluations - Evaluable patients

There is no statistically significant difference between the treatment groups in the distribution of symptomatic response, the 95% CI for the difference (Dirithromycin - Erythromycin) is $_{90,83}(-0.114,0.003)_{94.5\%,100\%}$. However, it is to be noted that this confidence interval does not satisfy the guidelines of DAIDP.

When considering only the 35 dirithromycin-treated patients with pneumonia caused by conventional bacterial pathogens, 32 (91.4%) patients at posttherapy had presumed or proven eradication of the infecting pathogen. In the erythromycin-treated group, 36 (87.8%) of the 41 patients with pneumonia caused by conventional organisms had proven or presumed eradication of the pathogen at the posttherapy visit. There is no statistically significant difference between the treatment groups in the distribution of bacteriologic response in patients with pneumonia caused by conventional bacterial pathogens, the 95% CI for the difference (Dirithromycin - Erythromycin) is $_{35,41}(-0.127,0.199)_{91.4\%,87.8\%}$. However, it is to be noted that this confidence interval does not satisfy the guidelines of DAIDP.

41 (45.6%) of the 90 qualified dirithromycin-treated patients had serological evidence of acute *Mycoplasma pneumoniae*; a favorable posttherapy clinical response was achieved in 38 (92.7%) of these patients. In the comparator group, 32 (38.6%) of the 83 qualified erythromycin-treated patients had serology consistent with acute *Mycoplasma pneumoniae* infection and a favorable clinical response was achieved in each of these patients. There is no statistically significant difference between the two treatment groups in the distribution of clinical response in patients who had serological evidence of acute *Mycoplasma pneumoniae*, the 95% CI for the difference (Dirithromycin - Erythromycin) is $_{41,38}(-0.181,0.034)_{92.7\%,100\%}$. However, it is to be noted that this confidence interval does not satisfy the guidelines of DAIDP. 14 (15.6%) dirithromycin-treated patients were diagnosed with pneumonia caused by *Legionella* and each of these patients were assigned a favorable clinical response at the posttherapy evaluation. *Legionella pneumoniae* was diagnosed in 10 (12.0%) of the 83 qualified erythromycin-treated patients, with a favorable clinical response assigned to each at the posttherapy evaluation. There is no statistically significant difference between the treatment groups in the distribution of clinical response in patients who had serological evidence of *Legionella pneumoniae*, the 95% CI for the difference (Dirithromycin - Erythromycin) is $_{14,10}(-0.086,0.086)_{100\%,100\%}$.

ii. Late-Posttherapy Evaluations - Evaluable patients¹³

There is no statistically significant difference between the treatment groups in the distribution of clinical and bacteriologic response in patients with pneumonia caused by conventional bacterial pathogens, the 95% CI for the difference (Dirithromycin - Erythromycin) is, 28,26 (-0.136,0.245) 89.7%,94.2%.

There is no statistically significant difference between the two treatment groups in the distribution of clinical response in patients who had serological evidence of acute *Mycoplasma pneumoniae*, the 95% CI for the difference (Dirithromycin - Erythromycin) is 36,31 (-0.060,0.124) 100%,95.1%.

There is no statistically significant difference between the treatment groups in the distribution of clinical response in patients who had serological evidence of *Legionella pneumoniae*, the 95% CI for the difference (Dirithromycin - Erythromycin) is 14,8 (-0.1,0.1) 100%,100%.

d. Safety analyses (by the sponsor and checked by the reviewer)

Analysis of treatment-emergent events showed the overall frequency of adverse events recorded from the 2 study groups to be comparable ($p > 0.05$). Analysis of individual events revealed that the incidence of abdominal pain was higher among patients treated with dirithromycin ($p = 0.01$). Fourteen dirithromycin-treated and 14 erythromycin-treated patients discontinued study participation early due to adverse events. Analyses of clinical laboratory data revealed no significant differences between the treatment groups that were considered drug-related.

2. Protocol B9Z-EW-E003

a. Study design, Dosage administration and Efficacy criteria

This was a multicenter, double-blind, randomized, parallel study. The objective of this study was to compare dirithromycin administered once daily (500 mg/day) with erythromycin administered four times daily (1000 mg/day) for effectiveness and safety in the treatment of bacterial pneumonia. Patients were evaluated for symptomatic and bacteriologic responses to treatment. Safety was measured by clinical assessment and laboratory tests.

b. Study population and demographic characteristics

The study population consisted of 591 randomized patients enrolled by 76 investigators worldwide. 295 (49.9%) patients were randomized to the dirithromycin group, and 296 (50.1) patients were randomized to the erythromycin group. Of the 295 patients treated with dirithromycin, 127 (43.1%) qualified for efficacy analysis, compared with 118 of 296 (39.9%) qualified patients in the erythromycin. Bacteriologic reasons for disqualification (e.g. negative pretherapy culture, sensitivity not done, causative organism resistant, causative organism

¹³ Late-Posttherapy Evaluation is the Efficacy End Point Measure according to the reviewing Medical Officer.

unidentified, no initial culture) were cited most frequently in both treatment groups.

The groups were well matched with respect to age distribution (the mean age of the patients in each group was approximately 46.0 years), gender, height, weight, origin, presenting clinical condition, tobacco and alcohol habits, exposure to smoking in their family environment, historical diagnoses, chronic illnesses, admission events, and drug usage before, during, and after the administration of the study drug ($p > 0.05$).

127 patients in the dirithromycin group had posttherapy evaluations. Of these, 110 patients had a late-posttherapy evaluation. 118 patients in the erythromycin group were assessed posttherapy. Of these, 101 patients had a late-posttherapy evaluation.

c. Efficacy analyses (by the reviewer)

i. Posttherapy evaluations - Evaluable patients

There is no statistically significant difference between the treatment groups in the distribution of clinical response (cure + improvement) at the posttherapy visit, the 95% confidence interval for the difference (Dirithromycin - Erythromycin) is $_{127,118}(-0.071, 0.083)_{92.1\%, 91.5\%}$.

There is no statistically significant difference between the treatment groups in the distribution of bacteriologic response in patients with pneumonia caused by conventional bacterial pathogens, the 95% CI for the difference (Dirithromycin - Erythromycin) is, $_{83,70}(-0.142, 0.119)_{83.1\%, 84.3\%}$.

There is no statistically significant difference between the treatment groups in the distribution of clinical response in patients with pneumonia caused by Mycoplasma, Chlamydia or Legionella, the 95% CI for the difference (Dirithromycin - Erythromycin) is, $_{44,48}(-0.115, 0.145)_{93.2\%, 91.2\%}$. However, this confidence interval does not satisfy the guidelines of DAIDP.

ii. Late Posttherapy evaluations - Evaluable patients¹⁴

There is no statistically significant difference between the treatment groups in the distribution of clinical and bacteriologic responses in patients with pneumonia caused by conventional bacterial pathogens, the 95% CI for the difference (Dirithromycin - Erythromycin) is, $_{71,82}(-0.118, 0.114)_{90.1\%, 90.3\%}$. However, this confidence interval does not satisfy the guidelines of DAIDP.

There is no statistically significant difference between the treatment groups in the distribution of clinical response in patients with pneumonia caused by Mycoplasma, Chlamydia or Legionella, the 95% CI for the difference (Dirithromycin - Erythromycin) is, $_{39,38}(-0.072, 0.178)_{97.4\%, 92.1\%}$.

¹⁴ Late-Posttherapy Evaluation is the Efficacy End Point Measure according to the reviewing Medical Officer.

d. Safety analyses (by the sponsor and checked by the reviewer)

Analysis of treatment-emergent events showed the overall frequency of adverse events recorded from the 2 study groups to be comparable ($p > 0.05$). Analysis of individual events revealed that increase in sputum was higher among patients treated with erythromycin during therapy ($p = 0.046$). Diarrhea, with a higher incidence in the dirithromycin group approached significance ($p = 0.068$). There was one death during the study. 18 dirithromycin-treated and 21 erythromycin-treated patients discontinued early due to adverse events. Analyses of clinical laboratory data revealed no significant differences between the treatment groups that were considered drug-related.

III. Overall conclusions (which may be conveyed to the sponsor)

Pharyngitis/Tonsillitis

Study B9Z-MC-AQAB shows that for Late Posttherapy and Overall Study Termination Evaluations, there is no statistically significant difference between Dirithromycin and Erythromycin tablets in the distribution of clinical/symptomatic response. However, relative to bacteriologic response at the Late Posttherapy and Overall Study Termination Evaluations, there is a statistically significant difference between Dirithromycin (69.9%) and Erythromycin (86.0%) treatment groups (95% CIs on pages 2 and 3 under efficacy analyses section).

Study B9Z-MC-AQAS shows that for Late Posttherapy and Overall Study Termination Evaluations, there are no statistically significant differences between Dirithromycin and Erythromycin tablets in the distribution of clinical/symptomatic and bacteriologic responses (95% CIs on pages 4 and 5 under efficacy analyses section). It is to be noted that, relative to bacteriologic response for the Overall Study Termination Evaluation, the 95% CI (page 5) does not satisfy the guidelines of DAIDP. However, the results of the analysis of bacteriologic response support the results of the analysis of clinical/symptomatic response.

Study B9Z-EW-E001 shows that for Late-Posttherapy Evaluation, there are no statistically significant differences between Dirithromycin and Erythromycin tablets in the distribution of clinical/symptomatic and bacteriologic responses (95% CIs on page 7). It is to be noted that these CIs do not satisfy the guidelines of DAIDP. The sponsor has not submitted the results of Overall Study Termination Evaluation.

Thus, only one out of three studies provides adequate statistical support to the sponsor's claim that Dirithromycin (500 mg) is therapeutically not worse than the comparator, Erythromycin (1000 mg) in the treatment of patients with Pharyngitis/Tonsillitis. The sponsor needs to submit the results of another well-controlled clinical trial in order to get approval for Pharyngitis/Tonsillitis indication. Further, analysis of treatment-emergent events showed fewer patients reporting adverse events in the Dirithromycin than the Erythromycin group. Analysis of clinical laboratory data revealed no significant differences between the treatment groups that was considered drug-related.

Skin and Skin Structure Infections

Study B9Z-MC-AQAB shows that for Posttherapy Evaluation, there are no statistically significant differences between Dirithromycin and Erythromycin tablets, relative to clinical/symptomatic and bacteriologic responses, bacteriologic outcomes (pathogen eliminated or not applicable) and bacteriologic summary by the pathogen, *S. Aureus* (95% CIs on page 10 under efficacy analyses section).

Study B9Z-EQ-E004 shows that for Posttherapy Evaluation, there are no statistically significant differences between Dirithromycin and Erythromycin tablets relative to clinical/symptomatic responses, clinical/symptomatic (cure + improvement) by the infecting pathogen, *S. Aureus*, bacteriologic outcomes (pathogen eliminated or not applicable) or bacteriologic response summary by the pathogen, *S. Aureus* (95% CI on page 13 under efficacy analyses). It is to be noted that the 95% CI for the difference for bacteriologic summary by the pathogen *S. Aureus* does not satisfy the guidelines of DAIDP. However, the results of the analysis of bacteriologic summary by pathogen *S. aureus* support the results of the analysis of clinical/symptomatic response.

Thus, these two studies provide enough statistical support to the sponsor's claim that Dirithromycin (500 mg) is therapeutically not worse than Erythromycin (1000 mg) in the treatment of patients with Skin and Skin Structure Infections. Further, analysis of treatment-emergent events showed that both the treatment groups are comparable with respect to the number of patients reporting adverse events. Analysis of clinical laboratory data revealed no significant differences between the treatment groups that were considered drug-related.

Acute Bronchitis

Study B9Z-EW-E002 shows that for Posttherapy Evaluation, there are no statistically significant differences between the two treatment groups relative to the distribution of clinical/bacteriologic responses (95% CIs on page 15 under efficacy analyses section). It is to be noted that the 95% CI for the difference (Dirithromycin - Erythromycin) for the clinical/symptomatic response rates does not satisfy the guidelines of DAIDP. However, the results of the analysis of clinical/symptomatic response rates support the results of analysis of bacteriologic response rates.

Acute Superimposed on Chronic Bronchitis

Study B9Z-EW-E002 shows that for Posttherapy Evaluation, there are no statistically significant differences in the distribution of clinical and bacteriologic responses (95% CI on page 16 under efficacy analyses section). It is to be noted that the 95% CI for the difference (Dirithromycin - Erythromycin) in the clinical response does not satisfy the DAIDP guidelines. However, the results of the analysis of clinical/symptomatic response rates support the results of the analysis of bacteriologic response rates.

Study B9Z-MC-AQAB shows that there are no statistically significant difference in the distribution of clinical and bacteriologic responses at the Posttherapy Evaluation (95% CI for the difference between the two treatment groups on page 18 under efficacy analyses section).

Thus, these 3 studies, one for Acute Bronchitis and two for Acute Superimposed on Chronic Bronchitis provide enough statistical support to the sponsor's claim that Dirithromycin (500 mg) is therapeutically not worse than Erythromycin (1000 mg) in the treatment of patients with Acute Bronchitis/Acute Superimposed on Chronic Bronchitis. However, in order to get approval for the Acute Bronchitis indication, the sponsor needs to submit the results of another well-controlled clinical trial. The incidence of adverse events was in general comparable in the two treatment groups.

Bacterial Pneumonia

Study B9Z-MC-AQAB shows that there are no statistically significant differences between Dirithromycin and Erythromycin tablets in the distribution of clinical and bacteriologic responses in patients with pneumonia caused by conventional bacterial pathogens and in patients who had serological evidence of Mycoplasma Pneumonia and Legionella Pneumonia at the Late Posttherapy Evaluation (95% CI on the difference between the two treatment groups on page 21 under efficacy analyses section).

Study B9Z-EW-E003 shows that there are no statistically significant differences between Dirithromycin and Erythromycin in the distribution of clinical and bacteriologic responses in patients with pneumonia caused by conventional pathogens and in patients with pneumonia caused by Mycoplasma, Chlamydia and Legionella (95% CI for the difference between the two treatment groups on page 22 under efficacy analyses section). It is to be noted that the 95% for the difference in the distribution of clinical and bacteriologic responses in patients caused by conventional pathogens, does not satisfy the guidelines of DAIDP. However, the results of the analysis of clinical/bacteriologic responses in patients with pneumonia caused by conventional pathogens support the results of analysis of clinical/bacteriologic responses in patients with pneumonia caused by Mycoplasma, Chlamydia and Legionella pathogens.

Analysis of treatment-emergent events showed an overall frequency of adverse events recorded from the two treatment groups to be comparable ($p > 0.05$). Also, the analysis of clinical laboratory data reveals no significant differences between the two treatment groups, Dirithromycin and Erythromycin, that are considered drug-related.

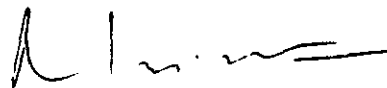
Thus, these two studies, provide statistical support to the sponsor's claim that Dirithromycin (500 mg) is therapeutically not worse than its comparator, Erythromycin (1000 mg) in the treatment of patients with Bacterial Pneumonia.

Thus, these studies provide adequate statistical support to the sponsor's claim that Dirithromycin (500 mg) is therapeutically not worse than Erythromycin (1000 mg) and is safe in the treatment of patients with skin and skin structure infection, acute superimposed on chronic bronchitis and bacterial pneumonia.

For the Pharyngitis/Tonsillitis indication, only one of the three studies submitted by the sponsor provides statistical support to the sponsor's claim that Dirithromycin (500 mg) is therapeutically not worse than Erythromycin (1000 mg). The sponsor needs to submit results of another well-controlled clinical trial for Pharyngitis/Tonsillitis in order to get approval for this indication.

For the approval of Acute Bronchitis indication, the sponsor needs to submit the results of another well-controlled clinical study.

At this point of time, the data is not available to do efficacy analysis with respect to age, gender and race.



R. Srinivasan, Ph.D
Mathematical Statistician, Group 7

Ralph Harkins, Ph.D 7/12/94

Concur: Dr. Ralph Harkins

Dr. Satya Dubey

6/7-14-94

cc:
Orig. NDA 50-678

HFD-520
HFD-520/Dr. Gavrilovich
HFD-520/Dr. Albuerne
HFD-520/Dr. Molidina
HFD-713/Dr. Dubey [File DRU 1.3.2]
HFD-713/Dr. Harkins
HFD-713/Dr. Srinivasan
HFD-520/Ms. DeSantis
HFD-344/Dr. Lisook

Chron.

This review contains 26 pages.

Srinivasan/07/11/94/X4594/WPTEXT/C:\reviews.nda\Dyanabac.nda

Pharmacokinetic/
Bio Reviews

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NDA: 50-678 **SUBMISSION DATE:** August 30, 1994
Dirithromycin (enteric coated tablets)

BRAND NAME: DYNABAC^R **REVIEWER:** Funmilayo Ajayi, Ph.D

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

TYPE OF SUBMISSION: Amendment.

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Background: In this submission, the sponsor provides responses to comments from the Division of Biopharmaceutics regarding the dissolution method and specification, suggested Phase IV studies, and the variation ranges of the inactive ingredients in the tablet core.

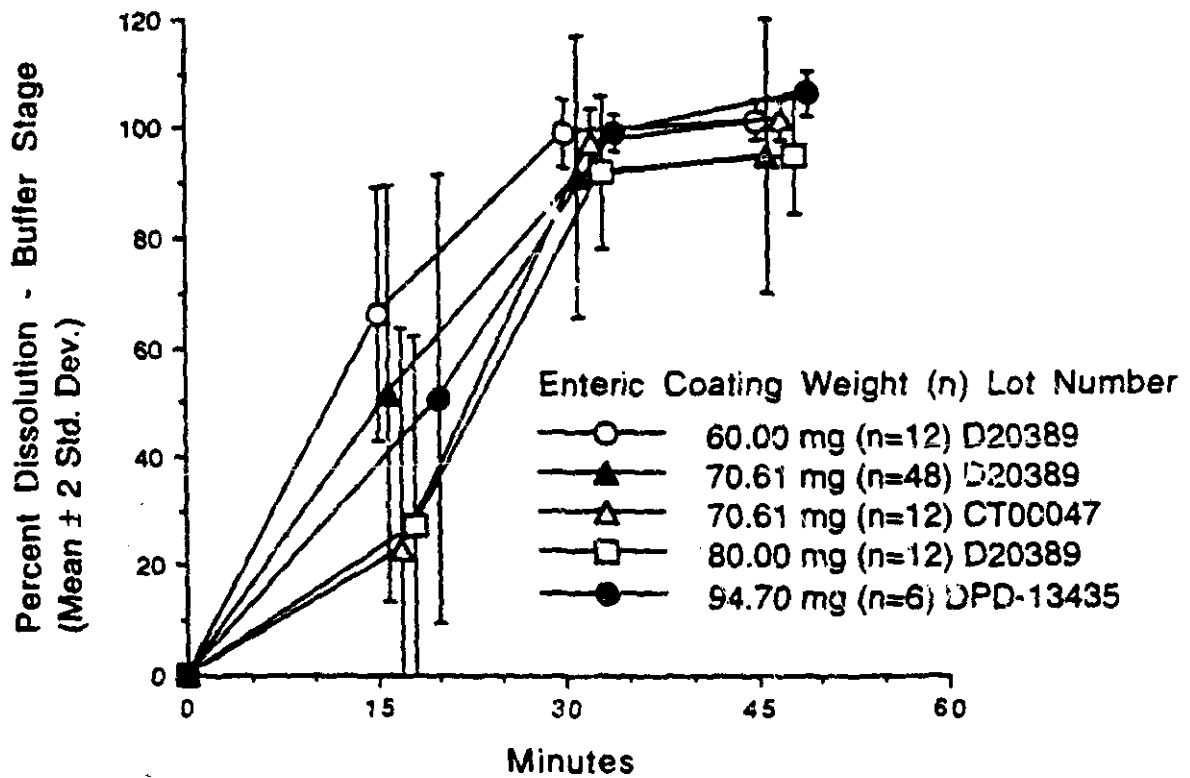
Findings:

Item 1: Dissolution. Following the review of the original submission for this NDA, the dissolution specification (Q) was set at NLT % in minutes. Based on the dissolution data obtained during the validation for the scale-up of the manufacturing process, the sponsor was concerned that the to-be-marketed formulation may not meet this Q in % of the cases. Subsequently, a review of the dissolution data from the scale-up batches contained in the June 22, 1994 submission, revealed that the tablets should be able to meet a Q of NLT % in minutes. In the current submission, the sponsor is concerned that the tablets may not meet a Q of NLT % in minutes for the buffer stage set by the Agency (see the Biopharm review of June 22, 1994 submission). Rather, a Q of NLT % in minutes, originally proposed in the NDA, is favored.

The sponsor performed statistical analysis of the dissolution data from the stability assessment of the product with a view of producing a prediction of future dissolution performance at different dissolution specifications (see the Attachments). Following a review of this information and the Biopharm concerns, the product should be able to meet a Q of NLT % in minutes. In any event, the Division of Biopharmaceutics believes that any dissolution specification for this product that is lower than NLT % in minutes is unacceptable. Ideally, the Division of Biopharmaceutics likes to have specifications for immediate release products in the order of NLT % to % label claim dissolved in the shortest time possible.

Dissolution specification should be based on the dissolution profiles for the to-be-marketed formulation. It was observed from the data on the effect of different levels of coating on dissolution (e.g. Lot D20389) that as expected, the dissolution profiles are different in rate from each other especially within the first minutes (Fig 1). Although marked with high variability, the differences in the dissolution profiles over the first minutes for CT00047 (market image) with a coating of 70.61 and D20389 with similar coating further lend credence to our previous comments to the reviewing chemist regarding the tightening of the proposed tolerance range for the coating and some components of the formulation that are important to product release. In this submission, the sponsor is of the opinion that the dissolution profiles are similar for all the Lots tested and that the proposed tolerance range (mg/tablet) be maintained for the coating.

FIG 1: Dissolution Profile Comparison of Tablets Dynabac with Four Levels of Enteric Coating



Data was generated at 15, 30, and 45 minutes in the buffer stage for each dissolution profile except for lot DPD-13435. Data for this lot was generated at 20, 30, and 45 minutes. Since data for this lot was generated as part of the release testing, only six tablets were used.

Item 2: Suggested Phase IV Studies. Evaluation of the pharmacokinetics of dirithromycin in patients with moderate to severe hepatic impairment and in nursing mothers were suggested phase IV studies. The sponsor is not willing to carry out such studies at this time. Instead, it was suggested that the labeling reflect the lack of such information with the usual wordings in the Precautions section of the product label.

Labeling Comments:

CONTRAINDICATIONS (should read thus)..

Most macrolides are contraindicated in patients receiving terfenadine therapy who have preexisting cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischemic heart disease, congestive heart failure, etc.) or electrolyte disturbances. Although clinical drug interaction studies are pending, a drug interaction study in 6 healthy volunteers that received multiple doses of terfenadine plus dirithromycin did not reveal inhibition of the metabolism of terfenadine or significant changes in any of the indices of cardiovascular function such as QT interval.

PRECAUTIONS

Theophylline: (should read thus)..

Following co-administration of two 250-mg dirithromycin tablets administered once daily with 200-mg theophylline tablets administered twice daily for 10 days to 14 healthy subjects, the steady-state plasma concentration of theophylline was not significantly altered. In general, most patients treated with dirithromycin who are receiving concomitant theophylline therapy may not require empiric adjustment of theophylline dosage or monitoring of theophylline plasma concentrations. However, theophylline plasma concentrations should be monitored with dosage adjustment as appropriate for patients with more severe pulmonary disease who are dependent on maintaining a given theophylline plasma concentration for optimal pulmonary function or for patients with theophylline concentrations at the higher end of the therapeutic range.

Hepatic Insufficiency: (should read thus)..

Because dirithromycin is principally eliminated via the liver, caution should be exercised when dirithromycin is administered to patients with moderate to severe impaired hepatic function. No dosage adjustment should be necessary in patients with mildly impaired hepatic function.

Nursing Mothers: (should read thus)..

It is not known whether dirithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dirithromycin is administered to a nursing woman.

Recommendation: Following a review of the current information in the above submission, The Division of Biopharmaceutics believes that the product should meet a Q of NLT % in minutes any dissolution specification that is lower than NLT % in minutes is unacceptable. The suggested labeling changes regarding nursing mothers and patients with moderate to severe hepatic impairment are acceptable in lieu of formal pharmacokinetics studies to address these issues as previously suggested. Please see the Labeling Comments for full details. The reviewing chemist should please look into the proposed tolerance ranges for the different components of the tablet e.g. the coating with respect to variability in dissolution rates.

Funmilayo O. Ajayi 3/3/95
Funmilayo O. Ajayi, Ph.D
Pharmacokinetic Evaluation Branch

FT initialed by Frank Pelsor, PharmD.....

Frank Pelsor 3/3/95

cc: NDA 50-676, HFD-520 (Clinical Division), HFD-427 (M.Chen, Pelsor, Ajayi), Chron, Drug, Reviewer, FOI (HFD-19), ~~HFD-240 (HFD)~~

Attachments

FDA Request

10. "A statement acknowledging that with regards to the dissolution data from the scale-up validation of the to-be-marketed formulation, the dissolution specification (Q) should be set at NLT % dissolved in buffer stage in minutes."

Lilly Response

An analysis of the full shelf-life stability data in the NDA and the data from the validation study is provided on the following pages. We believe the dissolution specification submitted in the NDA to be an appropriate control of the manufacturing process for this enteric-coated tablet. The NDA specification for the buffer phase dissolution is % (Q) in minutes. We find that the FDA proposed specification of % (Q) in minutes would result in an unacceptable number of lots that would not pass the proposed specification during stability testing, and therefore, would be subject to recalls. Reducing the specification to % (Q) or even % (Q) in minutes does not markedly reduce the number of lots that would be subject to recall.

