HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BIAXIN safely and effectively. See full prescribing information for BIAXIN.

BIAXIN® Filmtab® (clarithromycin) tablets, for oral use
BIAXIN® XL Filmtab® (clarithromycin extended-release tablets), for oral use
BIAXIN® Granules (clarithromycin) for oral suspension
Initial U.S. Approval: 1991

RECENT MAJOR CHANGES

Warnings and Precautions, Acute Hypersensitivity Reactions (5.1)	6/2017
Warnings and Precautions, All-Cause Mortality in Patients With Coronary Artery Disease Years After BIAXIN Exposure (5.5)	6/2017

INDICATIONS AND USAGE

BIAXIN is a macrolide antimicrobial indicated for mild to moderate infections caused by designated, susceptible bacteria in the following:

- Acute Bacterial Exacerbation of Chronic Bronchitis in Adults (1.1)
- Acute Maxillary Sinusitis (1.2)
- Community-Acquired Pneumonia (1.3)
- Pharyngitis/Tonsillitis (1.4)
- Uncomplicated Skin and Skin Structure Infections (1.5)
- Acute Otitis Media in Pediatric Patients (1.6)
- Treatment and Prophylaxis of Disseminated Mycobacterial Infections (1.7)
- *Helicobacter pylori* Infection and Duodenal Ulcer Disease in Adults (1.8)

Limitations of Use

BIAXIN XL Filmtab is indicated only for acute bacterial exacerbation of chronic bronchitis, acute maxillary sinusitis, and community-acquired pneumonia in adults. (1.9)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of BIAXIN and other antibacterial drugs, BIAXIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.9)

DOSAGE AND ADMINISTRATION

- Adults: BIAXIN 250 mg or 500 mg every 12 hours for 7–14 days; BIAXIN XL 1 gram every 24 hours for 7–14 days (2.2)
- *H. pylori* eradication (in combination with lansoprazole/amoxicillin, omeprazole/amoxicillin, or omeprazole): BIAXIN 500 mg every 8 or 12 hours for 10–14 days. See full prescribing information (FPI) for additional information. (2.3)
- Pediatric Patients: BIAXIN 15 mg/kg/day divided every 12 hours for 10 days (2.4)
- Mycobacterial Infections: BIAXIN 500 mg every 12 hours; BIAXIN 7.5 mg/kg up to 500 mg every 12 hours in pediatric patients (2.5)
- Reduce dose in moderate renal impairment with concomitant atazanavir or ritonavir-containing regimens and in severe renal impairment (2.6)

DOSAGE FORMS AND STRENGTHS

- Tablets: 250 mg and 500 mg (3)
- Extended-release Tablets: 500 mg (3)
- Granules for Oral Suspension: 125 mg/5 mL and 250 mg/5 mL (3)

CONTRAINDICATIONS

- Hypersensitivity to clarithromycin or any macrolide drug (4.1)
- Cisapride, pimozide, lovastatin/simvastatin, ergotamine/dihydroergotamine (4.2, 4.5, 4.6)
- History of cholestatic jaundice/hepatic dysfunction with use of clarithromycin (4.3)
- Colchicine in renal or hepatic impairment (4.4)

WARNINGS AND PRECAUTIONS

- Severe acute hypersensitivity reactions: Discontinue BIAXIN if occurs (5.1)
- QT prolongation: Avoid BIAXIN in patients with known QT prolongation or receiving drugs known to prolong the QT interval, ventricular arrhythmia (torsade de pointes), hypokalemia/hypomagnesemia, significant bradycardia, or taking Class IA or III antiarrhythmics (5.2)
- Hepatotoxicity: Discontinue if signs and symptoms of hepatitis occur (5.3)
- Serious adverse reactions can occur due to drug interactions of BIAXIN with colchicine, some HMG CoA reductase inhibitors, some calcium channel blockers, and other drugs (5.4)
- Risk of all-cause mortality one year or more after the end of treatment in patients with coronary artery disease (5.5)
- *Clostridium difficile* associated diarrhea (CDAD): Evaluate if diarrhea occurs (5.6)
- Embryofetal toxicity: BIAXIN should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate (5.7)
- Exacerbation of myasthenia gravis (5.8)

ADVERSE REACTIONS

Most frequent adverse reactions for both adult and pediatric populations in clinical trials: abdominal pain, diarrhea, nausea, vomiting, dysgeusia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of BIAXIN can alter the concentrations of other drugs. The potential for drug-drug interactions must be considered prior to and during therapy. (4, 5.2, 5.4, 7)

USE IN SPECIFIC POPULATIONS

Geriatric: Increased risk of *torsades de pointes* (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Bacterial Exacerbation of Chronic Bronchitis

BIAXIN (Filmtab, Granules) and BIAXIN XL Filmtab are indicated in adults for the treatment of mild to moderate infections caused by susceptible isolates due to *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae [see Indications and Usage (1.9)]*.

1.2 Acute Maxillary Sinusitis

BIAXIN (Filmtab, Granules) and BIAXIN XL Filmtab (in adults) are indicated for the treatment of mild to moderate infections caused by susceptible isolates due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae [see Indications and Usage (1.9)]*.

1.3 Community-Acquired Pneumonia

BIAXIN (Filmtab, Granules) and BIAXIN XL Filmtab are indicated *[see Indications and Usage (1.9)]* for the treatment of mild to moderate infections caused by susceptible isolates due to:

- *Haemophilus influenzae* (in adults)
- *Haemophilus parainfluenzae* (BIAXIN XL Filmtab in adults)
- *Moraxella catarrhalis* (BIAXIN XL Filmtab in adults)
- *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Chlamydophila pneumoniae* (BIAXIN XL Filmtab [in adults]; BIAXIN Filmtab and BIAXIN Granules [in adults and pediatric patients])

1.4 Pharyngitis/Tonsillitis

BIAXIN Filmtab and BIAXIN Granules are indicated for the treatment of mild to moderate infections caused by susceptible isolates due to *Streptococcus pyogenes* as an alternative in individuals who cannot use first line therapy.

1.5 Uncomplicated Skin and Skin Structure Infections

BIAXIN Filmtab and BIAXIN Granules are indicated for the treatment of mild to moderate infections caused by susceptible isolates due to *Staphylococcus aureus*, or *Streptococcus pyogenes*.

1.6 Acute Otitis Media

BIAXIN Filmtab and BIAXIN Granules are indicated in pediatric patients for the treatment of mild to moderate infections caused by susceptible isolates due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae [see Clinical Studies (14.2)]*.

1.7 Treatment and Prophylaxis of Disseminated Mycobacterial Infections

BIAXIN Filmtab and BIAXIN Granules are indicated for the treatment of mild to moderate infections caused by susceptible isolates due to *Mycobacterium avium* or *Mycobacterium intracellulare* in patients with advanced HIV infection *[see Clinical Studies (14.1)]*.

1.8 *Helicobacter pylori* Infection and Duodenal Ulcer Disease

BIAXIN Filmtab is given in combination with other drugs in adults as described below to eradicate *H. pylori*. The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence *[see Clinical Studies (14.3)]*.

- BIAXIN Filmtab in combination with amoxicillin and PREVACID (lansoprazole) or PRILOSEC (omeprazole) Delayed-Release Capsules, as triple therapy, are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or five-year history of duodenal ulcer) to eradicate *H. pylori*.
- BIAXIN Filmtab in combination with PRILOSEC (omeprazole) capsules are indicated for the treatment of patients with an active duodenal ulcer associated with *H. pylori* infection. Regimens which contain BIAXIN Filmtab as the single antibacterial agent are more likely to be associated with the development of clarithromycin resistance among patients who fail therapy. Clarithromycin-containing regimens should not be used in patients with known or suspected clarithromycin resistant isolates because the efficacy of treatment is reduced in this setting.

1.9 Limitations of Use

BIAXIN XL Filmtab is indicated only for acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, and community-acquired pneumonia in adults. The efficacy and safety of BIAXIN XL Filmtab in treating other infections for which BIAXIN Filmtab and BIAXIN Granules are approved have not been established.

There is resistance to macrolides in certain bacterial infections caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*. Susceptibility testing should be performed when clinically indicated.

1.10 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of BIAXIN and other antibacterial drugs, BIAXIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

BIAXIN Filmtab and BIAXIN Granules may be given with or without food.

BIAXIN XL Filmtab should be taken with food. Swallow BIAXIN XL Filmtab whole; do not chew, break or crush BIAXIN XL Filmtab.

2.2 Adult Dosage

The recommended dosages of BIAXIN Filmtab and BIAXIN XL Filmtab for the treatment of mild to moderate infections in adults are listed in Table 1.

