CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-670/S-015

50-693/S003

50-730/S005

MICROBIOLOGY REVIEW

HFD-530
Willard

NOV 13 2000

Microbiology Review

Division of Special Pathogens and Immunologic Products

(HFD-530)

NDA# 50,730

Reviewer : Linda Gosey
Correspondence Date : 1-13-2000
CDER Receipt Date : 1-13-2000
Review Assigned Date: 1-18-2000
Review Complete Date: 11-07-2000

Sponsor: Pfizer
Eastern Point Road
Groton, Ct. 06340

Submission Reviewed: Supplement SLR-005

Drug Category: Antimycobacterial and antiparasitic

Indication: Prophylactic therapy for Mycobacterium avium complex infections.

Dosage Form: Oral tablet

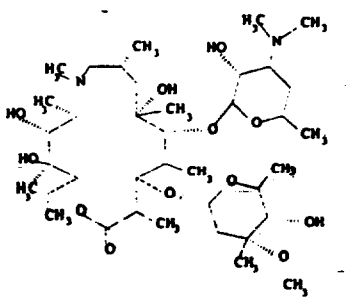
Product Names:

a. Proprietary: Azalide

b. Nonproprietary: Azithromycin

c. Chemical: 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A

Structural Formula:



NDA 50-730.SLR5
Azithromycin /MAC
Pfizer

Supporting Documents: [redacted]

Background:

In this supplement the sponsor is providing clinical trial data from study 66-189 evaluating azithromycin in combination with ethambutol for the treatment of disseminated *Mycobacterium avium* complex (MAC) infections in HIV positive patients. In 1996 azithromycin was approved for prophylaxis of disseminated MAC in HIV positive patients.

The content of this microbiology review pertains to the evaluation of the microbiologic data obtained from clinical trial 66-189 and 66-189B. The overview of the protocol design and the assessment of the clinical data can be found in the medical officer's review. This review also contains a summary of the preclinical activity profile of azithromycin against MAC organisms, as well as the mechanism of action and drug resistance.

Summary of Preclinical Microbiology Data:

Azithromycin, an erythromycin derivative, inhibits cell-free protein synthesis by binding to the conserved domain V of the 23S rRNA. Because the mechanism of action is the same for all the macrolides cross resistance between these agents is observed. Thus, MAC organisms developing resistance to clarithromycin would also be resistant to azithromycin and vice versa. It is estimated that the frequency of macrolide-resistant MAC mutants is between 10^{-8} to 10^{-10}.

As with other macrolides, azithromycin MICs can vary depending on the conditions of the susceptibility test. Macrolide MICs are pH sensitive. The higher the pH (i.e. 7.4 versus 6.6) the lower the MIC values.

In vitro azithromycin does not appear to be very active with MICs ranging from [redacted] for MAC isolates. However, azithromycin accumulates intracellularly where MAC organisms reside. Using the macrophage model, investigators have demonstrated that azithromycin in combination with rifabutin, rifapentine, tumor necrosis factor or granulocyte-macrophage colony-stimulating factor (GMCSF)

produced greater intracellular killing of MAC than any of the agents alone.

In the paper "Rationale for the use of Azithromycin as *Mycobacterium avium* Chemoprophylaxis". 1997. Am. J. Med.;102(5C):37-49, Dunne et. al. summarized the data from the published literature on the pharmacokinetics, in vitro activity and intracellular activity of azithromycin. In general, while azithromycin MICs were 2-32 fold higher than clarithromycin, both demonstrated equivalent activity in the beige mouse infection model of disseminated MAC.

When azithromycin or clarithromycin mono-therapy was administered to MAC infected beige mice, comparable activity was demonstrated between the two treatments. However, it was noted that a higher incidence of drug resistance development occurred in the clarithromycin mono-therapy arm versus the azithromycin arm. When cross resistance was evaluated it was determined that complete cross resistance occurred due to a single point mutation at position 2058 or 2059 of the 23 rRNA. The lower incidence of drug resistance development in the azithromycin arm may be due to the high intracellular concentrations obtained with azithromycin versus clarithromycin.