The risk of not passing dissolution during stability testing is not due to a decrease in dissolution capability over the shelf-life of the product. There is no significant decrease in mean dissolution over time and no trend toward an increase in the number of tests that do not meet the dissolution specification.

An analysis of the validation batches produced similar results (new stability data for individual dissolution values are attached). The following predictions are made for stability failures at several specifications:

<u>Specification</u>	<u>Percent of Tests Not Passing USP Stage 3</u>	<u>Percent of Lots Not Passing USP Stage 3 During Stability Protocol</u>
% (Q) in minutes	1.3%	5%
% (Q) in minutes	1.5%	6%
% (Q) in minutes	0.3%	1%
% (Q) in minutes	0.04%	0.2%

In the stability protocol submitted in the NDA, representative lots are tested at 0, 6, 12, 18, and 24 months. From the table above, each test has a 1.3% chance of not meeting the FDA proposed specification of % (Q) in minutes. Over the course of the stability program, the probabilities compound so that each lot has a 5% chance of not meeting the criteria in at least one of the four tests during shelf-life. It should be kept in mind that dissolution testing is being conducted at minutes for validation lots on stability. Dissolution data at minutes has not been generated for stability samples of validation lots since this was not the specification used for clinical lots.

Only specifications of % (Q) or % (Q) in minutes are supported by the data. Lilly does not object to setting a discriminating specification for dissolution and we believe this is accomplished with the specification of % (Q) in minutes. We have shown that this is the tightest specification supported by the data. Setting a tighter specification either at minutes or minutes will result in unacceptable recalls.

Statistical Review of NDA Dirithromycin Dissolution Stability Data and all Available Validation Data

NDA STABILITY ANALYSIS

The 25°C and 30°C stability data included in the NDA were observed and the number of tests not passing dissolution at various specifications and times were tabulated (see Table 1). Stability graphs 1.A and 1.B contain the mean and lowest individual percent dissolved in minutes (for all studies) plotted against age of batch. Stability graphs 2.A and 2.B contain the mean and lowest individual percent dissolved in minutes (for all studies) plotted against age of batch. There is no significant decrease in the mean dissolution over the full shelf-life. Furthermore, there is no trend toward an increase in the number of tests that do not meet the dissolution specification over time. The low results occur at random, between 9 and 39 months. The data collected at minutes have an RSD (statistical measurement used to compare the variation of methods) of about 12%, while the dissolution data at minutes have an RSD of less than 6%.

Table 1

Q mean required (Stage 3)	minimum required (Stage 3)	# that do not pass mean & minimum	# that do not pass mean only	# that do not pass minimum only	total # not passing Stage 3	% of 252 total tests not passing	% of 30 studies with failing results
In minutes							
		6	0	3	9	3.6%	30%
		5	1	1	7	2.8%	23%
		3	2	1	6	2.4%	20%
		1	0	1	2	0.8%	7%
In minutes							
		1	0	3	4	1.6%	13%
		0	0	3	3	1.2%	10%
		0	0	3	3	1.2%	10%
		0	0	1	1	0.4%	3%

note: "*" represents the number of tests (6 to 24 tablets) observed in the NDA data. The studies are per batch, per package, per temperature.

Dissolution specifications of % or more in minutes result in more than twice the percent of tests not passing than the proposed specification of % in minutes. It is also noted that the percent dissolved in minutes have many tests that fail both the mean and minimum dissolution requirements.

VALIDATION DATA ANALYSIS

An analysis of all validation data was conducted to confirm the results observed in the NDA data. The analysis consisted of a characterization of the data and a prediction of future dissolution performance. The following data were analyzed:

dissolution in minutes:

14 test results as part of the validation dissolution profiles

dissolution in minutes:

39 test results as part of validation batch data

12 stability studies with: initial results; 1, 2, and 3 month results at 40°C/75% relative humidity; 3 and 6 month results at 30°C.

No significant change in dissolution was observed over time, so all minute data were combined. Several dissolution specifications were modeled:

For a specification of Q= % in minutes, the validation data predicts that 31% of future tests will not pass USP Stage 1 and 1.3% of tests will not pass USP Stage 3 testing. If a batch meets this specification at release and is placed on the stability protocol with testing at 0, 6, 12, 18, and 24 months, there is a 5% chance that the batch will not pass USP Stage 3 testing at some point in the study.

For a specification of Q: % in minutes, the validation data predicts that 29% of future tests will not pass USP Stage 1 and 1.5% of tests will not pass USP Stage 3 testing. If a batch meets this specification at release and is placed on the stability protocol with testing at 0, 6, 12, 18, and 24 months, there is a 6% chance that the batch will not pass USP stage 3 testing at some point in the study.

For a specification of Q % in minutes, the validation data predicts that 14% of future tests will not pass USP Stage 1 and 0.3% of tests will not pass USP Stage 3 testing. If a batch meets this specification at release and is placed on the stability protocol with testing at 0, 6, 12, 18, and 24 months, there is a 1% chance that the batch will not pass USP Stage 3 testing at some point in the study.

For a specification of Q: % in minutes, the validation data predicts that 5% of future tests will not pass USP Stage 1 and 0.04% of tests will not pass USP Stage 3 testing. If a batch meets this specification at release and is placed on the stability protocol with testing at 0, 6, 12, 18, and 24 months, there is a 0.2% chance that the batch will not pass USP Stage 3 testing at some point in the study.

In summary, 5% of lots placed on stability are predicted to not pass USP Stage 3 dissolution testing at some point in the stability schedule with the FDA proposed specification of Q % in minutes. For dissolution testing at minutes, specifications of Q %, Q: %, and Q: % would result in 6%, 1%, and 0.2% of lots, respectively, that are predicted to not pass USP Stage 3 testing at some point in the stability schedule.

CONCLUSION

Table 2	% of tests not passing the specification at USP Stage 3	
Specification	observed in NDA data	predicted by validation
minutes		
Q:	3.6%	1.3%
minutes		
Q	1.2%	1.5%
Q	1.2%	0.3%
Q:	0.4%	0.04%

In both datasets, the validation data and the NDA data, there is significantly less capability of meeting a specification of Q in minutes than Q in minutes.

NDA #50-678 DIRITHROMYCIN

PREFACE: This NDA deals with the use of Dirithromycin in 5 clinical infections: pharyngitis and tonsillitis, secondary bacterial infection of acute bronchitis, acute bacterial exacerbation of chronic bronchitis, pneumonia, and skin and skin-structure infections. The reports that follow review the two major studies submitted for evaluation of dirithromycin in skin and skin-structure infections, and summarize three smaller supporting studies.

CLINICAL STUDY REPORT PROTOCOL B9Z-MC-AQAB, SKIN AND SKIN-STRUCTURE INFECTION INDICATION

1. INTRODUCTION

This study was designed to assess the efficacy and safety of dirithromycin in the treatment of bacterial skin and skin structure infections. The protocol, B9Z-MC-AQAB, included four indications (pharyngitis, acute bacterial exacerbation of chronic bronchitis, pneumonia, and skin and skin-structure infections), but only the methods and results for the skin infection indication will be discussed here. Each indication had a different group of patients.

Dirithromycin was compared to erythromycin base. This drug (erythromycin) was chosen because it is the prototypical macrolide antibiotic with an extensive safety and efficacy database.

To assess efficacy, dirithromycin-treated patients were evaluated for symptomatic and bacteriologic responses, and their results were compared with those of erythromycin-treated patients. The safety of dirithromycin therapy was evaluated by analyzing adverse clinical events and the results of blood chemistry, hematology, electrocardiograms, and urine tests. These were also compared to the values found in the erythromycin-treated patients.

2. OBJECTIVE

The objective of this study was to compare dirithromycin administered once daily (500 mg/day) with erythromycin administered four times daily (1000 mg/day) for effectiveness and safety in the treatment of bacterial skin and skin structure infections.

3. INVESTIGATIONAL PLAN

a. SUMMARY OF STUDY DESIGN

This was a double-blind, double-dummy, randomized, parallel study. Patients who met the entry criteria and signed a consent form were to be assigned by randomization to one of the 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, which were to be done prior to therapy, during therapy and then after completion of therapy. There was no minimum treatment period for patients who did not respond to therapy, but for those who did, the duration of therapy was to be 7 days.

b. INVESTIGATORS

Investigators were from 30 different study centers from both private practice

and in academia. All investigators were approved by Institutional Review Boards and conducted their trials according to IRB guidelines. The investigators needed to be versed in the diagnosis and treatment of infectious diseases and were practitioners in one of the following specialties: dermatologists, infectious disease specialists, general internists, or family practitioners.

c. DOSAGE AND ADMINISTRATION

Patients randomly assigned to the dirithromycin treatment group were to receive two 250-mg dirithromycin tablets in the morning (total dose of 500 mg) and one tablet of placebo four times daily for 7 days. The placebo tablet was identical in appearance to the erythromycin tablet.

Patients randomly assigned to the erythromycin treatment group were to receive one 250-mg erythromycin tablet four times daily (total of 1000 mg daily) and two tablets of placebo in the morning for 7 days. The placebo tablet was identical in appearance to the dirithromycin tablet.

Formulations used in study: In the early stages of the study, the original formulation (referred to as the "Thomae" formulation) was used. However, a new formulation was developed (referred to as the "Lilly" formulation) and was used in patients in the latter stages of the study. The switch in formulations was done for the following reasons:

1. The Lilly formulation had an improved enteric coating with better long-term stability (an eudragit coating replaced a cellulose-acetate-phthalate coating).
2. The new manufacturing process did not induce dirithromycin epimer formation.
3. The new manufacturing process was environmentally desirable because it used aqueous solvents in place of hydrocarbon solvents.

Medical Officer's Comments: The sponsor has submitted data in the NDA application showing that the two formulations have similar biopharmaceutical profiles and antimicrobial activity. Thus, the medical officer treated all patients in the dirithromycin treated group as a whole and did not separate them into two subgroups.

d. CONCOMITANT MEDICATION

Concomitant medications needed for treatment of underlying diseases or conditions were acceptable with the exception of systemic antibiotics. If a systemic antibiotic was required, the study antibiotic was to be discontinued and appropriate cultures and laboratory tests performed. The case was to be classified as a clinical failure and possibly a bacteriologic failure. Patients requiring topical antimicrobial or topical or systemic steroids were not to be enrolled.

e. DISEASE DIAGNOSTIC CRITERIA

Patients with the following bacterial skin and skin-structure infections were included:

1. subcutaneous abscess,
2. impetigo,
3. pyoderma,
4. infected skin ulcer,
5. post-surgical wound infection.
6. post-traumatic wound infection,
7. cellulitis.

If patients had an acute infection superimposed on an area of chronic skin disease, and thus making evaluation of clinical response difficult, they were to be excluded from the study.

All patients were to have a culture obtained at the pretherapy visit. Patients with cellulitis were to have a needle-aspirate culture of the cellulitic area obtained. If an incision and drainage was performed, it was to be recorded in the case report form.

f. EFFICACY CRITERIA

Patients were to be evaluated from two points of view, clinical or symptomatic response and bacteriologic response. Responses were to be assessed by the investigators.

Clinical response could be classified in one of five ways:

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

NOTE: The use of "failure" for cases requiring the addition of another antibiotic was to be reserved for those cases where a different antibiotic was given due to worsening or lack of improvement of the patient's clinical condition. Thus, in patients who had a favorable clinical response ("cure" or "improved"), but an unfavorable bacteriologic response (relapse or failure) and thus treated with a new antibiotic, the patient's clinical response remained as "cure" or "improvement".

Bacteriologic response could be classified in one of seven ways:

- Pathogen Eliminated: Eradication of the pathogen.
- Recurrence Same Pathogen: Original pathogen eliminated during treatment but recurred during the follow-up period.
- Recurrence Same Pathogen, Resistance Developed: Original pathogen susceptible to erythromycin was eliminated during treatment but recurred in the follow-up period and tested as resistant to erythromycin.
- Recurrence New Pathogen: Original pathogen susceptible to erythromycin was eliminated during treatment, but a new pathogen was isolated in the follow-up period.
- Failure: Original pathogen was not eradicated.
- Not Applicable: Patient obtained either a cure or improvement clinically, and the follow-up culture was not clinically indicated or the culture source was eliminated.

Unable to Evaluate: Term used when cultures were not obtained or when a systemic or topical (nonstudy) antimicrobial agent with activity against cutaneous bacterial pathogens or a systemic or topical corticosteroid agent was used.

NOTE: Superimposed infections, that is, the presence of a new pathogen (bacterial, viral, fungal) resistant to study medication, and with signs and/or symptoms of infection present, were regarded as adverse events and listed as such.

Medical Officer's Comments: As done by the sponsor, patients were evaluated in two ways: clinical response and bacteriologic response. Clinical response was divided into three categories only, compare to the five used by the sponsor. These categories were:

Cure: Elimination of signs and symptoms of infection with no recurrence in the follow-up period.

Not Cured: This included patients with: incomplete resolution of signs and symptoms of infection, worsening of signs and symptoms after initial improvement on therapy, or no improvement of signs and symptoms during therapy. All patients requiring the addition of another antibiotic (be it systemic or topical) were considered as "not cured". Thus, even patients who had clinical resolution of signs and symptoms but who required another antibiotic because of relapse or failure bacteriologically were classified as "not cured".

Unable to Evaluate: Unable to evaluate a symptomatic response due to extenuating circumstances. This response disqualified a case for efficacy analysis only. Included in this category were ALL patients who received either topical or systemic steroids since such treatment could mask the clinical picture.

In regards to the bacteriological response category, the medical officer used the same 7 possible groups as the sponsor but renamed the "not applicable" as "presumed eradicated". However, if a systemic or topical antimicrobial agent other than the study drug, with activity against cutaneous bacterial pathogens was used, the bacteriologic response was classified as a "failure" and not as "unable to evaluate" as the sponsor may have done.

g. PATIENT DISPOSITION CRITERIA

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

- The patient completed the protocol.
- 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 to respond to treatment.
- If, in the investigator's opinion, a significant adverse event or significant alteration in a laboratory test result occurred, the study medication was discontinued.
- 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 stated on the CRF.
- Study drug identity was unblinded for safety reasons.
- Pretherapy serum creatinine $\geq$ 133 μ mol/L (1.5 mg/dL).

Note that all patients discontinued from the study had laboratory tests repeated at discontinuation.

SAFETY

All patients who gave consent to participate in this study and were randomized to a treatment group were to be included in the safety evaluation, even if they were not treated with a study medication (i.e., an intent-to-treat analysis).

EFFICACY

Cases were classified by the sponsor as "qualified" if they met the following criteria for analysis of efficacy:

- the patient met the inclusion/exclusion criteria (will be discussed in the next section),
- the pretherapy culture, obtained within 24 hours prior to start of study drug medication, was positive for a cutaneous pathogen susceptible to erythromycin,
- the patient completed an adequate course of therapy (5 to 7 days),
- posttherapy clinical and microbiological evaluations were performed,
- the symptomatic response could be evaluated.

h. INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

Patients included males and females and were required to be 12 years of age or older, weigh at least 37 kg, and be able to swallow tablets. Women with child-bearing potential were to have a negative pregnancy test prior to therapy and be on effective birth control during the course of therapy. Patients were to be included if they had a clinical diagnosis of bacterial skin or skin-structure infection that could be cultured. Thus, infections such as lymphangitis, where material for culturing is difficult to obtain, were excluded.

The investigators attempted to select those patients and/or parents or guardians who had a history of complying with instructions.

EXCLUSION CRITERIA

Patients were to be excluded for any of the following reasons:

- History of renal impairment (serum creatinine ≥ 133 $\mu\text{mol/L}$, 1.5 mg/dL).
- Significant underlying disease or concomitant infection which, in the opinion of the investigator, could have precluded evaluation of response.
- An anticipated requirement of systemic antibiotics other than the study antibiotic or systemic corticosteroid during therapy.
- Use of any antimicrobial therapy within 1 week preceding the pretherapy evaluation.
- Use of other investigational agents within 21 days prior to entry into the study.
- Patient would not be able to come back routinely for follow-up.
- History of hypersensitivity to macrolides.
- Pregnancy, and postpartum/lactating females who were nursing.

4. PROCEDURES AND METHODS

In general, there were to be 4 patient visits during the course of therapy. They were:

1. Pretherapy Visit: Within 24 hours preceding the first dose
2. During Therapy Visit: Between days 3-5 of therapy

3. Posttherapy Visit: 3-5 days after completion of therapy
4. Late-Posttherapy Visit: 10-14 days after therapy was completed.

a. EFFICACY EVALUATION

Procedures that were to be done at each visit so as to evaluate clinical response were as follows:

- Pretherapy: A complete history and physical examination were to be done
During Therapy: Evaluate symptomatic response to therapy and assess patient compliance with instructions for taking medication
Posttherapy: Physical examination was to be performed to evaluate symptomatic response to therapy
Late-Posttherapy: Physical examination was to be performed to evaluate symptomatic response to therapy.

Procedures that were to be done at each visit for evaluation of bacteriologic response were:

- Pretherapy: Culture of cutaneous infection. Patients with cellulitis required a biopsy for culture purposes. Susceptibility of the microorganism(s) isolated to both dirithromycin and erythromycin was to be determined by the NCCLS standardized disk method and/or MIC determination as specified by the NCCLS. The pathogen(s) had to be susceptible to erythromycin for the patient to remain in the study. Susceptibility was defined as ≥ 18 mm zone size or ≤ 0.5 $\mu\text{g/mL}$ MIC.
During Therapy: Culture of cutaneous infection, if source available.
Posttherapy: Culture of cutaneous infection, if source available.
Late-Posttherapy: Culture of cutaneous infection, if source available.

b. SAFETY EVALUATION

Safety assessments were to include clinical evaluations (both by examination and by history looking for adverse events) and laboratory tests. Electrocardiograms (ECGs) were to be performed in the early stages of the trial (when still at Stage II) but were not required in the Stage III studies.

In terms of adverse events, all patients (or parents or guardians, if the patient was a minor) were to be instructed to contact the investigator or clinical personnel by phone if they experienced an adverse event. Additionally, at each visit patients were to be specifically asked about any adverse events. All adverse events were to be recorded in the clinical report form using the patient's words or the investigator's terms. These were to be classified then by the sponsor based on COSTART definitions in a database referred to as ELECT (Eli Lilly and Company Classification Terms). Adverse events were to be categorized by body system using the algorithm found in the ELECT dictionary.

All laboratory work was to be sent and processed at a central laboratory. The following laboratory tests were to be obtained at each visit:

TABLE AQAB.4.3
LABORATORY TESTS TO EVALUATE SAFETY

INDICATION: SKIN AND SKIN-STRUCTURE INFECTIONS

Study Phase	Procedure		
Pretherapy (Within 24 Hours of Receiving the First Dose):	<u>Hematology</u>	<u>Blood Chemistry</u>	<u>Urinalysis</u>
	Hemoglobin	Phosphorus	Appearance
	Hematocrit	Calcium	Specific Gravity
	RBC Count	Glucose	pH
	MCV	Cholesterol	Protein
	MCH	Total Bilirubin	Glucose
	MCHC	Alkaline Phosphatase	Ketones
	WBC Count	GGT	Bilirubin
	Differential Count	ALT (SGPT)	Urobilinogen
	Platelet Count	AST (SGOT)	Blood
	Morphology	Urea Nitrogen	Nitrite
		Creatinine	Leukocyte Esterase
		Uric Acid	Microscopic - WBC
		Total Protein	RBC
	Albumin	Casts	
	Creatine Kinase*		

During Therapy (days 3-5): Laboratory tests were to be repeated as clinically indicated. Urine samples were to be assayed for presence of antimicrobial activity.

Posttherapy: 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: Laboratory tests were to be repeated during Phase II. Laboratory tests were to be repeated during Phase III, if clinically indicated.

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

For patients on concomitant theophylline, carbamazepine, or cyclosporine, appropriate drug levels were to be obtained at the pretherapy and during-therapy visits. If clinically indicated, they were to be done at other times also. Patients on warfarin were to have a prothrombin time obtained at the pretherapy and during-therapy visits and to be done at other times as clinically indicated.

ECG's were to be obtained in the Phase II stages of the study. ECG's were to be taken at the pretherapy and posttherapy visits and mailed to a central laboratory for interpretation.

c. DATA ANALYSIS METHODS

All data obtained from each patient entering the study were to be included in the primary statistical evaluations. Symptomatic and bacteriologic response rates and adverse event frequency rates in the two groups (dirithromycin treated and erythromycin treated) were to be compared by means of chi-square methodology. Laboratory monitoring data were to be analyzed using appropriate continuous data procedures, such as a two-sample t-test on ranked data. Additionally, all analyses were to examine consistency of results among participating clinics. The two formulations of dirithromycin used ("Thomae" and "Lilly" formulations) were to be compared also.

d. COMPLIANCE

Investigators were to attempt to select those patients and parents or guardians who had a history of complying with instructions. Urine samples were to be obtained from all patients at the during-therapy visit to look for the presence of antimicrobial activity. Additionally, the number of tablets remaining was to be recorded at the posttherapy visit.

5. EVALUABILITY

Based on the above information concerning protocol, efficacy evaluations, and safety evaluations, we can now chronologically look at the actual breakdown of patient evaluability. The easiest and most logical way to do this is to actually look at what occurred at each visit.

a. PRE-THERAPY VISIT: The purpose of this visit was to qualify patients for the study, randomize them into the two treatment groups, determine presenting diagnoses, obtain adequate cultures, obtain routine laboratory tests, perform an initial examination, and obtain signed informed consent forms. Patients qualified if they met the following criteria:

- Had a skin or skin-tissue infection which was acute in nature, appeared to be treatable by the study antimicrobials and was culturable,
- Had a culture of the affected area obtained (either by swab or aspirate, and two blood cultures obtained simultaneously in patients with cellulitis),
- Met inclusion/exclusion criteria,
- Had a history of being reliable and thought to be capable of follow-up visits,
- Signed a consent form approved by a local IRB:

If all these were met, the patient was then randomly (by a randomization scheme devised by the sponsor) assigned to either the dirithromycin or erythromycin group.

Medical Officer's Comments:

The sponsor did not state explicitly how cultures were to be obtained. For the medical officer, swabs sent for culture were adequate for patients with open or draining lesions. However, for patients with cellulitis or other deep and not open infections, either leading edge or actual area needle aspirate cultures were required. Also, of note, the sponsor did not include patients with infected burns because of the usual severe nature of such infections.

b. DURING THERAPY VISIT: The purpose of this visit was to disqualify patients based on culture or routine laboratory abnormalities, to check the progress of the subjects while on study drug, to follow-up on any abnormal entry laboratory values, and to ask and look for any adverse clinical events. The investigators could disqualify a subject from

efficacy evaluation if any of the following were noted:

- Microbiologic disqualification occurred. This included all patients who had one or more of the following:
 1. no growth on culture,
 2. organism(s) grown were resistant to erythromycin,
 3. organism(s) grown were not recognized skin pathogen(s),
 4. culture obtained too late,
 5. culture improperly obtained.
- Disqualification secondary to use of other antimicrobials, be it systemic or topical. If the patient was started on another antimicrobial because of failure of the study drug, then this patient was classified as a "treatment failure".
- Development of adverse event(s) or reporting of an abnormal laboratory measurement requiring termination from the study.
- A violation of inclusion/exclusion criteria was found during therapy.
- Blinding of either the patient or investigator was broken.

Patients discontinued at this time were not eligible for efficacy evaluability, but were included in evaluation for adverse events. Additionally, all patients ~~disqualified at this time~~ had a repeat of their entry laboratory work done.

Medical Officer's Comments:

The sponsor did not specifically list which organisms were classified as recognized skin pathogens. For the medical officer, any culture obtained properly that grew either *Staphylococcus aureus* or *Streptococcus pyogenes* (Group A *Streptococcus*) was seen as evaluable. The majority of cases where *Staphylococcus epidermidis*, or other coagulase negative strains of *Staphylococcus*, was isolated from culture were NOT seen as evaluable by the medical officer. *Staphylococcus epidermidis* is a well recognized "contaminant" or "colonizer" of skin and skin structures, and is usually ONLY seen as a true pathogen in the following patients:

- a. patients who are immunodeficient or who have some compromise of their immune response secondary to chronic disease (such as in diabetics),
- b. patients with central venous or arterial access,
- c. patients with permanent foreign bodies, such as prostheses, heart valves, etc.

Additionally, unless the patient's clinical condition or history revealed a reason to be predisposed, most other organisms were also not accepted as true pathogens. In patients with insulin-dependent diabetes mellitus or with some other chronic disorder predisposing to immunologic difficulties, or with a skin infection known to have flora not *Streptococcal* or *Staphylococcus aureus* in origin (such as infected ulcers or burns), other organisms were accepted.

c. POST-THERAPY VISIT: The purpose of this visit was to evaluate patients for efficacy (both clinical and microbiologic), check for any adverse clinical events, repeat laboratory tests to look for any development of abnormal laboratory values during the clinical trial, and to disqualify those patients from efficacy evaluation that met one of the following criteria:

- Disqualification secondary to use of other antimicrobials, be it systemic or topical. If the patient was started on another antimicrobial because of failure of the study drug, then this patient was classified as a "treatment failure".
- Lost to follow-up, or the patient or investigator terminated the patient from the study secondary to personal reasons.
- Development of adverse event(s) or reporting of an abnormal

- laboratory measurement requiring termination from the study.
- A late finding that the patient had a violation of initial entry inclusion/exclusion criteria.
- Blinding of either patient or investigator was broken.

Those not disqualified were evaluated for both clinical and microbiologic efficacy, using the criteria noted before in section #3, subsection f. All patients that returned for a post therapy visit were evaluated for safety and laboratory value analysis, regardless if found to be evaluable or not.

At the post-therapy visit, any patient with clinical failure was classified as such and repeat cultures were obtained prior to starting another antimicrobial agent. Patients who were not failures were recultured if applicable or if a source still existed. They were then asked to return for the late post-therapy visit.

