CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-678/SE1-003

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Microbiological Review of Efficacy Supplement

NDA #: 50-678 **REVIEW #:** 1 **REVIEW DATE:** 01-APR-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT SEI-003	18-DEC-96	20-DEC-96	02-JAN-97

NAME & ADDRESS OF APPLICANT:

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

CONTACT PERSON:
Jennifer L. Stotka, M.D.
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DRUG PRODUCT NAME:

Proprietary:	Dynabac™
Nonproprietary:	Dirithromycin tablets
Chemical Type:	Macrolide Antibiotic Drugs
Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status:
Not Applicable

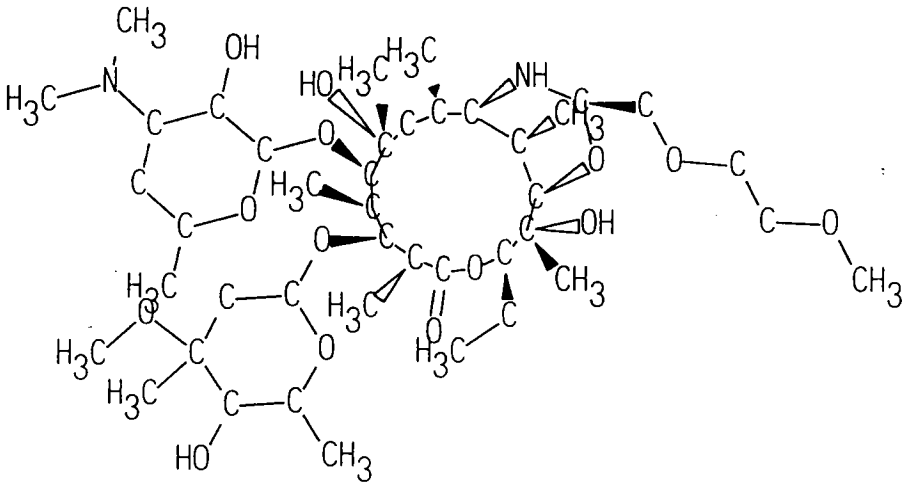
PHARMACOLOGICAL CATEGORY/INDICATION:
Macrolide antibiotic drug/acute bacterial exacerbations of chronic bronchitis, secondary bacterial infection of acute bronchitis, community acquired pneumonia, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections.

DOSAGE FORM:	Tablets
STRENGTHS:	250mg/tablet
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	_X_ **Rx** ___ **OTC**

CHEMICAL NAME, STRUCTURAL AND MOLECULAR FORMULA, MOL.WT:

Chemical Name: (9*S*)-9-Deoxo-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy)-ethylidene]oxy]erythromycin

Chemical Structure:



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

SUPPORTING DOCUMENTS:
None

RELATED DOCUMENTS (if applicable):
None

CONSULTS: None

REMARKS/COMMENTS:

This submission contains data to support the use of dirithromycin for 5 days for acute exacerbations of chronic bronchitis and skin and skin tissue infections. This drug is approved for both of these indications for 7 days of treatment.

The sponsor also wishes to add *Haemophilus influenzae* to the bronchitis claim for this drug and *Streptococcus pyogenes* to the skin and skin tissue indication. *Streptococcus pyogenes* is already in the label due to the pharyngitis/tonsillitis claim and is, therefore, already in the microbiology subsection in the first listing of organisms. The sponsor has completed two additional bronchitis studies correlating *Haemophilus influenzae* MIC and zone diameter data with clinical and bacteriological outcome. The sponsor has proposed breakpoints for this organism. A study has also been performed to determine quality control limits for *Haemophilus influenzae* ATCC 49247.

In the review of the original NDA submission, FDA expressed concerns about acute exacerbations of chronic bronchitis caused by *H. influenzae*. One issue was the percentage of "resistant" isolates. The second issue was the unavailability of tests to determine whether strains were susceptible or resistant. Most strains of *H. influenzae* have high MIC's when tested against almost all of the macrolides. In clinical trails of bronchitis, however, this organism is eradicated and the patient has a successful clinical response. For almost all strains of *H. influenza,* the MIC's of macrolides vary from 0.25 to 16 μg/mL.

In Vitro Activity against *Haemophilus influenzae*

Barry et al (1) used NCCLS procedures and *Haemophilus* Test Medium (HTM) and tested 308 *H. influenzae* isolates including 92 β-lactamase producing strains and 20 ampicillin-resistant β-lactamase-nonproducers (BLNAR strains). Both clarithromycin alone and clarithromycin and its 14-hydroxy metabolite in a 3:1 ratio was tested. Results for the macrolides tested were as follow:

	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Azithromycin	1.0	2.0
Clarithromycin	8.0	16.0
Clarithromycin +14-OHC	4.0	8.0
Erythromycin	4.0	16.0

In this study azithromycin was four- to eight-times more potent than clarithromycin parent compound and two- to four-times more potent than the combination of clarithromycin and 14-hydroxy clarithromycin. At 4.0 μg/mL azithromycin inhibited all but one strain. At the breakpoint concentration of 8.0 μg/mL only 71% of the strains

were inhibited by clarithromycin. When 14-hydroxy was added the activity was increased. Almost all strains were resistant to erythromycin at a breakpoint of 0.5 μg/mL, but MIC values were lower for erythromycin than for clarithromycin.

Erwin and Jones (2) tested over 100 clinical strains of *H. influenzae* against roxithromycin by NCCLS methods. MIC's ranged from μg/mL with a modal MIC of 8 μg/mL. There was a mono-modal MIC population distribution indicating no true resistant strains. Clinical cure rates of 84% to 100% were reported for roxithromycin in respiratory tract infections. This indicates that most strains of *H. influenzae* are probably susceptible to roxithromycin.

In another study Barry et al (3) determined the MIC's of 318 isolates of *H. influenzae* against clarithromycin. There were 75 isolates with an MIC of 16 μg/mL and 17 with an MIC of ≥ 32 μg/mL when tested in HTM against clarithromycin.

In a study (4) performed by Barry et al the *in vitro* activity of dirithromycin and erythromycin against 150 *H. influenzae* isolates was tested. They found that diffusion tests with HTM plates incubated in 5-7% CO_2 produced no zones of inhibition or very small zones with the 150 isolates tested against dirithromycin. Broth microdilution, unlike disk diffusion, tests with HTM broth do not need an increased CO_2 atmosphere for growth. When trays were incubated in 5-7% CO_2, control strains of *S. aureus* and *E. faecalis* showed four- to eight-fold increases in dirithromycin MIC's as compared to MIC's determined without added CO_2. Erythromycin showed two- to four-fold increases in MIC's when incubated in CO_2. The following MIC's were found for the 150 *H. influenzae* strains tested:

	Cumulative % inhibited by (μg/mL)						
	≤0.5	1.0	2.0	4.0	8.0	16.0	Geometric Mean MIC (μg/mL)
Erythromycin	5	8	22	81	99	100	3.5
Dirithromycin	3	3	6	27	88	100	6.5
Erythromycylamine	3	3	5	23	93	100	6.5

All these studies show that the patterns of susceptibilities of *H. influenzae* strains to different macrolides are generally similar, with most strains being inhibited by each macrolide at a concentration of μg/mL. Azithromycin is the most active compound against *H. influenzae* with MIC's of μg/mL for most strains.

