CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-662/A029

MICROBIOLOGY REVIEW

Division of Anti-Infective Drug Products
Clinical Microbiological Review

NDA NUMBER:	REVIEW DATE:	SUBMISSION/TYPE:
50662	2-11-00	Efficacy Supplement SE1-029
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12-17-99	12-20-99	2-2-00

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DRUG PRODUCT NAME

Proprietary:	BIAXIN® FILMTAB®
Nonproprietary/USAN:	Clarithromycin
Code Names/#'s:	Abbott-56268
Therapeutic Class:	Antimicrobial

PHARMACOLOGICAL CATEGORY: Macrolide

DOSAGE FORM: Tablets
STRENGTHS: 250 and 500 mg tablet
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx __ OTC

RELATED DOCUMENTS (if applicable):

[redacted]

REMARKS/COMMENTS:

This is an efficacy supplement for addition of *Haemophilus influenzae* to the pneumonia indication. There is no new microbiological data included in this submission for review. However, the microbiology section of the label needs to be updated as follows:

Microbiology:

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis.

Clarithromycin is active in vitro against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms as well as most *Mycobacterium avium* complex (MAC) microorganisms.

Additionally, the 14-OH clarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OH clarithromycin is twice as active against *Haemophilus influenzae* microorganisms as the parent compound. However, for *Mycobacterium avium* complex (MAC) isolates the 14-OH metabolite is 4 to 7 times less active than clarithromycin. The clinical significance of this activity against *Mycobacterium avium* complex is unknown.

Clarithromycin 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:

Aerobic Gram-positive microorganisms
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic Gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis

Other microorganisms
Mycoplasma pneumoniae
Chlamydia pneumoniae (TWAR)

Mycobacteria
Mycobacterium avium complex (MAC) consisting of:
Mycobacterium avium
Mycobacterium intracellulare

Beta-lactamase production should have no effect on clarithromycin activity.

NOTE: Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

Omeprazole/clarithromycin dual therapy; ranitidine bismuth citrate/clarithromycin dual therapy; omeprazole/clarithromycin/amoxicillin triple therapy; and lansoprazole/clarithromycin/amoxicillin triple therapy have been shown to be active against most strains of *Helicobacter pylori* in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Helicobacter
Helicobacter pylori

Pretreatment Resistance
Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual-therapy studies (M93-067, M93-100) and 9.3% (41/439) in the omeprazole/clarithromycin/ amoxicillin triple-therapy studies (126, 127, M96-446). Clarithromycin pretreatment resistance was 12.6% (44/348) in the ranitidine bismuth citrate/clarithromycin b.i.d. versus t.i.d. clinical study (H2BA3001). Clarithromycin pretreatment resistance rates were 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the lansoprazole/clarithromycin/amoxicillin triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (<0.25 μg/mL) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin clinical studies (126, 127, M96-446). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 μg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin/amoxicillin study arm. Amoxicillin pretreatment susceptible isolates (< 0.25 μg/mL) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the lansoprazole/clarithromycin/amoxicillin triple-therapy clinical trials by E-test and agar dilution, respectively. Twenty-one of the 957 patients (2.2%) by E-test and 2 of 100 patients (2.0%) by agar dilution had amoxicillin pretreatment MICs of > 0.25 μg/mL. Two patients had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 μg/mL by E-test.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a]

Clarithromycin Pretreatment Results	Clarithromycin Post-treatment Results				
	H. pylori negative - eradicated	*H. pylori* positive - not eradicated Post-treatment susceptibility results			
		S[b]	I[b]	R[b]	No MIC
Omeprazole 40 mg q.d./clarithromycin 500 mg t.i.d. for 14 days followed by omeprazole 20 mg q.d. for another 14 days (M93-067, M93-100)					
Susceptible[b] 108	72	1		26	9
Intermediate[b] 1				1	
Resistant[b] 4				4	
Ranitidine bismuth citrate 400 mg b.i.d./clarithromycin 500 mg t.i.d. for 14 days followed by ranitidine bismuth citrate 400 mg b.i.d. for another 14 days (H2BA3001)					
Susceptible[b] 124	98	4		14	8
Intermediate[b] 3	2				1