Table 1. Adult Dosage Guidelines

	BIAXIN Filmtab		BIAXIN XL Filmtab	
Infection	**Dosage (every 12 hours)**	**Duration (days)**	**Dosage (every 24 hours)**	**Duration (days)**
Acute bacterial exacerbation of chronic bronchitis	250 to 500 mg[a]	7[b]-14	1 gram	7
Acute maxillary sinusitis	500 mg	14	1 gram	14
Community-acquired pneumonia	250 mg[c]	7[d]-14	1 gram[c]	7
Pharyngitis/Tonsillitis	250 mg	10	-	-
Uncomplicated skin and skin structure infections	250 mg	7-14	-	-
Treatment and prophylaxis of disseminated *Mycobacterium avium* disease *[see Dosage and Administration (2.5)]*	500 mg[e]	-	-	-
H.pylori eradication to reduce the risk of duodenal ulcer recurrence with amoxicillin and omeprazole or lansoprazole *[see Dosage and Administration (2.3)]*	500 mg	10-14	-	-
H.pylori eradication to reduce the risk of duodenal ulcer recurrence with omeprazole *[see Dosage and Administration (2.3)]*	500 mg every 8 hours	14	-	-

[a] For *M. catarrhalis* and *S. pneumoniae* use 250 mg. For *H. influenzae* and *H. parainfluenzae*, use 500 mg.
[b] For *H parainfluenzae*, the duration of therapy is 7 days.
[c] For *H. parainfluenzae* and *M. catarrhalis* use BIAXIN XL tablets only.
[d] For *H. influenzae*, the duration of therapy is 7 days.
[e] BIAXIN therapy should continue if clinical response is observed. BIAXIN can be discontinued when the patient is considered at low risk of disseminated infection.

2.3 Combination Dosing Regimens for *H. pylori* Infection

- **Triple therapy: BIAXIN Filmtab/lansoprazole/amoxicillin**
  The recommended adult dosage is 500 mg BIAXIN Filmtab, 30 mg lansoprazole, and 1 gram amoxicillin, all given every 12 hours for 10 or 14 days *[see Indications and Usage (1.8) and Clinical Studies (14.3)]*.
- **Triple therapy: BIAXIN Filmtab/omeprazole/amoxicillin**
  The recommended adult dosage is 500 mg BIAXIN Filmtab, 20 mg omeprazole, and 1 gram amoxicillin; all given every 12 hours for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief *[see Indications and Usage (1.8) and Clinical Studies (14.3)]*.
- **Dual therapy: BIAXIN Filmtab/omeprazole**
  The recommended adult dosage is 500 mg BIAXIN Filmtab given every 8 hours and 40 mg omeprazole given once every morning for 14 days. An additional 14 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief *[see Indications and Usage (1.8) and Clinical Studies (14.3)]*.

2.4 Pediatric Dosage

The recommended daily dosage is 15 mg/kg/day divided every 12 hours for 10 days (up to the adult dose). Refer to dosage regimens for mycobacterial infections in pediatric patients for additional dosage information *[see Dosage and Administration (2.5)]*.

2.5 Dosage Regimens for Mycobacterial Infections

For the treatment of disseminated infection due to *Mycobacterium avium* complex (MAC), BIAXIN Filmtab and BIAXIN Granules are recommended as the primary agents. BIAXIN Filmtab and BIAXIN Granules should be used in combination with other antimycobacterial drugs (e.g. ethambutol) that have shown *in vitro* activity against MAC or clinical benefit in MAC treatment *[see Clinical Studies (14.1)]*.

Adult Patients

For treatment and prophylaxis of mycobacterial infections in adults, the recommended dose of BIAXIN is 500 mg every 12 hours.

Pediatric Patients

For treatment and prophylaxis of mycobacterial infections in pediatric patients, the recommended dose is 7.5 mg/kg every 12 hours up to 500 mg every 12 hours. *[See Use in Specific Populations (8.4) and Clinical Studies (14.1)]*.

BIAXIN therapy should continue if clinical response is observed. BIAXIN can be discontinued when the patient is considered at low risk of disseminated infection.

2.6 Dosage Adjustment in Patients with Renal Impairment

See Table 2 for dosage adjustment in patients with moderate or severe renal impairment with or without concomitant atazanavir or ritonavir-containing regimens *[see Drug Interactions (7)]*.

Table 2. BIAXIN Dosage Adjustments in Patients with Renal Impairment

	Recommended BIAXIN Dosage Reduction
Patients with severe renal impairment (CL_{cr} of <30 mL/min)	Reduce the dosage of BIAXIN by 50%
Patients with moderate renal impairment (CL_{cr} of 30 to 60 mL/min) taking concomitant atazanavir or ritonavir-containing regimens	Reduce the dosage of BIAXIN by 50%
Patients with severe renal impairment (CL_{cr} of <30 mL/min) taking concomitant atazanavir or ritonavir-containing regimens	Reduce the dosage of BIAXIN by 75%

2.7 Dosage Adjustment Due to Drug Interactions

Decrease the dose of BIAXIN by 50 % when co-administered with atazanavir *[see Drug Interactions (7)]*. Dosage adjustments for other drugs when co-administered with BIAXIN may be recommended due to drug interactions *[see Drug Interactions (7)]*.

2.8 Reconstitution of BIAXIN Granules

The supplied BIAXIN Granules must be reconstituted with water prior to administration of BIAXIN for oral suspension. Table 3 below indicates the volume of water to be added when reconstituting. To reconstitute:

a. Add half the volume of water to the bottle containing the BIAXIN granules and shake vigorously.
b. Add the remainder of water to the bottle and shake.

Shake well before each use. After mixing, store at 15° to 30°C (59° to 86°F) and use within 14 days. Do not refrigerate.

Table 3. Volume of Water to be Added When Reconstituting BIAXIN Granules

Total Volume After Reconstitution	**Clarithromycin Concentration After Reconstitution**	**Amount of Water to be Added**
50 mL	125 mg/5 mL	27 mL
100 mL	125 mg/5 mL	55 mL
50 mL	250 mg/5 mL	27 mL
100 mL	250 mg/5 mL	55 mL

3 DOSAGE FORMS AND STRENGTHS

BIAXIN is available as:

- BIAXIN Filmtab (yellow oval film-coated tablet):
  - 250 mg: imprinted in blue with the “a” logo and KT
  - 500 mg: debossed with the “a” logo on one side and KL on the opposite side
- BIAXIN XL Filmtab (yellow oval film-coated extended-release tablet):
  - 500 mg: debossed with the “a” logo and KJ

- BIAXIN Granules (white to off-white granules before reconstitution; white to off-white opaque suspension after reconstitution):
  - 125 mg/5 mL concentration available in 50 mL and 100 mL bottles
  - 250 mg/5 mL concentration available in 50 mL and 100 mL bottles

4 CONTRAINDICATIONS

4.1 Hypersensitivity

BIAXIN is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibacterial drugs *[see Warnings and Precautions (5.1)]*.

4.2 Cardiac Arrhythmias

Concomitant administration of BIAXIN with cisapride and pimozide is contraindicated *[see Drug Interactions (7)]*.

There have been postmarketing reports of drug interactions when clarithromycin is co-administered with cisapride or pimozide, resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and *torsades de pointes*) most likely due to inhibition of metabolism of these drugs by BIAXIN. Fatalities have been reported.

4.3 Cholestatic Jaundice/Hepatic Dysfunction

BIAXIN is contraindicated in patients with a history of cholestatic jaundice or hepatic dysfunction associated with prior use of clarithromycin.

4.4 Colchicine

Concomitant administration of BIAXIN and colchicine is contraindicated in patients with renal or hepatic impairment.

4.5 HMG-CoA Reductase Inhibitors

Do not use BIAXIN concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis *[see Warnings and Precautions (5.4) and Drug Interactions (7)]*.

4.6 Ergot Alkaloids

Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated *[see Drug Interactions (7)]*.

4.7 Contraindications for Co-administered Drugs

For information about contraindications of other drugs indicated in combination with BIAXIN, refer to their full prescribing information (contraindications section).

5 WARNINGS AND PRECAUTIONS

5.1 Acute Hypersensitivity Reactions

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schonlein purpura, and acute generalized exanthematous pustulosis, discontinue BIAXIN therapy immediately and institute appropriate treatment.

5.2 QT Prolongation

BIAXIN has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of *torsades de pointes* have been spontaneously reported during postmarketing surveillance in patients receiving BIAXIN. Fatalities have been reported.