Pharmacokinetics/Bioavailability

Dirithromycin is 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 dirithromycin tablets once daily for 10 days were as follows:

Pharmacokinetic Parameter (n=10 subjects	Mean (1 S.D.)	
	Day 1	Day 10
C_{max} (μg/mL)	0.3 (0.2)	0.4 (0.2)
T_{max} (h)	3.9 (0.9)	4.1 (1.3)
AUC_{0-24h} (μg.h/mL)	0.9 (0.7)	1.8 (1.1)

The protein binding of erythromycin ranges from % . Erythromycylamine is widely distributed throughout the body with a mean apparent volume of distribution (Vdss) of 800 L. The following steady-state tissue concentration were seen:

Steady-State Tissue Concentrations of Erythromycylamine Following Two 250-mg Tablets of Dirithromycin Given Orally Once Daily

Tissue	Time After Last Dose (h)	Mean Tissue Concentration (μg/mL or $\mu g/10^7$ cells)	Corresponding Mean Plasma or Serum Concentration (μg/mL)	Tissue/ Plasma (Serum) Ratio
Tonsil	14	3.47	0.17	20.4
Healthy lung	12	3.79	0.13	29.2
Infected lung	12	3.85	0.13	29.6
Infected bronchial secretions	48	2.15	0.31	6.9
Infected bronchial mucosa	48	2.59	0.31	8.4
Infected bronchial mucosa	72	1.74	0.33	5.3
Alveolar macrophages	5	0.37	0.35	1.1

The above information shows that as with most macrolides, plasma levels are very low. The drug is concentrated in lung and bronchial tissues. The amount in these tissues never gets close to dirithromycin MIC's for *H. influenzae* which are usually μg/mL. Treatment, however, leads to clinical success in most cases.

Erythromycylamine is primarily eliminated in the bile and undergoes little or no hepatic metabolism. The primary route of elimination is fecal/hepatic with 81% to 97% of the dose eliminated in this manner. About 2% of the administered dose is eliminated through the kidney. The mean plasma half-life of erythromycylamine is about 8 hours.

Bacteriological Efficacy (Correlation of Tests Results with Outcome)

The data submitted with this supplement tested *H. influenzae* strains by both the disk diffusion and broth microdilution NCCLS methods using HTM. For disk diffusion tests, NCCLS recommends incubating the organisms in 5-7% CO_2. The activity of dirithromycin is inhibited by acidic pH and incubation in CO_2 lowers the pH of the growth medium. This leads to very small zone diameters and makes disk diffusion testing unless. In the two studies submitted most zones were 7-12 mm (when any zone diameters were seen) and did not correlate with MIC results. An MIC of 16 μg/mL could have a zone size of 7 mm or one of 12 mm and a low MIC value of 0.5 μg/mL had the same variation in zone diameters. Broth dilution tests do not need incubation in CO_2 and are, therefore, more reliable.

When the original NDA 50-678 was submitted isolates of *H. influenzae* were not tested for susceptibility in Studies AQAB and E002 submitted with the NDA for bronchitis. Two new studies have now been performed, AQAT and AQAW, in which *H. influenzae* susceptibility has been tested using NCCLS methods. These two studies were double-blind, randomized trials of dirithromycin 500 mg QD for 5 days versus erythromycin 250 mg QID for 7 days. In the combined studies a total of 531 patients were treated with dirithromycin. Of the 531 patients treated with dirithromycin, a total of 228 were bacteriologically evaluable. Of these 228 patients, 178 (78.0%) had a favorable bacteriological response (9 eradications and 169 presumptive eradications) at posttherapy. Of the 228 bacteriologically evaluable patients, 44 patients were treated for infection caused by multiple pathogens and the remaining 184 patients were treated for infection caused by a single pathogen. *S. pneumoniae* was isolated in 18 (9.7%) of the 184 single-pathogen cases, *M. catarrhalis* was isolated in 15 (8.1%) cases, *H. influenzae* was isolated in 59 (32.1%) cases, and *S. aureus* was isolated as sole pathogen in 7 (3.8%) cases.

The data correlating the MIC's with outcomes is shown in TABLE 1.

TABLE 1
Correlation of MIC's with Outcomes--Studies AQAT and AQAW

MIC (μg/mL)	Number of patients (%)	Clinical Response		Bacteriological Response	
		Favorable (%)	Failure	Eradication[a] (%)	Persistence
0.4	1 (2)	1 (100%)	0	1 (100%)	0
1	1 (2)	1 (100%)	0	1 (100%)	0
2	8 (14)	8 (100%)	0	7 (87.5%)	1
4	18 (31)	14 (77.7%)	4	13 (72.2%)	5
8	22 (37)	15 (68.2%)	7	15 (68.2%)	7
12	1 (2)	0	1	1 (100%)	0
16	6 (10)	4 (66.6%)	2	4 (66.6%)	2
32	1 (2)	1 (100%)	0	1 (100%)	0
NA	1 (2)	1 (100%)	0	1 (100%)	0
Total	59	45 (76%)	14 (24%)	44 (75%)	15 (25%)

[a] Includes the categories eradicated and presumed eradicated.

The above table shows that the MIC's of dirithromycin fell within the range of μg/mL for 95% of the isolates and between μg/mL for 68% of the isolates. These data correlate well with Barry's study (4) in which 88% of 150 *H. influenzae* isolates were inhibited by 8.0 μg/mL dirithromycin and 100% by 16.0 μg/mL. The response rate of isolates with an MIC of 16.0 μg/mL was about the same as that at 8.0 μg/mL and only slightly less than that at 4.0 μg/mL. It appears that all these isolates should be grouped together since response rates are similar and no mechanism of resistance seems to come into play at the higher MIC values. There is only one isolate at 32 μg/mL and although it is eradicated the number of isolates is too small to make a prediction of what is the true response at this MIC value. There appears to be no reason to separate the isolates at 8.0 μg/mL from those at 16 μg/mL. Since there appears to be a few isolates with an MIC value > 16 μg/mL, an intermediate and resistant breakpoint may prove useful. The following breakpoints should be used:

MIC (μg/mL)	Interpretation
$\leq$ 16	Susceptible (S)
32	Intermediate (I)
$\geq$ 64	Resistant (R)

These breakpoints are only applicable to aerobically incubated broth dilution tests.