Resistant[b]	17	1	15		1
Ranitidine bismuth citrate 400 mg b.i.d./clarithromycin 500 mg b.i.d. for 14 days followed by ranitidine bismuth citrate 400 mg b.i.d. for another 14 days (H2BA3001)					
Susceptible[b]	125	106	1	12	5
Intermediate[b]	2	2			
Resistant[b]	20	1		19	
Omeprazole 20 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 10 days (126, 127, M96-446)					
Susceptible[b]	171	153	7	3	8
Intermediate[b]					
Resistant[b]	14	4	1	6	3
Lansoprazole 30 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 14 days (M95-399, M93-131, M95-392)					
Susceptible[b]	112	105			7
Intermediate[b]	3	3			
Resistant[b]	17	6		7	4
Lansoprazole 30 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 10 days (M95-399)					
Susceptible[b]	42	40	1	1	
Intermediate[b]					
Resistant[b]	4	1		3	

[a] Includes only patients with pretreatment clarithromycin susceptibility tests
[b] Susceptible (S) MIC < 0.25 μg/mL, Intermediate (I) MIC 0.5 - 1.0 μg/mL, Resistant (R) MIC > 2 μg/mL

Patients not eradicated of *H. pylori* following omeprazole/clarithromycin, ranitidine bismuth citrate/clarithromycin, omeprazole/clarithromycin/amoxicillin, or lansoprazole/clarithromycin/ amoxicillin therapy would likely have clarithromycin resistant *H. pylori* isolates. Therefore, for patients who fail therapy, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin resistant *H. pylori* should not be treated with any of the following: omeprazole/clarithromycin dual therapy; ranitidine bismuth citrate/clarithromycin dual therapy; omeprazole/clarithromycin/amoxicillin triple therapy; lansoprazole/clarithromycin/amoxicillin triple therapy; or other regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the omeprazole/clarithromycin/amoxicillin triple-therapy clinical trials, 84.9% (157/185) of the patients who had pretreatment amoxicillin susceptible MICs (< 0.25 μg/mL) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28

patients who failed triple therapy 11 had no post-treatment susceptibility test results, and 17 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

In the lansoprazole/clarithromycin amoxicillin triple-therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (< 0.25 μg/mL) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of > 0.25 μg/mL, three of six had the *H. pylori* eradicated. A total of 12.8% (22/172) of the patients failed the 10- and 14-day triple-therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple-therapy regimen also had clarithromycin resistant *H. pylori* isolates.

The following in vitro data are available, **but their clinical significance is unknown.** Clarithromycin exhibits in vitro activity against most strains of the following microorganisms; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Streptococcus agalactiae
Streptococci (Groups C, F, G)
Viridans group streptococci

Aerobic Gram-negative microorganisms
Bordetella pertussis
Legionella pneumophila
Pasteurella multocida

Anaerobic Gram-positive microorganisms
Clostridium perfringens
Peptococcus niger
Propionibacterium acnes

Anaerobic Gram-negative microorganisms
Prevotella melaninogenica (formerly *Bacteriodes melaninogenicus*)

Susceptibility Testing Excluding Mycobacteria and Helicobacter:

Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or

equivalent with standardized inoculum concentrations and standardized concentrations of clarithromycin powder. The MIC values should be interpreted according to the following criteria:

For Testing *Staphylococcus* spp.

MIC (µg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*[a]

MIC (µg/mL)	Interpretation
≤ 0.25	Susceptible (S)
0.5	Intermediate (I)
≥ 1.0	Resistant (R)

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 - 5 % lysed horse blood.

For testing *Haemophilus* spp.[b]

MIC (µg/mL)	Interpretation
≤ 8.0	Susceptible (S)
16.0	Intermediate (I)
≥ 32.0	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM)[1]

Note: When testing *Haemophilus* spp. and *Streptococcus* spp. including *Streptococcus pneumoniae* susceptibility and resistance to clarithromycin can be predicted by using erythromycin.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the 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 clarithromycin powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
S. aureus ATCC 29213	0.12 to 0.5
S. pneumoniae[c] ATCC 49619	0.03 to 0.12
Haemophilus influenzae[d] ATCC 49247	4 to 16

[c] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

[d] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM[1].

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 procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-µg clarithromycin to test the susceptibility of microorganisms to clarithromycin.
Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15-µg clarithromycin disk should be interpreted according to the following criteria:

For testing *Staphylococcus* spp.