Avoid BIAXIN in the following patients:

- patients with known prolongation of the QT interval, ventricular cardiac arrhythmia, including *torsades de pointes*
- patients receiving drugs known to prolong the QT interval *[see also Contraindications (4.2)]*
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval *[see Use in Specific Populations (8.5)]*.

5.3 Hepatotoxicity

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Symptoms of hepatitis can include anorexia, jaundice, dark urine, pruritus, or tender abdomen. Discontinue BIAXIN immediately if signs and symptoms of hepatitis occur.

5.4 Serious Adverse Reactions Due to Concomitant Use with Other Drugs

Drugs metabolized by CYP3A4: Serious adverse reactions have been reported in patients taking BIAXIN concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; hypoglycemia with disopyramide; hypotension and acute kidney injury with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem, nifedipine). Most reports of acute kidney injury with calcium channel blockers metabolized by CYP3A4 involved elderly patients 65 years of age or older. Use BIAXIN with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme. The use of BIAXIN with simvastatin, lovastatin, ergotamine, or dihydroergotamine is contraindicated *[see Contraindications (4.5, 4.6) and Drug Interactions (7)]*.

Colchicine: Life-threatening and fatal drug interactions have been reported in patients treated with BIAXIN and colchicine. Clarithromycin is a strong CYP3A4 inhibitor and this interaction may occur while using both drugs at their recommended doses. If co-administration of BIAXIN and colchicine is necessary in patients with normal renal and hepatic function, reduce the dose of colchicine. Monitor patients for clinical symptoms of colchicine toxicity. Concomitant administration of BIAXIN and colchicine is contraindicated in patients with renal or hepatic impairment *[see Contraindications (4.4) and Drug Interactions (7)]*.

HMG-CoA Reductase Inhibitors (statins): Concomitant use of BIAXIN with lovastatin or simvastatin is contraindicated *[see Contraindications (4.5)]* as these statins are extensively metabolized by CYP3A4, and concomitant treatment with BIAXIN increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Cases of rhabdomyolysis have been reported in patients taking BIAXIN concomitantly with these statins. If treatment with BIAXIN cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Exercise caution when prescribing BIAXIN with atorvastatin or pravastatin. In situations where the concomitant use of BIAXIN with atorvastatin or pravastatin cannot be avoided, atorvastatin dose should not exceed 20 mg daily and pravastatin dose should not exceed 40 mg daily. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered. It is recommended to prescribe the lowest registered dose if concomitant use cannot be avoided.

Oral Hypoglycemic Agents/Insulin: The concomitant use of BIAXIN and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended *[see Drug Interactions (7)]*.

Quetiapine: Use quetiapine and clarithromycin concomitantly with caution. Co-administration could result in increased quetiapine exposure and quetiapine related toxicities such as somnolence, orthostatic hypotension, altered state of consciousness, neuroleptic malignant syndrome, and QT prolongation. Refer to quetiapine prescribing information for recommendations on dose reduction if co-administered with CYP3A4 inhibitors such as clarithromycin *[see Drug Interactions (7)]*.

Oral Anticoagulants: There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when BIAXIN is co-administered with warfarin. Monitor INR and prothrombin times frequently while patients are receiving BIAXIN and oral anticoagulants concurrently *[see Drug Interactions (7)]*.

Benzodiazepines: Increased sedation and prolongation of sedation have been reported with concomitant administration of BIAXIN and triazolobenzodiazepines, such as triazolam and midazolam *[see Drug Interactions (7)]*.

5.5 All-Cause Mortality in Patients With Coronary Artery Disease 1 to 10 Years After BIAXIN Exposure

In one clinical trial evaluating treatment with clarithromycin on outcomes in patients with coronary artery disease, an increase in risk of all-cause mortality one year or more after the end of treatment was observed in patients randomized to receive clarithromycin.[1] Clarithromycin for treatment of coronary artery disease is not an approved indication. The cause of the increased risk has not been established. Other epidemiologic studies evaluating this risk have shown variable results *[see Adverse Reactions (6.1)]*. Consider balancing this potential risk with the treatment benefits when prescribing BIAXIN in patients who have suspected or confirmed coronary artery disease.

5.6 *Clostridium difficile* Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including BIAXIN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.7 Embryofetal Toxicity

Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If BIAXIN is used during pregnancy, or if pregnancy occurs while the patient is taking this drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects on pregnancy outcome and/or embryo-fetal development in monkeys, rats, mice, and rabbits at doses that produced plasma levels 2 times to 17 times the serum levels achieved in humans treated at the maximum recommended human doses *[see Use in Specific Populations (8.1)]*.

5.8 Exacerbation of Myasthenia Gravis

Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic syndrome has been reported in patients receiving BIAXIN therapy.

5.9 Development of Drug Resistant Bacteria

Prescribing BIAXIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Acute Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- QT Prolongation *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Serious Adverse Reactions Due to Concomitant Use with Other Drugs *[see Warnings and Precautions (5.4)]*
- *Clostridium difficile* Associated Diarrhea *[see Warnings and Precautions (5.6)]*
- Exacerbation of Myasthenia Gravis *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Based on pooled data across all indications, the most frequent adverse reactions for both adult and pediatric populations observed in clinical trials are abdominal pain, diarrhea, nausea, vomiting and dysgeusia. Also reported were dyspepsia, liver function test abnormal, anaphylactic reaction, candidiasis, headache, insomnia, and rash.

The subsequent subsections list the most common adverse reactions for prophylaxis and treatment of mycobacterial infections and duodenal ulcer associated with *H. pylori* infection. In general, these profiles are consistent with the pooled data described above.

Prophylaxis of Mycobacterial Infections

In AIDS patients treated with BIAXIN over long periods of time for prophylaxis against *M. avium*, it was often difficult to distinguish adverse reactions possibly associated with BIAXIN administration from underlying HIV disease or intercurrent illness. Median duration of treatment was 10.6 months for the BIAXIN group and 8.2 months for the placebo group.

Table 4. Incidence Rates (%) of Selected Adverse Reactions[a] in Immunocompromised Adult Patients Receiving Prophylaxis Against *M. avium Complex*

Body System[b] **Adverse Reaction**	**BIAXIN (n=339) %**	**Placebo (n=339) %**
Body as a Whole		
Abdominal pain	5%	4%

Headache	3%	1%
Digestive		
Diarrhea	8%	4%
Dyspepsia	4%	3%
Flatulence	2%	1%
Nausea	11%	7%
Vomiting	6%	3%
Skin & Appendages		
Rash	3%	4%
Special Senses		
Taste Perversion	8%[c]	0.3%

a Includes those events possibly or probably related to study drug and excludes concurrent conditions
b 2% or greater Adverse Reaction Incidence Rates for either treatment group
c Significant higher incidence compared to the placebo-treated group

Discontinuation due to adverse reactions occurred in 18% of patients receiving BIAXIN compared to 17% of patients receiving placebo in this trial. Primary reasons for discontinuation in BIAXIN treated patients include headache, nausea, vomiting, depression, and taste perversion.

Changes in Laboratory Values

Selected laboratory adverse experiences that were reported during therapy in greater than 2 % of adult patients treated with BIAXIN in a randomized double-blind clinical trial involving 682 patients are presented in Table 5.

In immunocompromised patients receiving prophylaxis against *M. avium*, evaluations of laboratory values were made by analyzing those values outside the seriously abnormal value (i.e., the extreme high or low limit) for the specified test.

Table 5. Percentage of Patients[a] Exceeding Extreme Laboratory Values in Patients Receiving Prophylaxis Against *M. avium* Complex

		BIAXIN 500 mg twice a day	**Placebo**
WBC Count	$<1 \times 10^9$/L	2/103 (4%)	0/95
SGOT	>5 x ULN[b]	7/196 (4%)	5/208 (2%)
SGPT	>5 x ULN[b]	6/217 (3%)	4/232 (2%)

a Includes only patients with baseline values within the normal range or borderline high (hematology variables) and within normal range or borderline low (chemistry variables)
b ULN= Upper Limit of Normal

Treatment of Mycobacterial Infections

The adverse reaction profiles for both the 500 mg and 1000 mg twice a day dose regimens were similar.

In AIDS patients and other immunocompromised patients treated with the higher doses of BIAXIN over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse reactions possibly associated with BIAXIN administration from underlying signs of HIV disease or intercurrent illness.

The following analysis summarizes experience during the first 12 weeks of therapy with BIAXIN. Data are reported separately for trial 1 (randomized, double-blind) and trial 2 (open-labeled, compassionate use) and also combined. Adverse reactions were reported less frequently in trial 2, which may be due in part to differences in monitoring between the two studies.