No zone diameter breakpoint should be used since this test requires incubation in an atmosphere of 5-7% CO_2, which causes very small or no zone of inhibition.

Quality Control Studies

In November, 1996, Barry and Brown performed a study to reevaluate the MIC control limits for dirithromycin versus *Staphylococcus aureus* ATCC 29213 and to evaluate the quality control parameters for *Haemophilus influenzae* ATCC 49247. The data from this study are submitted in this supplement. Ten laboratories were used in this study. In the *S. aureus* part of the study azithromycin and erythromycin were included as control drugs in one lot of media, six different lots of Mueller-Hinton broth were used, and agar dilution tests were also performed to determine whether broth and agar dilution MIC's with the control strain were comparable. In the *H. influenzae* part of the study the same ten laboratories were used, both dirithromycin and clarithromycin were tested in HTM broth, five different lots of media were used, and clarithromycin was tested as a control in one of the five lots of media. Disk diffusion tests were not assessed because previous experience had shown that there were no substantial zones around 15-μg dirithromycin disks when *H. influenzae* are tested on HTM agar and incubated under CO_2. Each day two microdilution trays were inoculated with the *S. aureus* control strain. This provided 12 dirithromycin MIC's, 2 azithromycin MIC's, and 2 erythromycin MIC's. Two microdilution trays (HTM broth) were inoculated with the *H. influenzae* control strain. This provided 10 dirithromycin MIC's and 2 clarithromycin MIC's. Tests were repeated on five different days for *S. aureus* ATCC 29213 and on ten different days for *H. influenzae* ATCC 49247.

Against *S. aureus* ATCC 29213 all MIC's were between 1 and 4 μg/mL. There were 90 MIC's at 1 μg/mL, 478 MIC's at 2 μg/mL and 31 MIC's at 4 μg/mL. All erythromycin MIC's were within the set control limits of 0.25 to 1 μg/mL. All azithromycin MIC's were within the set control limits of 0.5-2 μg/mL. A range of μg/mL for *S. aureus* ATCC 29213 was proposed. This range includes 100% of the data from this study. Agar dilution and broth microdilution test of dirithromycin were comparable when incubated in air.

Against *H. influenzae* ATCC 49247 there was one MIC of 4.0 μg/mL, 50 of 8.0 μg/mL, 400 at 16 μg/mL, and 49 at 32 μg/mL. All clarithromycin MIC's were within the set limits of 4 to 16 μg/mL. A proposed quality control range of μg/mL was set. This included 99.4% of the data from this study.

NDA REFERENCES

1. Barry AL, PC Fuchs, and SD Brown. Relative potencies of azithromycin, clarithromycin, and five other orally administered antibiotics. J Antimicrob Chemother 1995;**35:**552-555.

2. Erwin ME and RN Jones. Roxithromycin *in vitro* susceptibility testing of *Haemophilus influenzae* by NCCLS methods. J Antimicrob Chemother 1993;**32:** 652-654.

3. Barry AL, TS Schultheiss, SD Brown, and PC Fuchs. Reassessment of methods for testing the susceptibility of *Haemophilus influenzae* to clarithromycin. J Antimicrob Chemother 1996;**37:**845-847.

4. Barry AL, MA Pfaller, and PC Fuchs. Dirithromycin disc susceptibility tests: interpretive criteria and quality control parameters. J Antimicrob Chemother 1993;**31(suppl. C):**27-37.

CONCLUSIONS & RECOMMENDATIONS:

This supplement should be APPROVED from the microbiological viewpoint. The microbiology subsection should read as follows:

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information

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically--Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January, 1997.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.

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Microbiologist, HFD-520

cc: Orig. NDA 50-678/SEI-003
HFD-520/Division File
HFD-520/MICRO/Dionne
HFD-520/MO/Davidson
HFD-520/CHEM/Timper
HFD-520/PHARM/Seethaler
HFD-520/CSO/Cintron

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/GLMicro/ATSheldon
4/1/97 TB
12/15/97 TB
MB 12/16/97

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Addendum to Microbiological Review of Efficacy Supplement

NDA #: 50-678 **REVIEW #:** 1A **REVIEW DATE:** 12-DEC-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT SEI-003	18-DEC-96	20-DEC-96	02-JAN-97

NAME & ADDRESS OF APPLICANT:

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

CONTACT PERSON:

Jennifer L. Stotka, M.D.
Director U.S. Regulatory Affairs
Phone Number: (317) 276-1249
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DRUG PRODUCT NAME:

Proprietary:	Dynabac™
Nonproprietary:	Dirithromycin tablets
Chemical Type:	Macrolide Antibiotic Drugs
Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status:

Not Applicable

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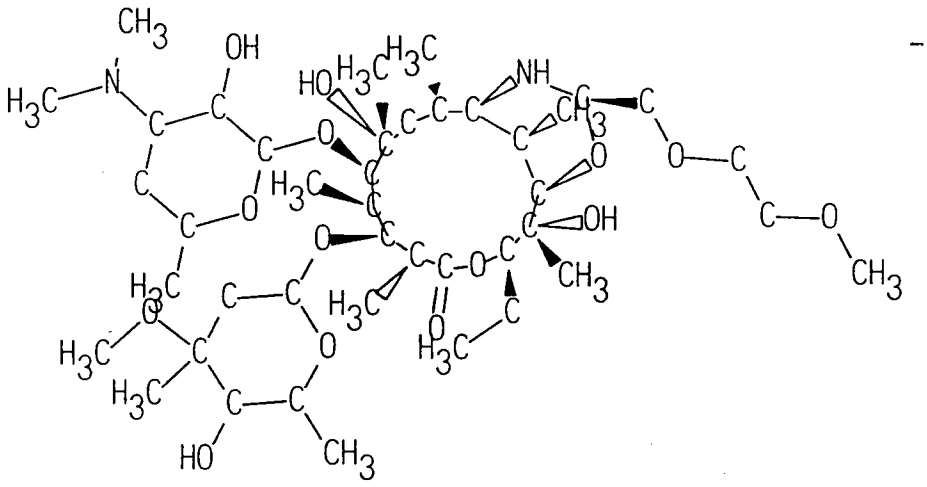
STRENGTHS:	250mg/tablet
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	_X_ **Rx** ___ **OTC**

CHEMICAL NAME, STRUCTURAL AND MOLECULAR FORMULA, MOL.WT:

Chemical Name: (9*S*)-9-Deoxo-11-deoxy-9,11-[imino[(1R)-2-(2-methoxyethoxy)-ethylidene]oxy]erythromycin

Chemical Structure:



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

SUPPORTING DOCUMENTS:
None

RELATED DOCUMENTS (if applicable):
None

CONSULTS: None

REMARKS/COMMENTS:

This submission contains data to support the use of dirithromycin for 5 days for acute exacerbations of chronic bronchitis and skin and skin tissue infections. This drug is approved for both of these indications for 7 days of treatment.