Medical Officer's Comments:

There are two points of difference between the sponsor and medical officer at this point. For one, the sponsor evaluated patients twice for efficacy: once at the post-therapy visit and then again at the late post-therapy visit. The results were reported separately by the sponsor, and they were not tied together. The medical officer only used the results from the late post-therapy visit for efficacy evaluation. Of note, all patients deemed as failures in visits prior to the late post-therapy visit were carried through to this visit for purposes of statistical evaluation. This is as per the recent recommendations of both the Division of Anti-Infectives at the FDA and the Infectious Disease Society of America (as published in Supplement #1 of the Clinical Infectious Diseases in 1992) to evaluate patients 10-14 days after completion of therapy to look for late recurrences.

The other point of difference is the clinical efficacy criteria used. The sponsor used 5 possible criteria (cured/improved/relapsed/failed/unable to evaluate) while the medical officer used only three (cure/not cured/unable to evaluate). For both the medical officer and sponsor, a patient classified clinically as being "unable to be evaluated" was not included into the final efficacy evaluation.

d. LATE POST-THERAPY VISIT: The purpose of this visit was to allow the sponsor to evaluate the clinical and microbiologic response of the subjects about 10-14 days after completion of therapy. For the sponsor, each evaluable subject that came to both the post-therapy and late post-therapy visits received two sets of efficacy evaluations. Laboratory studies or repeat cultures were sent only if needed.

6. RESULTS

Initially, there were 578 patients who gave informed consent and were randomized to treatment groups. Of these, 304 (53%) were randomized to receive dirithromycin and 274 (47%) were randomized to the erythromycin treatment group.

The demographics, according to the sponsor, for the two treatment groups (this considers all patients entered initially into a treatment group, were similar in respect to age, gender, weight and height, with the following values obtained:

- a. Age: the mean age in the dirithromycin group was 41.10 years and was 39.55 in the erythromycin group.
- b. Gender: in the dirithromycin group, 50.3% of subjects were females and in the erythromycin group, 49.3% were females.
- c. Height: average height of the dirithromycin group was 170.59 cm in comparison to the erythromycin group's mean height of 170.98 cm.
- d. Weight: average weight for the dirithromycin group was 79.15 kg and it was 76.82 kg in the erythromycin group.

Additionally, the groups were well matched for racial origin.

a. EVALUABILITY:

The following table shows the number of patients found evaluable for each of the 30 study centers. The table shows both the values obtained by the medical officer and by the sponsor.

CENTER#/INVESTIGATOR/LOCATION	NUMBER OF EVALUABLE PATIENTS (%)					
	NO. PTS. ENROLLED		DIRITHROMYCIN		ERYTHROMYCIN	
	DIRITHROMYCIN	ERYTHROMYCIN	SPONSOR	M.O.	SPONSOR	M.O.
004/ D Lehman/ Sacramento, CA	9	5	3 (33%)	3 (33%)	0 (0%)	0 (0%)
006/ J Seltzer/ San Diego, CA	2	0	1 (50%)	1 (50%)	-----	-----
010/ S Heatley/ Redwood City, CA	4	4	1 (25%)	1 (25%)	1 (25%)	1 (25%)
011/ R Stoltz/ Evansville, IN	8	14	5 (63%)	5 (63%)	9 (64%)	7 (50%)
012/ D Breeman/ Cincinnati, OH	30	29	20 (67%)	18 (60%)	17 (59%)	17 (59%)
014/ D Wright/ Austin TX	5	4	2 (40%)	2 (40%)	2 (50%)	2 (50%)

016/ C Weart/ Charleston, SC	6	2	1 (17%)	0 (0%)	1 (50%)	1 (50%)
017/ G Fisher/ Pensacola, FL	2	4	2 (100%)	2 (100%)	3 (75%)	2 (50%)
018/ R Schneider/ Charlotte, NC	0	1	-----	-----	1 (100%)	0 (0%)
023/ M Morman/ Rutherford NJ	11	10	7 (64%)	6 (55%)	5 (50%)	3 (30%)
024/ H Katz/ Fridley MN	5	5	3 (60%)	3 (60%)	2 (40%)	2 (40%)
026/ A Puopolo/ Milford MA	20	20	9 (45%)	6 (30%)	8 (40%)	5 (25%)
029/ C Goswick/ Bryan, TX	8	9	6 (75%)	6 (75%)	3 (33%)	4 (44%)
034/ M Barrero/ Binghamton, NY	2	3	0 (0%)	-----	0 (0%)	0 (0%)
036/ W Gardner/ Akron, OH	2	1	1 (50%)	2 (100%)	1 (100%)	1 (100%)

016/ C Weart/ Charleston, SC	6	2 -	1 (17%)	0 (0%)	1 (50%)	1 (50%)
017/ G Fisher/ Pensacola, FL	2	4	2 (100%)	2 (100%)	3 (75%)	2 (50%)
018/ R Schneider/ Charlotte, NC	0	1	-----	-----	1 (100%)	0 (0%)
023/ M Norman/ Rutherford NJ	11	10	7 (64%)	6 (55%)	5 (50%)	3 (30%)
024/ H Katz/ Fridley MN	5	5	3 (60%)	3 (60%)	2 (40%)	2 (40%)
026/ A Puopolo/ Milford MA	20	20	9 (45%)	6 (30%)	8 (40%)	5 (25%)
029/ C Goswick/ Bryan, TX	8	9	6 (75%)	6 (75%)	3 (33%)	4 (44%)
034/ M Barrero/ Binghamton, NY	2	3	0 (0%)	-----	0 (0%)	0 (0%)
036/ W Gardner/ Akron, OH	2	1	1 (50%)	2 (100%)	1 (100%)	1 (100%)

043/ C Chand- ler/ Monroe, LA	16	16	8 (50%)	8 (50%)	7 (44%)	6 (38%)
046/ E Fenn- ell/ Johnson City, TN	0	1	-----	-----	0 (0%)	0 (0%)
051/ S Crosby/ Jackson, AL	4	2	2 (50%)	2 (50%)	0 (0%)	1 (50%)
062/ R Geiger/ Vero Beach, FL	19	22	8 (42%)	7 (37%)	10 (46%)	9 (41%)
073/ D Simons- Morton/ Houston, TX	10	1	4 (40%)	3 (30%)	0 (0%)	1 (100%)
080/ C Hetsko/ Madison, WN	2	0	1 (50%)	1 (50%)	-----	-----
086/ F Guerra/ El Paso, TX	9	10	7 (78%)	4 (44%)	6 (60%)	4 (40%)
087/ G Golla- pudi/ Midland. TX	13	12	3 (23%)	3 (23%)	3 (25%)	4 (33%)

088/ T Rist/ Knoxville, TN	38	38	22 (58%)	7 (18%)	22 (58%)	10 (26%)
091/ D Wall- ack/ Little- ton, CO	26	25	13 (50%)	11 (42%)	13 (52%)	12 (48%)
092/ D Miller/ Mooresv- ille, PA	22	14	12 (55%)	10 (45%)	4 (29%)	3 (21%)
100/ M Gold/ Nashvil- le, TN	6	6	3 (50%)	1 (17%)	2 (33%)	0 (0%)
101/ F Whit- tier/ Canton, OH	1	0	1 (100%)	1 (100%)	-----	-----
102/ D Bartels/ Belvid- ere, IL	1	0	0 (0%)	0 (0%)	-----	-----
115/ J McCarty/ Fresno, CA	23	16	11 (48%)	13 (57%)	7 (44%)	6 (38%)
TOTALS	304	274	156 (51%)	126 (41%)	127 (46%)	101 (37%)

In terms of reasons why subjects were classified as unevaluable, there was a discrepancy in the way the medical officer and sponsor performed this evaluation. The sponsor listed every reason why a subject was found to be unevaluable, and, thus, approximately 20% of unevaluable subjects had more than one reason listed. The medical officer only listed the major reason why a subject was found to be unevaluable, and, thus, each subject had only one reason listed. The following two tables present the sponsor's and medical officer's summaries of why patients were found unevaluable:

ALL UNEVALUABLE PATIENTS	148	(43.7%)	147	(40.5%)	295	(51.1%)
PATS. WITH > 1 REASON	10	(20.7%)	97	(24.8%)	107	(20.4%)
CAUSATIVE ORGANISM RESISTANT	56	(38.4%)	57	(31.5%)	115	(39.9%)
UNEVALUABLE BY						
INVESTIGATOR	41	(13.5%)	41	(15.0%)	82	(14.2%)
INSUFFICIENT THERAPY	38	(12.5%)	31	(11.0%)	69	(12.9%)
CAUSATIVE ORGANISM						
UNIDENTIFIED	36	(11.8%)	24	(8.9%)	60	(10.4%)
UNACCEPTABLE PATHOGEN	16	(5.3%)	28	(10.2%)	44	(7.5%)
PROTOCOL VIOLATED	9	(3.0%)	11	(4.0%)	20	(3.5%)
SENSITIVITY NOT DONE	9	(3.0%)	10	(3.6%)	19	(3.3%)
NO POSTTHERAPY CULTURE	9	(2.6%)	8	(2.9%)	16	(2.8%)
CAUSATIVE ORGANISM UNAPPROVED	4	(1.3%)	4	(2.9%)	12	(2.1%)
CONCOMITANT ANTIBIOTIC	4	(1.3%)	9	(3.5%)	9	(1.6%)
SEQUENTIAL THERAPY	5	(1.6%)	2	(0.7%)	7	(1.2%)
INCOMPLETE DATA	3	(1.0%)	3	(1.1%)	6	(1.0%)
BACTERIOLOGY INCOMPLETE	2	(0.7%)	3	(1.1%)	5	(0.9%)
CONCOMITANT MEDICATION	3	(1.0%)	2	(0.7%)	5	(0.9%)
INITIAL CULTURE EARLY	1	(0.3%)	3	(1.1%)	4	(0.7%)
NO DURING CULTURE	2	(0.7%)	2	(0.7%)	4	(0.7%)
NO POST FOLLOW-UP	3	(1.0%)	1	(0.4%)	4	(0.7%)
NO INITIAL CULTURE	0		2	(0.7%)	2	(0.3%)
BLIND BROKEN	0		1	(0.4%)	1	(0.2%)
NO THERAPY	0		1	(0.4%)	1	(0.2%)
POSTTHERAPY CULTURE LATE	1	(0.3%)	0		1	(0.2%)
NO FOLLOW-UP CULTURE*	1	(0.3%)	0		1	(0.2%)
UNDERLYING CONDITION	1	(0.3%)	0		1	(0.2%)
POOR COMPLIANCE	0		1	(0.4%)	1	(0.2%)
WRONG DOSAGE	1	(0.3%)	0		1	(0.2%)

MEDICAL OFFICER'S REASON UNEVALUABLE SUMMARY

	<u>Dirithromycin</u>	<u>Erythromycin</u>
1. MICROBIOLOGIC		
A. no culture	0	0
B. no growth	25 (14%)	22 (13%)
C. resistant org.	46 (26%)	48 (28%)
D. unacceptable org.	72 (40%)	73 (42%)
E. miscellaneous	7 (4%)	7 (4%)
2. CONCOMITANT MEDICATIONS	5 (3%)	5 (3%)
3. POOR FOLLOW-UP	13 (7%)	13 (8%)
4. ADVERSE EVENTS	3 (2%)	2 (1%)
5. OTHERS	7 (4%)	3 (2%)
A. no reason given	2	1
B. broken blind	0	1
C. insufficient tx	1	0
D. prolonged tx	1	0
E. wrong dosage	1	0
F. mistake made by microbiology lab	0	1
G. other inclusion/exclusion criteria violation	2	0
TOTALS	178	173

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Notes: In this chart the % given is the % of unevaluable patients, not % of the entire patient population. Also, the sponsor tested all pathogens for susceptibility to both erythromycin and dirithromycin, but officially reported organisms as being either sensitive or resistant based on the zones obtained with erythromycin. This was done because erythromycin and dirithromycin had similar susceptibility patterns with typical skin infection pathogens (such as *Staphylococcus aureus* and *Streptococcus pyogenes*) so the class antibiotic was chosen (that is, erythromycin).

Medical Officer Comments

There is a wide discrepancy between the number of patients found evaluable by the medical officer and the number found evaluable by the sponsor. The major reason for this appears to be related to the definition of acceptable organisms. As noted above, the vast majority (85%) of patients found unacceptable by the medical officer were classified as such due to microbiologic reasons. The criteria used by the medical officer to classify an organism as acceptable or not were noted in a prior section.

As per the medical officer, there was a total of 242 positive initial cultures with growth of *Staphylococcus aureus*, of which 41 were either resistant to (85% of the 41 were resistant) or of intermediate susceptibility to erythromycin. This is a resistance rate of 17%. The sponsor submitted data which evaluates the susceptibility patterns based on dirithromycin disk diffusion tests. The resistance rate with dirithromycin is 16%. Considering that *Staphylococcus aureus* is the predominant organism found in skin and skin-structure infections, this high percentage of resistant organisms is concerning.

b. DEMOGRAPHICS:

The following section deals with the demographics of the patients found evaluable by the medical officer. The sponsor presented demographics dealing with all enrolled subjects (presented previously) but did not give specific demographics for evaluable patients only.

1. Gender: 49% of the dirithromycin evaluable group was female and 50% of the erythromycin evaluable group was female.

2. Age: For dirithromycin, the following age distribution was obtained:

YRS	#	%
15-24	32	25%
25-34	28	22%
35-44	22	17%
45-54	19	15%
55-64	11	8.7%
>=65	14	11%

For erythromycin, the following distribution was obtained:

YRS	#	%
<15	1	1%
15-24	26	26%
25-34	20	20%
35-44	23	23%
45-54	6	6%
55-64	13	13%
>=65	12	12%

3. Weights: For dirithromycin, the following weight distribution was found:

<u>wt. (kg)</u>	<u>#</u>	<u>%</u>
<40	0	0%
40-49	2	1.6%
50-59	14	11%
60-69	22	17%
70-79	35	28%
80-89	16	13%
90-99	13	10%
>=100	24	19%

For erythromycin, the following distribution was obtained:

<u>wt. (kg)</u>	<u>#</u>	<u>%</u>
<40	0	0%
40-49	2	2%
50-59	18	18%
60-69	29	29%
70-79	18	18%
80-89	12	12%
90-99	5	5%
>=100	17	17%

4. Concomitant medications and illnesses: All patients on other systemic antibiotics or topical antimicrobials, or using steroid preparations were seen as unevaluable (unless the other antimicrobial was started due to failure of the study drug, at which time the patient was seen as a failure). In the evaluable population, the most commonly used concomitant medication was paracetamol, which was used essentially evenly among the dirithromycin and erythromycin treatment groups. Other medications consisted of oral contraceptives or medications used specifically for underlying illnesses (such as hypertension). There was no difference of significance among the two treatment groups with regard to illness or with regard to a specific medication.

5. Duration of therapy: Subjects with insufficient therapy or with prolonged therapy were seen as unevaluable unless a subject discontinued the study drug because of poor response and thus was seen as a failure. The duration of therapy that the sponsor is interested in is 7 days. The following distribution of duration of therapy was obtained for dirithromycin:

<u>duration (days)</u>	<u>#</u>	<u>%</u>
<=4	2	2%
5-6	6	5%
7-8	97	77%
9-10	14	11%
11-12	3	2%
>12	4	3%

The following distribution was obtained for the erythromycin group:

<u>duration (days)</u>	<u>#</u>	<u>%</u>
<=4	2	2%
5-6	1	1%
7-8	78	77%
9-10	12	12%
11-12	6	6%
>12	2	2%

6. Diabetes mellitus: There were 21 evaluable patients with diabetes mellitus, 13 in the dirithromycin treatment group (10% of that group) and 8 in the erythromycin group (8% of that group).

Medical Officer's Comments:

Overall, the two treatment groups were similar in basic demographics.

c. DISEASE TYPES:

There were 7 different disease types represented by the 227 patients found evaluable by the medical officer with the following distribution:

DIAGNOSIS	DIRITHROMYCIN	ERYTHROMYCIN	TOTAL
SQ ABSCESS	29 (23%)	27 (27%)	56
CELLULITIS	12 (10%)	7 (7%)	19
INFECTED ULCER	7 (6%)	8 (8%)	15
IMPETIGO	27 (21%)	22 (22%)	49
POST-SURGICAL WOUND INFECTION	7 (6%)	6 (6%)	13
POST-TRAUMA WOUND INFECTION	15 (12%)	5 (5%)	20
PYODERMA	29 (23%)	26 (26%)	55
TOTAL	126	101	227

The sponsor did not perform a breakdown of the evaluable patients into disease entities but did look at this in regard to all enrolled patients. The following table shows the sponsor's data:

TABLE AQAB.5.13
PRESENTING DIAGNOSIS
ALL PATIENTS

INDICATION: SKIN

	DIRITHROMYCIN (N=304)		ERYTHROMYCIN (N=274)		TOTAL (N=578)	
	n	(%)	n	(%)	n	(%)
ABSCESSES, SUBCUTANEOUS	113	(38.3%)	103	(37.6%)	221	(39.2%)
CELLULITIS	10	(3.3%)	15	(5.5%)	25	(4.3%)
IMPETIGO	49	(16.1%)	47	(17.2%)	96	(16.6%)
INFECTION, POSTOPERATIVE WOUND	15	(5.0%)	14	(5.1%)	30	(5.2%)
INFECTION, TRAUMATIC WOUND	23	(7.6%)	20	(7.3%)	43	(7.4%)
PYODERMA	54	(17.8%)	51	(19.0%)	107	(18.5%)
SKIN, ULCER INFECTED	25	(8.2%)	21	(7.7%)	46	(8.0%)

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Medical Officer's Comments:

In regards to the disease type, there are no statistically significant differences between the two treatment groups in the patients found evaluable by the medical officer.

d. EFFICACY:

This section will present the results obtained by the medical officer. It is essentially divided into two tables. The first table is a combination table where the disease types are matched with specific organisms and then a total efficacy rate for the disease type is presented. The second table presents efficacy rates for each individual organism, irregardless of the disease they caused.

Several points of clarification are necessary prior to the presentation of the tables. All evaluations are done based on the data from the late post-therapy visit. As noted previously, the clinical results were classified as either "Cured" or "Not Cured". The term "Improved" was not used by the medical officer. Patients with a very major improvement were classified as "Cured" while all other "Improved" patients were seen as "Not Cured". In regards to the microbiologic response, the categories presented before were combined into three major categories, which were:

1. Assumed eradicated: All subjects in which a repeat culture showed elimination of the initial pathogen and all subjects in which a repeat culture was not obtained due to lack of a site (the "Not Applicable" group) were included here.
2. Not eradicated: This includes all patients in which the repeat culture showed either persistence of the initial organism, growth of a new pathogen, or regrowth of the initial organism but now with a resistance to the study drugs.
3. Unable to Evaluate: This group includes all patients in which the investigator did not state what was done microbiologically with the subject at the late post-therapy visit.

The percent rate of microbiologic cure is thus based on the ratio of "Assumed eradicated" patients divided by the sum of the "Not eradicated" and "Assumed eradicated" patients. The group labelled "Unable to Evaluate" was not included in the ratio.

The criteria for accepting an organism as a true pathogen were presented previously. The accepted pathogens obtained were divided into 5 groups:

1. *Staphylococcus aureus*: all subjects where this was the only pathogen isolated.
2. *Streptococcus pyogenes*: all subjects where this was the only pathogen isolated.
3. Other streptococcal species: all subjects with *Streptococcus* species other than *pyogenes* isolated as the only pathogen.
4. Mixed flora: all subjects where an accepted combination of pathogens were obtained on initial culture. An example is a subject with impetigo having both *Streptococcus pyogenes* and *Staphylococcus aureus* growing on initial culture.
5. Other organisms: subjects, especially diabetics, where more unusual organisms (as far as skin infections are concerned) were accepted as being true pathogens. An example would be a diabetic patient with *Escherichia coli* growing in a culture from an infected ulcer.

For the two tables that follow, "A.E." stands for "Assumed Eradicated" and "UTE" for "Unable to Evaluate".

The first table follows:

DIRITHROMYCIN			ERYTHROMYCIN		
CELLULITIS					
Organism (# pts.)	Clinical Response	Micro Response	Organism (# pts.)	Clinical Response	Micro Response
<i>S. aureus</i> (9)	8 CURED (89%)	8 A.E. 1 UTE (100%)	<i>S. aureus</i> (5)	3 CURED (60%)	4 A.E. 1 UTE (100%)
Mixed flora (1)	0 CURED (0%)	0 A.E. 0 UTE (0%)	Mixed flora (1)	1 CURED (100%)	1 A.E. (100%)
Other strep (?)	2 CURED (100%)	1 A.E. 1 UTE (100%)	Other strep (?)	1 CURED (100%)	1 A.E. (100%)
TOTALS (12)	10 CURED (83%)	9 A.E. 2 UTE (90%)	TOTALS (7)	5 CURED (71%)	6 A.E. 1 UTE (100%)
INFECTED ULCERS					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (7)	3 CURED (43%)	5 A.E. (71%)	<i>S. aureus</i> (5)	1 CURED (20%)	2 A.E. (40%)
			Mixed flora (2)	0 CURED (0%)	0 A.E. (0%)
			Other strep (1)	0 CURED (0%)	1 UTE (0%)
TOTALS (7)	3 CURED (43%)	5 A.E. (71%)	TOTALS (8)	1 CURED (13%)	2 A.E. 1 UTE (29%)
IMPETIGO					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (25)	20 CURED (80%)	22 A.E. 2 UTE (96%)	<i>S. aureus</i> (19)	15 CURED (79%)	15 A.E. 1 UTE (83%)
<i>Strep pyogenes</i> (2)	1 CURED (50%)	1 A.E. 1 UTE (100%)	<i>Strep pyoge</i> (1)	1 CURED (100%)	1 A.E. (100%)
			Mixed flora (2)	1 CURED (50%)	1 A.E. (50%)
TOTALS (27)	21 CURED (78%)	23 A.E. 3 UTE (96%)	TOTALS (22)	17 CURED (77%)	17 A.E. 1 UTE (81%)

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POST-SURGICAL WOUND INFECTIONS					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (4)	4 CURED (100%)	4 A.E. (100%)	<i>S. aureus</i> (6)	5 CURED (83%)	5 A.E. (83%)
<i>Strep pyogenes</i> (1)	1 CURED (100%)	1 A.E. (100%)			
Other organisms (2)	2 CURED (100%)	2 A.E. (100%)			
TOTALS (7)	7 CURED (100%)	7 A.E. (100%)	TOTALS (6)	5 CURED (83%)	5 A.E. (83%)
POST-TRAUMA WOUND INFECTIONS					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (11)	8 CURED (73%)	10 A.E. (91%)	<i>S. aureus</i> (4)	3 CURED (75%)	4 A.E. (100%)
<i>Strep pyogenes</i> (2)	1 CURED (50%)	1 A.E. (50%)			
Other <i>strep</i> (1)	1 CURED (100%)	1 A.E. (100%)	Other <i>strep</i> (1)	1 CURED (100%)	1 A.E. (100%)
Mixed flora (1)	1 CURED (100%)	1 A.E. (100%)			
TOTALS (15)	11 CURED (73%)	13 A.E. (87%)	TOTALS (5)	4 CURED (80%)	5 A.E. (100%)
PYODERMA					
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (24)	17 CURED (71%)	16 A.E. (67%)	<i>S. aureus</i> (21)	11 CURED (52%)	12 A.E. 1 UTE (60%)
<i>Strep pyogenes</i> (3)	1 CURED (33%)	1 A.E. 1 UTE (50%)			
			Other <i>strep</i> (2)	2 CURED (100%)	2 A.E. (100%)
Mixed flora (2)	1 CURED (50%)	1 A.E. (50%)	Mixed flora (2)	2 CURED (100%)	2 A.E. (100%)

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			Other organisms (1)	1 CURED (100%)	1 A.E. (100%)
TOTALS (29)	19 CURED (66%)	18 A.E. 1 UTE (64%)	TOTALS (26)	16 CURED (62%)	17 A.E. 1 UTE (68%)
SUBCUTANEOUS ABSCESS					
ORGANISMS (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISMS (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (24)	21 CURED (88%)	21 A.E. 1 UTE (91%)	<i>S. aureus</i> (22)	18 CURED (82%)	19 A.E. 2 UTE (95%)
			<i>Strep pyogenes</i> (2)	2 CURED (100%)	2 A.E. (100%)
Other strep (1)	1 CURED (100%)	1 A.E. (100%)	Other strep (1)	1 CURED (100%)	1 A.E. (100%)
Mixed flora (2)	2 CURED (100%)	2 A.E. (100%)	Mixed flora (2)	2 CURED (100%)	2 A.E. (100%)
Other organisms (2)	1 CURED (50%)	1 A.E. 1 UTE (100%)			
TOTALS (29)	25 CURED (86%)	25 A.E. 2 UTE (93%)	TOTALS (27)	23 CURED (85%)	24 A.E. 2 UTE (96%)
TOTALS (126)	96 CURED (76%)	101 A.E. 8 UTE (86%)	TOTALS (101)	71 CURED (70%)	76 A.E. 6 UTE (80%)

The following table looks at the results obtained in regards to specific organisms:

DIRITHROMYCIN			ERYTHROMYCIN		
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (#pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (104)	81 CURED (78%)	86 A.E. 4 UTE (86%)	<i>S. aureus</i> (82)	56 CURED (68%)	61 A.E. 5 UTE (79%)
<i>Strep pyogenes</i> (8)	4 CURED (50%)	4 A.E. 2 UTE (67%)	<i>Strep pyogenes</i> (3)	3 CURED (100%)	3 A.E. (100%)
Other strep (4)	4 CURED (100%)	3 A.E. 1 UTE (100%)	Other strep (6)	5 CURED (83%)	5 A.E. 1 UTE (100%)
Mixed flora (6)	4 CURED (67%)	4 A.E. (67%)	Mixed flora (9)	6 CURED (67%)	6 A.E. (67%)
Other organisms (4)	3 CURED (75%)	3 A.E. 1 UTE (100%)	Other organisms (1)	1 CURED (100%)	1 A.E. (100%)
TOTALS (126)	96 CURED (76%)	101 A.E. 8 UTE (86%)	TOTALS (101)	71 CURED (70%)	76 A.E. 6 UTE (80%)

The following pathogens were found in the mixed flora group:

1. Dirithromycin treatment group: 6 patients with "mixed flora" in their initial culture. All 6 had *Staphylococcus aureus*. The other pathogen found was *Streptococcus pyogenes* in 2 patients, and *Streptococcus* species in the other 4 patients. In regard to response to therapy, the following was found:

a. *Staphylococcus aureus* & *Streptococcus pyogenes* combination: 2 patients, one of which was both clinically cured and with assumed eradication of pathogen. The other patient failed both clinically and microbiologically.

b. *Staphylococcus aureus* & *Streptococcus* species: 4 patients, with 3 of these having both a clinical and microbiologic cure, and one patient with failure.