In adult patients receiving BIAXIN 500 mg twice a day, the most frequently reported adverse reactions, considered possibly or possibly related to study drug, with an incidence of 5% or greater, are listed below (Table 6). Approximately 8% of the patients who received 500 mg twice a day and 12% of the patients who received 1000 mg twice a day discontinued therapy due to drug related adverse reactions during the first 12 weeks of therapy; adverse reactions leading to discontinuation in at least 2 patients included nausea, vomiting, abdominal pain, diarrhea, rash, and asthenia.

Table 6. Selected Treatment-Related[a] Adverse Reaction Incidence Rates (%) in Immunocompromised Adult Patients During the First 12 Weeks of Therapy with 500 mg Twice a Day BIAXIN Dose

Adverse Reaction	Trial 1 (n=53)	Trial 2 (n=255)	Combined (n=308)
Abdominal Pain	8	2	3
Diarrhea	9	2	3
Flatulence	8	0	1
Headache	8	0	2
Nausea	28	9	12
Rash	9	2	3
Taste Perversion	19	0	4
Vomiting	25	4	8

a Includes those events possibly or probably related to study drug and excludes concurrent conditions

A limited number of pediatric AIDS patients have been treated with BIAXIN suspension for mycobacterial infections. The most frequently reported adverse reactions excluding those due to the patient's concurrent conditions were consistent with those observed in adult patients.

Changes in Laboratory Values

In the first 12 weeks of starting on BIAXIN 500 mg twice a day, 3% of patients has SGOT increases and 2% of patients has SGPT increases > 5 times the upper limit of normal in trial 2 (469 enrolled adult patients) while trial 1 (154 enrolled patients) had no elevation of transaminases. This includes only patients with baseline values within the normal range or borderline low.

Duodenal ulcer associated with *H. pylori* Infection

In clinical trials using combination therapy with BIAXIN plus omeprazole and amoxicillin, no adverse reactions specific to the combination of these drugs have been observed. Adverse reactions that have occurred have been limited to those that have been previously reported with BIAXIN, omeprazole or amoxicillin.

The adverse reaction profiles are shown below (Table 7) for four randomized double-blind clinical trials in which patients received the combination of BIAXIN 500 mg three times a day, and omeprazole 40 mg daily for 14 days, followed by omeprazole 20 mg once a day, (three studies) or 40 mg once a day (one study) for an additional 14 days. Of the 346 patients who received the combination, 3.5% of patients discontinued drug due to adverse reactions.

Table 7. Adverse Reactions with an Incidence of 3% or Greater

Adverse Reaction	BIAXIN + Omeprazole (n=346) % of Patients	Omeprazole (n=355) % of Patients	BIAXIN (n=166) % of Patients[a]
Taste Perversion	15	1	16
Nausea	5	1	3
Headache	5	6	9
Diarrhea	4	3	7
Vomiting	4	<1	1
Abdominal Pain	3	2	1
Infection	3	4	2
a Only two of four studies			

Changes in Laboratory Values

Changes in laboratory values with possible clinical significance in patients taking BIAXIN and omeprazole in four randomized double-blind trials in 945 patients are as follows:

Hepatic: elevated direct bilirubin <1%; GGT <1%; SGOT (AST) <1%; SGPT (ALT) <1%, Renal: elevated serum creatinine <1%.

Less Frequent Adverse Reactions Observed During Clinical Trials of Clarithromycin

Based on pooled data across all indications, the following adverse reactions were observed in clinical trials with clarithromycin at a rate less than 1%:

Blood and Lymphatic System Disorders: Leukopenia, neutropenia, thrombocythemia, eosinophilia

Cardiac Disorders: Electrocardiogram QT prolonged, cardiac arrest, atrial fibrillation, extrasystoles, palpitations

Ear and Labyrinth Disorders: Vertigo, tinnitus, hearing impaired

Gastrointestinal Disorders: Stomatitis, glossitis, esophagitis, gastrooesophageal reflux disease, gastritis, proctalgia, abdominal distension, constipation, dry mouth, eructation, flatulence

General Disorders and Administration Site Conditions: Malaise, pyrexia, asthenia, chest pain, chills, fatigue

Hepatobiliary Disorders: Cholestasis, hepatitis

Immune System Disorders: Hypersensitivity

Infections and Infestations: Cellulitis, gastroenteritis, infection, vaginal infection

Investigations: Blood bilirubin increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, albumin globulin ratio abnormal

Metabolism and Nutrition Disorders: Anorexia, decreased appetite

Musculoskeletal and Connective Tissue Disorders: Myalgia, muscle spasms, nuchal rigidity

Nervous System Disorders: Dizziness, tremor, loss of consciousness, dyskinesia, somnolence

Psychiatric Disorders: Anxiety, nervousness

Renal and Urinary Disorders: Blood creatinine increased, blood urea increased

Respiratory, Thoracic and Mediastinal Disorders: Asthma, epistaxis, pulmonary embolism

Skin and Subcutaneous Tissue Disorders: Urticaria, dermatitis bullous, pruritus, hyperhidrosis, rash maculo-papular

Gastrointestinal Adverse Reactions

In the acute exacerbation of chronic bronchitis and acute maxillary sinusitis studies overall gastrointestinal adverse reactions were reported by a similar proportion of patients taking either BIAXIN Filmtab or BIAXIN XL Filmtab; however, patients taking BIAXIN XL Filmtab reported significantly less severe gastrointestinal symptoms compared to patients taking BIAXIN Filmtab. In addition, patients taking BIAXIN XL Filmtab had significantly fewer premature discontinuations for drug-related gastrointestinal or abnormal taste adverse reactions compared to BIAXIN Filmtab.

All-Cause Mortality in Patients with Coronary Artery Disease 1 to 10 Years Following BIAXIN Exposure

In one clinical trial evaluating treatment with clarithromycin on outcomes in patients with coronary artery disease, an increase in risk of all-cause mortality was observed in patients randomized to clarithromycin. Clarithromycin for treatment of coronary artery disease is not an approved indication. Patients were treated with clarithromycin or placebo for 14 days and observed for primary outcome events (e.g., all-cause mortality or non-fatal cardiac events) for several years.[1] A numerically higher number of primary outcome events in patients randomized to receive clarithromycin was observed with a hazard ratio of 1.06 (95% confidence interval 0.98 to 1.14). However, at follow-up 10 years post-treatment, there were 866 (40%) deaths in the clarithromycin group and 815 (37%) deaths in the placebo group that represented a hazard ratio for all-cause mortality of 1.10 (95% confidence interval 1.00 to 1.21). The difference in the number of deaths emerged after one year or more after the end of treatment.

The cause of the difference in all-cause mortality has not been established. Other epidemiologic studies evaluating this risk have shown variable results *[see Warnings and Precautions (5.5)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BIAXIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System: Thrombocytopenia, agranulocytosis

Cardiac: Ventricular arrhythmia, ventricular tachycardia, *torsades de pointes*

Ear and Labyrinth: Deafness was reported chiefly in elderly women and was usually reversible.

Gastrointestinal: Pancreatitis acute, tongue discoloration, tooth discoloration was reported and was usually reversible with professional cleaning upon discontinuation of the drug.

There have been reports of BIAXIN XL Filmtab in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibacterial drug.

Hepatobiliary: Hepatic failure, jaundice hepatocellular. Adverse reactions related to hepatic dysfunction have been reported with clarithromycin *[see Warnings and Precautions (5.2)]*.

Infections and Infestations: Pseudomembranous colitis *[see Warnings and Precautions (5.6)]*

Immune System: Anaphylactic reactions, angioedema

Investigations: Prothrombin time prolonged, white blood cell count decreased, international normalized ratio increased. Abnormal urine color has been reported, associated with hepatic failure.

Metabolism and Nutrition: Hypoglycemia has been reported in patients taking oral hypoglycemic agents or insulin.

Musculoskeletal and Connective Tissue: Myopathy rhabdomyolysis was reported and in some of the reports, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol *[see Contraindications (4.5) and Warnings and Precautions (5.4)]*.

Nervous System: Parosmia, anosmia, ageusia, paresthesia and convulsions

Psychiatric: Abnormal behavior, confusional state, depersonalization, disorientation, hallucination, depression, manic behavior, abnormal dream, psychotic disorder. These disorders usually resolve upon discontinuation of the drug.

Renal and Urinary: Nephritis interstitial, renal failure

Skin and Subcutaneous Tissue: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schonlein purpura, acne, acute generalized exanthematous pustulosis

Vascular: Hemorrhage

7 DRUG INTERACTIONS

Co-administration of BIAXIN is known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.

BIAXIN should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively metabolized by this enzyme. Adjust dosage when appropriate and monitor serum concentrations of drugs primarily metabolized by CYP3A closely in patients concurrently receiving clarithromycin.