Intermittent dosing with azithromycin is achievable due to the drug's long half-life and the high intracellular concentrations. In one human pharmacokinetic study mean leukocyte concentrations following a single 1200 mg oral dose were >32 μg/mL for 3 days and >16 μg/mL for 5 days.

Assessment of Microbiology Data from Clinical Study 189 and 189B: Treatment of Disseminated MAC

Clinical trial 66-189/189B was a randomized double-blind study assessing the efficacy of daily dosing of azithromycin at 250 mg or 600 mg compared to clarithromycin 500 mg, with each being given in combination with ethambutol, for the treatment of disseminated MAC. HIV positive patients with culture proven MAC bacteremia were enrolled and treated for 24 weeks. The primary endpoint in this study was the percent of patients who achieved sterility of blood. Secondary endpoints included durability of sterility of blood and the relationship between microbiologic sterility, clinical response and survival. Two other points of interest included

drug resistance development and the relationship between prior macrolide therapy and macrolide MIC values on baseline MAC isolates.

Incidence of Microbiologically proven MAC events:

A total of 68 and 57 subjects were enrolled in the azithromycin and clarithromycin arms of study 66-189, respectively. As per the protocol design subjects were to receive therapy for a total of 24 weeks. After completing 24 weeks of therapy subjects were enrolled in study 66-189B and followed for relapse. After looking at the data it was noted that a number of the subjects enrolled in the study did not have routine blood drawn for mycobacterial culture at weeks, 3, 6, 9, 12, 16, 20 and 24. This is unfortunate, as these data were needed to address the primary and secondary microbiologic objectives.

In an effort to address the microbiologic objectives (i.e. microbiologic outcome after 24 weeks of treatment, durability of sterility of blood and the incidence of relapse) this reviewer chose to focus on subjects that had blood cultures routinely evaluated for MAC up to weeks 20 or 24. However, to include as many subjects as possible in this analysis 4 additional patients were added. Three additional patients were added to the clarithromycin arm, one who completed 12 weeks and 2 who completed 16 weeks of therapy. One patient that completed 17 weeks of therapy was added to the azithromycin arm. As a consequence, there were 40/68 (59%) azithromycin and 32/57 (56%) clarithromycin patients that were considered microbiologically evaluable.

For study 66-189 microbiologic efficacy was defined as follows:

Microbiologic cure: patients whose blood was MAC free at the end of therapy

Microbiologic failure: patients who continued to have MAC in their blood at week 20 or 24

Relapse: patients who were MAC free at the end of therapy but had a positive blood culture for MAC during the post therapy follow-up period

A number of observations were made regarding this FDA microbiologically evaluable subset of subjects. The first evaluation as demonstrated in the following 2 tables measured the number of microbiologic cures, failures and relapses broken down by the baseline mycobacterial burden.

Clarithromycin Therapeutic Response Rates Separated by Baseline Mycobacterial Burden

BASELINE MAC CFU/mL	CURE	RELAPSE	FAILURE	TOTAL
1-10	8	4	0	12
11-25	1	2	0	3
26-50	2	0	0	2
51-100	3	0	2	5
101-200	1	0	0	1
201-500	2	1	1	4
501-1000	0	0	0	0
>1001	2*	2	1	5
TOTAL	19	9	4	32

*- One patient developed a drug resistant strain on day 141 of therapy and only had one additional culture on day 197, which was negative for MAC.