The sponsor also wishes to add *Haemophilus influenzae* to the bronchitis claim for this drug and *Streptococcus pyogenes* to the skin and skin tissue indication. *Streptococcus pyogenes* is already in the label due to the pharyngitis/tonsillitis claim and is, therefore, already in the microbiology subsection in the first listing of organisms. The sponsor has completed two additional bronchitis studies correlating *Haemophilus influenzae* MIC and zone diameter data with clinical and bacteriological outcome. The sponsor has proposed breakpoints for this organism. A study has also been performed to determine quality control limits for *Haemophilus influenzae* ATCC 49247.

In the review of the original NDA submission, FDA expressed concerns about acute exacerbations of chronic bronchitis caused by *H. influenzae*. One issue was the percentage of "resistant" isolates. The second issue was the unavailability of tests to determine whether strains were susceptible or resistant. Most strains of *H. influenzae* have high MIC's when tested against almost all of the macrolides. In clinical trails of bronchitis, however, this organism is eradicated and the patient has a successful clinical response. For almost all strains of *H. influenza,* the MIC's of macrolides vary from
μg/mL.

The Medical Officer has now completed review of this supplement. Based on the Medical Officer's Review of Evaluable Patients with *Haemophilus influenzae* infection the following data are available correlating MIC's of dirithromycin with Clinical Outcome in Study Protocols AQAT and AQAW.

Since the date of this submission separate breakpoints have been established for *Streptococcus* species. These breakpoints have been added to the label for this product.

Table 1 shows the number of patients and cures at each dirithromycin MIC value for the dirithromycin treated patients.

TABLE 1
Correlation of Dirithromycin MICs of *H. influenzae* and Clinical Outcome
For Dirithromycin Treated Patients Protocols B9Z-MC-AQAT and B9Z-MC-AQAW

MIC (μg/mL)	Number of Patients	Number of Cures	% Cured
0.06	1	0	0
1	1	1	100
2	9	8	88.9
4	30	24	80
8	31	21	67.7
12	1	0	0
16	8	6	75
32	1	1	100

Figure 1 shows the number of dirithromycin treated patients at each dirithromycin MIC value.

Figure 1
Number of Dirithromycin Treated Patients at Each MIC

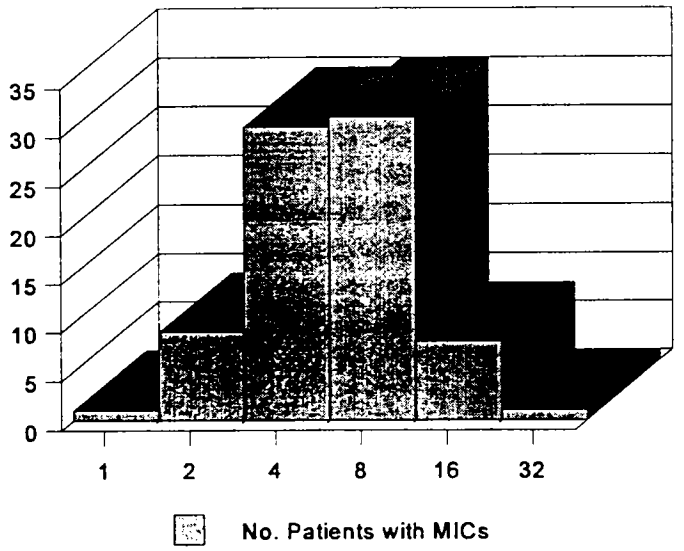


Figure 2 shows the number of cures for dirithromycin treated patients at each dirithromycin MIC value.

Figure 2
Number of Cures in Dirithromycin Treated Patients at each MIC value

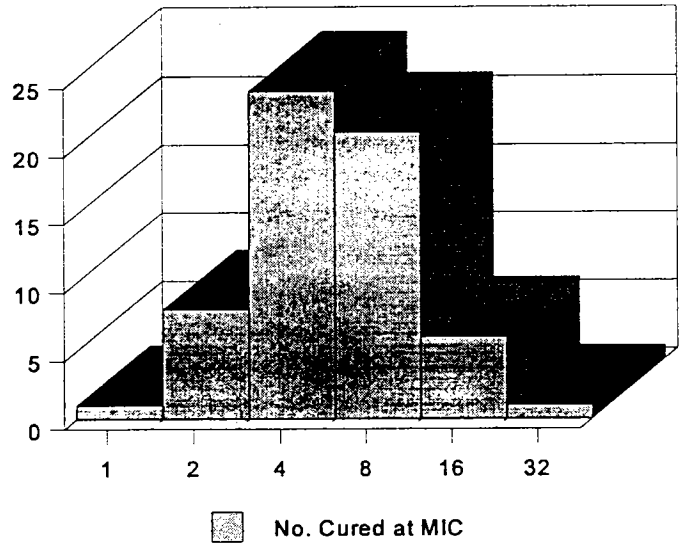
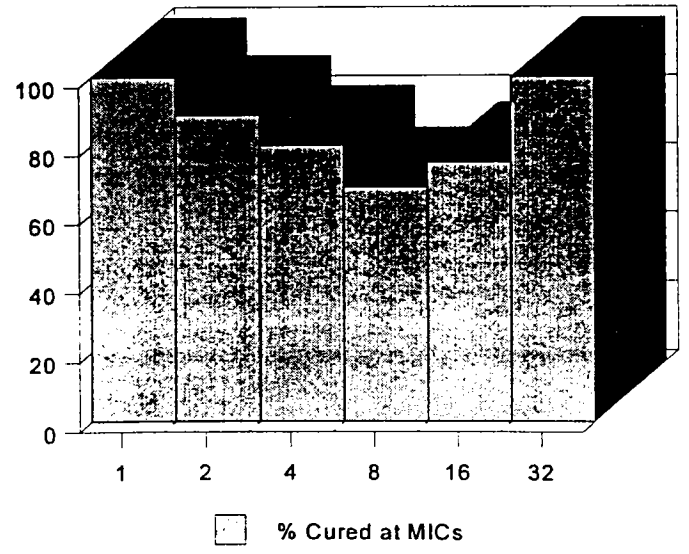


Figure 3 shows the percentage of dirithromycin treated patients cured at each dirithromycin MIC value.