2. Erythromycin treatment group: 9 patients with "mixed flora" in their initial culture. All 9 had *Staphylococcus aureus*. The other pathogen found was *Streptococcus pyogenes* in 6 patients and *Streptococcus* species in 3 subjects.

In regard to response to therapy, the following was found:

a. *Staphylococcus aureus* & *Streptococcus pyogenes* combination: 6 patients, 5 of which were both clinically cured and with assumed eradication of pathogen. The other patient failed both clinically and microbiologically.

b. *Staphylococcus aureus* & *Streptococcus* species: 3 patients, with 1 of these having both a clinical and microbiologic cure, and the other 2 patients with both clinical and microbiologic failure.

If the organisms found in the "mixed flora" are considered individually, the results found were:

DIRITHORMYCIN			ERYTHROMYCIN		
ORGANISM (# pts.)	CLINICAL RESPONSE	MICRO RESPONSE	ORGANISM (#pts.)	CLINICAL RESPONSE	MICRO RESPONSE
<i>S. aureus</i> (110)	85 CURED (77%)	90 A.E. 4 UTE (85%)	<i>S. aureus</i> (91)	62 CURED (68%)	67 A.E. 5 UTE (78%)
<i>Strep pyogenes</i> (10)	5 CURED (50%)	5 A.E. 2 UTE (63%)	<i>Strep pyogenes</i> (9)	8 CURED (89%)	8 A.E. (89%)
Other <i>strep</i> (8)	7 CURED (88%)	6 A.E. 1 UTE (86%)	Other <i>strep</i> (9)	6 CURED (67%)	6 A.E. 1 UTE (75%)

Medical Officer's Comments:

Based on the microbiologic breakdown, *Staphylococcus aureus* and *Streptococcus pyogenes* were the only pathogens found in enough patients (greater than 10 in each of the two treatment groups) to be able to comment on the efficacy of dirithromycin in clearing skin and skin structure infections caused by these organisms. The number of patients found to have infections caused by any of the other organisms was too small to be able to compare with certainty the two antimicrobials. However, *Staphylococcus aureus* and *Streptococcus pyogenes* are the two MAJOR skin and skin structure infection pathogens, and the number of patients with these organisms as the pathogen was adequate.

The efficacy rates obtained by both antimicrobials in patients with infected skin ulcers was suboptimal. This is not surprising considering that the majority of these patients had diabetes mellitus as an underlying condition.

Using the Chi-square test, the dirithromycin and erythromycin treatment groups' efficacy results were compared for total outcome, patients with *Streptococcus pyogenes*, and patients with *Staphylococcus aureus*. In all three comparisons, there was no statistically significant difference (using a two-sided tail p value of 0.5) among the treatment groups in both the clinical and microbiologic response rates. However, of concern, is the low efficacy rate of dirithromycin in treatment of infections caused by *Streptococcus pyogenes*. Though not statistically inferior to erythromycin, the 50% cure rate found is concerning.

e. ADVERSE CLINICAL EVENTS:

The individual investigators listed all clinical adverse events that occurred during the course of the clinical trial. The investigators were also responsible for stating whether the adverse event was probably, possibly, or not related or of unknown relation to the study drug. The sponsor later, when evaluating the data, agreed or disagreed with the investigators' evaluation of the adverse clinical events. The medical officer also went through the investigators' reports and either agreed or disagreed with the investigators' evaluations. The results obtained by the medical officer and by the sponsor were very similar, so only one list of adverse clinical events will be presented in this section (showing the medical officer's evaluation). The adverse events listed in this section are only those seen as possibly, probably or definitely related to the study drug or of unknown relation. Adverse events not related to the study drugs are not listed.

All adverse events of a mild or moderate degree are listed together. Severe or serious adverse clinical events will be presented individually.

Of the 578 enrolled subjects, a total of 165 experienced one or more adverse clinical events, or a total of 29% of the subjects. Of the 578 enrolled subjects, 304 received dirithromycin and 274 received erythromycin. Of the dirithromycin treatment group, 91 subjects experienced an adverse clinical event, or 30%. Of the erythromycin treatment group, 74 subjects experienced an adverse clinical event, or 27%. In terms of the actual adverse clinical events seen, the following table provides a list of each event and the frequency with which it was encountered:

EVENTS	<u>Dirithro</u>	<u>Erythro</u>
A. GI SYSTEM		
1. Nausea/Dyspepsia	37 (12%)	37 (14%)
2. Diarrhea	16 (5%)	8 (3%)
3. Flatulence	6 (2%)	6 (2%)
4. Emesis	4 (1%)	3 (1%)
5. Combination of Nausea/ Vomiting/Diarrhea	0 (0%)	2 (1%)
6. Constipation	1 (1%)	0 (0%)
B. CNS		
1. Headache	16 (5%)	10 (4%)
2. Dizziness	6 (2%)	4 (2%)
3. Somnolence	1 (1%)	3 (1%)
4. Dry Mouth	1 (1%)	0 (0%)
5. Insomnia	1 (1%)	0 (0%)
6. Tinnitus	1 (1%)	0 (0%)
7. Weakness	2 (1%)	0 (0%)
8. Myalgia	1 (1%)	1 (1%)
9. Flu-like sx	2 (1%)	0 (0%)
C. GENITOURINARY SYSTEM		
1. Vaginitis	2 (1%)	2 (1%)
2. Urinary Tract Infection	0 (0%)	1 (1%)
D. SKIN		
1. Pruritis	0 (0%)	5 (2%)
2. Rash	3 (1%)	2 (1%)
3. Urticaria	1 (1%)	0 (0%)
4. Pruritic Rash	2 (1%)	0 (0%)
5. Dry Skin	0 (0%)	1 (1%)
6. Sweating	0 (0%)	1 (1%)
7. Alopecia	1 (1%)	0 (0%)
8. Ulcers in mouth	1 (1%)	0 (0%)
9. Swelling around eyes	0 (0%)	1 (1%)
E. CARDIAC & MISCELLANEOUS		
1. Hypoglycemia	1 (1%)	1 (1%)
2. Chest Pain	0 (0%)	1 (1%)
3. Palpitations	0 (0%)	1 (1%)
4. Extrasystolic beats	1 (1%)	0 (0%)

There were a total of 16 clinical adverse events, in addition to those listed above, which were singled out because they were listed as being severe/serious in nature. Of these 16 events, there were 8 each in the two treatment groups. The actual severe/serious adverse events found in each treatment group were: DIRITHROMYCIN: 2 patients with nausea, and 1 each with depression, diarrhea, emesis, flatulence, pruritic rash and a combination of nausea/ vomiting/ diarrhea. ERYTHROMYCIN: 2 patients with nausea, 2 with flatulence, and 1 each with diarrhea, headache, migraine, and pruritic.

Two patients listed above, though rated as having only mild/moderate degrees of these clinical adverse events, were flagged by the medical officer because of the nature of the event and because of a lack of information available to fully explain why the adverse event may have occurred. These two patients were in the dirithromycin group.

1. pt. who had a mild degree of extrasystolic beats noted, yet had no history of cardiac difficulties in the past, and
2. pt. who had a mild amount of alopecia, but with no history of this in the past and no other obvious risk factors for developing alopecia other than study drug use.

Medical Officer's Comments:

Overall, the distribution of adverse clinical events was distributed fairly evenly among the individual study centers. However, there were two centers, #088 and #091, that had far fewer adverse clinical events reported than anticipated. Both of these centers, however, had a fairly equal distribution of patients into the two treatment groups, so this should not have affected the overall adverse clinical event rates for the two treatment groups.

As expected, the most common adverse event class was gastrointestinal. There were no statistically significant differences in the rates of any of the classes when comparing the two treatment groups.

The medical officer does have concern about the two patients mentioned previously that had mild alopecia and mild extrasystolic beats as adverse clinical events. Both of these patients were in the dirithromycin treatment group, and in both cases the adverse events were not expected for a macrolide. More information is required.

f. LABORATORY VALUES:

Upon evaluating all laboratory results obtained on all of the patients, 22 of the 578 enrolled subjects (or 3.8%) were noted to have significant laboratory value changes possibly or probably associated with study drug use. This was determined by the medical officer based on the following criteria:

1. There was a clinically significant change in a laboratory test value compared to a baseline value while on the study drug or noted up until the time of the late posttherapy visit.
2. This change in the laboratory value was not secondary to either the disease process that entered the subject into the study, or secondary to a chronic condition. Exceptions to this were made if the study drug caused a change in patients with a chronic condition who were stable at the time of entry into the study. For example, a patient with a history of high cholesterol levels, but under control, who had a sudden increase in cholesterol levels during the clinical trial would be considered as having had a significant laboratory value change probably related to the study drug.
3. This laboratory change did not stand out on its own but was

consistent with other changes. For example, a patient with a mildly elevated ALT level who had otherwise normal liver function tests would not be considered as having a study drug related laboratory abnormality but a laboratory value variation.

Of these 22 patients, 12 were in the dirithromycin treatment group (or 3.9% of those subjects) and 10 were in the erythromycin treatment group (or 3.6% of those subjects). None of the laboratory value abnormalities were seen as being serious in nature. All of the changes were either mild or moderate in nature, and had the following distribution:

<u>LABORATORY VALUE CHANGE</u>	<u>#DIRITHRO</u>	<u>#ERYTHRO</u>
1. decreased platelets	1	0
2. increased eosinophils	1	1
3. increased basophils	1	0
4. decreased calcium	3	4
5. increased CPK	1	4
6. increased blood glucose	5	1

CPK=creatinine phosphokinase

Of note, all of the subjects noted to have an elevation of blood glucose levels were insulin-dependent diabetics who were in good control prior to onset of study drug use. Diabetics who had elevated blood glucose levels noted on pre-therapy laboratory work were not considered as being well controlled at the time of this clinical trial, and thus were not listed as having had study drug induced elevation in blood glucose levels.

MAR 31 1994

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NDA: 50-678

SUBMISSION DATE: 4 June, 1992

Dirithromycin (enteric coated tablets)

BRAND NAME: DYNABAC[®]

REVIEWER: Funmilayo Ajayi, Ph.D

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

TYPE OF SUBMISSION: Original NME

CODE: 1,S
=====

SYNOPSIS: NDA 50-678 was first submitted on June 4, 1992 for Dirithromycin enteric coated tablets. The application was filed on 4/29/93 following major and minor amendments. The product is being proposed for the treatment of pharyngitis & tonsillitis, 2° bacterial infection of acute bronchitis, and skin & skin structure infections. Studies were conducted to evaluate the pharmacokinetics in healthy volunteers, bioavailability/BE, metabolism, kinetics in special populations, tissue distribution, and drug interactions. Dirithromycin, a prodrug, is rapidly hydrolyzed to erythromyclamine immediately after administration. Erythromyclamine is well distributed to tissues, has an estimated volume of distribution of about 800 liters, a terminal elimination half-life of approximately 44 hours and is primarily eliminated via the hepatic/fecal route. Like most macrolides, the plasma concentration is low and highly variable. However, unlike erythromycin and troleandomycin, the drug interaction potential of dirithromycin is low.

RECOMMENDATION: A review of the data submitted in the Human Pharmacokinetics and Bioavailability section of NDA 50-678 for Dirithromycin showed that the Biopharmaceutics requirements were met. Please forward the appropriate comments to: (i) the reviewing Chemist (page 6); and (ii) the Firm (page 6).

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ORGANIZATION OF REVIEW: Following the background is a description of the drug formulation. The summary of the studies is followed by the general comments and comments to the Firm.

BACKGROUND: Dirithromycin is an oral antibacterial agent derived from erythromycin. It is the C-9 oxazine derivative of erythromyclamine formed by the condensation of methoxyacetaldehyde and erythromyclamine. Erythromyclamine is formed by the reductive amination of the C-9 ketone of erythromycin. It is acid-labile and belongs to the macrolide antibiotic agents. Following oral administration, Dirithromycin is non-enzymatically hydrolyzed to erythromyclamine; an antibiotic equivalent in potency to the parent compound. The empirical formula of dirithromycin is $C_{42}H_{78}N_2O_{14}$ with a molecular weight of 835.09 and structural formula shown in Fig 1. This new molecular entity is being proposed for oral administration of 500mg daily dose.

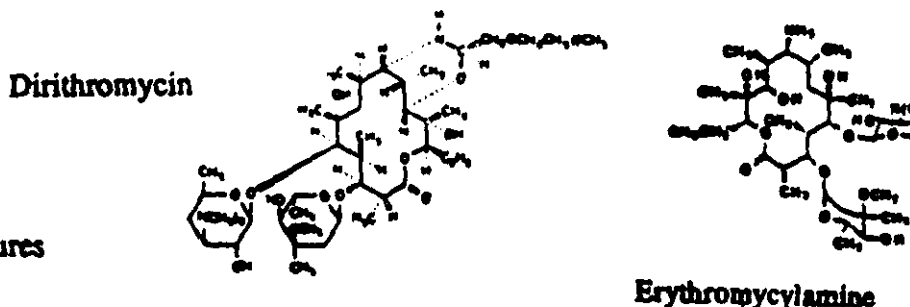


Figure 1: Chemical structures

DRUG FORMULATION: The drug substance is presented as enteric coated tablet formulation containing buffering agents in order to maximize the absorption of the acid-labile compound. A number of different formulations were used in clinical efficacy studies. The to-be-marketed is one of the 5 Lilly II formulations. A synopsis of the different formulations can be found in appendix II. Below is the composition of the to-be-marketed enteric coated tablet.

Name of Ingredients	Quantity (mg/tablet)	Reasonable Variation (mg/tablet)	Function
Active Ingredient			
Dirithromycin	250.0 ^{1,2}	(0.3% excess)	Active Ingredient
Other Ingredients			
Core Tablet			
1 Magnesium Carbonate, USP			Buffering agent
1 Microcrystalline Cellulose			Binder, disintegrant, diluent
1 Sodium Starch Glycolate, NF			Disintegrant
1 Hydroxypropyl Cellulose			Binder
1 Croscarmellose Sodium, NF			Disintegrant
1 Magnesium Stearate, NF			Lubricant
Core Tablet Weights			
Subcoating (Theoretical)			
1 Hydroxypropyl Methylcellulose, USP			Film coating polymer
1 Polyethylene Glycol (3350), NF			Plasticizer
1 Triethylene Glycol, USP			Plasticizer
1 Benzyl Alcohol, NF			See note ³
Enteric Coating (Theoretical)			
1 Methacrylic Acid Copolymer			Film coating polymer
			Coloring agent
1 Triethyl Citrate, NF			Plasticizer
Talc, USP			Polishing aid
			Product information

¹ The sum of dirithromycin and microcrystalline cellulose is 250.0 mg.
² Adjusted for potency.
³ Benzyl alcohol is contained in the subcoating solution as a preservative prior to use. Some benzyl alcohol will volatilize in the coating process.

DRUG DISSOLUTION: The proposed method utilizes USP dissolution apparatus I, a rotation speed of rpm, ml 0.1N HCl at 37°C for 2 hours (1st stage), ml pH 6.8 phosphate buffer (2nd stage), and a dissolution specification (Q) of not less than % dissolved in buffer stage in minutes. Samples were analyzed by using a colorimetric derivatization procedure with absorbance measurements at nm.

ANALYTICAL METHODS: A microbiological assay methodology was employed for the estimation of dirithromycin and or erythromycylamine in plasma, urine, and tissues using Micrococcus luteus as the test organism. The measured moiety is erythromycylamine because dirithromycin is non-specifically and rapidly converted to erythromycylamine at pH below 10. The range of the standard curve for the microbiological assay was ug/ml for dirithromycin and ug/ml for erythromycylamine. An HPLC method that employed roxithromycin as the internal standard was also used in some studies. Estimation of the amount of erythromycylamine and the residual dirithromycin in biological samples was by an electrochemical detector following extraction with methy t-butyl ether. The range of the standard curve was ug/ml for this method. There is a good correlation between the HPLC and microbiological methods - $r^2 = 0.95$. However in some studies, the microbiological assay was observed to yield higher values than the HPLC method suggesting non-specificity of the microbiological method coupled with the possibility of a loss of material during the extraction procedure for the HPLC (recovery = 81%). Erythromycylamine was shown to be stable in storage and during 3 cycles of freeze/thaw. The stability of extracted samples of erythromycylamine held for 8 days at room temperature was demonstrated.

SUMMARY OF STUDIES:

1. **Pharmacokinetics:** The microbiological assay was employed in most of the studies. As with the other macrolide antibiotic agents, dirithromycin is highly distributed into deep compartments; resulting in the plasma levels being near or below the detection limit of the analytical methods which led to high variability in the estimated PK parameters. Although there is some degree of correlation between the HPLC and the microbiological methods ($r^2 = 0.95$), the former gave lower measurements in some studies. In most cases, the plasma concentrations are near or at the lower limit of detection. Thus, careful interpretation should be given to the following results:

1.1 **Mass-balance study:** The level of radioactivity became detectable in plasma from 3 to 5 hours following oral administration of a single dose of ^{14}C radiolabelled dirithromycin and remain measurable up to 216 h. The fecal excretion amounts to 65 - 95% of the dose with the bulk of radioactivity occurring during the first 48 h after drug administration. Approximately 2 - 4% of the dose is recovered in urine mainly within the first 12 hours. Thus giving an indication that about 10% (5.5 - 13%) of the oral dose is absorbed. Urinary excretion of radioactivity persisted for up to 10 days suggesting a slow return from the extravascular tissue compartment. Following IV administration of the radiolabelled drug, dirithromycin was rapidly hydrolyzed to erythromycylamine, an active metabolite with similar potency, which is widely distributed within 2 hours after the infusion. The urinary excretion amounts to about 20% of the IV dose; while the remaining radioactivity was found in the feces. The terminal half-life ($t_{1/2}$) of both the microbiological activity and the radioactivity ranged from 16 to 65 hours with a

mean of 40 h. As a result of the entero-hepatic recirculation, the $t_{1/2}$ is likely to be slightly over-estimated. The protein binding of dirithromycin and erythromyclamine is approximately 19%. This low binding to plasma proteins might be one of the factors that favor the fast distribution of erythromyclamine into tissue.

1.2 Absolute bioavailability: Evaluation of the absolute bioavailability was made on erythromyclamine because of the rapid, non-enzymatic hydrolysis of dirithromycin to this active metabolite within an hour of IV dosing. Also, following oral dosing, dirithromycin was undetectable in all plasma samples. The most consistent estimate of bioavailability was from the urinary excretion data. In one study, the estimated absolute bioavailability from dose-corrected urinary excretion data following a single 500 mg dose ranged from % . In another study, the absolute bioavailability was estimated to be 10%, 15%, and 10% following 500mg, 750mg, and 1000mg administered as single oral doses. Similar results, 12%, 9%, 13%, and 9%, were obtained from the urinary excretion data for 250mg, 500mg, 750mg and 1000mg dose levels.

1.3 Dose proportionality: An attempt was made to demonstrate linearity of dose in a study where 4 dose levels (250, 500, 750, & 1000 mg) of dirithromycin were administered as single oral doses to 12 subjects using a cross-over design with a washout period of 2 weeks. The concentrations of erythromyclamine were at or below the limit of detection following the 250 mg oral dose. For other doses, dirithromycin was undetected in all plasma samples while the plasma concentrations of erythromyclamine were very low. The apparent terminal elimination $t_{1/2}$ estimated from the plasma data tends to increase with dose (2.3 h, 5.2 h, & 7.6 h for 500mg, 750 mg & 1000mg doses, respectively). Using the sigma-minus method, the apparent terminal elimination $t_{1/2}$ from the urinary data are similar: 29.6 h, 32.5 h, 30.6 h, & 31.9 h for the 250, 500, 750, & 1000 mg doses, respectively. Although the urinary $t_{1/2}$ values are much longer than those in plasma, most (~ 76%) of the erythromyclamine recovered in urine was excreted during the initial 36 hour. The amount of erythromyclamine excreted in urine are 2.2, 2, 2.5, & 1.7 % of 250mg, 500mg, 750mg & 1000mg dose, respectively. The percent of the overall urinary excretion of erythromyclamine which was recovered over a period of 36 hour following drug administration was similar: 73%, 70%, & 71% for the 500mg, 750mg, & 1000mg doses. There is a high variability in the observed pharmacokinetic parameters which is likely related to the analytical limitations encountered at the low range of concentrations observed in the study. Results from the urinary data can be interpreted as an indication of dose linearity.

1.4 Multiple dosing: There was no apparent drug accumulation when volunteers were dosed to steady-state over a period of 14 days.

1.5 Bioequivalence: Following a series of single and multiple dose bioequivalency studies, the Sponsor could not prove equivalence between the clinical and the to-be marketed formulations. Analysis of a recent study indicated that the to-be-marketed tablets appear to be more bioavailable than one of the clinical lots (Study # B9Z-LC-AQBI).

1.6 Food effect study: The effect of food on the bioavailability of dirithromycin was evaluated following administration immediately after a normal breakfast, and administration 1 or 4 hours before food. The effects of high and low fat meals on dirithromycin bioavailability were also investigated. Results obtained indicated a slight increase in the absorption when dirithromycin

was administered immediately after food with the dietary fat having little or no effect. However, a notable decrease in C_{max} (33%) and AUC (31%) was observed when administered 1-hour before food compared to when administered immediately after food. Thus, dirithromycin should be administered immediately after food or on an empty stomach.

1.7 Tissue concentration: Tissue concentrations of erythromyclamine were generally 20 to 30 fold higher than those obtained in plasma and persist for longer periods of time. This finding is typical for the macrolide antibiotics. It was noted in patients with biliary stenosis that the bile concentration of erythromyclamine is much higher than the plasma concentration. Therefore, it is likely that the predominant route of excretion of erythromyclamine is via the bile.

2. Drug interaction:

2.1 Cimetidine and antacid (Maalox): The absorption of dirithromycin was slightly enhanced when given immediately after the administration of Maalox or cimetidine.

2.2 Theophylline or antipyrine: Following co-administration of dirithromycin with each of these agents in separate studies, a significant change was not observed in the kinetics of 200 mg t.i.d. oral dose of theophylline, or 1 gram daily oral dose of antipyrine.

3. Special population:

3.1 Elderly: Dirithromycin, 500 mg daily oral dose, was administered to 10 young (19-50 yrs.), and 20 elderly healthy male and female volunteers for 10 days. The elderly subjects were distributed into 4 age brackets (55-69, 70-74, 75-79, & >80 years). There was considerable variability in the absorption of dirithromycin as indicated by the variability in C_{max} in each of the age groups. There was a trend for increased C_{max} and AUC with age following multiple dosing. However, neither C_{max} nor AUC were significantly altered with age. Therefore, no dosage adjustment should be necessary based on pharmacokinetic considerations alone.

3.2 Patients: Dirithromycin was administered to patients with cardiovascular, renal (including those on dialysis), or hepatic (biliary or parenchymal) disease. Results from these studies indicated that dosage adjustment is not necessary for patients with any of these disease states.

3.3 Gender: Although there is no specific study to address gender differences, data from studies where males and females were enrolled failed to reveal significant differences in the pharmacokinetics of dirithromycin or erythromyclamine, the measured / circulating moiety.

4. Pharmacokinetic / pharmacodynamic (PK/PD) relationship:

4.1. There is no study that adequately address the PK/PD relationship. However, the study described below provided some interesting information. A total of 125 patients with acute bronchitis or acute exacerbations of chronic bronchitis took part in a study where trough and plasma concentrations of dirithromycin were assessed at steady-state. A daily, single oral dose of 500 mg dirithromycin was administered for a period of 7 days. The blood samples were taken before and 4 hours after the day 7 dose. Of the 119 evaluable patients, 55 were cured, 59

improved, there were 3 failures, and 2 relapses. The mean steady-state 4-hour post-dose and trough concentrations (mg/l) of dirithromycin in these various groups are, respectively, for those cured; for those that improved; for those that failed to respond; and for the 2 patients who had a relapse. This study would have provided a basis for determining any PK/PD relationship if plasma concentrations were determined at more time points and, there was a better-defined, well-monitored PD marker.

4.2. An MIC value of 2 ug/ml is recommended for most susceptible organisms except for *H. influenzae*. Although the link between the plasma concentration of macrolides and the rate of bacterial kill (outcome or efficacy) is not known, it should be noted that the observed mean peak plasma concentration, C_{max} , of erythromyclamine in the reported PK studies (approximately 0.34 ug/ml) is lower than the MIC value for most susceptible organisms.

GENERAL COMMENTS (NEED NOT BE SENT TO THE FIRM):

Dirithromycin is rapidly hydrolyzed to erythromyclamine which is the circulating active moiety. The high degree of intersubject variability observed in all the studies might be partly explained by the low concentrations of erythromyclamine in serum and urine.

As with other macrolides, the plasma concentration of erythromyclamine is very low and highly variable. Also, erythromyclamine is rapidly and highly distributed to tissues. Reports from the submitted drug interaction studies as well as from literature indicated that dirithromycin has a low potential for drug interaction.