Zone diameter (mm)	Interpretation
≥ 18	Susceptible (S)
14 to 17	Intermediate (I)
≤ 13	Resistant (R)

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*[e]

Zone diameter (mm)	Interpretation
≥ 21	Susceptible (S)
17 to 20	Intermediate (I)
≤ 16	Resistant (R)

[c] These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2

For testing *Haemophilus* spp.[f]

Zone diameter (mm)	Interpretation
≥ 13	Susceptible (S)
11 to 12	Intermediate (I)
≤ 10	Resistant (R)

[f] These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM[2].

Note: When testing *Haemophilus* spp. and *Streptococcus* spp. including *Streptococcus pneumoniae* susceptibility and resistance to clarithromycin can be predicted by using erythromycin.

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 trovafloxacin.

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 clarithromycin.

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-µg clarithromycin disk should provide the following zone diameters in this laboratory test quality control strain:

Microorganism	Zone diameter (mm)
S. aureus ATCC 25923	26 to 32
S. pneumoniae[g] ATCC 49619	25 to 31
Haemophilus influenzae[h] ATCC 49247	11 to 17

[g] This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

[h] This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM[2].

***In vitro* Activity of Clarithromycin against Mycobacteria:**
Clarithromycin has demonstrated in vitro activity against *Mycobacterium avium* complex (MAC) microorganisms isolated from both AIDS and non-AIDS patients. 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.

Various in vitro methodologies employing broth or solid media at different pH's, with and without oleic acid-albumin-dextrose-catalase (OADC), have been used to determine clarithromycin MIC values for mycobacterial species. In general, MIC values decrease more than 16-fold as the pH of Middlebrook 7H12 broth media increases from 5.0 to 7.4. At pH 7.4, MIC values determined with Mueller-Hinton agar were 4- to 8-fold higher than those observed with Middlebrook 7H12 media. Utilization of oleic acid-albumin-dextrose-catalase (OADC) in these assays has been shown to further alter MIC values.

Clarithromycin activity against 80 MAC isolates from AIDS patients and 211 MAC isolates from non-AIDS patients was evaluated using a microdilution method with Middlebrook 7H9 broth. Results showed an MIC value of ≤ 4.0 μg/mL in 81% and 89% of the AIDS and non-AIDS MAC isolates, respectively. Twelve percent of the non-AIDS isolates had an MIC value ≤ 0.5 μg/mL. Clarithromycin was also shown to be active against phagocytized *M. avium* complex (MAC) in mouse and human macrophage cell cultures as well as in the beige mouse infection model.

Clarithromycin activity was evaluated against *Mycobacterium tuberculosis* microorganisms. In one study utilizing the agar dilution method with Middlebrook 7H10 media, 3 of 30 clinical isolates had an MIC of 2.5 μg/mL. Clarithromycin inhibited all isolates at > 10.0 μg/mL.

Susceptibility Testing for *Mycobacterium avium* Complex (MAC):
The disk diffusion and dilution techniques for susceptibility testing against gram-positive and gram-negative bacteria should not be used for determining clarithromycin 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. Clarithromycin MIC values will vary depending on the susceptibility testing method employed, composition and pH of the media, and the utilization of nutritional supplements. Breakpoints to determine whether clinical isolates of *M. avium* or *M. intracellulare* are susceptible or resistant to clarithromycin have not been established.

Susceptibility Test for *Helicobacter pylori*
The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[3] One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 - 1×10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (> 2-weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for *Campylobacter* species. After 3 days of incubation, the MICs are recorded as the lowest concentration of

antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Clarithromycin MIC (μg/mL)[i]	Interpretation
< 0.25	Susceptible (S)
0.5 - 1.0	Intermediate (I)
> 2.0	Resistant (R)

Amoxicillin MIC (μg/mL)[i,j]	Interpretation
< 0.25	Susceptible (S)

i. These are tentative breakpoints for the agar dilution methodology, and they should not be used to interpret results obtained using alternative methods

j. There were not enough organisms with MICs > 0.25 μg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Microorganisms	Antimicrobial Agent	MIC (μg/mL)[k]
H. pylori ATCC 43504	Clarithromycin	0.015 - 0.12 μg/mL
H. pylori ATCC 43504	Amoxicillin	0.015 - 0.12 μg/mL

k. These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

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-A5, Vol. 20, No. 2, NCCLS, Villanova, PA, January, 2000.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--Sixth Edition; Approved Standard, NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Villanova, PA, January 2000.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY section of the package insert. These revisions are found

on page 1-11 of this review. The sponsor should be notified of the needed changes in the product insert.

/S/

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