Figure 3
Percentage Cure Rates at each Dirithromycin MIC



The above data demonstrate that most dirithromycin MICs were betweer μg/mL μg/mL. The vast majority of isolates had MIC values or μg/mL. The cure rate at 4 μg/mL was 80% and the cure rate at 8 μg/mL was lower at 67.7%. The number of isolates is small, however, and a change in the number of cures by one or two would make the cure rates at each MIC value about the same. The cure rate at 16 μg/mL was 75%, but there were only eight isolates with this MIC value. Since there does not appear to be any significant difference in the cure rate at the higher MIC values, there is no reason to separate the MICs into different interpretative categories. There is about an equal number of isolates with MICs or 4 μg/mL or 8 μg/mL, and separating these two MICs into separate categories does not appear justified. There are only a few isolates at 16 μg/mL and almost none at 32 μg/mL. The 16 μg/mL isolates can be separated into an intermediate category since there are only a few available to determine the cure rate and this category gives a buffer between susceptible and resistant isolates.

It appears from these data that the best breakpoints for dirithromycin when testing *Haemophilus influenzae* are:

Susceptible = ≤ 8 μg/mL
Intermediate = 16 μg/mL
Resistant = 32 μg/mL

The breakpoints in the Microbiology Review #1 should be revised as indicated above.

Table 2 shows the number of patients and cures at each erythromycin MIC value for patients treated with erythromycin. Since erythromycin is not a drug of choice for *Haemophilus influenzae* infections, no breakpoints have been established for erythromycin against *H. influenzae.*

TABLE 2
Correlation of Erythromycin MICs of *H. influenzae* and Clinical Outcome For Erythromycin Treated Patients Protocols B9Z-MC-AQAT and B9Z-MC-AQAW

MIC (μg/mL)	Number of Patients	Number of Cures	% Cured
0.06	2	1	50
0.15	1	0	0
0.5	5	5	100
1	13	6	46.2
2	23	15	65.2
4	37	26	70.3
8	3	2	66.7
14	1	0	0

Figure 4 shows the number of erythromycin treated patients at each erythromycin MIC value.

Figure 4
Number of Erythromycin Treated Patients at Each MIC

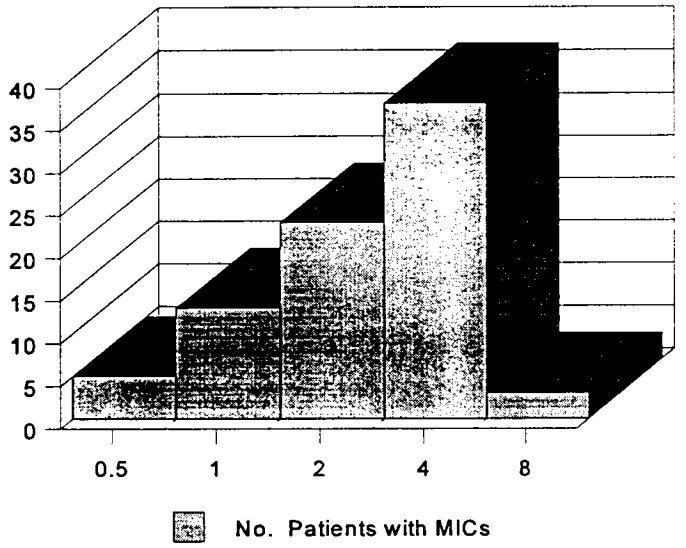


Figure 5 shows the number of cures for erythromycin treated patients at each erythromycin MIC value.

Figure 5
Number of Cures in Erythromcyin Treated Patients at Each MIC Value

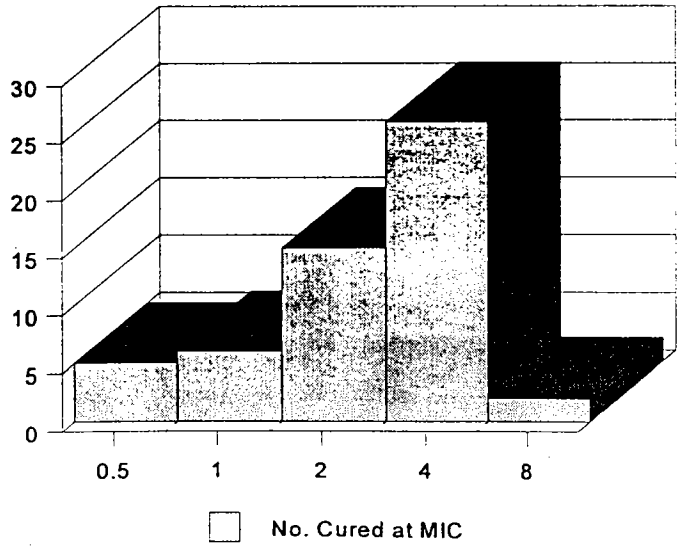
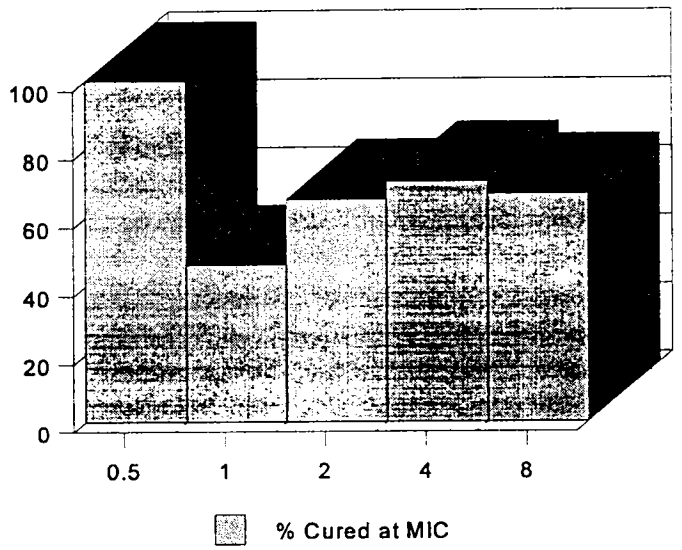


Figure 6 shows the percentage of erythromycin treated patients cured at each erythromycin MIC value.

Figure 6
Percentage Cure Rates at each Erythromycin MIC



These data demonstrate that most of the patients treated with erythromycin had isolates with erythromycin MICs of 2 μg/mL or 4 μg/mL. The cure rates also appear to be slightly better at the higher MIC values, but once again the number of isolates is small and a change from failure to cure of only two or three isolates can cause a significant change in cure rate. The overall cure rate for dirithromycin treated patients (61/82 = 74.4%) is better than for the erythromycin treated patients (55/85 = 64.7%).