Table 8: Clinically Significant Drug Interactions with BIAXIN

Drugs That Are Affected By BIAXIN		
Drug(s) with Pharmacokinetics Affected by BIAXIN	**Recommendation**	**Comments**
Antiarrhythmics: Disopyramide Quinidine Dofetilide Amiodarone Sotalol Procainamide	Not Recommended	Disopyramide, Quinidine: There have been postmarketing reports of *torsades de pointes* occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs *[see Warnings and Precautions (5.3)]*. Serum concentrations of these medications should also be monitored. There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with disopyramide and quinidine. There have been postmarketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore, blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.
Digoxin	Use With Caution	Digoxin: Digoxin is a substrate for P-glycoprotein (Pgp) and clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are co-administered, inhibition of Pgp by clarithromycin may lead to increased exposure of digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have been

		reported in postmarketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Monitoring of serum digoxin concentrations should be considered, especially for patients with digoxin concentrations in the upper therapeutic range.
Oral Anticoagulants: Warfarin	Use With Caution	Oral anticoagulants: Spontaneous reports in the postmarketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously *[see Warnings and Precautions (5.4)]*.
Antiepileptics: Carbamazepine	Use With Caution	Carbamazepine: Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered. Increased serum concentrations of carbamazepine were observed in clinical trials with clarithromycin. There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with carbamazepine.
Antifungals: Itraconazole	Use With Caution	Itraconazole: Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, potentially leading to a bi-directional drug interaction when administered concomitantly (see also Itraconazole under “Drugs That Affect BIAXIN” in the table below). Clarithromycin may increase the plasma concentrations of itraconazole. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged adverse reactions.

Fluconazole	No Dose Adjustment	Fluconazole: *[see Pharmacokinetics (12.3)]*
Anti-Gout Agents: Colchicine (in patients with renal or hepatic impairment) Colchicine (in patients with normal renal and hepatic function)	 Contraindicated Use With Caution	 Colchicine: Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. The dose of colchicine should be reduced when co-administered with clarithromycin in patients with normal renal and hepatic function *[see Contraindications (4.4) and Warnings and Precautions (5.4)]*.
Antipsychotics: Pimozide Quetiapine	 Contraindicated	 Pimozide: *[See Contraindications (4.2)]* Quetiapine: Quetiapine is a substrate for CYP3A4, which is inhibited by clarithromycin. Co-administration with clarithromycin could result in increased quetiapine exposure and possible quetiapine related toxicities. There have been postmarketing reports of somnolence, orthostatic hypotension, altered state of consciousness, neuroleptic malignant syndrome, and QT prolongation during concomitant administration. Refer to quetiapine prescribing information for recommendations on dose reduction if co-administered with CYP3A4 inhibitors such as clarithromycin.
Antispasmodics: Tolterodine (patients deficient in CYP2D6 activity)	 Use With Caution	 Tolterodine: The primary route of metabolism for tolterodine is via CYP2D6. However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. Tolterodine 1 mg twice daily is recommended in patients deficient in CYP2D6 activity (poor metabolizers) when co-administered with clarithromycin.

Antivirals:		
Atazanavir	Use With Caution	Atazanavir: Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction (see Atazanavir under "Drugs That Affect BIAXIN" in the table below) *[see Pharmacokinetics (12.3)]*.
Saquinavir (in patients with decreased renal function)		Saquinavir: Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A and there is evidence of a bi-directional drug interaction (see Saquinavir under "Drugs That Affect BIAXIN" in the table below) *[see Pharmacokinetics (12.3)]*.
Ritonavir Etravirine		Ritonavir, Etravirine: (see Ritonavir and Etravirine under "Drugs That Affect BIAXIN" in the table below) *[see Pharmacokinetics (12.3)]*.
Maraviroc		Maraviroc: Clarithromycin may result in increases in maraviroc exposures by inhibition of CYP3A metabolism. See Selzentry® prescribing information for dose recommendation when given with strong CYP3A inhibitors such as clarithromycin.
Boceprevir (in patients with normal renal function) Didanosine	No Dose Adjustment	Boceprevir: Both clarithromycin and boceprevir are substrates and inhibitors of CYP3A, potentially leading to a bi-directional drug interaction when co-administered. No dose adjustments are necessary for patients with normal renal function (see Victrelis® prescribing information).
Zidovudine		Zidovudine: Simultaneous oral administration of clarithromycin immediate-release tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Administration of clarithromycin and zidovudine should be separated by at least two hours *[see Pharmacokinetics (12.3)]*. The impact of co-administration of clarithromycin extended-release tablets or granules and zidovudine has not been evaluated.
Calcium Channel Blockers:		

Verapamil Amlodipine Diltiazem Nifedipine	Use With Caution	Verapamil: Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, *[see Warnings and Precautions (5.4)]*. Amlodipine, Diltiazem: *[See Warnings and Precautions (5.4)]* Nifedipine: Nifedipine is a substrate for CYP3A. Clarithromycin and other macrolides are known to inhibit CYP3A. There is potential of CYP3A-mediated interaction between nifedipine and clarithromycin. Hypotension and peripheral edema were observed when clarithromycin was taken concomitantly with nifedipine *[see Warnings and Precautions (5.4)]*.
Ergot Alkaloids: Ergotamine Dihydroergotamine	Contraindicated	Ergotamine, Dihydroergotamine: Postmarketing reports indicate that coadministration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4.6)]*.
Gastroprokinetic Agents: Cisapride	Contraindicated	Cisapride: *[See Contraindications (4.2)]*
HMG-CoA Reductase Inhibitors: Lovastatin Simvastatin Atorvastatin Pravastatin Fluvastatin	Contraindicated Use With Caution No Dose Adjustment	Lovastatin, Simvastatin, Atorvastatin, Pravastatin, Fluvastatin: *[See Contraindications (4.5) and Warnings and Precautions (5.4)]*

Hypoglycemic Agents: Nateglinide Pioglitazone Repaglinide Rosiglitazone Insulin	Use With Caution	Nateglinide, Pioglitazone, Repaglinide, Rosiglitazone: *[See Warnings and Precautions (5.4) and Adverse Reactions (6.2)]* Insulin: *[See Warnings and Precautions (5.4) and Adverse Reactions (6.2)]*
Immunosuppressants: Cyclosporine Tacrolimus	Use With Caution	Cyclosporine: There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with cyclosporine. Tacrolimus: There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with tacrolimus.
Phosphodiesterase inhibitors: Sildenafil Tadalafil Vardenafil	Use With Caution	Sildenafil, Tadalafil, Vardenafil: Each of these phosphodiesterase inhibitors is primarily metabolized by CYP3A, and CYP3A will be inhibited by concomitant administration of clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil, or vardenafil will result in increased exposure of these phosphodiesterase inhibitors. Co-administration of these phosphodiesterase inhibitors with clarithromycin is not recommended. Increased systemic exposure of these drugs may occur with clarithromycin; reduction of dosage for phosphodiesterase inhibitors should be considered (see their respective prescribing information).
Proton Pump Inhibitors: Omeprazole	No Dose Adjustment	Omeprazole: The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when coadministered with clarithromycin as a result of increased omeprazole exposures *[see*

		Pharmacokinetics (12.3)] (see also Omeprazole under "Drugs That Affect BIAXIN" in the table below).
Xanthine Derivatives: Theophylline	Use With Caution	Theophylline: Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations *[see Pharmacokinetics (12.3)]*. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range.
Triazolobenzodiazepines and Other Related Benzodiazepines: Midazolam	Use With Caution	Midazolam: When oral midazolam is co-administered with clarithromycin, dose adjustments may be necessary and possible prolongation and intensity of effect should be anticipated *[see Warnings and Precautions (5.4) and Pharmacokinetics (12.3)]*.
Alprazolam Triazolam		Triazolam, Alprazolam: Caution and appropriate dose adjustments should be considered when triazolam or alprazolam is co-administered with clarithromycin. There have been postmarketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested. In postmarketing experience, erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines.
Temazepam Nitrazepam Lorazepam	No Dose Adjustment	Temazepam, Nitrazepam, Lorazepam: For benzodiazepines which are not metabolized by CYP3A (e.g., temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin

		is unlikely.
Cytochrome P450 Inducers: Rifabutin	Use With Caution	Rifabutin: Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis (see Rifabutin under "Drugs That Affect BIAXIN" in the table below).
Other Drugs Metabolized by CYP3A: Alfentanil Bromocriptine Cilostazol Methylprednisole Vinblastine Phenobarbital St. John's Wort	Use With Caution	There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with alfentanil, methylprednisolone, cilostazol, bromocriptine, vinblastine, phenobarbital, and St. John's Wort.
Other Drugs Metabolized by CYP450 Isoforms Other than CYP3A: Hexobarbital Phenytoin Valproate	Use With Caution	There have been postmarketing reports of interactions of clarithromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.
Drugs that Affect BIAXIN		
Drug(s) that Affect the Pharmacokinetics of BIAXIN	**Recommendation**	**Comments**
Antifungals: Itraconazole	Use With Caution	Itraconazole: Itraconazole may increase the plasma concentrations of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged adverse reactions (see also Itraconazole under "Drugs That Are Affected By