Therapeutic Response Rates Based on Baseline MAC burden and Azithromycin Therapy

BASELINE MAC CFU/ml	CURE	RELAPSE	FAILURE	TOTAL
1-10	4	4	1	9
11-25	6	4	2	12
26-50	2	0	0	2
51-100	0	0	1	1
101-200	3	3	0	6
201-500	3	1	2	6
501-1000	0	0	0	0
>1001	1	1	2	4
TOTAL	19	13	8	40

It is well known that MAC burden in the blood is a [redacted] for severity of disease. Thus the higher the MAC burden at baseline the more likely these patients will either fail or relapse. To challenge this hypothesis MAC burden at baseline was looked at in $\log_{10}$ increments. In the azithromycin and clarithromycin arms the total number of subjects that failed were 8/40 (20%) and 4/32 (12.5%), respectively. For azithromycin patients with baseline MAC cultures of ≤10, ≤100, ≤1000 and >1000 CFU/mL there was a failure rare of 11%, 33%, 8% and 50%, respectively. In the clarithromycin arm the failure rate was 0%, 29%, 20% and 20% for patients with baseline MAC burdens of ≤10, ≤100, ≤1000 and >1000 CFU/mL, respectively. While these numbers are small there is a slight trend suggesting that patients who received azithromycin versus clarithromycin therapy were more likely to fail.

Assessment of Relapse:

At the end of 24 weeks of therapy (in a few cases the end of therapy was at week 20) 32/40 (80%) subjects in the azithromycin arm and 28/32 (87.5%) subjects in the clarithromycin arm had cleared MAC from their blood. Patients receiving complete therapy and remained MAC free through week 24 were chosen to determine if the proposed therapeutic dosing would be adequate not only to sterilize the blood but reduce the incidence of relapse. In this study it was noted that a number of patients had episodes of transient MAC bacteremia either during treatment or during follow-up. At this time it is unclear how to interpret these results as transient positive blood cultures could be an early sign for relapse or an indication that the body is clearing MAC over time. Of the 32 azithromycin patients that cleared MAC from the blood 13 (41%) relapsed. Only 9/28 (32%) of the clarithromycin subjects that were MAC free at week 24 relapsed.

Patients were further evaluated to determine the length of time patients remained MAC free, as well as the time relapse occurred. For these evaluations a time point of 6 months post therapy (180 days post therapy) was chosen.

Rate of Relapse in Microbiologically Evaluable Patients who had Sterile Blood Cultures after Receiving 20 or 24 weeks of Azithromycin or Clarithromycin Therapy

NUMBER OF PATIENTS	AZITHROMYCIN	CLARITHROMYCIN
PATIENTS WITH < 180 DAYS FOLLOW-UP DATA	15	8
STERILE BLOOD CULTURES or ASYMPTOMATIC	7	5*
RELAPSE - MAC POSITIVE BLOOD CULTURES	8	3
PATIENTS WITH > 180 DAYS FOLLOW-UP DATA	10	16
STERILE BLOOD CULTURES or ASYMPTOMATIC	5	10
RELAPSE - MAC POSITIVE BLOOD CULTURES	5	6
NO FOLLOW-UP DATA	7	4

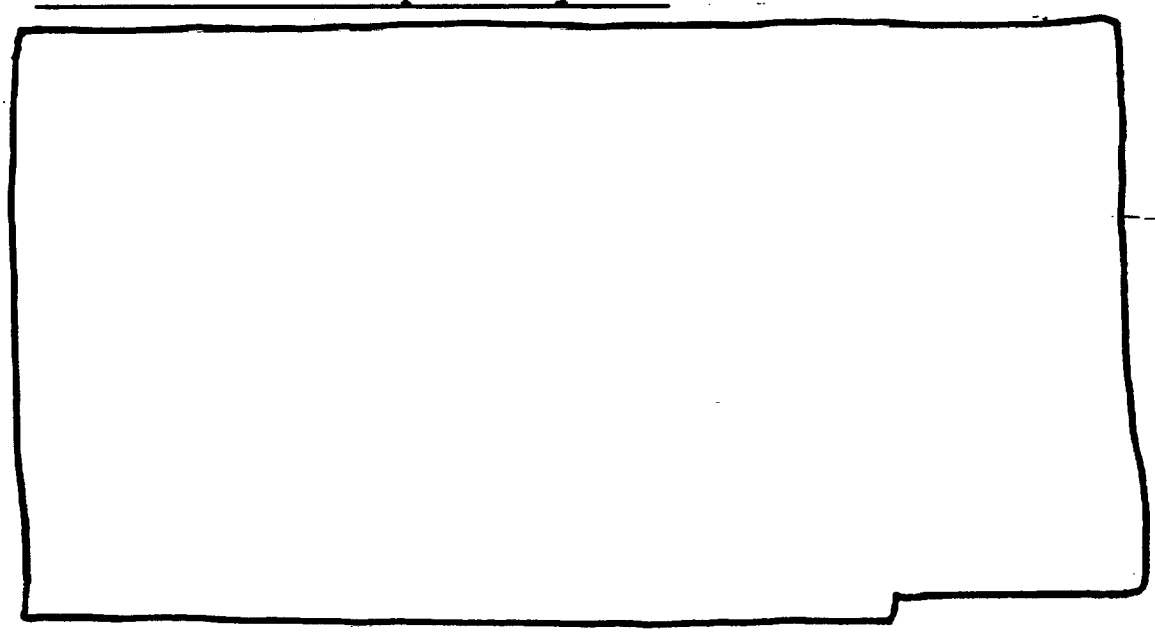
*- One patient devoped a drug resistant strain on day 141 of therapy and only had one additional culture on day 197, which was negative for MAC.