COMMENTS TO REVIEWING CHEMIST:

The proposed tolerance range, referred to as "reasonable variation" by the sponsor, in the formulation is too wide. There is a concern about the bioavailability of products made in the extreme situation. For instance:

1. Magnesium stearate, mg/tablet (proposed range = mg/tablet): Bioavailability can be adversely affected because this component is crucial to product release.

2. Methacrylic acid copolymer, mg/tablet (proposed range = mg/tablet): Bioavailability can be adversely affected because coating is an essential part of the formulation.

3. Please refer to an Article entitled "Workshop II Report: Scale-up of Oral Extended Release Dosage Forms" in European Journal of Pharm. and Biopharm. (1993) vol. 39(4), page 162-167.

COMMENTS TO FIRM:

1. The dissolution method utilized USP Apparatus I (); please provide the reason(-) for not using the standard

2. The proposed dissolution method, USP dissolution apparatus I / at a rotation speed of rpm, containing ml 0.1N HCl at 37°C for 2 hours (1st stage), and ml pH

6.8 phosphate buffer (2nd stage), is acceptable to the Division of Biopharmaceutics. However, dissolution specification (Q) should be set at NLT % dissolved in buffer stage in minute

3. It is recommended that phase IV studies should include evaluation of:

- (i) the pharmacokinetics of dirithromycin in patients with moderate to severe hepatic impairment who have a potential for antibacterial therapy.
- (ii) the pharmacokinetics of dirithromycin in nursing mothers to assess the degree of excretion into milk.
- (iii) the pharmacokinetics of dirithromycin following administration to children.

LABELING COMMENTS: Changes are shaded and are in italics.

CLINICAL PHARMACOLOGY:

Systemic Bioavailability--

[The following text is heavily obscured by a large black redaction box.]

Metabolism--Dirithromycin is rapidly converted by nonenzymatic hydrolysis during absorption to erythromycylamine, which is microbiologically active. Dirithromycin and erythromycylamine are primarily eliminated in the bile and undergo little or no hepatic metabolism. Thus, the primary route of elimination is fecal/hepatic, with 81% to 97% of the dose eliminated in this manner. Approximately 2% of the administered dose is eliminated renally *mainly within the first 36 hours following drug administration.*

Pharmacokinetics--*Following oral administration of a 500 mg dose of dirithromycin, a peak plasma concentration of the microbiologically active metabolite (erythromycylamine), approximately 0.84 µg/ml, is reached in about 4 hours post dose. The plasma half-life of erythromycylamine was estimated to be about 8 hours; while a urinary terminal elimination half-life of 44 (16 to 65) hours, apparent total body clearance of approximately 23 L/min, and an apparent volume of distribution (V_{dss}) of 800 (504 to 1,041) liters was observed in patients with normal renal function.*

The bioavailability parameters of dirithromycin in plasma after single- and multiple-dose oral administration of 500 mg once daily for 10 days in fasting healthy young adults (19 to 50 years of age) *are comparable, giving indication of little or no accumulation.*

Protein Binding--The protein binding of circulating dirithromycin and its metabolite, erythromycylamine, ranges between 15% to 30%.

Tissue Concentrations—Following a 500 mg dose of dirithromycin, erythromyclamine is rapidly distributed into tissues and achieves high concentrations within cells, significantly higher concentrations in tissues than in plasma or serum. There are no data available on cerebrospinal fluid penetration.—
-----etc. etc. etc.

PRECAUTIONS:

Drug Interactions—

In general, most patients treated with dirithromycin who are receiving concomitant theophylline therapy do not require empiric adjustment of theophylline dosage or monitoring of theophylline plasma concentrations. theophylline plasma concentrations should be monitored with dosage adjustment as appropriate for patients with more severe pulmonary disease who are dependent on maintaining a given theophylline plasma concentration for optimal pulmonary function or for patients with theophylline concentrations at the higher end of the therapeutic range.

When dirithromycin is administered immediately following antacid or H2-receptor antagonists,-----
-----etc. etc. etc.

Funmilayo O. Ajayi 3/29/94
Funmilayo O. Ajayi, Ph.D
Pharmacokinetic Evaluation Branch

Biopharm Day (3/3/94; Collins, Ludden, Fleischer, Pelsor, Ajayi)

FT initialed by Frank Pelsor, PharmD.....

F. Pelsor 3/30/94

cc: NDA 50-678, (Clinical Division), HFD-426 (Fleischer, Pelsor, Ajayi), Chron, Drug, Reviewer, FOI (HFD-19), GA, C, F, DI.

JUL 20 1994

=====

NDA: 50-678
Dirithromycin (enteric coated tablets)

SUBMISSION DATE: 22 June, 1994

BRAND NAME: DYNABAC[®]

REVIEWER: Funmilayo Ajayi, Ph.D

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

TYPE OF SUBMISSION: Amendment

CODE: 1,S

=====

Background: The comments from the Division of Biopharmaceutics regarding the dissolution method and specification were forwarded to the sponsor by the clinical review division. The comments are:

1. The dissolution method utilized USP Apparatus I please provide the
reason(s) for not using the standard
2. The proposed dissolution method, USP dissolution apparatus I at a
rotation speed of rpm, containing ml 0.1N HCl at 37°C for 2 hours (1st stage), and
ml pH 6.8 phosphate buffer (2nd stage), is acceptable to the Division of
Biopharmaceutics. However, dissolution specification (Q) should be set at NLT %
dissolved in buffer stage in minutes.

The sponsor, in this submission, provides their response to the two issues above.

Findings:

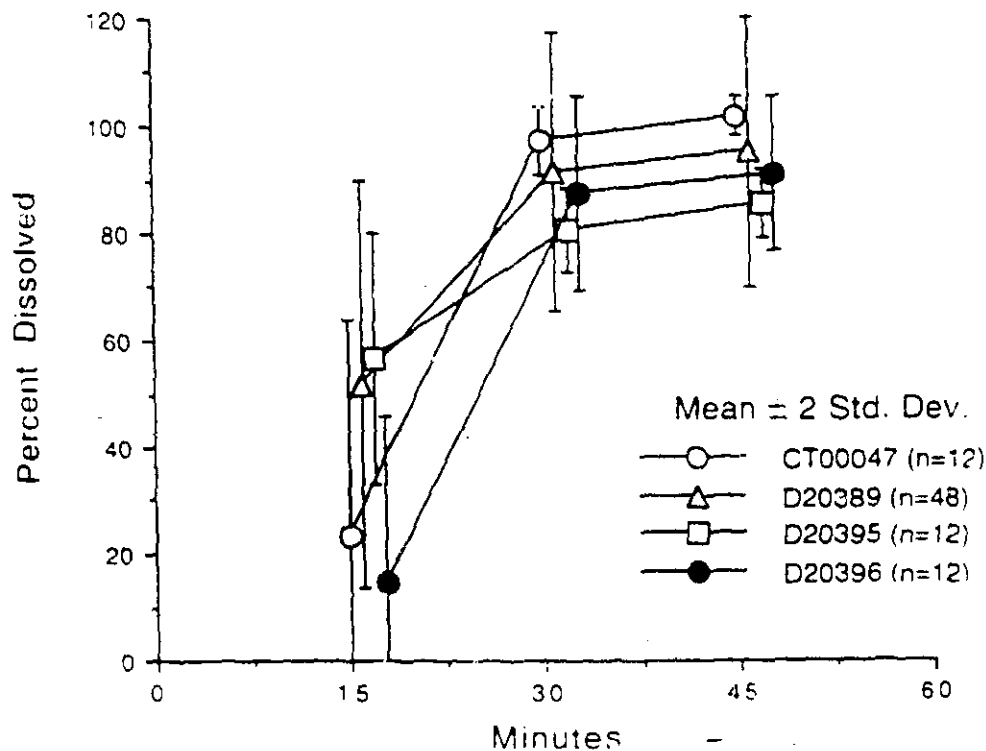
Item 1. The sponsor stated that the USP Apparatus I is preferred to the
because the latter is more likely to become blinded with enteric coating from
large tablets during dissolution testing (previous experience). Other stated reasons for using
the are: less susceptibility to trapping air bubbles under the basket, studier,
easier to rinse the HCl off when changing media, and easier observation of the disintegration
of tablets.

Item 2. The validation for the scale-up of the manufacturing process for the to-be-marketed
formulation was recently completed by the sponsor. The dissolution method and specification
used for the validation was as reported in the NDA for the clinical trial batches. Based on the
dissolution results obtained during the validation process, the sponsor is concerned that the
to-be-marketed formulation may not meet the dissolution specification (Q) of % in min
set by the Division of Biopharmaceutics following its review of the NDA, in about 16% of
tests, through Stage III testing.

The following were the observations made from a review of the dissolution profiles from the validation of the scale-up of the manufacturing process:

1. There is a high degree of variability in the dissolution profiles of tablets from the same (within) and from different (between) Lots.
2. The dissolution observed after the scale-up is different in rate and extent (%) from that observed for the clinical trial batches (Fig 1). The impact of this difference, if any, on the bioavailability and hence the therapeutic performance of this product is unknown. Unfortunately, the bioavailability of the product is known to be highly variable.

FIGURE 1: Dissolution Profile Comparison of Market Image Lot CT00047 and Full-scale Validation Lots D20389, D20395, and D20396



3. Although the to-be-marketed formulation may not meet a dissolution specification (Q) of % in minutes, a tighter Q is necessary in order to provide an attempt to reduce the high variability. Based on the current dissolution results from the scale-up batches, the tablets should be able to meet a Q of % in minutes (Table 1).

TABLE 1.

Lot # (section)	% of Test that meet Q (Q % in min.). n = 12.
D 20389 (A)	100
D 20389 (B)	100
D 20389 (C)	92
D 20389 (D,E,F,G,H)	92
D 20395 (ALL)	92
D 20396 (ALL)	83

General Comments:

1. The high degree of variability in the dissolution profile observed for the to-be-marketed formulation is of concern because of the well established variability in the degree of exposure to the product following administration in well-controlled situations (Bioequivalence studies). Also, the dissolution profile is different in rate and extent from the Clinical trial batch. Although this might be attributed to minor scale-up changes, and may not appear to be dramatic, the effect on the systemic availability and possibly, clinical outcome may be pronounced. The findings from the review of the dissolution data further lend credence to our previous comments to the reviewing Chemist regarding the tightening of the proposed tolerance range for some components of the formulation that are important to product release. For convenience and ease of reference, these comments are inserted in this review (see below) for appropriate action by the reviewing Chemist.

Previous comments to the chemist:

"The proposed tolerance range, referred to as "reasonable variation" by the sponsor, in the formulation is too wide. There is a concern about the bioavailability of products made in the extreme situation. For instance:

1. Magnesium stearate, mg/tablet (proposed range mg/tablet): Bioavailability can be adversely affected because this component is crucial to-product release.

2. Methacrylic acid copolymer, mg/tablet (proposed range mg/tablet): Bioavailability can be adversely affected because coating is an essential part of the formulation.

3. Please refer to an Article entitled "Workshop II Report: Scale-up of Oral Extended Release Dosage Forms" in European Journal of Pharm. and Biopharm. (1993) vol. 39(4), page 162-167."

Recommendation: Following a review of the dissolution data from the scale-up validation of the to-be-marketed formulation by the Division of Biopharmaceutics, the dissolution specification (Q) should be set at NLT % dissolved in buffer stage in minutes. The explanation for using the instead of the standard is acceptable.

Ajayi 7/20/94
Funmilayo O. Ajayi, Ph.D
Pharmacokinetic Evaluation Branch

FT initialed by Frank Pelsor, PharmD. *[Signature]*

cc: NDA 50-678, HFD-520 (Clinical Division), HFD-426 (Fleischer) HFD-427 (M. Chen, Pelsor, Ajayi), Chron, Drug, Reviewer, FOI (HFD-19), HFD-340 (Vish).

JUN 29 1993

=====

NDA: 50-678

SUBMISSION DATE: April 27, 1993

Dirithromycin (enteric coated tablets)

BRAND NAME: DYNABAC[®]

REVIEWER: Funmilayo Ajayi, Ph.D

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

TYPE OF SUBMISSION: Amendment to Original NME **CODE:** 1,S

=====

The following information is needed to make the above submission complete:

1. **Drug Batch:** (i) A clarification of the Lot numbering used in the **present study**. (ii) The link with the original production batch. (iii) The expiration dates.
2. Data from a recent dissolution test for the two batches used in the submitted bioequivalence study. If the batch is expired or close to expiration, a batch recertification will be required.
3. Tables 1-4 Vol. 1 pg 66-69 are not explicit. Represent each table by grouping the data with respect to the dosing periods.
4. The individual serum dirithromycin data (Attachment A, vol. 1, pg 92) is not included. Please provide this information.

General: Batch production record

(a) Please link all the Lot/CT numbers that have been used in the clinical and pharmacokinetic studies to their respective production batches.

(b) A breakdown of the usage of the tablets produced as Batch # 3 is required.

Funmilayo 6/29/93
Funmilayo O. Ajayi, Ph.D
Pharmacokinetic Evaluation Branch

RD/FT initialed by Frank Pelsor, PharmD. *Frank Pelsor* 4/29/93

cc: NDA 50-678, HFD-520 (Clinical Division), HFD-426 (Fleischer, See, Pelsor, Ajayi).

FDA Corres

To Co.



NDA 50-678

NOV 30 1994

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref.: No. 94 HFD-340-1103

Steven K. Zorn, M.D.
Pulmonary Medicine, P.C.
4060 Westown Parkway
West Des Moines, Iowa 50266

Dear Dr. Zorn:

On August 23-29, 1994, Mr. Michael J. Verdi, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as Principal Investigator, of a clinical study (protocol B92-MC-AQAB) of the investigational drug dirithromycin (LY237216), performed for Eli Lilly Research Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

We have evaluated Mr. Verdi's inspection report, the documents collected, and the four page statement of his investigational observations (FDA-483; copy enclosed) which was presented and discussed with your research coordinator, Mr. Staples, at the close of the inspection. We conclude that you significantly violated Title 21 of the Code of Federal Regulations (CFR) sections 312.60, 312.62 (a) (b), 312.64 (b), 312.66 and 50.25 covering your conduct of clinical investigations of FDA regulated products and the protection of human study subjects as follows:

A. SUMMARY OF PROTOCOL VIOLATIONS: (21 CFR 312.60).

1. You failed to follow the protocol in that the protocol requires urine samples to be provided by the patient at the "during therapy" visits to assure that the patients are actually taking the medications. We note that eleven patients had no record of urine samples collected or assays performed.

2. Section 8(d) of the protocol requires that "records of laboratory tests, clinical notes and patient medical records will be kept in the patient file as original source documents for the study." There was no available source record(s) to verify the gram stain results (for the PMN's and epithelial cells/hpf) as reported in the case report forms (CRFs). In addition, no source documentation was available to support the numeric values listed under the bronchitis/pneumonia ratings (cough, productive sputum, dyspnea, tachypnea, rhonchi, rales and chills) in the CRFs on certain visits for patients

3. Under "exclusionary criteria" the protocol notes "any condition, including significant underlying disease...,"; a "Dear Doctor" memo dated May 3, 1989 states that patients with a history of cardiac disease and on multiple cardiac medications should not be enrolled in the dirithromycin study. Nine patients

had such backgrounds (congestive heart failure, coronary artery disease, myocardial infarction ventricular arrhythmia/atrial fibrillation, cerebrovascular accident and breast cancer (#4272)) and were receiving cardiac medications such as Lanoxin, Cardizem, Lasix, Nitrostat, Dyazide and clonidine. All these patients should have been excluded from enrollment.

B. SUMMARY OF VIOLATIONS RELATED TO REQUIREMENTS FOR PREPARING AND MAINTAINING ADEQUATE AND ACCURATE CASE HISTORIES (21 CFR 312.62(b))

1. There is no available record or evidence that you reviewed the data in CRFs for their accuracy and completeness.

2. It is very important to accurately record the outcome/completion status of each subject enrolled in the study. The protocol states "if the patient's symptomatic response is "cure" or "improvement," the patient must have completed at least five days therapy." We note six patients, five of whom had four days of therapy and one three days of therapy. The symptomatic response for five of these patients was rated as "improvement" and one as "cure."

In addition, patient _____ was rated as "cured" in the CRF, yet in comparing the pre-therapy respiratory diagnostic rating criteria to post-therapy evaluation, we found an increased (moderate to severe) rating for cough, dyspnea, tachypnea, an unchanged rating for chills, and an improved rating (moderate to mild) for productive sputum. Therefore, the symptomatic response should have been a "failure" instead of "cure."

C. SUMMARY OF VIOLATIONS RELATED TO REQUIREMENTS FOR INVESTIGATOR REPORTING TO SPONSOR AND/OR IRB: (21 CFR 312.64 and 312.66).

You failed to report adverse events to your IRB and to the sponsor. Patient _____ was hospitalized for severe cough, shortness of breath and increased sputum production; patient _____ was hospitalized for rash, confusion and pneumonia. Documentation was not available to show that the sponsor and/or the IRB were notified of these events.

D. SUMMARY OF VIOLATIONS RELATED TO DRUG ACCOUNTABILITY RECORDS (21 CFR 312.62 (a)).

Discrepancies were found between the number of tablets taken in consideration of the number of days the patient was reported to have been on the study. Patient _____ CRF shows the patient on study drug for four days while the drug inventory indicates the patient had 9 days of dirithromycin and 6 days of erythromycin; patient _____ CRF shows the patient on study drug for 5 days while the drug inventory indicates the patient had 7 days of test medication; patient _____ CRF shows the patient on study drug for 3 days while the drug inventory indicates the patient had 7 days of test medication. Therefore, the number of days and the number of tablets each patient received could not be determined based on the available records, and no explanation was provided to reconcile the differences.

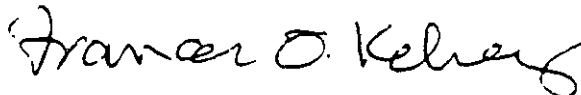
E. SUMMARY OF VIOLATIONS RELATED TO CONSENT FORM PROCEDURES (21 CFR Part 50.25).

The consent form used in this study was deficient in that:

1. it did not state that one purpose of the study was to determine safety of the investigational drug;
2. it did not provide an explanation of whom the subject should contact in the event of a research-related injury to the subject.

The above listed violations are not intended to be an all-inclusive list of violations and deficiencies. We request that you notify this office in writing within 15 working days of receipt of this letter of actions that you have taken or plan to take to correct/or prevent similar violations in future studies that you might conduct. If you do not take appropriate action to assure strict adherence to the investigational new drug regulations, we may consider steps that will lead to your disqualification in accordance with 21 CFR 312.70.

Sincerely yours,



Frances O. Kelsey, Ph.D., M.D.
Director
Division of Scientific
Investigations, HFD-340
Office of Compliance
Center for Drug Evaluation
and Research

Enclosures (2)

1. FDA-483
2. 21 CFR Part 50.25 - Elements of Informed Consent

Page 5 - Steven K. Zorn, M.D.

CFN: 1932926

Field classification: B

Headquarters classification: OAI

If Headquarters classification is different classification,
explain why:

Deficiencies noted:

inadequate consent form
 inadequate drug accountability
 failure to adhere to protocol
 inadequate records
 failure to report ADRS _____
_____ other (specify)

cc:

HFA-224

HFI-35 (w/o distribution page)

HFR-SW300

HFR-SW340

HFR-SW350

HFC-132

HFC-230

HFD-019 Hooton

HFD-300 Rats#

HFD-340 R/F

HFD-342

HFD-344 files w/original records

HFD-344/c/r/s/Lisook

HFD-340 Kelsey/Richardson

HFM-640 Salewski

HfV-234 Pocurull

HfZ-324 Grayson

HFD-520: Review Division Div. Dir./Doc. Rm.: NDA #50,678

Dr. Alex/CSO: Dillon-Parker

IND #

Drafted: AEl-Hage 11/3/94

DSI:CIB

Document: Zorn.aeh

typed:mgk 11/16/94

edited: AEH

r/t: mgk 11/28/94

r/t: mgk 11/29/94

Edited: FOKelsey

r/t: mgk 11/30/94

NDA 50-678

**M.W. Talbott, Ph.D.
Director
Medical Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285**

AUG 4 1992

Dear Dr. Talbott:

Reference is made to your New Drug Application (NDA) dated June 4, 1992, and submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for Dynabac (dirithromycin) 250 mg enteric coated tablet for oral administration.

On the basis of our initial review of your application referred to above, received on Jun. 5, 1992, and acknowledged on June 23, 1992, we have determined that the application is not acceptable for filing under 21 CFR 314.101.

Specifically, the application has been determined to be incomplete because it does not contain on its face information required under section 507 of the Act and 21 CFR 314.50 (3) as follows:

- 1. Appropriate data that establish the bioequivalence of the "to-be-marketed" formulation of dirithromycin and the various formulations of dirithromycin used in the clinical trials have not been submitted.**
- 2. Appropriate data that validate the correlation between the microbiological assay and the HPLC assay have not been submitted. Appropriate data that validate the use of dirithromycin in the microbiological assay, rather than its hydrolyzed active metabolite, erythromycylamine, have not been submitted.**
- 3. All the dosage forms used in the clinical trials and all of the dosage forms used in the bioavailability and bioequivalence studies need to be tabulated by lot number, lot size, and production date and submitted.**

Complete information, as specified in this letter, will be necessary, at a minimum, before this application can be filed for review. At the time of the review, further information may be requested depending on the adequacy of the data submitted.

Within 30 days of the date of this letter, you may request in writing an informal conference about Food and Drug Administration's (FDA's) refusal to file the application.

NDA 50-678

To file this application over Food and Drug Administration's protest, you must avail yourself of this informal conference.

Should you have questions concerning this application, please contact Ms. Kennerly K. Chapman, Project Manager, at 301-443-2057.

Sincerely yours,

MML 8/4/92

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Orig NDA 50-678

HFC-130

HFD-82

HFD-500

HFD-638

HFD-735

HFD-520

HFD-520/DDir/Lumpkin/1/4/92

HFD-520/DeputyDir/Gavrilovich

HFD-520/MO/Moledina/7/30/92

HFD-520/Pharm/Browder

HFD-520/Chem/Katague

HFD-520/Micro/Creedon

HFD-714/Biometrics/Harkins

HFD-426/Biopharm/Lam/7/30/92

HFD-521/PMS/Chapman/12/50678.11 *4/28/92*

Concurrences:

HFD-520/SMO/Albuerne/7/22/92

HFD-520/SPharm/Osterberg

HFD-520/SCchem/DeCamp

HFD-521/SPMS/Bona/7/22

REFUSE TO FILE

NDA 50-678

M.W. Talbott, Ph.D.
Director
Medical Regulatory Affairs
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

NOV 4 1992

Dear Dr. Talbott:

Reference is made to your New Drug Application (NDA) dated June 4, 1992, submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for Dynabac (dirithromycin) 250 mg enteric coated tablet for oral administration.

Reference is further made to our letter dated August 4, 1992, in which you were informed that the application was judged to be incomplete and, therefore, not acceptable for filing under 21 CFR 314.101.

Subsequent to amendments dated August 27, and September 4, 1992, and to our meeting held on September 3, 1992, it was concluded that additional information with regard to the pharmacokinetics and bioavailability section of the application is necessary:

1. A bioequivalence study for dirithromycin incorporating a two-way crossover design with repeat sampling should be submitted.
2. A minimum of thirty-six subjects should be utilized comparing the marketed image lot with lots with the most clinical data.
3. A study design comparing inter- and intra subject variability should be submitted.
4. HPLC methodology should be utilized to analyze the samples. Additionally, some of the samples should be analyzed via a microbiological and HPLC assay to establish a correlation between the two methodologies. These results should be submitted.
5. Data analyzed incorporating log transformation and non-transformation should be submitted. Bioequivalence should be established using a two one-sided T test for AUC's and C_{max} .

With regard to the microbiology section of the application, the following information is requested:

1. Raw data which should include HPLC chromatograms of calibration and patient serum samples indicating the dirithromycin and erythromyclamine peaks, to validate the use of the HPLC assay for the bioavailability and pharmacokinetic studies, should be submitted.
2. The HPLC assay which had been used for the different studies should be identified and details of the chromatographic conditions should be submitted. A statement whether the assay used in a given study can differentiate dirithromycin from erthromyclamine should be submitted.
3. The microbiological assay used for monitoring activity in biological samples should clearly identify which organisms have been used as test organisms, and whether different results are obtained if a different organism is used. Such information should be in compliance with 21 CFR 436, subpart D of the regulations.
4. Data on the rate of hydrolysis of dirithromycin to erythromyclamine in human plasma (not rat plasma) should be submitted.

Complete information as specified in this letter will be necessary, at a minimum, before this application can be filed for review. At the time of the review, further information may be requested depending on the adequacy of the data submitted.

Should you have any questions concerning this application, please contact Ms. Kennerly K. Chapman, Project Manager, at 301-443-0257.

Sincerely yours,

MML 11/04/92

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Orig NDA 50-678

HF-35

HFC-130

HFD-82

HFD-473

HFD-500

HFD-638

HFD-735

HFD-520

HFD-520/DDir/Lumpkin/rd11/2/92

HFD-520/MO/Moledina/rd10/27/92

HFD-520/Pharm/Browder

HFD-520/Micro/Creedonrd10/26/92

HFD-520/Chem/Katague

HFD-473/Biopharm/Lam/rd10/28/92

HFD-521/PMS/Chapman/n50678.rfa

Concurrence only:

HFD-520/SMO/Albuerne/10/28/92

HFD-520/SPharm/Osterberg/10/26/92

HFD-520/SCchem/DeCamp/pappas10/26/92

HFD-520/SMicro/Sheldon/10/26/92

HFD-521/SPMS/Bona/10/26/92

REFUSE TO FILE CORRESPONDENCE

NDA 50-678

23

M.W. Talbott, Ph.D.
Director
Medical Regulatory Affairs
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Talbott:

We have received your New Drug Application (NDA) submitted to Section 507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Dynabac (dirithromycin) Tablets, 250 mg
Date of Application: June 4, 1992
Date of Receipt: June 5, 1992
Our Reference Number: NDA 50-678

Unless we find the application not acceptable for filing, the filing date will be August 5, 1992.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning the NDA, please contact Ms. Kennerly Chapman, Project Manager, at 301-443-6797.