		BIAXIN" in the table above).
Antivirals:		
Atazanavir	Use With Caution	Atazanavir: When clarithromycin is co-administered with atazanavir, the dose of clarithromycin should be decreased by 50% *[see Clinical Pharmacology (12.3)]*. Since concentrations of 14-OH clarithromycin are significantly reduced when clarithromycin is co-administered with atazanavir, alternative antibacterial therapy should be considered for indications other than infections due to *Mycobacterium avium* complex. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.
Ritonavir (in patients with decreased renal function)		Ritonavir: Since concentrations of 14-OH clarithromycin are significantly reduced when clarithromycin is co-administered with ritonavir, alternative antibacterial therapy should be considered for indications other than infections due to *Mycobacterium avium [see Pharmacokinetics (12.3)]*. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.
Saquinavir (in patients with decreased renal function)		Saquinavir: When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (refer to ritonavir above) *[see Pharmacokinetics (12.3)]*.
Etravirine		Etravirine: Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.
Saquinavir (in patients with normal renal	No Dose Adjustment	

function) Ritonavir (in patients with normal renal function)		
Proton Pump Inhibitors: Omeprazole	Use With Caution	Omeprazole: Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole *[see Pharmacokinetics (12.3)]*.
Miscellaneous Cytochrome P450 Inducers: Efavirenz Nevirapine Rifampicin Rifabutin Rifapentine	Use With Caution	Inducers of CYP3A enzymes, such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine will increase the metabolism of clarithromycin, thus decreasing plasma concentrations of clarithromycin, while increasing those of 14-OH-clarithromycin. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers. Alternative antibacterial treatment should be considered when treating patients receiving inducers of CYP3A. There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with rifabutin (see Rifabutin under "Drugs That Are Affected By BIAXIN" in the table above).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C

Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.7)]*.

Four teratogenicity studies in rats (three with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to 125 mg/kg/day (approximately twice the recommended maximum human dose based on mg/m^2) or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18 failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were twice the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day (2 and 4 times the recommended maximum human dose based on mg/m^2, respectively) during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day produced fetal growth retardation at plasma levels that were twice the human serum levels.

8.3 Nursing Mothers

Caution should be exercised when BIAXIN is administered to nursing women. The development and health benefits of human milk feeding should be considered along with the mother's clinical need for BIAXIN and any potential adverse effects on the human milk fed child from the drug or from the underlying maternal condition.

Clarithromycin and its active metabolite 14-hydroxy clarithromycin are excreted in human milk. Serum and milk samples were obtained after 3 days of treatment, at steady state, from one published study of 12 lactating women who were taking BIAXIN 250 mg orally twice daily. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively human milk fed infant would receive an estimated average of 136 mcg/kg/day of clarithromycin and its active metabolite, with this maternal dosage regimen. This is less than 2% of the maternal weight-adjusted dose (7.8 mg/kg/day, based on the average maternal weight of 64 kg), and less than 1% of the pediatric dose (15 mg/kg/day) for children greater than 6 months of age.

A prospective observational study of 55 breastfed infants of mothers taking a macrolide antibacterial (6 were exposed to clarithromycin) were compared to 36 breastfed infants of mothers taking amoxicillin. Adverse reactions were comparable in both groups. Adverse reactions occurred in 12.7% of infants exposed to macrolides and included rash, diarrhea, loss of appetite, and somnolence.

8.4 Pediatric Use

The safety and effectiveness of BIAXIN Filmtab and BIAXIN Granules have been established for the treatment of the following conditions or diseases in pediatric patients 6 months and older. Use in these indications is based on clinical trials in pediatric patients or adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients:

- Pharyngitis/Tonsillitis
- Community-Acquired Pneumonia
- Acute maxillary sinusitis
- Acute otitis media *[see Clinical Studies (14.2)]*

- Uncomplicated skin and skin structure infections

The safety and effectiveness of BIAXIN Filmtab and BIAXIN Granules have been established for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in pediatric patients 20 months and older with advanced HIV infection. No studies of BIAXIN for MAC prophylaxis have been performed in pediatric populations and the doses recommended for prophylaxis are derived from MAC pediatric treatment studies.

The safety and effectiveness of BIAXIN XL Filmtab in the treatment of pediatric patients has not been established.

Safety and effectiveness of BIAXIN in pediatric patients under 6 months of age have not been established. The safety of BIAXIN has not been studied in MAC patients under the age of 20 months.

8.5 Geriatric Use

In a steady-state study in which healthy elderly subjects (65 years to 81 years of age) were given 500 mg of BIAXIN every 12 hours, the maximum serum concentrations and area under the curves of clarithromycin and 14-OH clarithromycin were increased compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse reactions when compared to younger patients. Consider dosage adjustment in elderly patients with severe renal impairment. Elderly patients may be more susceptible to development of *torsades de pointes* arrhythmias than younger patients *[see Warnings and Precautions (5.3)]*.

Most reports of acute kidney injury with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem, nifedipine) involved elderly patients 65 years of age or older *[see Warnings and Precautions (5.4)]*.

Especially in elderly patients, there have been reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, some of which occurred in patients with renal insufficiency. Deaths have been reported in some patients *[see Contraindications (4.4) and Warnings and Precautions (5.4)]*.

8.6 Renal and Hepatic Impairment

BIAXIN is principally excreted via the liver and kidney. BIAXIN may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate *[see Dosage and Administration (2.5)]*.

10 OVERDOSAGE

Overdosage of BIAXIN can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea.

Treat adverse reactions accompanying overdosage by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, BIAXIN serum concentrations are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

11 DESCRIPTION

Clarithromycin is a semi-synthetic macrolide antimicrobial for oral use. Chemically, it is 6-*O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. The structural formula is:

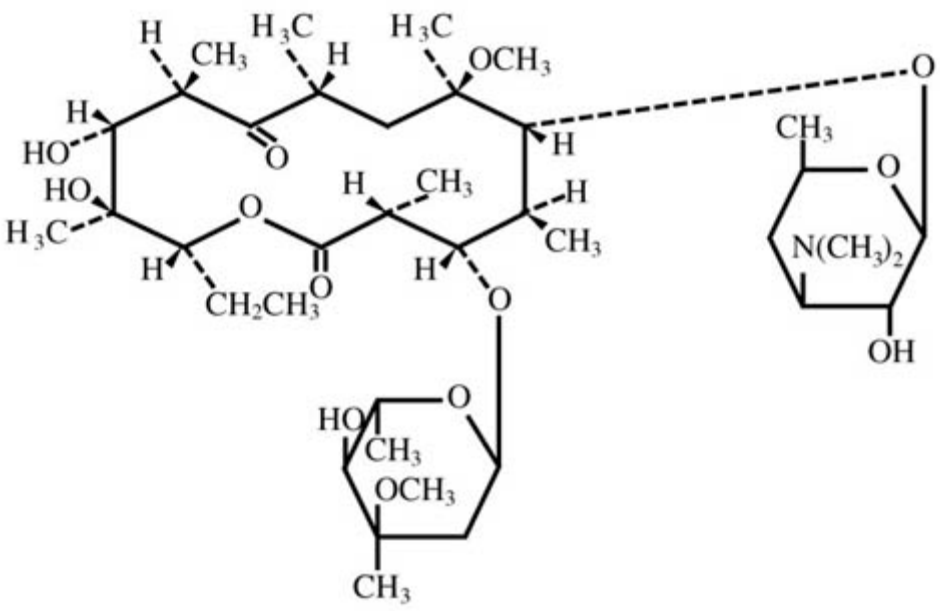

Figure 1: Structure of Clarithromycin

Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water.

BIAXIN is available as immediate-release tablets, extended-release tablets, and granules for oral suspension.

Each yellow oval film-coated immediate-release BIAXIN Filmtab tablet (clarithromycin tablets, USP) contains 250 mg or 500 mg of clarithromycin and the following inactive ingredients:

- 250 mg tablets: hypromellose, hydroxypropyl cellulose, croscarmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide, and vanillin.
- 500 mg tablets: hypromellose, hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sorbic acid, sorbitan monooleate, titanium dioxide, and vanillin.