APPEARS THIS WAY
ON ORIGINAL

The data from the above table shows that 25/32 (78%) and 24/28 (86%) of the patients who obtained sterile blood cultures at the end of therapy and received azithromycin and clarithromycin therapy, respectively, had follow-up data. In the azithromycin arm 10/25 (40%) subjects were followed for greater than 180 days post therapy. In the clarithromycin arm 16/24 (67%) of the patients completing therapy were followed for greater that 6 months post therapy.

When relapse rates were assessed it was observed that 13/25 (52%) and 9/28 (32%) of the subjects in the azithromycin and clarithromycin arms, respectively, relapsed. In the azithromycin arm approximately one-half of the subjects followed for < 180 days, as well as > 180 days post therapy relapsed. In the clarithromycin arm, 3/8 and 6/16 (38% each) of the subjects followed for less than 180 days and greater than 180 days relapsed. While the number of subjects followed post therapy are small the data do suggest that patients who received clarithromycin therapy are less likely to relapse than those who received azithromycin therapy are. The data also suggest that the time to relapse is longer for those subjects who received clarithromycin versus azithromycin.

Assessment of Susceptibility Data:



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[redacted]

The use of a unique susceptibility testing method [redacted] to obtain azithromycin MIC values brings up a larger concern; the determination and interpretation of azithromycin breakpoints. Depending on the susceptibility method employed different MIC values may be used to define the resistance breakpoint. To bring consistency to the clinical laboratories and reduce confusion, the Division has consistently recommended that antimycobacterial breakpoints be determined using the agar dilution and [redacted] broth method devised [redacted] These methods were chosen because approximately 30% and 70% of the clinical laboratories in the U.S. use the agar dilution and radiometric method, respectively. In addition, these susceptibility methods have been used for years in clinical laboratories and are somewhat standardized for MAC isolates though not approved by the FDA.

It is unfortunate that different susceptibility testing methods were used to determine azithromycin and clarithromycin MIC values. At the present time, it is not known how azithromycin MIC values obtained using [redacted] method correlate to clinical response or to azithromycin MIC values obtained by the Inderlied susceptibility testing method. It is this reviewers opinion that the sponsor should establish and validate azithromycin MIC values for MAC organisms using [redacted] radiometric methodology and the agar proportion method as these antimycobacterial susceptibility testing methods are used in the majority of the U.S. clinical laboratories. Azithromycin breakpoints determined using these methods should be described in the package insert.

In clinical trial 189 susceptibility testing was conducted against the MAC isolates recovered at baseline, at the time of relapse (post therapy) or failure. Azithromycin MIC values ranged from [redacted]

[redacted] and clarithromycin MICs ranged from [redacted] The individual MAC susceptibility results demonstrated that azithromycin MIC values could be 4 to 32 fold higher than clarithromycin MIC values.