Sincerely yours,

J. Bona 6/16/92

James D. Bona, R.Ph.
Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA 50-678
HFD-520
HFD-520/MO/NMoledina
HFD-520/PHARM/NBrowder
HFD-520/MICRO/KCreedon
HFD-520/PMS/KChapman *KC*
SJohnson/6/15/92
F/T: 6/15/92

NDA 50-678

JAN 14 1994

M. W. Talbott, Ph.D.
Director, Medical Regulatory Affairs
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Talbott:

We acknowledge the receipt of your resubmitted new drug application (NDA) dated April 27, 1993, received by the Food & Drug Administration (FDA) on April 29, 1993, for Dynabac (dirithromycin) 250 mg enteric coated tablet for oral administration.

Unless we find the resubmission unacceptable for filing, the filing date will be June 29, 1993.

The new due date is April 29, 1994.

If questions arise concerning this application, please contact Ms. Maureen Dillon-Parker, Project Manager, at 301-443-6797.

Sincerely yours,

PD 1-14-94

Patricia L. DeSantis
Acting Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 50-678
HFD-520
HFD-520/SMO/Albuerne/rd init 1/13/94
HFD-520/MO/Moledina/rd init 1/12/94
HFD-520/MO/Rakowsky
HFD-520/SPharm/Osterberg
HFD-520/Pharm/Joshi
HFD-520/SMicro/Sheldon
HFD-520/Micro/Creedon
HFD-520/Chem/Katague
HFD-713/Stat/Harkins
HFD-426/SBiopharm/Pelsor
HFD-426/Biopharm/Srinivasan
HFD-521/SPMS/DeSantis/rd init 1/11/94
HFD-521/PMS/Dillon-Parker\rd 1-6-94
FT\1-14-94\C:\WP51\EXT\N50-678.NDD

ACKNOWLEDGEMENT

NDA 50-678

M.W. Talbott, Ph.D.
Director
Medical Regulatory Affairs
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

JUL 16 1993

Dear Dr. Talbott:

Reference is made to your New Drug Application (NDA) dated June 4, 1992, submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for Dynabac (dirithromycin) 250 mg enteric coated tablet for oral administration.

Reference is further made to our letter dated August 4, 1992, in which you were informed that the application was judged to be incomplete and, therefore, not acceptable for filing under 21 CFR 314.101.

We further acknowledge submissions dated August 27, September 4, and December 16, 1992; April 27, and June 30, 1993.

We have reviewed your application and have determined that the application is acceptable for filing under 21 CFR 314.101.

Additionally, please be advised that additional information with regard to the pharmacokinetics and bioavailability section of the application is necessary:

1. Drug Batch

- a. A clarification of the lot numbering used in the present study should be provided
- b. The link with the original production batch should be provided
- c. Expiration dates should be provided

2. Data from a recent dissolution test for the two batches used in the submitted bioequivalence study should be provided. A batch recertification will be required if the batch has expired or is close to expiration.

3. Tables 1-4 in volume 1, pages 66-69 are not explicit. Tables should be represented by grouping the data with respect to the dosing periods.

4. Individual serum dirithromycin data should be provided.
5. Batch production record
 - a. All Lot/CT numbers that have been used in the clinical and pharmacokinetic studies should be linked to their respective production batches.
 - b. A breakdown of the usage of the tablets produced as Batch number 3 should be provided.

At the time of review, appropriate data that establish the bioequivalence of the "to-be-marketed" formulation of dirithromycin and the formulation of dirithromycin used in the clinical studies will be assessed. Further recommendations may be forthcoming depending on the adequacy of the data submitted.

All future communications should be submitted in triplicate and identified with the NDA referred to above.

Should you have questions concerning this application, please contact Ms. Kennerly K. Chapman, Project Manager, at 301-443-0257.

Sincerely yours,

MM 7/16/93

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Orig NDA 50-678

HFD-520

HFD-520/DDir/Lumpkin

HFD-520/DDpty/Gavrilovich

HFD-520/MO/Moledina/rd7/7/93

HFD-520/Pharm/via Osterberg

HFD-520/Chem/Katague

HFD-520/Micro/Creedon

HFD-714/Biometrics/Harkins

HFD-426/Biopharm/Ajayi/rd6/29/93

HFD-521/PMS/Chapman/n50678.ok6/29/93 *see 7/14/93*

Concurrence only:

HFD-520/SMO/Albuerne

HFD-520/SPMS/Bona

NDA 50-678

M.W. Talbott, Ph.D.
Director
Medical Regulatory Affairs
Eli Lilly and Company
Lily Corporate Center
Indianapolis, IN 46285

DEC 18 1992

Dear Dr. Talbott:

Reference is made to your New Drug Application (NDA) for Dynabac (dirithromycin) and to your letter dated November 10, 1992, concerning the design of Protocol B9Z-LC-AQB1, "Dirithromycin (LY237216): Bioequivalence of Two Batches".

Reference is further made to your letter dated November 16, 1992, requesting a waiver from the requirements of 21 CFR 320.32(a) due to insufficient quantities of tablets in Batch 4 (CT-0009-9B) at

This letter confirms the agreement between you and the Division to grant a waiver of the requirements of 21 CFR 320.32(a).

If you have further questions, please contact Ms. Kennerly K. Chapman, Project Manager, at 301-443-0257.

Sincerely yours,

MML 12/18/92

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Orig NDA 50-678

~~XXXXXXXXXX~~
HFD-520/DDir/Lumpkin
HFD-520/MO/Moledina/12/18/92
HFD-520/SPharm/Osterberg
HFD-520/Pharm/Browder
HFD-520/SMicro/Sheldon
HFD-520/Micro/Creedon
HFD-520/SCchem/DeCamp
HFD-520/Chem/Katague
HFD-521/PMS/Chapman *me 12/18/92*

Concurrence only:

HFD-520/SMO/Albuerne
HFD-521/PMS/Bona/rd12/18/92
HFD-426/Biopharm/Lam/12/18/92

WAIVER REQUEST

(attachment)

JUL 20 1994

Tovio Rist, M.D.
Dermatology Associates of Knoxville, P.C.
816 St. Mary's Professional Building
930 Emerald Avenue
Knoxville, Tennessee 37917

Dear Dr. Rist:

On May 2-5 and 13, 1994, Mr. Edward H. Maticka, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as Principal Investigator, of a clinical study (protocol # B92-MC-AQAB) of the investigational drug diryثromycin (LY237216), performed for Eli Lilly Research Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you did not adhere to pertinent Federal regulations governing your conduct of clinical investigations. We are aware that Mr. Maticka's findings were presented to you on Form FDA-483 and were discussed with you at the close of the inspection. We note your responses and acknowledge receiving on 6/28/94 an undated and unsigned letter from your firm. This reply to the FDA-483 items will be included as a permanent part of the inspection report. We would like to emphasize the following:

1. The protocol states that "patients requiring a topical anti-microbial, or topical or systemic steroid will be prohibited". You admitted patient _____ to the study, a patient who was using Temovate cream. We note your statement that Temovate was used on different area of the body than the site being studied.
2. Patient _____ had a cyst removed from the right earlobe (site being studied) and was prescribed tetracycline. In your letter you stated that the patient did not start tetracycline until she completed the study. Neither tetracycline nor the removal of the cyst were reported in the case report form (CRF) as they should have been.

Page 2 - Tovia Rist, M.D.

3. Your drug accountability records were incomplete in that no records could be found to document the amount of unused test material returned to the sponsor. The investigator is required to maintain adequate and accurate disposition records for used and unused drug including dates and quantities used and received.
4. In at least thirteen patients you failed to maintain documents to support entries/changes made in the case report forms (CRFs). You must retain copies in support of all changes made in the CRFs and copies of pertinent information related to the study.
5. The consent form failed to identify whom to contact for answers to pertinent questions about the research subjects' rights. This statement is required by Part 50.25 of our regulations (copy enclosed). Please note item (a) 7.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Maticka during inspection.

Sincerely yours,



Alan B. Lisook, M.D.
Chief, Clinical Investigations Branch
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place, Rm. #125, MPN #1
Rockville, Maryland 20855

Enclosure
21 CFR Part 50.25

CFN: 1057430

Field classification: A

Headquarters classification:

- 1) NAI
- 2) VAI-no response required
- 3) VAI-response requested

If Headquarters classification is different classification, explain why:

Deficiencies noted:

- inadequate consent form
- inadequate drug accountability
- failure to adhere to protocol
- inadequate records
- failure to report ADRS _____
- other (specify) _____

cc:

HFA-224

HFD-344 files w/original records

HFD-340 r/f

HFD-342

HFD-340 Kelsey/Richardson

HFR-SE300

HFR-SE340

HFR-SE350

✓HFD-520: Division Div. Dir./Doc. Rm.: NDA # 50-678
Dr. Moledina/CSO:Dillon-Parker

HFC-230

IND #

HFC-132

Drafted: AEl-Hage: 7/5/94: DSI: CIB

typed: mgk: 7/15/94

retyped: mgk: 7/18/94

retyped: cmm: 7/20/94

Document: Rist.aeh

NDA 50-678

MAR 15 1994

M. W. Talbott, Ph.D.
Director of Worldwide Regulatory Affairs
Lilly Research Laboratories
Indianapolis, IN 46285

Dear Dr. Talbott:

Reference is made to your supplemental new drug application (NDA) and to your amendment dated February 3, 1994, received by the Food and Drug Administration (FDA) on February 4, 1994, for Dynabac Tablets.

We consider your submission a major amendment under 21 CFR 314.60 and have determined that 175 additional days will be required for its review.

The new due date is July 29, 1994.

If questions arise concerning this NDA, please contact Ms. Maureen Dillon-Parker, Project Management Staff, at 301-443-6797.

Sincerely yours,

MML
gn L G 3/14/94

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Orig NDA 50-678,
HFD-520
HFD-520/SMO/NMoledina
HFD-520/PHARM/Jcchi
HFD-520/CHEM/DKatague
HFD-520/MICRO/KCreedon
HFD-713/STAT/Srinivasan
HFD-426/BIOPHARM/Pelsor
HFD-521/PMS/MDillon-Parker
KKonkolewski/3/14/94
F/T:

MML
3/14/94



NOV 16 1994

Randall R. Stoltz, M.D.
GFI Pharmaceutical Services, Incorporated
800 St. Mary's Drive
Evansville, Indiana 47714

Dear Dr. Stoltz:

On July 26-27, 1994, Mr. Douglas W. Gronski, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as Principal Investigator, of a clinical study (protocol #B9Z-MC-AQAB/011) of the investigational drug dirithromycin, performed for Eli Lilly Research Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you adhered to pertinent Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. However, the consent form that you used for this trial did not specifically state that the purpose of the study is to evaluate both the safety and the efficacy of the drug. Your form omits the safety aspect.

We appreciate the cooperation shown Investigator Gronski during inspection:

Sincerely yours,

Alan B. Lisook, M.D.
Chief, Clinical Investigations Branch,
HFD-344
Division of Scientific
Investigations -
Office of Compliance
Center for Drug Evaluation
and Research

Page 2 - Randall R. Stoltz, M.D.

CFN: None

Field classification: N

Headquarters classification:

- 1) NAI
- 2) VAI-no response required
- 3) VAI-response requested

If Headquarters classification is different classification, explain why:

Deficiencies noted:

- inadequate consent form
- inadequate drug accountability
- failure to adhere to protocol
- inadequate records
- failure to report ADRS _____
- other (specify)

DO NOT TYPE ANYTHING IN BOLD PRINT

cc:

HFA-224

HFD-344 files w/original records

HFD-340 r/f

HFD-342

HFD-340 Kelsey/Richardson

HFR-MW200

HFR-MW250

HFD-520:Review Division Div. Dir./Doc. Rm.:

NDA# 50,678

HFC-230 Dr. Moledina/CSO:Dillion-Parker

IND#

HFC-132

Drafted: AE1-Hage

DSI:CIB

Typed:mgk 11/14/94

r/t: mgk 11/15/94

Document: Stoltz.aeh

CO. Corres TO

FDA

Lilly

Lilly Research Laboratories
Eli Lilly and Company

December 16, 1992

Dr. Murray Lumpkin
Center for Drug Evaluation and Research
Division of Anti-Infective Drug
Products, HFD-520 - Room 12B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Lumpkin:

Re: NDA 50-678, Dynabac® (dirithromycin)

Please refer to your letter of November 4, 1992 concerning the filing of the referenced NDA. Refer also to my letter of November 10, 1992, which summarized the agreements reached by Dr. See Lam, HFD-426, FDA, and Dr. Karl DeSante, Eli Lilly and Company, concerning the design of the bioequivalence study, the submission of which is required for the filing of NDA 50-678. This letter also confirms the agreement that due to insufficient quantities of tablets in some batches, the requirement for 10X release samples may be waived. Also refer to my letter of December 16, 1992, which is the cover letter to the submission of Protocol B9Z-LC-AQBI, "Dirithromycin (LY237216): Bioavailability of Two Batches", and is the protocol to be used by

to carry out the study agreed to by Drs. Lam and DeSante.

The study will compare two batches of the Lilly II formulation. These are CT-0009-9B, Batch 4 and CT-00047, Batch 5. These two batches differ only in color, Batch 5 being white and is the "market image".

Of these two batches, total tablets in Batch 4 remain after supplying previous clinical studies. Adequate supplies of Batch 5 are available. The tablets of Batch 4 have been packaged into bottles of 10, and 18 bottles will be shipped to along with sufficient tablets from Batch 5. Eighteen bottles of Batch 4 will remain at Eli Lilly and Company as in-house samples and one bottle will be used for final assay. Of the 18 bottles at tablets), will be used in study B9Z-LC-AQBI. Therefore, only tablets will remain for in-house samples at Since an insufficient number of tablets of Batch 4 will remain, it is requested that a waiver be granted for this requirement at

Please call me at (317) 276-2574 or Dr. Larry Day at (317) 276-5037 if there are questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Allan J. Weinstein

M. W. Talbott, Ph.D.
Director
Medical Regulatory Affairs

cc: Ms. K. Chapman
Dr. S. Lam
Dr. N. Moledina

NDA 50-678 E.A. & FONSI

MDFA 50-678

E.A. + Fonsi

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
NDA 50-678
DYNABAC[®]
(DIRITHROMYCIN)
TABLETS
250 MG

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

HFD-520

FINDING OF NO SIGNIFICANT IMPACT

NDA 50-678

Dynabac®

(Dirithromycin)

Tablets

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Dynabac®**, **Eli Lilly and Company** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Dynabac is a semi-synthetic antibiotic administered as an oral tablet in the treatment of pharyngitis and tonsillitis, acute bronchitis and acute exacerbation of chronic bronchitis, pneumonia and infections of the skin and skin structures. The drug substance will be manufactured at Eli Lilly and Company in Mayaguez, Puerto Rico or near Lafayette, Indiana. The drug product will be manufactured by Eli Lilly and Company in Indianapolis, Indiana. The finished drug product will be used in hospitals and homes.

Dirithromycin rapidly metabolizes *in vivo* and degrades in the environment to erythromyclamine.

Chemical and physical testing results indicate that the hydrolysis product of dirithromycin, erythromyclamine, will most likely be restricted to the aquatic environment with no appreciable partitioning into the atmospheric or terrestrial environments. Erythromyclamine is not significantly metabolized *in vivo* nor does it rapidly degrade in the aquatic environment.

As erythromyclamine is expected to persist in the aquatic environment for some time, the toxicity of the compound in aquatic organisms was characterized. Acute static toxicity studies in *Daphnia magna* and rainbow trout (*Oncorhynchus mykiss*), and a 14 day toxicity study in green algae (*Selenastrum capricornutum*) were conducted. The data indicates that erythromyclamine is generally not toxic to aquatic organisms at concentrations of at least 1-3 orders of magnitude greater than the maximum expected environmental concentration (MEEC) at Waste Water Treatment Facilities.

Erythromyclamine is part of a family of macrolide antibiotics that can inhibit bacterial species of *Staphylococcus*, *Streptococcus*, *Legionella*, and other genera. Minimum inhibitory concentrations (MIC) for sensitive species range from about 15-128,000 ppb. The MIC for about two-thirds of the species ranges from 60-1000 ppb, which is 1-3 orders magnitude greater than the maximum expected environmental concentration (MEEC) at Waste Water Treatment Facilities.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Expired, rejected and returned drug substance and drug product will normally be disposed of by incineration. At U.S. hospitals, empty or partially empty packages will be disposed of according to hospital regulations. In the home, empty or partially empty containers will be disposed of by a community's solid waste management system or minimal quantities of unused drug product may be disposed of in the sewer system.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

12-11-94 Nancy B. Sager
DATE Prepared By
Nancy B. Sager
Review Chemist
Center for Drug Evaluation and Research

12/13/94 Phillip G. Vincent
DATE Approved
Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

12/13/94 Charles S. Kumkumian
DATE Concurred
Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (dirithromycin)
Material Safety Data Sheet (erythromyclamine)
Emission Permit Status

CC: Original NDA 50-678/FLeSane copy to NDA/HFD-520
FONSI File 50-678/HFD-102
P. Vincent/HFD-102
Docket File 50-678/HFD-102
FOI/HFD-019

50678.FON
F/T by NBS

FDA COMMENT
NDA 50-678

FDA has included Appendices A and B in the public document. The other non-confidential appendices were not included as this information is adequately summarized in the environmental assessment.

**ENVIRONMENTAL ASSESSMENT FOR THE
USE OF DYNABAC® (DIRITHROMYCIN) IN THE
TREATMENT OF INFECTIONS IN HUMANS**

**Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285**

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**ENVIRONMENTAL ASSESSMENT FOR THE
USE OF DYNABAC[®] (DIRITHROMYCIN) IN THE
TREATMENT OF INFECTIONS IN HUMANS**

1. **DATE** November 1994
2. **APPLICANT** Eli Lilly and Company
3. **ADDRESS** Lilly Corporate Center, Indianapolis, Indiana 46285

4. **DESCRIPTION OF THE PROPOSED ACTION**

A new drug approval has been requested for the use of Dynabac[®] in the treatment of infections in humans. The active ingredient in Dynabac is dirithromycin. Dirithromycin is a macrolide antibiotic intended for use in the treatment of pharyngitis and tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis, pneumonia, and infections of the skin and skin structures. Dynabac will be produced as enteric coated tablets which contain 250 mg of dirithromycin. The recommended adult dosage is 500 mg (two 250-mg tablets) once a day for up to 14 days. Approval of this new drug would authorize the production facilities of Eli Lilly Industries, Inc. (mail: P.O. Box 1748, Mayaguez, PR 00681; street: Km. 146.7 State Road 2, Mayaguez, PR 00680) in Puerto Rico, and near Lafayette, Indiana (mail: P.O. Box 685, Lafayette, IN 47902; street: Lilly Road, Shadeland, IN 47905) to manufacture dirithromycin for sale within the United States. Formulation and packaging of dirithromycin will be done at facilities of Eli Lilly and Company in Indianapolis, Indiana (mail: Lilly Corporate Center, Indianapolis, IN 46221; street: 1200-1555 Kentucky Avenue, Indianapolis, IN 46221). Expired, rejected, and returned drug substance and drug product will normally be disposed of by incineration.

Based on the proposed action, dirithromycin would be used by individuals at home and in hospitals and could potentially be introduced into the following environments:

- a. The environments adjacent to the manufacturing plants and formulation and packaging plant. The manufacturing site in Puerto Rico is in a tropical climate and an urban setting. The manufacturing plant in Indiana is located in a temperate climate and a rural setting. The formulation and packaging facilities in Indianapolis are in an urban setting.
- b. Sewage treatment facilities receiving wastes from hospitals and homes where dirithromycin is used.
- c. Septic tanks receiving wastes from homes where dirithromycin is used.

5. IDENTIFICATION OF THE CHEMICAL SUBSTANCE

A. FORMULATION

Dirithromycin will be available in the form of enteric coated tablets. The tablet will contain 250 mg of dirithromycin and excipients that are categorized as Generally Recognized as Safe.

B. DIRITHROMYCIN

Dirithromycin is a white to off-white solid. Dirithromycin is made in a chemical process from erythromycin or from 9-(S)-erythromyclamine. A representative lot (DPD13925) had a potency of 97.6%. The potency of this material consists of dirithromycin and its epimer, epidirithromycin, which contributes to the potency of the drug. Approximately 2.5% of this material was made up of related substances, such as 9-(S)-erythromyclamine. Specifications for the drug substance and impurities are listed in confidential appendices.

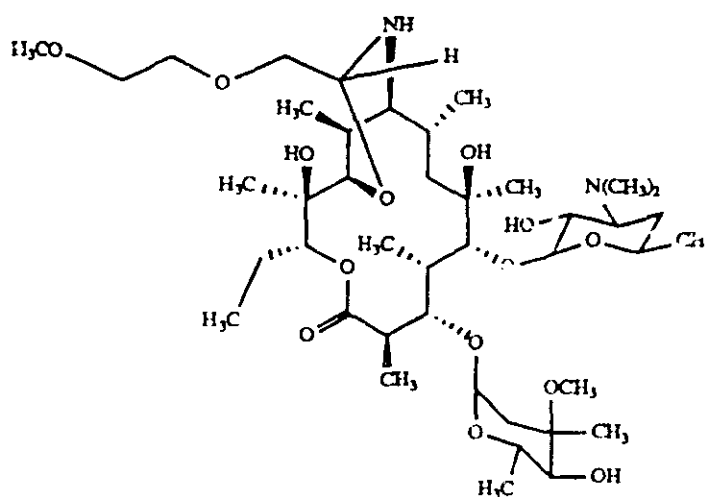
Chemical Name: (9S)-9-Deoxo-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy)ethylidene]oxy]-erythromycin

CAS Registry Number: 62013-04-1

Empirical Formula: $C_{42}H_{78}N_2O_{14}$

Molecular Weight: 835.09

Structural Formula:



Melting Temperature (Appendix C): 186.6 - 187.3°C

Ultraviolet-Visible Light Absorption (Appendix D): No appreciable absorption at wavelengths from 290 - 800 nm

Dissociation Constants (Appendix E): Average $pK_a = 9.12$; another ionizable group was too weak to allow determination of a second pK_a . Furthermore, dirithromycin degrades rapidly at lower pH levels.

Solubility in Water (Appendix F): pH 5 = Hydrolysis too rapid to determine solubility
pH 7 = Hydrolysis too rapid to determine solubility
pH 9 = $1456 \pm 54 \mu\text{g/mL}$

Octanol/Water Partition Coefficient: Hydrolysis is too rapid at pH 5 and pH 7 to determine K_{ow} . At pH 9, detection interference kept accurate measurements from being made.

Hydrolysis Half-Life (Appendix G): pH 5 = 7.5 minutes
pH 7 = 2.6 hours
pH 9 = 15.5 hours

Dirithromycin hydrolyzes to 9-(S)-erythromyclamine

Vapor Pressure: Dirithromycin is a nonvolatile solid. Differential thermal analysis indicates an endotherm at about 190°C that is near the measured melting temperature range. Thermogravimetric analysis shows only about a 0.4% weight loss from 25°C to 106°C.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

A. INTRODUCTION OF SUBSTANCES FROM THE MANUFACTURING SITES

The processes for manufacturing dirithromycin, the operations for formulating and packaging, and the pollution control practices at the corresponding plant sites are designed to result in minimal environmental impact. Dirithromycin (Appendix A) is produced in a chemical process with erythromycin or 9-(S)-erythromycylamine (Appendix A) as a starting material. Erythromycylamine may be produced by Eli Lilly and Company or purchased from Abbott Laboratories. Authorization to reference the drug master file for Abbott Laboratories has been provided to the U. S. Food and Drug Administration. Erythromycin, which is commercially available, may also be purchased. Materials used to manufacture dirithromycin are listed in confidential appendices. Production of dirithromycin will occur at the facilities of Eli Lilly Industries, Inc. (mail: P.O. Box 1748, Mayaguez, PR 00681; street: Km. 146.7 State Road 2, Mayaguez, PR 00680) in Puerto Rico or the production facility of Eli Lilly and Company near Lafayette, Indiana (mail: P.O. Box 685, Lafayette, IN 47902; street: Lilly Road, Shadeland, IN 47905). Dirithromycin will be formulated and packaged at the Lilly Technology Center of Eli Lilly and Company in Indianapolis, Indiana (mail: Lilly Corporate Center, Indianapolis, IN 46221; street: 1200-1555 Kentucky Avenue, Indianapolis, IN 46221). Materials used in the formulation of the drug product are listed in confidential appendices. Production of drug substance and drug product will be done under Good Manufacturing Practices.

Eli Lilly Industries, Inc. and Eli Lilly and Company will comply with all applicable federal, state, and local regulations concerning emission control and waste treatment at all production, formulation, and packaging facilities. Releases into the environment of wastewater or liquid, solid, or gaseous emissions resulting from the production of dirithromycin will be controlled. Liquid process waste streams discharged directly from the chemical synthesis of dirithromycin will either be recovered for reuse or will be

treated by incineration and thermal oxidation. Solids and particulate filters may also be collected for incineration. Dilute wash waters and filtrate from production processes are incinerated or treated in biological wastewater treatment facilities. If filtrate (up to 13,500 L/day) is sent to biological wastewater treatment facilities, any dirithromycin or erythromyclamine present will be treated, possibly with strong acid and then neutralized, to reduce to concentrations below a practical detection limit (10 mg/L). Eight chemicals (acetone, ethanol, hydrazine hydrate, hydrochloric acid, isopropyl acetate, isopropyl alcohol, methanol, and sodium hydroxide) used or produced in the manufacture of dirithromycin are on the OSHA Air Contaminants List (Appendix W). The production facilities that will be used to produce dirithromycin are already designed and being operated for the production of human drugs, so emission control equipment and treatment systems are in place for these manufacturing operations.