Each yellow oval film-coated BIAXIN XL Filmtab tablet (clarithromycin extended-release tablets) contains 500 mg of clarithromycin and the following inactive ingredients: cellulosic

polymers, D&C Yellow No. 10, lactose monohydrate, magnesium stearate, propylene glycol, sorbic acid, sorbitan monooleate, talc, titanium dioxide, and vanillin.

Each 5 mL of BIAXIN reconstituted suspension (clarithromycin for oral suspension, USP) contains 125 mg or 250 mg of clarithromycin. Each bottle of BIAXIN granules contains 1250 mg (50 mL size), 2500 mg (50 and 100 mL sizes) or 5000 mg (100 mL size) of clarithromycin and the following inactive ingredients: carbomer, castor oil, citric acid, hypromellose phthalate, maltodextrin, potassium sorbate, povidone, silicon dioxide, sucrose, xanthan gum, titanium dioxide and fruit punch flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clarithromycin is a macrolide antimicrobial drug *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Absorption

BIAXIN Filmtab Immediate-Release Tablets

The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, BIAXIN Filmtab may be given without regard to food. In non-fasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing.

BIAXIN XL Filmtab Extended-Release Tablets

Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration. Relative to an equal total daily dose of immediate-release clarithromycin tablets, clarithromycin extended-release tablets provide lower and later steady-state peak plasma concentrations but equivalent 24-hour AUCs for both clarithromycin and its microbiologically-active metabolite, 14-OH clarithromycin. While the extent of formation of 14-OH clarithromycin following administration of BIAXIN XL Filmtab (2 x 500 mg tablets once daily) is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC relative to administration with food. Therefore, BIAXIN XL Filmtab should be taken with food.

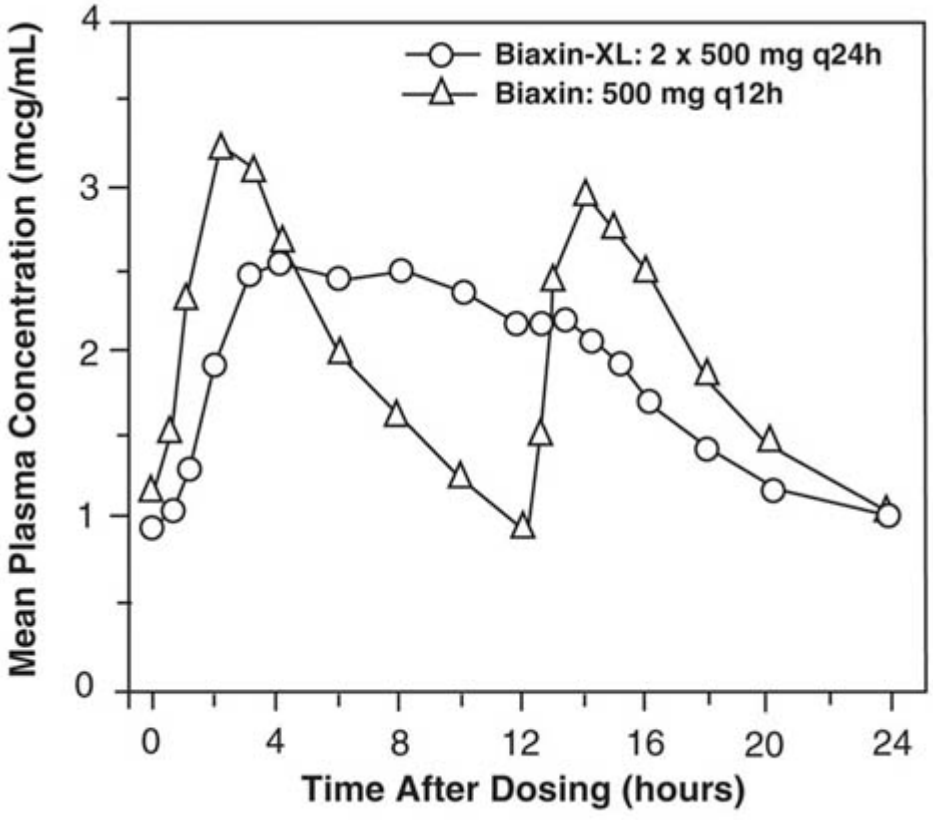

Figure 2: Steady-State Clarithromycin Plasma Concentration-Time Profiles

BIAXIN Granules For Oral Suspension

When 250 mg doses of clarithromycin as BIAXIN as an oral suspension were administered to fasting healthy adult subjects, peak plasma concentrations were attained around 3 hours after dosing.

For adult patients, the bioavailability of 10 mL of the 125 mg/5 mL suspension or 10 mL of the 250 mg/5 mL suspension is similar to a 250 mg or 500 mg tablet, respectively.

In adults given 250 mg clarithromycin as suspension (n = 22), food appeared to decrease mean peak plasma clarithromycin concentrations from 1.2 (± 0.4) mcg/mL to 1.0 (± 0.4) mcg/mL and the extent of absorption from 7.2 (± 2.5) hr•mcg/mL to 6.5 (± 3.7) hr•mcg/mL.

Distribution

Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. There are no data available on cerebrospinal fluid penetration. Because of high intracellular concentrations, tissue concentrations are higher than serum concentrations. Examples of tissue and serum concentrations are presented below.

Table 9. Tissue and Serum Concentrations of Clarithromycin

CONCENTRATION (after 250 mg every 12 hours)		
Tissue Type	**Tissue (mcg/g)**	**Serum (mcg/mL)**
Tonsil	1.6	0.8
Lung	8.8	1.7

Metabolism and Elimination

BIAXIN Filmtab Immediate-Release Tablets

Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 mcg/mL to 2 mcg/mL with a 250 mg dose administered every 12 hours and 3 mcg/mL to 4 mcg/mL with a 500 mg dose administered every 8 hours to 12 hours. The elimination half-life of clarithromycin was about 3 hours to 4 hours with 250 mg administered every 12 hours but increased to 5 hours to 7 hours with 500 mg administered every 8 hours to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 hours to 12 hours. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 mcg/mL and has an elimination half-life of 5 hours to 6 hours. With a 500 mg every 8 hours to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 mcg/mL), and its elimination half-life is about 7 hours to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 days to 4 days.

After a 250 mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500 mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. In comparison, after an oral dose of 250 mg (125 mg/5 mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with either a 250 mg or a 500 mg tablet administered every 12 hours.

BIAXIN XL Filmtab Extended-Release Tablets

In healthy human subjects, steady-state peak plasma clarithromycin concentrations of approximately 2 mcg/mL to 3 mcg/mL were achieved about 5 hours to 8 hours after oral administration of 1000 mg BIAXIN XL Filmtab once daily; for 14-OH clarithromycin, steady-state peak plasma concentrations of approximately 0.8 mcg/mL were attained about 6 hours to 9 hours after dosing. Steady-state peak plasma clarithromycin concentrations of approximately 1 mcg/mL to 2 mcg/mL were achieved about 5 hours to 6 hours after oral administration of a single 500 mg BIAXIN XL Filmtab once daily; for 14-OH clarithromycin, steady-state peak plasma concentrations of approximately 0.6 mcg/mL were attained about 6 hours after dosing.

Steady-state peak plasma concentrations were attained in 2 days to 3 days and were approximately 2 mcg/mL for clarithromycin and 0.7 mcg/mL for 14-OH clarithromycin when 250-mg doses of the clarithromycin suspension were administered every 12 hours. Elimination half-life of clarithromycin (3 hours to 4 hours) and that of 14-OH clarithromycin (5 hours to 7

hours) were similar to those observed at steady state following administration of equivalent doses of BIAXIN Filmtab.

Specific Populations for BIAXIN Filmtab, BIAXIN XL Filmtab, and BIAXIN Granules Formulations

BIAXIN Granules For Oral Suspension in Pediatric Patients

Clarithromycin penetrates into the middle ear fluid of pediatric patients with secretory otitis media.

Table 10. Middle Ear Fluid and Serum Concentrations of Clarithromycin and 14-OH-Clarithromycin in Pediatric Patients

CONCENTRATION (after 7.5 mg/kg every 12 hours for 5 doses)		
Analyte	**Middle Ear Fluid (mcg/mL)**	**Serum (mcg/mL)**
Clarithromycin	2.5	1.7
14-OH Clarithromycin	1.3	0.8

When pediatric patients (n = 10) were administered a single oral dose of 7.5 mg/kg BIAXIN as an oral suspension, food increased mean peak plasma clarithromycin concentrations from 3.6 (± 1.5) mcg/mL to 4.6 (± 2.8) mcg/mL and the extent of absorption from 10.0 (± 5.5) hr•mcg/mL to 14.2 (± 9.4) hr•mcg/mL.