The ability to determine which MAC isolates were resistant to azithromycin or clarithromycin is impossible as the breakpoint for separating susceptible and resistant MAC isolates has not been established for either macrolide. However, it is of interest to note that all twelve MAC isolates that had clarithromycin MICs >32 μg/ml also had azithromycin ≥128 μg/ml, suggesting total cross resistance between the two drugs.

The ability to interpret MAC isolates with azithromycin MICs of >32 and <128 μg/ml is less clear as there were only a few isolates that fell into this drug susceptibility range. At this point in time it is unknown if MAC isolates with azithromycin MIC values in this range indicate resistance to azithromycin or reduced activity against MAC. As a consequence, clinicians should be cautious when interpreting azithromycin MIC values as an indicator for drug activity against MAC infections.

The reviewing microbiologist also assessed the relationship between azithromycin and clarithromycin MIC values to determine if MAC isolates with high azithromycin MICs also had high clarithromycin MICs. For the purpose of this review a sharp increase in MICs over time was used as a guide for suggest drug resistance development. The FDA microbiology reviewer grouped the MAC isolates from the evaluable patients under the following MICs values; azithromycin at <16, ≥16-<32, ≥32-<128, ≥128μ/mL and clarithromycin at <1, ≥1-<4, ≥4-<32, ≥32 μ/mL.

The two tables below show the number of MAC isolates from the evaluable subset of patients falling under the various drug categories. Because the number of patients that were microbiologically evaluable are small, the in vitro susceptibility data can, at best, only enlighten us as to the rate MAC organisms develop resistance to azithromycin as well as the frequency of cross resistance between azithromycin and clarithromycin.

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SUSCEPTIBILITY PATTERNS OF MAC ISOLATES AT VARIOUS TIME POINTS-AZITHROMYCIN ARM

	AZITHROMYCIN (μg/mL)					CLARITHROMYCIN (μg/mL)				
MAC ISOLATE	<16	≥16-<32	≥32-<128	>128	ND	<1	≥1-<4	≥4-<32	>32	ND
BASELINE	27	10	3			23	16	1		
RELAPSE	2	1*	1	4*	6	1	3*		4*	6
FAILURE	4	2	0	2		4	2	0	2	

*:One patient had a mixed culture with MAC isolates having high and low MICs

SUSCEPTIBILITY PATTERNS OF MAC ISOLATES AT VARIOUS TIME POINTS-CLARITHROMYCIN ARM

	AZITHROMYCIN (μg/mL)					CLARITHROMYCIN (μg/mL)				
MAC ISOLATE	<16	≥16-<32	≥32-<128	≥128	ND	<1	≥1-<4	≥4-<32	≥32	ND
BASELINE	23	6	3			15	16	1		
RELAPSE		1		4	4		1		4	4
FAILURE	1	2		1			3			

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Susceptibility test results obtained from the reference laboratory were used to assess potential drug resistance. There was a total of 6 MAC isolates in the azithromycin arm that had high MICs for both azithromycin and clarithromycin, >128 μg/mL and >32 μg/mL, respectively. In the clarithromycin arm there were five MAC isolates with high macrolide MIC values. It should be noted that the sponsor identified an additional patient with high macrolide MICs, however, the susceptibility testing was conducted at the local laboratory and the MIC data were not available for an independent review. These results suggest that the rate of drug resistance development is low in both treatment arms. A total of 4/6 (66%) and 4/5 (80%) of the MAC isolates with high macrolide MICs in the azithromycin and clarithromycin arms, respectively, occurred in patients who relapsed. The remaining MAC isolates occurred in patients who failed therapy. These data show that MAC isolates that develop high azithromycin MICs also develop high clarithromycin MICs indicating cross resistance.

Azithromycin Label

Below is the FDA's proposed labeling of the Microbiology section of the azithromycin label regarding the treatment of MAC. The sponsor is in agreement with this version of the label.