Practices related to treatment, storage and disposal for solid, liquid, and gaseous wastes from the production facility near Mayaguez, Puerto Rico are defined by the regulations administered, in certain instances, by the U.S. Environmental Protection Agency (EPA) and in other instances by the Puerto Rico Environmental Quality Board (EQB) and the Puerto Rico Aqueduct and Sewer Authority (PRASA). Permits for this facility are identified in Appendix B. Solvent wastes will be either recovered for reuse or destroyed by incineration. Aqueous process waste streams discharged from the synthesis will be treated by incineration or processed through a secondary wastewater treatment plant. Cooling waters and wastewater from the incinerator are combined with wash waters and aqueous streams that have been treated in a secondary wastewater treatment plant before discharge to the sewer (PRASA). Dirithromycin production will account for only about 2 percent of the discharge capacity authorized by the wastewater permit and about 4 percent of the incineration capacity for this production facility. Treated wastewater from the Regional Wastewater Treatment Plant is discharged into the ocean. Solids from the dirithromycin manufacturing process will be incinerated or disposed of in

an approved solids disposal facility. An air permit for this facility regulates its buildings, one boiler, and one incinerator that will support dirithromycin manufacturing. This facility intends to manufacture dirithromycin under Good Manufacturing Practices.

Treatment, storage and disposal practices for solid, liquid and gaseous wastes from the Indiana plant sites are defined by the regulations administered, in certain instances by the U.S. EPA and in other instances, by the Indiana Department of Environmental Management (IDEM). The Department of Public Works in the City of Indianapolis provides the permits which allow the emissions from the formulating and packaging facilities. Permits related to the manufacture and packaging of dirithromycin and issued by these regulatory agencies for the discharge of wastewater (NPDES or DPW) and the treatment, storage and disposal of materials (RCRA) are listed in Appendix B.

Formulation and packaging of dirithromycin will be carried out at the Lilly Technology Center of Eli Lilly and Company in Indianapolis, Indiana. The areas where formulation occur will meet the standards for Good Manufacturing Practices. All room air will pass through HEPA filters or bag filters, which will be packaged with solids, particulates, and dust for approved disposal. Wash water from the formulations facility will be collected and discharged under a permit issued by the Indianapolis Department of Public Works (DPW) to the Belmont Wastewater Treatment Plant. Wastewaters from formulation and packaging will account for less than 5 percent of the discharge capacity authorized by the wastewater permits issued by DPW. Treated wastewater from the Belmont Wastewater Treatment Plant is discharged to the White River.

Aqueous waste from the production facility near Lafayette, Indiana will be treated by biological treatment, or destroyed by incineration. Solvent wastes will be either recovered for reuse or destroyed by incineration. Any waste gases will be captured by liquid scrubbers or by a fume incineration collection system. If gases are captured by liquid scrubbers, the resulting spent scrubber solution will be either treated by biological treatment or destroyed by incineration. Wastewaters from production of dirithromycin

will account for less than 1 percent of the discharge capacity authorized by the wastewater permit for this production facility.

Liquid filtrate (up to 13,500 L) originally containing some dirithromycin may be discharged into a biological wastewater treatment system. The liquid filtrate will first be treated, possibly with strong acid and then neutralized to assure complete hydrolysis of dirithromycin. Neither dirithromycin nor erythromyclamine can be detected (10 mg/L) in this treated filtrate. Assuming that all dirithromycin is hydrolyzed to erythromyclamine by this process and that, as a worst case, erythromyclamine concentrations could be as high as 10 mg/L, the highest possible daily discharge of erythromyclamine from a production facility would then be 135 gm. Hypothetically, this material could be discharged into the total daily effluent (330,000 L) from the Mayaguez production facility and diluted in the 34×10^6 L of wastewater that flows from other sources into the Mayaguez Regional Wastewater Treatment Plant. Based on this hypothetical calculation, this wastewater treatment plant could be exposed to erythromyclamine concentrations of up to 4 $\mu\text{g/L}$. The Mayaguez Regional Wastewater Treatment Plant discharges into the ocean, where substantial dilution of any erythromyclamine would occur. If production of dirithromycin occurred at the facility near Lafayette, Indiana, erythromyclamine would be carried to biological treatment at a wastewater facility on site. This facility receives about 39.7×10^6 L of wastewater each day. The hypothetical concentration of erythromyclamine in this system could be up to about 3.4 $\mu\text{g/L}$. The Wabash River receives discharge from this wastewater facility. Even at the low flow of this river (1.37×10^9 L/day is average 3-day low flow in 10 years), the highest possible concentration of erythromyclamine that might occur is only about 0.1 $\mu\text{g/L}$.

B. INTRODUCTION OF SUBSTANCES FROM THE USE SITES

Dirithromycin is expected to be used by individuals in and out of a hospital setting. Accordingly, dirithromycin or metabolites of dirithromycin should be introduced into the environment with the same general geographical distribution patterns as those that exist for human populations. Dirithromycin manufactured in the United States will be sold in the United States. Most of the population in the United States lives within 100 miles of some coastline.

The dosage of dirithromycin recommended for adults is 500 mg/day, for up to 14 days, or a total of 7 gm. Projected total use of dirithromycin in any 1 year is less than 50,000 kg. If each person using dirithromycin ingested a total of 7 gm, less than 7.1 million people would be treated with dirithromycin each year. Treated individuals would constitute a small percentage (about 3%) of the human population even in the United States.

Clinical trials with dirithromycin show that, like in studies with rats and dogs, oral administration of dirithromycin in humans results in systemic plasma concentrations of erythromyclamine with very low or no systemic plasma concentrations of dirithromycin. Dirithromycin hydrolyzes to erythromyclamine in both buffer (Appendix G) and plasma at near neutral pH (Lindstrom and Ruterbories, 1991). Chromatographic analysis of plasma, urine, and fecal samples obtained from eight human volunteers dosed once daily with 500 mg dirithromycin for 16 days demonstrated that at no time could dirithromycin be detected in any of the biological samples, even though erythromyclamine was present in plasma, urine, and fecal samples (Fourtillan, 1985). In a subsequent study, five volunteers were dosed once daily with 500 mg dirithromycin for 5 days. Although no dirithromycin was detected in the plasma samples, erythromyclamine was present in the plasma of all volunteers (Lindstrom and Whitaker, 1987). Furthermore, in studies utilizing orally administered ring labeled ^{14}C -dirithromycin, 90% to 95% of the urinary radioactivity and 70 to 90% of the fecal radioactivity was demonstrated to be

erythromyclamine. Based on this information, almost all of the dirithromycin taken for treatment of infections in humans will be eliminated as erythromyclamine. Assuming 100% of the daily dirithromycin dose is excreted as erythromyclamine, an individual could eliminate up to 500 mg/day for 14 days into the environment. Nearly all of this material would be discharged into municipal sewage treatment systems or into septic tanks.

7. FATE OF EMITTED SUBSTANCE IN THE ENVIRONMENT

Significant amounts of dirithromycin will probably not reach the environment since it rapidly hydrolyzes to erythromyclamine at pH values below 9 (Appendix G).

Erythromyclamine is also eliminated by humans treated with dirithromycin. Since dirithromycin is not discharged at any significant level, it is not possible to determine the fate of this substance in the environment.

Erythromyclamine will be released into the environment and it is important to understand its characteristics and possible fate. As technical material, erythromyclamine is a white to off-white powder.

Chemical Name: (9S)-9-Amino-9-Deoxyerythromycin

CAS Registry Number: 26116-56-3

Empirical Formula: $C_{37}H_{70}N_2O_{12}$

Molecular Weight: 734.98

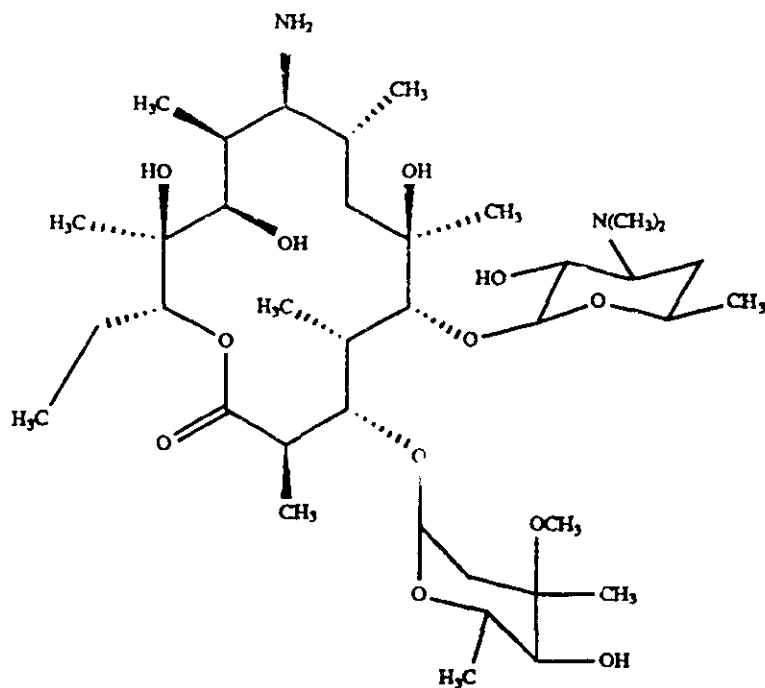
Melting Temperature (Appendix G): 132.5 - 149.0°C

Vapor Pressure (Appendix I): 3.696×10^{-6} to 2.243×10^{-6} Pascals at 298.15°K

Solubility in Water (Appendices J and K): In distilled water the solubility was found to be 1.22 g/L at 20°C (pH range 9.62-10.18). In another experiment, the solubility of this material was found to overwhelm the buffering capacity of solutions originally designed to maintain pH values of 5, 7, and 9. The solubility of erythromyclamine

in purified water, 0.001 N HCl, and 0.001 N NaOH was determined as 5.98, 6.14, and 0.309 g/L, respectively. This material is extremely soluble (225 g/L) in highly acidic media (1 N HCl).

Structural Formula:



Dissociation Constants (Appendix L): Two ionizable groups were detected with pK_a values of 9.08 ± 0.22 and 8.88 ± 0.28 .

Octanol/Water Partition Coefficient (Appendices M and N): In a test in which the pH of buffered solutions ranged from 8.69 to 8.87 because of the high concentration of erythromyclamine used (7.256 g/L), the partition coefficient was determined to be 49.1 (Log P = 1.69). In a subsequent test in which much lower concentrations (2 to 20 mg/L) were used, buffered octanol/water solutions at pH 5, 7, and 9 resulted in average partition coefficients of < 10 (0.00346), < 10 (0.1011), and 54.7, respectively. The Log P values at pH 5, 7, and 9 were < 1, < 1, and 1.74, respectively.

Ultraviolet-Visible Light Absorption (Appendix Q): No appreciable absorption at wavelengths from 290 - 800 nm

Hydrolysis (Appendices P and Q): In a 5-day study, erythromyclamine did not undergo hydrolysis at pH 7 or 9 at 50°C, but underwent complete hydrolysis at pH 4. In another study, slow hydrolytic degradation was detected at pH 5 and 9 at 25°C. Hydrolysis was not detected at pH 7.

Half-life at pH 4 (50°C): < 5 days

Half-life at pH 5 (25°C): 341 days

Half-life at pH 7 (25°C): hydrolysis could not be detected

Half-life at pH 9 (25°C): 190 days

Biodegradation (Appendices R and S): Little or no biodegradation could be detected in studies with erythromyclamine. In a closed-bottle test conducted for 28 days, only about 9% biodegradation of erythromyclamine occurred. In a different study, about 94.7% of the ¹⁴C-erythromyclamine present at the beginning of the study was still present at the end of the study.

The fate of erythromyclamine in the environment will be influenced by its chemical characteristics. Erythromyclamine is a nonvolatile solid, so measurable concentrations will not occur in the atmosphere. Erythromyclamine is soluble in water and probably exists in ionic form at the pH of natural waters. The relatively low n-octanol/water partition coefficients of the compound reflect its high solubility in water. Hydrolysis is very slow in aqueous solutions at pH values ≥ 5 and may account for the little biodegradation that does occur in water. In a solution of pH 4, erythromyclamine hydrolyzes rapidly.

Water solubility and the n-octanol/water partition coefficient (K_{ow}) of compounds have been related empirically to sorption onto soil (Kenega and Goring, 1980). Sorption

to soil declines as solubility in water increases and the K_{ow} decreases. Significant sorption of erythromyclamine to neutral soils is not expected. Using the K_{ow} associated with a neutral solution (0.1011), the adsorption coefficient (K_{oc}) expressed on the basis of the organic carbon content of soil can be calculated ($\text{Log } K_{oc} = 0.544 \text{ Log } K_{ow} + 1.377$) to be about 6.8. At pH 9, the higher K_{ow} (54.7) would result in a higher calculated K_{oc} value, 210.

Significant photolysis of erythromyclamine is unlikely. Ultraviolet light is highly attenuated by ozone and water, and essentially no light at wavelengths less than 295 nm is transmitted through the atmosphere (Zepp and Cline, 1977). There is no significant absorption of light by erythromyclamine at wavelengths between 290 and 800 nm, so there is little possibility that photolysis will occur.

There is some evidence, however, that erythromyclamine may dissipate at a moderate rate from surface water. In a study with the green algae *Selenastrum capricornutum*, concentrations of erythromycin in neutral to somewhat basic solutions declined to levels that were from <1.5% to 61.8% of their original values in 2 weeks (Appendix T). A greater percentage of the erythromyclamine dissipated from the test solutions with higher algal densities than those with lower algal densities. This dissipation could have been due to absorption and/or metabolism by the algae.

The primary manner in which erythromyclamine will be introduced into the environment is through the treatment and disposal of human waste. Virtually all the erythromyclamine excreted by an individual will enter a private septic tank or a municipal waste treatment system.

A. POTENTIAL CONCENTRATIONS OF ERYTHROMYCYLAMINE IN SEPTIC TANKS

Assuming the average septic tank associated with a private home with four occupants holds about 1000 gallons, and the average person uses 50 gallons of water each day for cleaning, personal hygiene, and drinking, a septic tank could be filled in about 5 days. If

one occupant of the household excretes 500 mg of erythromyclamine each day for 14 days, the concentration of erythromyclamine in the septic tank could reach about 0.66 mg/L ($500 \text{ mg/day} \div (200 \text{ gal/day} \times 3.785 \text{ L/gal})$). If all of the occupants of a household were simultaneously using erythromyclamine, its concentration in a septic tank could reach about 2.6 mg/L. Since dirithromycin treatment is only used for up to about 14 days, these concentrations of erythromyclamine would not persist for a long time in the septic tank.

It is unlikely that erythromyclamine will be rapidly degraded or hydrolyzed. Subsurface discharge of the material from a septic system would carry erythromyclamine, probably with little adsorption onto soil. Based on information from hydrolysis and biodegradation studies, the small dilute discharge of erythromyclamine from a septic tank would take several years to be substantially hydrolyzed or biodegraded in the subsurface soils.

B. POTENTIAL CONCENTRATIONS OF ERYTHROMYCYLAMINE IN SEWAGE TREATMENT FACILITIES

Municipal sewage treatment facilities collect water and waste discharge from businesses, government facilities, and homes. Concentrations of erythromyclamine in the wastewater at sewage treatment facilities would be much lower than those that could be found in septic tanks. Erythromyclamine could, however, be discharged to sewage treatment facilities on a daily basis over an entire year.

Assuming up to 3% of a community could use dirithromycin throughout any given year, and assuming a minimum of 100 gallons of waste water is treated for each person in the community each day, the highest continuous concentration of erythromyclamine possible in a sewage treatment facility can be calculated. In a community of 100,000 people, 3000 would use dirithromycin in a year. With a maximum of 7 g of dirithromycin used per person, up to 57.5 g could be used on any 1 day ($(3000 \text{ people/year} \times 7 \text{ g/person}) \div 365 \text{ days}$). Given a minimum of 10 million gallons of waste

water is generated each day by the community, the highest concentration of erythromyclamine in the waste water coming into, and perhaps leaving, the sewage treatment facility would be 1.5 µg/L. Dilution and long-term hydrolysis or biodegradation should insure that levels of erythromyclamine in receiving waters for a sewage treatment facility would fall below 1 µg/L.

If aquatic organisms were exposed to very low levels of erythromyclamine in surface waters, substantial bioconcentration of erythromyclamine would not be expected based on its low Kow values. The Kow is a measure of the propensity of a chemical to partition into water or an organic matrix. As the Kow value of a chemical increases, it is more likely that it will move into organic materials like fish tissue. Chemicals with low Kow values do not generally bioconcentrate in aquatic organisms. Neely, Branson, and Blau (1974) developed a regression equation for projected steady-state residue concentrations in trout muscle versus measured n-octanol/water partition coefficients for a variety of synthetic compounds.

$$\text{Log BCF (bioconcentration factor)} = 0.542 (\text{log Kow}) + 0.124$$

Using this equation and assuming the Kow for erythromyclamine is at most 54.7, the predicted BCF for erythromyclamine is about 12. This calculated BCF indicates that the steady-state concentration of erythromyclamine in fish tissue would be 12 times higher than the concentration of erythromyclamine in the surrounding water. Since erythromyclamine concentrations in surface waters are expected to be below 1 µg/L, concentrations in fish tissue would be below 12 µg/L.

8. EFFECTS ON THE ENVIRONMENT OF RELEASED SUBSTANCES

A. MAMMALIAN TOXICITY STUDIES

An in-depth testing program has been completed with dirithromycin and erythromyclamine in various laboratory animal species. Complete reports of all of these studies have been submitted to support the proposed action. Studies which help determine the safety of erythromyclamine to the public and the environment are briefly described below and are listed in Material Safety Data Sheets (Appendix A).

Mutagenicity Studies with Dirithromycin

Ames Test: Dirithromycin was not mutagenic in the Ames Salmonella/*E.Coli* test for bacterial mutation with and without the presence of a metabolic activation system.

DNA Repair Synthesis: Dirithromycin did not induce DNA repair synthesis in cultured rat hepatocytes.

Mouse Lymphoma Assay: Dirithromycin was not mutagenic in mouse lymphoma cells.

***In Vitro* Gene Mutation Test:** Dirithromycin did not induce point mutations in the HGPRT locus of V79 mesenchymal fibroblasts of Chinese hamsters.

Sister Chromatid Exchange: Dirithromycin did not induce sister chromatid exchange *in vivo* in bone marrow of Chinese hamsters, or *in vitro* in human lymphocytes.

Mouse Marrow Micronuclei: Dirithromycin did not induce micronuclei *in vivo* in bone marrow of mice.

Mutagenicity Studies with Erythromyclamine

Ames Test: Erythromyclamine was not mutagenic in the Ames Salmonella/*E.Coli* mammalian microsome test for bacterial mutation.

Chinese Hamster Ovary Cells: Erythromyclamine did not induce chromosome aberrations *in vitro* in Chinese hamster ovary cells.

Mouse Marrow Micronuclei: Erythromyclamine did not induce micronuclei *in vivo* in bone marrow of mice.

Acute or Subchronic Studies with Dirithromycin

Single Oral Dose Administration to Rats: No rats died when given a single oral dirithromycin dose of 1000 mg/kg. Higher doses of up to 10,000 mg/kg caused mortality, with the frequency of mortality related to dose.

Dermal Toxicity and Irritation in Rabbits: A dose of 1 g/kg body weight was applied topically to New Zealand White rabbits. After 24 hours, the treatment site was washed and animals were observed for 14 days. Very slight erythema, that developed within 24 hours in one of three rabbits, cleared within 48 hours after treatment.

Ocular Irritation in Rabbits: Moderate corneal opacity, marked to severe iritis, and moderate to extreme conjunctivitis developed within 1 hour after exposure to a dose of 45 mg. Corneal vascularization was noted 8 days after exposure and persisted until the end of the study on Test Day 22. Corneal dullness was also noted in one animal at the end of the study. Rinsing the eyes after dosing slightly reduced the severity and duration of the irritation.

Inhalation Study with Dogs: A subchronic inhalation study was conducted in beagle dogs. There were no treatment-related effects on body weight, food consumption, hematology, heart rate, clinical chemistry, or pathology at a mean aerosol exposure concentration of 23 mg dirithromycin/m³.

Acute Studies with Erythromyclamine

Single Oral Dose Administration to Fischer Rats: Two of five male rats died when given the highest single oral dose of erythromyclamine tested, 3500 mg/kg. All

male rats survived after being given an oral dose of 1875 mg/kg. The median lethal dose of erythromyclamine for female rats was calculated to be 2573 mg/kg.

Dermal Toxicity in Rabbits: A dose of 2 g/kg body weight was applied topically to New Zealand white rabbits. After 24 hours, the treatment site was washed and animals were observed for 14 days. There were no overt signs of toxicity or deaths, and no adverse findings were observed when a gross pathological examination was conducted at the end of the study. Under these conditions, erythromyclamine was considered to be nontoxic.

Dermal Irritation in Rabbits: A dose of 0.5 g/animal was applied topically to the skin (6 cm² area) of three rabbits. No evidence of dermal irritation was observed throughout the study.

Sensitization Study in Guinea Pigs: A 50 mg dose of erythromyclamine was applied to the skin according to techniques of the modified Buehler topical patch method. There was no indication of contact sensitization or dermal irritation in guinea pigs exposed topically to erythromyclamine.

Ocular Irritation in Rabbits: Corneal dullness, marked to severe iritis, and moderate to severe conjunctivitis developed within 1 hour after exposure to a dose of 39 mg. All treated rabbits had clear eyes by 14 days post treatment. No permanent ocular damage was observed. Erythromyclamine did cause marked ocular irritation under the conditions employed in this study.

Chronic Toxicity and Reproduction Studies

Chronic toxicity studies were not conducted with erythromyclamine. Chronic studies were conducted with dirithromycin, which is transformed to erythromyclamine *in vivo*. There were no effects of toxicologic consequence in a 6-month study with rats gavaged daily with dirithromycin doses of 100 mg/kg. Toxicological effects were found for rats gavaged with 400 and 750 mg/kg/day. These effects were decreased body

weight, weight gain, food consumption, and efficiency of food utilization values. Increased alanine transaminase and aspartate transaminase were also noted. Morphologic changes including cardiac and skeletal muscle myopathy, swelling and vacuolation of smooth muscle, bile duct and renal tubular epithelial cells, and focal lymphoid histiocytosis were recorded. By electron microscopy, cytoplasmic lamellar inclusion bodies were found in parenchymal and interstitial cells of the heart, skeletal muscle, liver, and kidney. In two 6-month studies with dogs, a daily oral dose of 30 mg/kg resulted in no toxicologically important findings. Cardiovascular parameters were not affected. In the first study, dogs given 70 or 150 mg/kg/day had slight to moderate increases in serum levels of aspartate and alanine transaminases and slight increase in cytoplasmic lamellar inclusion bodies. Additional findings in the second chronic dog study were a dose-related increase in focal lymphoid histiocytosis and a mild focal vacuolar degenerative myopathy in the 150 mg/kg group.

Effects of dirithromycin on fertility and general reproduction, including perinatal and postnatal effects, were evaluated in rats given 0, 150, 587, or 1000 mg/kg/day orally. All males treated for 12 weeks prior to mating and through cohabitation, mated successfully, there were no effects on fertility, reproduction parameters, or the fetuses. Dirithromycin administered orally to females up to 1000 mg/kg/day for 2 weeks prior to mating and continuing to the end of lactation of Gestation Day 20 had no effect on reproductive performance or fertility and caused no significant effects on offspring. There was a dose-related increase in post dosing salivation among parental males and females, and nasal/muzzle staining among male rats. Body weight and food consumption were significantly decreased in parental animals given 1000 mg/kg dirithromycin. Minor and transitory differences in the degree of ossification of a few bones in the skull in F₁ offspring resulted in minor skeletal abnormalities in the high-dose group.

Teratology studies were also conducted with rats and rabbits. In the teratology study with rats, females were dosed orally with 0, 15, 150, or 1000 mg/kg dirithromycin on

gestation days 7 through 16. Overt signs of maternal toxicity occurred at the high dose and 2 of the 23 animals in this group died. At the middle dose, only less pronounced clinical signs were noted. Litter sizes, survival, and growth and development of the offspring were unaffected by dirithromycin. There was no evidence of a teratogenic effect in this rat study. Oral gavage doses of 15, 40, or 100 mg dirithromycin/kg were given to 18 rabbits on Gestation Days 6 through 18. Rabbits are very sensitive to the effects of antibiotics on the flora of the gastrointestinal tract. Defecation was absent or reduced in this study, and there were changes in the consistency of the feces in all groups given dirithromycin. The frequency and severity of the condition related to dose. These disturbances in gut flora were considered responsible for the poor condition of some rabbits and reduced weight gain which occurred in the middle- and high-dose groups. One rabbit in the high-dose group died, and two rabbits in the high- and low-dose groups aborted. Reduced litter size in the high dose due to an increase in resorptions was the only reproduction parameter affected. There were no fetal abnormalities associated with dirithromycin treatment in rabbits.

Except for some apparent antimicrobial effects in the gastrointestinal tract of rabbits, erythromyclamine or dirithromycin should have no significant effect on mammals when dosed daily with 15 mg/kg.