CONCLUSIONS & RECOMMENDATIONS:

This supplement should be APPROVED from the microbiological viewpoint. The microbiology subsection should read as follows:

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References

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cc: Orig. NDA 50-678/SEI-003
HFD-520/Division File
HFD-590/MICRO/Dionne
HFD-520/MO/Davidson
HFD-520/CHEM/Timper
HFD-520/PHARM/Seethaler
HFD-520/CSO/Cintron

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/GLMicro/ATSheldon
12/15/97
12/16/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-678/SE1-003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 16 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 50-678
Dirithromycin, tablets

SUBMISSION DATE: Dec. 18, 1996

BRAND NAME: DYNABAC^R

REVIEWER: Funmilayo Ajayi, Ph.D.

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

TYPE OF SUBMISSION: Supplement

Background: This submission is to gain approval for the 5-day use of dirithromycin for the treatment of acute exacerbations of chronic bronchitis and skin and soft tissue infections. Dirithromycin was approved in the US in June, 1995 and in 35 foreign countries. The 5-day dosing has been approved in Belgium, Austria, Canada, Aruba, Curacao, Mexico, and Dominican Republic.

Findings: The current submission to the Human Pharmacokinetics and Bioavailability section of the NDA contains the report of study B9Z-IT-BAL2 entitled "Pulmonary Penetration of Dirithromycin in Patients Suffering from Acute Exacerbation of Chronic Bronchitis" (See **Appendix I for details**).
Results from this study demonstrates the ability of dirithromycin to achieve high concentrations at infected sites in the lung for at least 3 days after the last dose of the 5-day treatment. Mean concentrations (N=5) in the bronchial mucosa at 24, 48 and 72 h after the last dose on Day 5 are 2.59, 2.59, and 1.96 μg/g, respectively. The mean serum concentration at the same time points are 0.44, 0.31, 0.33 μg/ml, respectively. The high tissue concentrations are in agreement with the ability of macrolides to accumulate within the lysosomes, where protonated species are trapped because they ionize in the low pH of this organelle.

Recommendation: The information provided in the Human Pharmacokinetics and Bioavailability section of NDA 50,678 for dirithromycin oral tablets is acceptable because it meets the requirements set forth in 21 CFR 320. Although tissue concentrations that are well above the MIC of dirithromycin for the main pathogens responsible for exacerbations of chronic bronchitis were attained, a proof of clinical efficacy may be warranted. The requested change to the Clinical Pharmacology Section of the labeling is granted (**See Labeling Comments**).

Labeling Comments:

6/16/97

Funmilayo O. Ajayi, PhD
Div. Pharmaceutical Evaluation III

FT initialed by Frank Pelsor, PharmD...,.....

cc:
NDA 50-678, HFD-520 (Clinical Division)
HFD-880 (DPE3, Pelsor, Ajayi)
HFD-340 (Viswanathan)
CDR (B. Murphy)

Appendix I
(Study Summary)

STUDY TITLE: Pulmonary Penetration of Dirithromycin in Patients Suffering from Acute Exacerbation of Chronic Bronchitis. **Study # B9Z-IT-BAL2**.

INVESTIGATOR AND CENTER:

OBJECTIVES: The objective of this study was to determine the concentration of dirithromycin in bronchial secretions (BS), bronchial mucosa (BM), epithelial lining fluid (ELF), and serum after a 5-day, once daily, dirithromycin treatment regimen in patients with acute exacerbation of chronic bronchitis.

STUDY DESIGN: This was an open-label, unblinded, unrandomized, single-therapy study where 500 mg dirithromycin was administered once daily for 5 days.

STUDY POPULATION: fifteen (15) patients took part in the study.

DRUG FORMULATION: Dirithromycin, 250 mg at a dose of 500 mg given once daily.

DATA ANALYSIS: Concentrations of dirithromycin in serum, brochial mucosa, bronchial secretion, and epithelial lining fluid was estimated from the eryhtromycylamine activity in the biological fluids, determined by a microbiological assay using agar diffusion method.

RESULTS: The mean (n=5) 24-h dirithromycin concentrations in the serum, bronchial secretion, bronchial mucosa, and epithelial lining fluid are 0.44 μg/ml, 2.67 μg/g, 2.59 μg/g, 2.21, μg/ml, respectively. The mean (n=5) 48-h dirithromycin concentrations in the serum, bronchial secretion, bronchial mucosa, and epithelial lining fluid are 0.31 μg/ml, 2.15 μg/g, 2.59 μg/g, 2.25 μg/ml, respectively. The mean (n=5) 72-h dirithromycin concentrations in the serum, bronchial secretion, bronchial mucosa, and epithelial lining fluid are 0.33 μg/ml, 1.74 μg/g, 1.96 μg/g, 1.57 μg/ml, respectively. The penetration ratio in the bronchial mucosa are 5.9 at 24-h, 8.4 at 48-h and 5.9 at 72-h after the last Day 5 dose.

CONCLUSIONS: Results from this study demonstrates the ability of dirithromycin to achieve high concentrations at infected sites in the lung for at least 3 days after the last dose of the 5-day treatment. The high tissue concentrations are in agreement with the ability of macrolides to accumulate within the lysosomes, where protonated species are trapped because they ionize in the low pH of this organelle.

COMMENTS: A report of this study was published by Cazzola *et.al.* in Pulmonary Pharmacology (1994), 7: 377-381.

Figure 1 - Mean dirithromycin concentrations (±SD) in bronchial secretions, bronchial mucosa and ELF at each considered time after the last dose.