PRECLINICAL PHARMACOLOGY:

Mechanism of Action:

acceptable

In vitro Activity of Azithromycin against Mycobacteria:

Azithromycin has demonstrated *in vitro* activity against *Mycobacterium avium* complex (MAC) organisms. While gene probe techniques may be used to distinguish *M. avium* species from *M. intracellulare*, many studies only reported results on *M. avium* complex (MAC) isolates. Azithromycin was also shown to be active against phagocytized *M. avium* complex (MAC) organism in mouse and human macrophage cell cultures as well as in the beige mouse infection model.

Various *in vitro* methodologies employing broth or solid media at different pHs, with and without oleic acid-albumin-dextrose-catalase (OADC), have been used to determine azithromycin MIC values for *Mycobacterium avium* complex strains. In general, azithromycin MIC values decreased 4 to 8 fold as the pH of [redacted] agar media increased from 6.6 to 7.4. At pH 7.4, azithromycin MIC values determined with Mueller-Hinton agar were 4 fold higher than that observed with [redacted] media at the same pH. Utilization of oleic acid-albumin-dextrose-catalase (OADC) in these assays has been shown to further alter MIC values. The relationship between azithromycin and clarithromycin MIC values is vague. Azithromycin MIC values can be 2 to 32 fold higher than clarithromycin MICs irregardless of the susceptibility testing method employed.

The ability to correlate plasma drug levels and MIC values is difficult as azithromycin concentrates in macrophages and tissues. (See CLINICAL PHARMACOLOGY)

Drug Resistance:

Complete cross-resistance between azithromycin and clarithromycin has been observed with *Mycobacterium avium* complex (MAC) isolates. In most isolates, a single point mutation at a position that is homologous to *Escherichia coli* position 2058 or 2059 on the 23S rRNA gene is the mechanism producing this cross-resistance pattern[1,2]. *Mycobacterium avium* complex (MAC) isolates exhibiting cross-resistance show an increase in azithromycin MICs to $\geq$ 128 µg/mL with clarithromycin MICs increasing to $\geq$ 32 µg/mL. These MIC values were determined employing the radiometric broth dilution susceptibility testing method with [redacted] medium. The clinical significance of azithromycin and clarithromycin cross resistance is not fully understood at this time but pre-clinical data suggest that reduced activity to both agents will occur after *M. avium* complex strains produce the 23S rRNA mutation.

Susceptibility testing for *Mycobacterium avium* complex (MAC):

The disk diffusion techniques and dilution methods for susceptibility testing against gram-positive and gram-negative bacteria should not be used for determining azithromycin MIC values against mycobacteria. *In vitro* susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentration (MIC) values against *Mycobacterium avium* complex (MAC) organisms have not been standardized or validated. Azithromycin MIC values will vary depending on the susceptibility testing method employed, composition and pH of media and the utilization of nutritional supplements. Breakpoints to determine whether clinical isolates of *M. avium* or *M. intracellulare* are susceptible or resistant to azithromycin have not been established.

The clinical relevance of azithromycin *in vitro* susceptibility test results for other mycobacterial species, including *Mycobacterium tuberculosis,* using any susceptibility testing method has not been determined.

References:

1. Dunne MW, Foulds G, Retsema JA, Rationale for the use of Azithromycin as *Mycobacterium avium* Chemoprophylaxis. American J. Medicine 1997;102(5C):37-49.

2. Meier A, Kirschner P, Springer B, et al,. Identifications of mutations in 23S rRNA gene of clarithromycin-resistant *Mycobacterium intracellulare,* Antimicrob. Agents Chemother. 1994;38:381-384.

The following microbiology information should be placed in the clinical trials section regarding the treatment of MAC:

Susceptibility Pattern of MAC isolates:

Susceptibility testing was performed on MAC isolates recovered at baseline, at the time of breakthrough on

therapy or during post-therapy follow-up. The [redacted] radiometric broth method was employed to determine azithromycin and clarithromycin MIC values.

Azithromycin MIC values ranged from [redacted] and clarithromycin MICs ranged from [redacted] The individual MAC susceptibility results demonstrated that azithromycin MIC values could be 4 to 32 fold higher than clarithromycin MIC values.