B. POTENTIAL EFFECTS OF THE PROPOSED ACTION ON HUMAN HEALTH

1) Dirithromycin will be produced at two manufacturing sites and formulated at another site. These sites are designed and currently used for production and formulation of pharmaceuticals according to Good Manufacturing Practices. Dirithromycin will also be produced and formulated under Good Manufacturing Practices. As with other macrolide antibiotics, some potential exists for hypersensitivity reactions to dirithromycin or erythromyclamine. Individuals identified as sensitive at production facilities will be appropriately protected from exposure. Protective clothing is generally provided in these

facilities and eye protection is required. Engineering controls will be designed to meet a recommended exposure guideline that would only allow dirithromycin aerosols to reach a maximum 12-hr average level of 0.2 mg/m^3 . This level is about 100 times lower than the no-effect concentration (23 mg/m^3) in a subchronic inhalation study with dirithromycin in dogs. This 0.2-mg/m^3 level is also about 70 times lower than the theoretical 12-hr airborne concentration of dirithromycin that would be equivalent to the recommended daily therapeutic dose of 500 mg. Considering the proposed engineering controls, personal protective measures, the margin of safety demonstrated by toxicology studies, and the fact that dirithromycin and erythromycylamine are not mutagens, teratogens, or reproductive toxins, it can be concluded that workers producing dirithromycin would not be adversely affected.

2) Exposure of Humans to Dirithromycin or Erythromycylamine via Surface Waters

Exposure of humans to dirithromycin is not expected. Dirithromycin hydrolyzes in water with pH values <9 to erythromycylamine in just a few hours. Any small amounts of erythromycylamine that could be discharged from a municipal sewage treatment system will not significantly bioconcentrate in fish and will probably hydrolyze over a period of several years. Erythromycylamine may also be absorbed or metabolized within weeks by algae. The concentrations of erythromycylamine in surface water and fish tissue are expected to be less than 1 and $12 \text{ } \mu\text{g/L}$, respectively (Section 7B). If an adult drank 2 L of water each day with $1 \text{ } \mu\text{g/L}$ of erythromycylamine, his daily consumption would be less than 0.0004% of the recommended therapeutic dose of dirithromycin. If an adult ate 1 kg of fish each day with $12 \text{ } \mu\text{g}$ erythromycin/kg, his daily consumption of erythromycylamine would be less than 0.003% of the recommended therapeutic dose of dirithromycin. Humans are not expected to be adversely affected by exposure to dirithromycin or erythromycylamine in surface waters.

C. POTENTIAL EFFECTS OF THE PROPOSED ACTION ON NONTARGET ORGANISMS

As for humans, terrestrial organisms are not expected to be adversely affected by exposure to any small amount of erythromyclamine that may be discharged into surface waters. Erythromyclamine is eliminated by mammals and it is not a mutagen, teratogen, or reproductive toxin. Except for some apparent antimicrobial effects in the gastrointestinal tract of rabbits, erythromyclamine should have no significant effect on mammals when dosed daily with 15 mg/kg. The concentrations of erythromyclamine in surface waters and fish tissue are expected to be less than 1 and 12 µg/L, respectively. If a terrestrial animal drank 0.2 L of water/kg body weight each day with 1 µg/L of erythromyclamine, it could consume up to 0.2 µg of erythromyclamine/kg body weight/day. This exposure level is 75,000 times lower than the daily dose which should have no significant toxicological effects on mammals. If a terrestrial animal ate 0.2 kg of fish tissue each day containing 12 µg erythromyclamine/kg, it could consume up to 2.4 µg erythromyclamine/kg body weight/day. This exposure level is 6250 times lower than the daily dose of erythromyclamine which should be safe to mammals. Given the very low theoretical concentrations possible in surface waters and fish tissue, and the margin of safety demonstrated by mammalian toxicology studies, it is quite unlikely that terrestrial organisms would be adversely affected by exposure to erythromyclamine.

Exposure to any erythromyclamine that occurs in surface water should not result in effects on aquatic animals. No effects on the behavior or survival of *Daphnia magna* were found in an acute laboratory study with erythromyclamine at concentrations in water up to 48.2 mg/L (Appendix U). In an acute study with rainbow trout, no toxicologically significant effects were found at an erythromyclamine concentration of 2880 mg/L (Appendix V). The acute no-observed effect concentrations for daphnids and trout are at least 48,200 times higher than the concentration of erythromyclamine that may occur in surface waters.

Algae are more sensitive to exposure to erythromyclamine. Erythromyclamine is related structurally to erythromycin and has the same amino-hexose moiety. Erythromycin, and other macrolide antibiotics with this amino-hexose moiety, binds to ribosomal RNA and inhibits protein synthesis. Exposure to erythromycin is known to result in reduced chlorophyll content in algae (Ebringer, 1972). Initial exposure concentrations of erythromyclamine that are ≥ 0.16 mg/L resulted in significant reductions in the growth rates of the green algae *Selenastrum capricornutum* (Appendix T). Exposure to an initial erythromyclamine concentration of 0.07 mg/L resulted in no effects on growth rate or final standing crop. Algae may be able to metabolize erythromyclamine, as initial concentrations in the test solutions declined substantially by the end of this 14-day study. While algae are sensitive to erythromyclamine, concentrations of this material are expected to be at least 70 times lower in surface waters than the no-effect concentration for *Selenastrum capricornutum*.

Erythromyclamine is part of a family of macrolide antibiotics that can inhibit bacterial species of *Staphylococcus*, *Streptococcus*, *Legionella*, and other genera. Minimum inhibitory concentrations (MIC) for sensitive species range from a low of about 0.015 mg/L to greater than 128 mg/L (Hardy et al., 1988). For about two-thirds of the species tested, the minimum inhibitory concentrations for 50% of the strains ranged between 0.06 and 1 mg/L. Assuming the sensitivity of the microbial flora in a municipal sewage treatment facility is similar to that represented by published MIC values, it is highly unlikely that the microbial flora of sewage treatment facilities would be inhibited by the highest expected exposure concentrations of erythromyclamine, about 1.5 to 4 μ g/L. Since erythromyclamine would not inhibit the microflora at treatment facilities, development of strains resistant to erythromyclamine at these facilities is not expected.

Erythromyclamine concentrations in septic tanks may reach up to a level (2.6 mg/L) that inhibits some of the microflora. Since the duration of microbial exposure to erythromyclamine in septic tanks is at most 14 days, and since they are constantly

inoculated with bacteria, it is unlikely that erythromycylamine will adversely affect the long-term microbial processes in septic tanks. Any selection for resistant microflora in septic tanks will be temporary and their subsurface discharge would minimize release of resistant microflora into the surface environment.

9. UTILIZATION OF NATURAL RESOURCES AND ENERGY

Production and formulation of dirithromycin will occur at facilities already designed for production and formulation of pharmaceuticals. All of these facilities are operated according to Good Manufacturing Practices.

Process waste streams from production of dirithromycin only utilize a portion of incineration and thermal oxidation capacity, or recovery capacity of facilities already installed for these and other process wastes. Disposal of waste from the manufacturing processes and operations will not require use of unusual amounts of energy or natural resources.

Production, formulation, and use of dirithromycin will not affect endangered or threatened species. Production, formulation, and use of dirithromycin will not affect properties listed in or eligible for listing in the National Register of Historic Places.

10. MITIGATION MEASURES

The proposed action would not be expected to have any substantial adverse effect on human health or the environment. Engineering controls will be in place to minimize release of dirithromycin and process products at the manufacturing and formulation facilities. Personal protective gear is worn, when necessary, to reduce the potential for exposure to dirithromycin or process products at these sites. Dirithromycin will be produced under Good Manufacturing Practices. Material Safety Data Sheets describing dirithromycin and the intermediate, erythromycylamine, are available (Appendix A). The manufacturing process for dirithromycin results in the use or production of eight

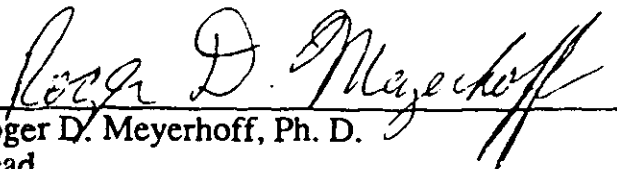
chemicals on the OSHA Air Contaminants List. Those materials and examples of the Material Safety Data Sheets available within the Company are provided in Appendix W.

11. ALTERNATIVES TO THE PROPOSED ACTION

As described in Section 8 of this document, the proposed action would not be expected to have any substantial adverse effect on human health or the environment. While there are no known environmental benefits from the production and use of Dynabac, there are, likewise, no known significant risks to the environment. No action to approve this new drug would not enhance the quality of the environment. The lack of action to approve this drug would only deny its use in the treatment of certain infections in humans.

12. LIST OF PREPARERS

The following personnel of Eli Lilly and Company are responsible for the preparation of this Environmental Assessment.



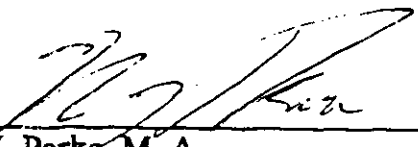
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Environmental Science & Hazard Communication

November 23, 1994
Date



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November 29, 1994
Date

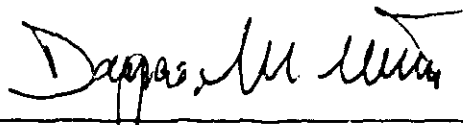


Neil J. Parke, M. A.
Senior Environmental Affairs Representative
Environmental Affairs

November 28, 1994
Date

13. CERTIFICATION

The undersigned official certifies that the information presented in this Environmental Assessment is true, accurate, and complete to the best of his knowledge.



Douglas M. Morton, Ph. D.
Vice President, Lilly Research Laboratories

Nov. 29, 1994

Date

14. REFERENCES

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APPENDIX A: Material Safety Data Sheets for Dirithromycin and Erythromyclamine

DIRITHROMYCIN

MSDS

MATERIAL SAFETY DATA SHEET



Page 1

COMMON NAME: Dirithromycin
(Lilly Nos.: ID0838, QA365Z, QA391P, QA393Q, QA394M,
QA399A, QA401B, SI0174, LSN237216)

REVISED DATE: August 26, 1993

SECTIONS REVISED: Sections 1, 4, 5, 7, 8

U.S. TELEPHONE NUMBERS: EMERGENCY 317-276-2000 CHEMTREC 800-424-9300

As of the date of issuance, we are providing available information relevant to the handling of this material in the workplace. All information contained herein is offered with the good faith belief that it is accurate. However, this safety data sheet does not constitute a warranty of any kind, express or implied. In the event of an adverse incident associated with this material, this safety data sheet is not intended to be a substitute for consultation with appropriately trained personnel. Nor is this safety data sheet intended to be a substitute for product literature which may accompany the finished product.

See attached glossary for abbreviations.

SECTION 1 - MATERIAL IDENTIFICATION

Common Name: Dirithromycin

Chemical Name: Erythromycin, 9-deoxy-11-deoxy-9,11-[imino{2-(2-methoxyethoxy)ethylidene}oxy]-, [9S(R)]-

Synonyms/Trade Names: Dynabac; Avatak; Dirithro; AS-E 136; Nortron; Noriclan

CAS Number: 62013-04-1

Molecular Formula: C42 H78 N2 O14

Chemical Family: Macrolide antibiotic

SECTION 2 - PHYSICAL DATA

Appearance: White to off-white powder

Odor: Odorless

Boiling Point: NA

MSDS

MATERIAL SAFETY DATA SHEET



COMMON NAME: Dirithromycin
(Lilly Nos.: ID0838, QA365Z, QA391P, QA393Q, QA394M,
QA399A, QA401B, SIO174, LSN237216)
REVISED DATE: August 26, 1993

----- SECTION 2 - PHYSICAL DATA (continued) -----

Melting Point: 189 C (372 F)
Specific Gravity: NAIF
pH: 9-10 (saturated solution)
Evaporation Rate: NAIF
Solubility in Water: Slightly soluble
Vapor Density: NAIF
Vapor Pressure: NAIF

----- SECTION 3 - FIRE AND EXPLOSION INFORMATION -----

Extinguishing Media: Use water, carbon dioxide, dry chemical, foam, or Halon.
Unusual Fire and Explosion Hazards: As a finely divided material, may form dust mixtures in air which could explode if subjected to an ignition source.
Flash Point: NAIF
Method: NA
UEL: NAIF
LEL: NAIF

----- SECTION 4 - REACTIVITY INFORMATION -----

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MATERIAL SAFETY DATA SHEET

Lilly

Page 3

COMMON NAME: Dirithromycin
(Lilly Nos.: ID0838, QA365Z, QA391P, QA393Q, QA394M,
QA399A, QA401B, SI0174, LSN237216)
REVISED DATE: August 26, 1993

----- SECTION 4 - REACTIVITY INFORMATION (continued) -----

Stability: This material should not be exposed to temperatures above 90 C (194 F). This temperature is based on a laboratory test and assumes near atmospheric pressures and quantities of less than 500 kg (1100 lb). For additional information refer to the CHL data base on EHSS or contact the Lilly Chemical Hazards Laboratory.

Incompatibility: May react with strong oxidizing agents (e.g., peroxides, permanganates, nitric acid, etc.).

Hazardous Decomposition: May emit toxic fumes when heated to decomposition.

Hazardous Polymerization: Not known to occur.

----- SECTION 5 - HEALTH HAZARD INFORMATION -----

Human - Occupational

Effects, Including Signs and Symptoms, of Exposure: None reported; however, based on animal data, may cause burns or permanent tissue damage to the eyes. Based on clinical experience, allergic reactions might be expected, including rash, itching, and hives. Clinical signs may include diarrhea, nausea, and abdominal pain.

Medical Conditions Aggravated By Exposure: Hypersensitivity to erythromycin or macrolide antibiotics.

Primary Route(s) of Entry: Inhalation and skin contact.

Exposure Guidelines: Dirithromycin - PEL and TLV not established.
LEG 0.2 mg/m³ TWA for 12 hours

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MSDS

MATERIAL SAFETY DATA SHEET



Page 4

COMMON NAME: Dirithromycin
(Lilly Nos.: ID0838, QA365Z, QA391P, QA393Q, QA394M,
QA399A, QA401B, SI0174, LSN237216)
REVISED DATE: August 26, 1993

----- SECTION 5 - HEALTH HAZARD INFORMATION (continued) -----

Animal Toxicity Data Single Exposure

Oral: Rat, median lethal dose estimated between 1881 mg/kg and 4703 mg/kg, reduced activity, diarrhea, lethargy, drooping eyelids, incoordination, coma.

Dog, 1000 mg/kg, no deaths, vomiting.

Skin: Rabbit, 1.0 g/kg, no deaths or toxicity.

Inhalation: Rat, 760 mg/m³ for four hours, no deaths.

Intravenous: Dog, median lethal dose estimated between 150 mg/kg and 250 mg/kg, increased respiration, vomiting, sleepiness, recumbency, convulsions.

Skin Contact: Rabbit, slight irritant

Eye Contact: Rabbit, corrosive

Animal Toxicity Data Repeat Exposure

Target Organ Effects: Muscle effects (tissue changes in heart and skeletal muscle).

Other Effects: Decreased body weight, weight gain, food consumption, and efficiency of food utilization. Increased alanine transaminase and aspartate transaminase values. Liver, kidney, and lymph node tissue damage.

Reproduction: No effects identified in animal studies.

Sensitization: NAIF

Mutagenicity: Not mutagenic in bacterial or mammalian cells.

Carcinogenicity: No carcinogenicity data found. Not listed as carcinogenic by IARC, NCI/NTP, ACGIH, or OSHA.

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MSDS

MATERIAL SAFETY DATA SHEET



COMMON NAME: Dirithromycin
(Lilly Nos.: ID0838, QA365Z, QA391P, QA393Q, QA394M,
QA399A, QA401B, SIO174, LSN237216)
REVISED DATE: August 26, 1993

----- SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES -----

Eyes: Hold eyelids open and flush with a steady, gentle stream of water for 15 minutes. See an ophthalmologist (eye doctor) or other physician immediately.

Skin: Remove contaminated clothing and clean before reuse. Wash all exposed areas of skin with plenty of soap and water. Get medical attention if irritation develops.

Inhalation: Move individual to fresh air. Get medical attention if breathing difficulty occurs. If not breathing, provide artificial respiration assistance (mouth-to-mouth) and call a physician immediately.

Ingestion: Do not induce vomiting. Call a physician or poison control center. If available, administer activated charcoal (6-8 heaping teaspoons) with two to three glasses of water. Do not give anything by mouth to an unconscious person. Immediately transport to a medical care facility and see a physician.

----- SECTION 7 - HANDLING PRECAUTIONS -----

Respiratory Protection: Use an approved respirator.

Eye Protection: Chemical goggles and/or face shield.

Ventilation: Laboratory fume hood or local exhaust ventilation.

Other Protective Equipment: Chemical-resistant gloves and body covering to minimize skin contact. If handled in a ventilated enclosure, as in a laboratory setting, respirator and goggles or face shield may not be required. Safety glasses are always required.

Other Handling Precautions: In production settings, airline-supplied, hood-type respirators are preferred. Shower and change clothing if skin contact occurs.

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MSDS



MATERIAL SAFETY DATA SHEET

COMMON NAME: Dirithromycin
(Lilly Nos.: ID0838, QA365Z, QA391P, QA393Q, QA394M,
QA399A, QA401B, SI0174, LSN237216)

REVISED DATE: August 26, 1993

----- SECTION 8 - SPILL, LEAK AND DISPOSAL PROCEDURES -----

Spills: Contain dry material by sweeping up or vacuuming. Vacuuming may disperse dust if appropriate dust collection filter is not part of the vacuum. Be aware of potential for dust explosion when using electrical equipment. Wear protective equipment, including eye protection, to avoid exposure (see Section 7 for specific handling precautions).

Waste Disposal: Dispose of any cleanup materials and waste residue according to applicable federal, state, and local regulations.

----- SECTION 9 - SHIPPING INFORMATION -----
(Proper Shipping Name / Hazard Class / UN Number)

DOT: Not regulated for surface transport.

ICAO: Not regulated for air transport.

IMO: Not regulated for water transport.

For additional information call: Occupational Health and Safety
Eli Lilly and Company 317-276-3494

ERYTHROMYCYLAMINE

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Material Safety Data Sheet

FOR USE ONLY BY LILLY EMPLOYEES
NOT FOR DISTRIBUTION OUTSIDE ELI LILLY & COMPANY

MATERIAL SAFETY DATA SHEET - FOR INTERNAL USE ONLY
NAME: 9-(S)-Erythromycylamine
(Lilly Nos.: QA3520, QA390F, LSN024410)
REVISED DATE: May 8, 1992

----- Section 1 - MATERIAL IDENTIFICATION -----

SECTION REVISED: Section 4

EMERGENCY TELEPHONE: (317) 276-2000 CHEMTREC TELEPHONE: 1-800-424-9300

Lilly Address: Lilly Corporate Center
Indianapolis, IN 46285

Common Name: 9-(S)-Erythromycylamine

Synonyms/Trade Names: Aminoerythromycin A; Erythromycylamine

CAS Number: 26116-56-3

Molecular Formula: C37 H70 N2 O12

Chemical Family: Macrolides (Erythromycins)

MATERIAL SAFETY DATA SHEET - FOR INTERNAL USE ONLY
NAME: 9-(S)-Erythromycylamine
(Lilly Nos.: QA352Q, QA290F, LSN024410)
REVISED DATE: May 8, 1992

----- Section 2 - PHYSICAL DATA -----

Appearance: White to off-white solid

Odor: Odorless

Boiling Point: NA

Melting Point: 128-135 C

Specific Gravity: NA

pH: NAIF

Evaporation Rate: NA

Solubility in Water: Slight

Vapor Density: NA

Vapor Pressure: NA

----- Section 3 - FIRE AND EXPLOSION INFORMATION -----

Extinguishing Media: Use water, CO2, dry chemical, foam, or Halon.

Unusual Fire and Explosion Hazards: As a finely divided material, may form dust mixtures in air which could explode if subjected to an ignition source.

Flash Point: NA

Method: NA

UEL: NA

LEL: NA

MATERIAL SAFETY DATA SHEET - FOR INTERNAL USE ONLY

NAME: 9-(S)-Erythromycylamine

(Lilly Nos.: QA352Q, QA390F, LSN024410)

REVISED DATE: May 8, 1992

----- Section 4 - REACTIVITY INFORMATION -----

Stability: Material could be thermally unstable above 55 C (130 F). Material should not be stored above 55 C (130 F). Decomposition potential should be considered on a case by case basis for processes which expose this material to temperatures above 55 C (130 F).

Incompatibility: May react violently with strong oxidizers.

Hazardous Decomposition: May emit toxic fumes when heated to decomposition.

Hazardous Polymerization: Does not occur.

----- Section 5 - HEALTH HAZARD INFORMATION -----

Human - Occupational

Effects, Including Signs and Symptoms, of Exposure: No adverse effects reported. Compounds of similar structure have been reported to cause transient alteration in heart rate and instances of allergenicity upon repeated exposure.

Medical Conditions Aggravated By Exposure: Erythromycin hypersensitivity.

Primary Route(s) of Entry: Inhalation and skin absorption.

Exposure Guidelines: Not established.

Animal Toxicity Data Single Exposure

Oral: Rat, median lethal dose 2573 mg/kg for females, estimated greater than 3500 mg/kg for males, mortality, diarrhea, reduced activity, labored respiration.

Skin: Rabbit, 2.0 g/kg, no deaths or toxicity.

Inhalation: Rat, 0.59 mg/L for four hours, no deaths.

Intravenous: Mouse, median lethal dose 575 mg/kg.

MATERIAL SAFETY DATA SHEET - FOR INTERNAL USE ONLY

NAME: 9-(S)-Erythromycylamine

(Lilly Nos.: QA352Q, QA390F, LSN024410)

REVISED DATE: May 8, 1992

----- Section 5 - HEALTH HAZARD INFORMATION (continued) -----

Skin Contact: Rabbit, nonirritant

Eye Contact: Rabbit, irritant

Animal Toxicity Data Repeat Exposure

Target Organ Effects: NAIF

Other Effects: NAIF

Reproduction/Teratology: NAIF

Sensitization: Guinea pig, not a contact sensitizer.

Mutagenicity: Not mutagenic in bacterial or mammalian cells.

Carcinogenicity: Not listed as a carcinogen by IARC, NCI/NTP, ACGIH, or OSHA.

----- Section 6 - EMERGENCY AND FIRST AID PROCEDURES -----

Eyes: Hold eyelids open and flush with a steady stream of water for 15 minutes. See an ophthalmologist (eye doctor) or physician immediately.

Skin: Remove contaminated clothing and clean before reuse. Wash all exposed areas of skin with plenty of soap and water. Get medical attention if irritation develops.

Inhalation: Move individual to fresh air. Get medical attention if breathing difficulty occurs. If not breathing, provide artificial respiration assistance (mouth-to-mouth) and call a physician immediately.

Ingestion: Call a physician or poison control center. Drink one or two

MATERIAL SAFETY DATA SHEET - FOR INTERNAL USE ONLY

NAME: 9-(S)-Erythromyclamine

(Lilly Nos.: QA352Q, QA390F, LSN024410)

REVISED DATE: May 8, 1992

----- Section 6 - EMERGENCY AND FIRST AID PROCEDURES (continued) -----

glasses of water and induce vomiting or use 1-2 tablespoons syrup of ipecac to induce vomiting. Do not induce vomiting or give anything by mouth to an unconscious person.

----- Section 7 - HANDLING PRECAUTIONS -----

Respiratory Protection: NIOSH approved respirator.

Eye Protection: Goggles or appropriate respirator.

Ventilation: Laboratory fume hood or local exhaust ventilation.

Other Protective Equipment: Impervious gloves; body cover to prevent skin contact.

Other Handling Precautions: In production settings, airline supplied hood-type respirators are preferred to provide face, eye, and respiratory protection. Shower and change clothing if skin contact occurs.

----- Section 8 - SPILL, LEAK, AND DISPOSAL PROCEDURES -----

Spills: Contain dry material by sweeping up. Vacuuming may disperse dust. Wear protective equipment, including eye protection, to avoid exposure.

Waste Disposal: Material is not a RCRA hazardous waste for disposal. Dispose of any cleanup materials and waste residue according to applicable federal, state, and local regulations.

MATERIAL SAFETY DATA SHEET - FOR INTERNAL USE ONLY
NAME: 9-(S)-Erythromyclamine
(Lilly Nos.: QA352Q, QA390F, LSN024410)
REVISED DATE: May 8, 1992

----- Section 9 - SHIPPING INFORMATION -----
(Proper Shipping Name / Hazard Class / UN Number)

DOT: Not regulated for domestic or international transport.

ICAO: Not regulated for domestic or international transport.

IMO: Not regulated for domestic or international transport.

For additional information call: Occupational Health and Safety
Eli Lilly and Company 317-276-2286

APPENDIX B: Permits Related to the Manufacture of Dirithromycin

Eli Lilly Industries, Inc. Facility at Mayaguez, Puerto Rico

<u>Permit Type</u>	<u>Expiration Date</u>
Water - PRASA (GDA-88-309-006)	6/2/94*
RCRA (PR0091024786)	12/1/94*
Air (PFE-02-50-893-001-1-D)	No expiration#

* A condition of the permit stipulates that the permit remains in force until the regulatory agency issues a new one, as long as timely application for a new permit is made before the expiration date. Eli Lilly Industries, Inc. has applied for renewal of this permit.

Permit is effective until new permit is issued under Title V of the Clean Air Act.

Eli Lilly and Co. Facility near Lafayette, Indiana (Tippecanoe)

<u>Permit Type</u>	<u>Expiration Date</u>
NPDES (IN0002861)	9/30/92*
RCRA (IND005050967)	4/30/93*

* A condition of the permit stipulates that the permit remains in force until the regulatory agency issues a new one, as long as timely application for a new permit is made before the expiration date. Eli Lilly and Company has applied for renewal of this permit.

Eli Lilly and Co. Facilities at Indianapolis, Indiana

<u>Permit Type</u>	<u>Expiration Date</u>
Water (283004) (Issued by the Department of Public Works, City of Indianapolis)	Dec. 31, 1995
Water (283001) (Issued by the Department of Public Works, City of Indianapolis)	Dec. 31, 1995