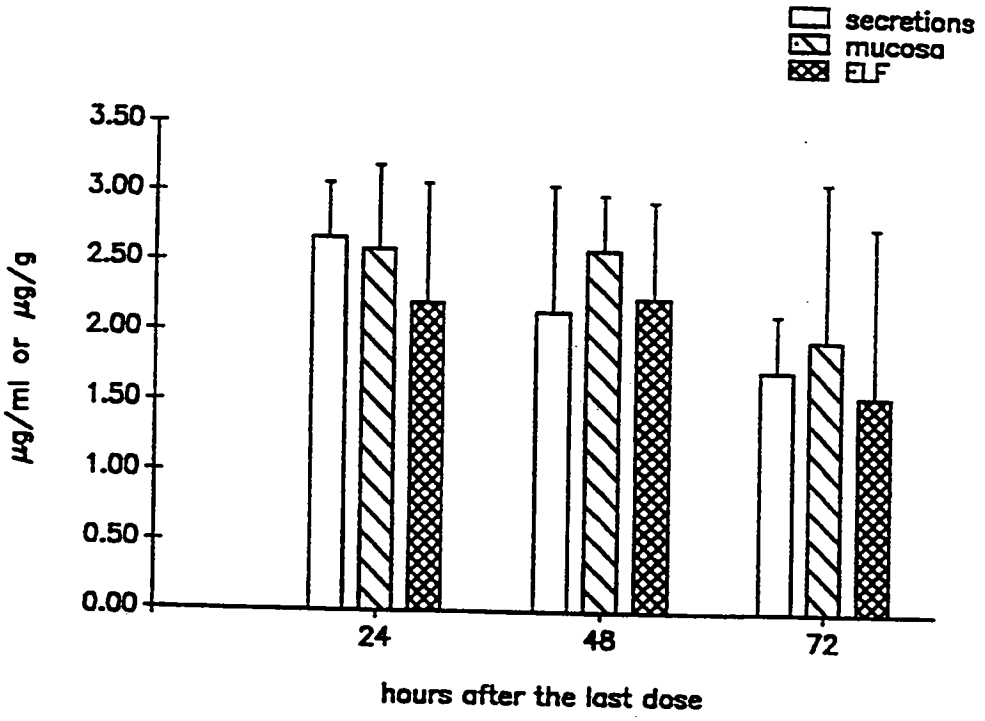


Figure 2 - Mean dirithromycin concentrations (±SD) in serum at each considered time after the last dose and MICs for *S. pneumoniae* (narrow crosshatch) and *M. catarrhalis* (narrow left diagonal).

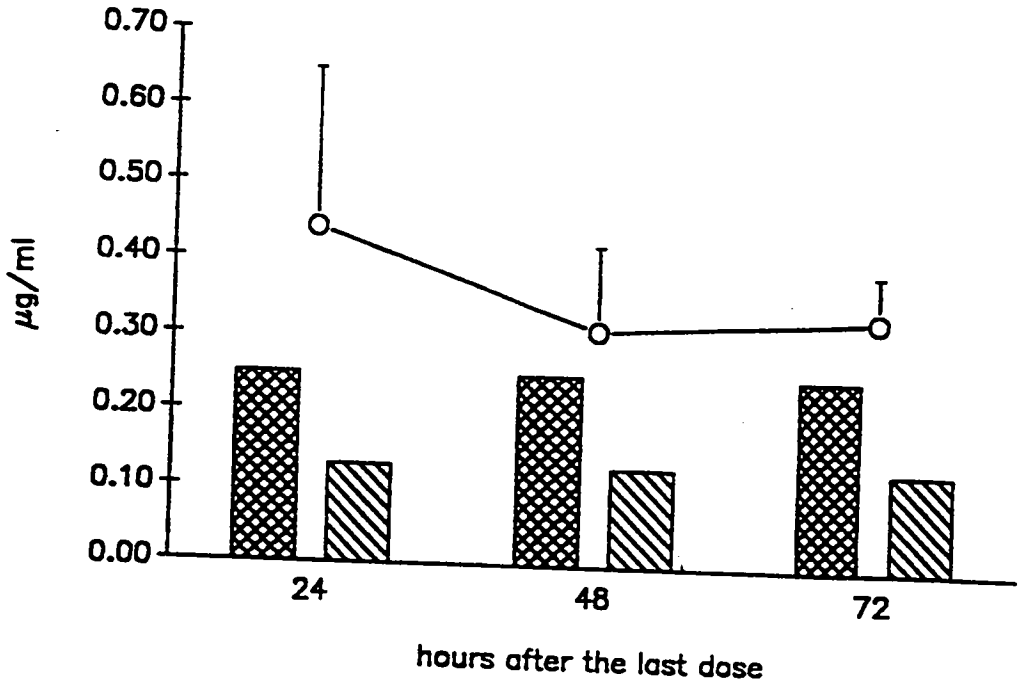


Figure 3 - Mean dirithromycin concentrations (±SD) in bronchial secretions, bronchial mucosa and ELF at each considered time after the last dose and MICs for key respiratory pathogens (*S aureus* = blank box; *S. pneumoniae* = narrow crosshatch; *M catarrhalis* = narrow left diagonal; *M pneumoniae* = narrow right diagonal; *L pneumophila* = wide crosshatch; *C pneumoniae* = wide left diagonal).

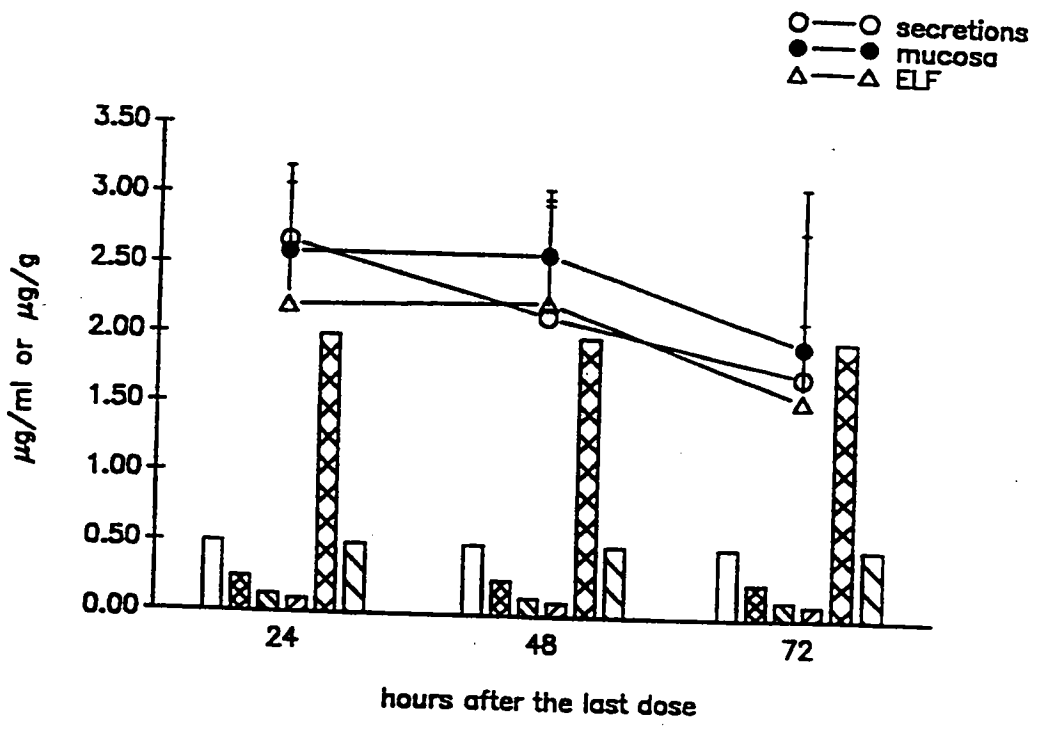
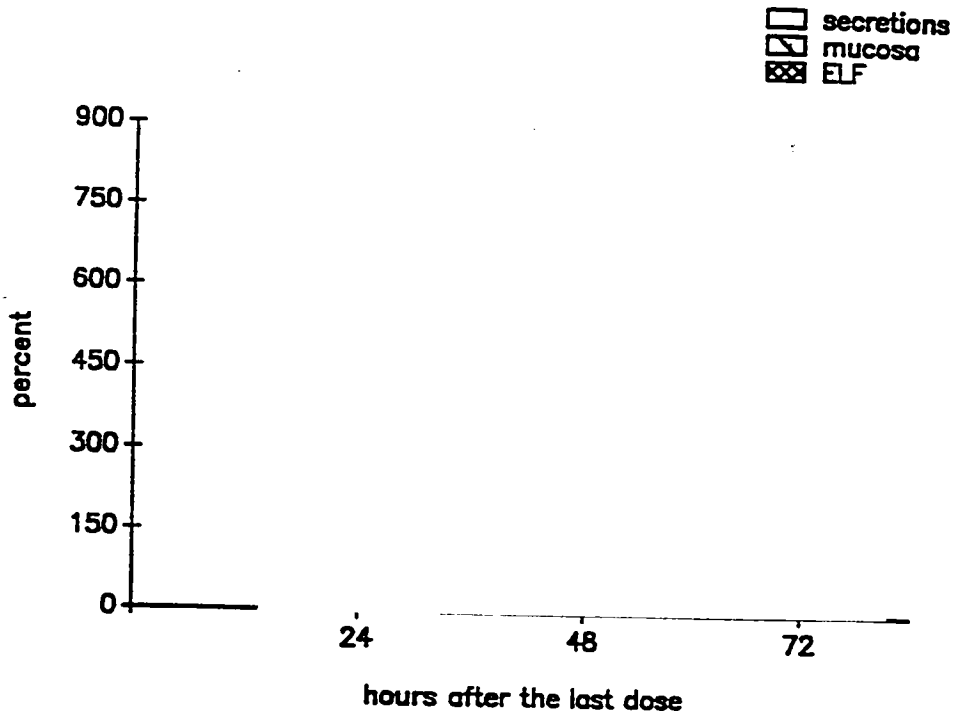