During treatment or the post-follow-up period a total of 6/68 (9%) and 6/57 (11%) of the patients who received daily azithromycin therapy at 600 mg with ethambutol and 500 mg clarithromycin bid with ethambutol, respectively, developed MAC bacteremia with isolates that had a sharp increase in MIC values. All twelve MAC isolates had azithromycin MICs $\geq$256 μg/ml and clarithromycin MICs >32 μg/ml. These high MIC values suggest development of drug resistance. However, at this time specific breakpoints for separating susceptible and resistant MAC isolates has not been established for either macrolide.

Conclusions:

This NDA contains the results from a phase III clinical trial, study 66-189, in support of azithromycin in combination with ethambutol for the treatment of disseminated MAC infection in HIV positive patients. Microbiologic issues evaluated in this NDA pertain to the rate of sterilization of *M. avium* complex from the blood after 24 weeks of therapy, azithromycin drug resistance development and the relationship between azithromycin and clarithromycin MIC values as it pertains to cross resistance.

In the original protocol design blood from enrolled subjects was to be collected in an Isolator tube, processed at the central laboratory and quantitatively cultured for MAC. [redacted] The methods used for culturing and quantitating MAC from blood, as well as the test method for speciating the MAC isolates are acceptable with respect to microbiology.

In this review statistical analyses of the microbiologic data were not performed due to the small number of microbiologically evaluable patients enrolled in both treatment arms. However, what can be discussed are trends in activity that were observed. The time to sterilization of MAC in blood could not be accurately determined from the study. What was observed is that 28/32 (87.5%) of the patients in the clarithromycin arm and 32/40 (80%) of the patients in the azithromycin arm obtained and maintained a negative blood culture by week 20 or 24. As per the protocol design subjects that had a sterile blood culture at the end of treatment were followed post-therapy to determine the rate of relapse. Of the azithromycin patients who sterilized their blood at the end of therapy 13/32 (40%) relapsed. There were 9/28 (32%) patients in the clarithromycin arm that relapsed. These observations suggest that the activity of azithromycin in combination with ethambutol is slightly less than clarithromycin and ethambutol for the sterilization of MAC from the blood of HIV positive patients. The trends also suggest that relapse of MAC bacteremia may occur slightly more often when azithromycin and ethambutol are administered for the treatment of disseminated MAC versus clarithromycin and ethambutol.

The ability to interpret the susceptibility test results from clinical trial 66-189 is difficult as breakpoints for azithromycin or clarithromycin resistant MAC isolates have not been established for any susceptibility testing method. In this study a [redacted] was employed to determine clarithromycin and azithromycin MIC values. Azithromycin MIC values ranged from [redacted] Clarithromycin MICs ranged from [redacted] Utilizing this method azithromycin MIC values were 4 to 32 fold higher than clarithromycin MICs.

The susceptibility test results obtained during this study suggest that MAC isolates exhibit total cross resistance between azithromycin and clarithromycin. During treatment and the post therapy follow-up period 6 patients in the azithromycin arm and 6 patients in the clarithromycin arm developed MAC bacteremia with isolates having azithromycin MICs >128 µg/mL. All twelve MAC isolates had clarithromycin MICs >32 µg/mL. Because MAC isolates have significantly higher azithromycin MIC values than clarithromycin care should be taken when interpreting azithromycin MIC values until a breakpoint for drug resistant MAC isolates can be established.

In conclusion, with respect to microbiology this NDA should be approved.

Recommendations:

There are no microbiology comments to be conveyed to the sponsor at this time.

/S/

Linda L. Gosey
Microbiologist

Concurrences:

/S/

HFD-590/DepDir _____Signature 11/13/00 Date
HFD-590/MicroTL /S/ _____ Signature 11-13-2000 Date

CC:
HFD-590/Division File
HFD-590/MO:Korvick
HFD-590/CSO:Willard
HFD-590/Chem:Holbert
HFD-590/Pharm:Hastings
HFD-590/Micro:Gosey
Key Words: Admin review, study micro, pop HIV, antimycobacterial, azithromycin,MAC