Figure 4 - Dirithromycin penetration ratio into bronchial secretions, bronchial mucosa and ELF relative to serum at each considered time after the last dose.



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-678/SE1-003

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 50-678 Supplement # 003 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Dynabac (dirithromycin) Tablets Action: AP AE NA

Applicant Eli Lilly Therapeutic Class Macrolide

Indication(s) previously approved Approval for the 5-day use of Dynabac for treating acute exarcerbations of chronic bronchitis and skin and soft tissue infections. (Haemophilus influenzae and Streptococcus pyogenes)
Pediatric information in labeling of approved indication(s) is adequate X inadequate __

Indication in this application CAP due Chlamydia pneumonia, Haemophilus influenzae, Mycoplasma pneumonia and Streptococcus pneumonia.
(Forsupplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or revious applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

XX 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required. **12 years and older**

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.
- __ (1) Studies are ongoing,
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Jose R. Cintron, R.Ph., M.A., Project Manager
Signature of Preparer and Title

December 12, 1997
Date

cc: Orig NDA/PLA/PMA # 50-678
HFD-520_____/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 12/12/97)

Certification

NDA Application Number: 50-678

Drug Name: Dynabac® (dirithromycin tablets)

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Dr. Jennifer L. Stotka, M.D., hereby certifies it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above-referenced application.

ELI LILLY AND COMPANY

By: _____

Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs

Date: 18 Dec 1996

ITEM 13: PATENT INFORMATION

The undersigned certifies that the drug and formulation or composition of such drug claimed by the following patents are the subject of the present New Drug Application

Patent Number	Expiration Date
4,048,306	Patent term extension pending. Interim extension granted to September 13, 1997.
4,755,385	July 5, 2005
5,556,839	September 17, 2013

ITEM 14: PATENT CERTIFICATION

We certify that we are unaware of any patent claiming the medicinal use of dirithromycin.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-678/SE1-003

CORRESPONDENCE

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

November 21, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attn.: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

CORRESPONDENCE

RE: NDA 50-678, Dynabac® (dirithromycin tablets)

This letter is submitted in response to the November 18, 1997, telefax from Mr. Jose Cintron, R.Ph, M.A., Division of Anti-Infective Drug Products, FDA. Responses to specific comments from Dr. Li Ming Dong (faxed to FDA on November 19, 1997) are attached. In addition, floppy disks containing all the datasets (including the updated ones) are provided.

The floppy diskettes are formatted for IBM as in our submission dated June 10, 1997. The diskettes contain the data in compressed form. Also included is the software necessary to transfer the files from the diskettes to your computer's hard drive. Three copies of the diskettes are being provided: one copy is included here for the NDA file and two desk copies are being sent under separate cover to Mr. Jose Cintron. Details about the contents of each diskette and instructions for accessing the data are attached.

Please call Mr. Gary Higdon at (317) 276-9136 or me at (317) 276-1249 with any questions or comments. Thank you for your assistance.

Sincerely,

ELI LILLY AND COMPANY

for Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs

Attachments

DUPLICATE

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

NDA SUPPL AMENDMENT

SE 1-003

April 17, 1997

CENTER FOR DRUG
REC'D
APR 21 1997
HFD-

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, Maryland 20852

RE: NDA 50-678 - Dynabac®, dirithromycin

Pursuant to 21 CFR 314.80(c)(2), enclosed is the Periodic Adverse Drug Experience Report for Dynabac, dirithromycin.

The time period covered by this report is December 20, 1996 through March 19, 1997.

Included in this submission are 2 initial and 0 follow-up U.S. non-alert reports. There were 4 initial and 2 follow-up international non-alert reports during the period covered by this report. In accordance with 21 CFR 314.80(c)(2)(iii), copies of these international reports are not included.

Further, as agreed in the April 15, 1997 telephone conversation between Mr. Jose Cintron, Division of Anti-infective Drug Products, FDA, and Dr. Wayne Millar, Eli Lilly and Company, it is our intent that this report also be the 4 month safety update for our December 18, 1996 submission as required under 21 CFR 314.50(d)(5)(vi)(b)(1). That submission was made to gain approval for the 5-day use of Dynabac for treating acute exacerbations of chronic bronchitis and skin and soft tissue infections.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Please call Dr. Wayne N. Millar at (317) 276-2084 or myself at (317) 276-1249 if there are any questions. Thank you for your continued cooperation and assistance.

Very truly yours,

ELI LILLY AND COMPANY

Jennifer L. Stotka, M.D.
Director
U.S. Regulatory Affairs

JLS:pmj

Enclosure

cc: Mr. Jose Cintron