In pediatric patients requiring antibacterial therapy, administration of 7.5 mg/kg every 12 hours of BIAXIN as an oral suspension generally resulted in steady-state peak plasma concentrations of 3 mcg/mL to 7 mcg/mL for clarithromycin and 1 mcg/mL to 2 mcg/mL for 14-OH clarithromycin.

In HIV-infected pediatric patients taking 15 mg/kg of BIAXIN as an oral suspension every 12 hours, steady-state clarithromycin peak concentrations generally ranged from 6 mcg/mL to 15 mcg/mL.

HIV Infection

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500 mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500-mg or 1000-mg doses of clarithromycin every 12 hours, steady-state clarithromycin C_{max} values ranged from 2 mcg/mL to 4 mcg/mL and 5 mcg/mL to 10 mcg/mL, respectively.

Hepatic Impairment

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

Renal Impairment

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function *[see Use in Specific Populations (8.6) and Dosage and Administration (2.5)]*.

Drug Interactions

Fluconazole

Following administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers, the steady-state clarithromycin C_{min} and AUC increased 33% and 18%, respectively. Clarithromycin exposures were increased and steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.

Colchicine

When a single dose of colchicine 0.6 mg was administered with clarithromycin 250 mg BID for 7 days, the colchicine C_{max} increased 197% and the $AUC_{0-\infty}$ increased 239% compared to administration of colchicine alone.

Atazanavir

Following administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily), the clarithromycin AUC increased 94%, the 14-OH clarithromycin AUC decreased 70% and the atazanavir AUC increased 28%.

Ritonavir

Concomitant administration of clarithromycin and ritonavir (n = 22) resulted in a 77% increase in clarithromycin AUC and a 100% decrease in the AUC of 14-OH clarithromycin.

Saquinavir

Following administration of clarithromycin (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers, the steady-state saquinavir AUC and C_{max} increased 177% and 187% respectively compared to administration of saquinavir alone. Clarithromycin AUC and C_{max} increased 45% and 39% respectively, whereas the 14–OH clarithromycin AUC and C_{max} decreased 24% and 34% respectively, compared to administration with clarithromycin alone.

Didanosine

Simultaneous administration of clarithromycin tablets and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

Zidovudine

Following administration of clarithromycin 500 mg tablets twice daily with zidovudine 100 mg every 4 hours, the steady-state zidovudine AUC decreased 12% compared to administration of zidovudine alone (n=4). Individual values ranged from a decrease of 34% to an increase of 14%. When clarithromycin tablets were administered two to four hours prior to zidovudine, the steady-state zidovudine C_{max} increased 100% whereas the AUC was unaffected (n=24).

Omeprazole

Clarithromycin 500 mg every 8 hours was given in combination with omeprazole 40 mg daily to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased

(C_{max}, AUC_{0-24}, and t½ increases of 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin.

The plasma levels of clarithromycin and 14–OH clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC_{0-8} was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14–OH clarithromycin, the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC_{0-8} was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Clarithromycin Tissue Concentrations 2 hours after Dose (mcg/mL)/(mcg/g)					
Treatment	**N**	**antrum**	**fundus**	**N**	**Mucus**
Clarithromycin	5	10.48 ± 2.01	20.81 ± 7.64	4	4.15 ± 7.74
Clarithromycin + Omeprazole	5	19.96 ± 4.71	24.25 ± 6.37	4	39.29 ± 32.79

Theophylline

In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of C_{max}, C_{min}, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Midazolam

When a single dose of midazolam was co-administered with clarithromycin tablets (500 mg twice daily for 7 days), midazolam AUC increased 174% after intravenous administration of midazolam and 600% after oral administration.

For information about other drugs indicated in combination with BIAXIN, refer to their full prescribing information, CLINICAL PHARMACOLOGY section.

12.4 Microbiology

Mechanism of Action

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

Resistance

The major routes of resistance are modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity or drug efflux pumps. Beta-lactamase production should have no effect on clarithromycin activity.

Most isolates of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

If *H. pylori* is not eradicated after treatment with clarithromycin-containing combination regimens, patients may develop clarithromycin resistance in *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; omeprazole/clarithromycin/amoxicillin triple therapy; lansoprazole/clarithromycin/amoxicillin triple therapy; or other regimens which include clarithromycin as the sole antibacterial agent.

Antimicrobial Activity

Clarithromycin has been shown to be active against most of the isolates of the following microorganisms both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Gram-Positive Bacteria

- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

Gram-Negative Bacteria

- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*

Other Microorganisms

- *Chlamydophila pneumoniae*
- *Helicobacter pylori*
- *Mycobacterium avium* complex (MAC) consisting of *M. avium* and *M. intracellulare*
- *Mycoplasma pneumoniae*

At least 90 percent of the microorganisms listed below exhibit *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the clarithromycin susceptible MIC breakpoint for organisms of similar type to those shown in Table 11. However, the efficacy of clarithromycin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria

- *Streptococcus agalactiae*
- Streptococci (Groups C, F, G)
- Viridans group streptococci

Gram-Negative Bacteria

- *Legionella pneumophila*
- *Pasteurella multocida*

Anaerobic Bacteria

- *Clostridium perfringens*
- *Peptococcus niger*
- *Prevotella melaninogenica*
- *Propionibacterium acnes*

Susceptibility Testing Methods (Excluding Mycobacteria and Helicobacter)

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and

community-acquired pathogens. These reports should aid the physician in selecting an antimicrobial drug for treatment.

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 test method[2,3] (broth and/or agar). The MIC values should be interpreted according to the criteria provided in Table 11.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.[3,4] This procedure uses paper disks impregnated with 15 mcg of clarithromycin to test the susceptibility of bacteria to clarithromycin. The disk diffusion interpretive criteria are provided in Table 11.

Susceptibility Testing for *Mycobacterium avium* Complex (MAC)

The reference methodology for susceptibility testing of *Mycobacterium avium* complex (MAC) is broth dilution (either microdilution or macrodilution method).[5] For broth microdilution testing, cation-adjusted Mueller-Hinton broth (CAMHB) supplemented with 5% OADC is recommended. Transparent colonies should be used for the inoculum, if present. Susceptibility testing at either pH 6.8 or pH 7.4 is acceptable, provided that interpretation is done based on the culture conditions employed. Microdilution trays are incubated at 35 ºC to 37 ºC in ambient air and examined after seven days. Trays should be incubated and read again at 10 to 14 days, if growth is poor on initial inspection.

Susceptibility Testing for *Helicobacter pylori*

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[6] 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 MIC values should be interpreted according to the criteria in Table 11.

Table 11. Susceptibility Test Interpretive Criteria for Clarithromycin

	Minimum Inhibitory Concentrations (mcg/mL)			**Disk Diffusion (zone diameters in mm)**		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus	≤ 2	4	≥ 8	≥ 18	14--17	≤ 13
Streptococcus pyogenes and *Streptococcus pneumoniae*	≤ 0.25[a]	0.5[a]	≥ 1[a]	≥ 21[b]	17--20[b]	≤ 16[b]

Haemophilus influenzae	≤ 8[c]	16[c]	≥ 32[c]	≥ 13[d]	11--12[d]	≤ 10[d]
Helicobacter pylori[e]	≤ 0.25	0.5	≥ 1	--	--	--

a These interpretive standards are applicable only to broth microdilution susceptibility tests using cation adjusted Mueller Hinton broth with 2-5% lysed horse blood[3].
b These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2[3].
c These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Testing Medium (HTM)[3].
d These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM[3].
e These are tentative breakpoints for clarithromycin for the agar dilution methodology and should not be used to interpret results obtained using alternative methods[6].
Note: When testing *Streptococcus pyogenes* and *Streptococcus pneumoniae*, susceptibility and resistance to clarithromycin can be predicted using erythromycin.

A report of *Susceptible* (S) indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate* (I) 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* (R) indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control bacteria to monitor and ensure the accuracy and precision of supplies and reagents in the assay, and the techniques of the individual performing the test.[2-6] Standard clarithromycin powder should provide the following range of MIC values as noted in Table 12. For the diffusion technique using the 15 mcg disk, the criteria in Table 12 should be achieved.

Table 12. Acceptable Quality Control Ranges for Clarithromycin

QC Strain	MIC (mcg/mL)	Zone diameter (mm)
Staphylococcus aureus ATCC 29213[a]	0.12 – 0.5	--
Staphylococcus aureus ATCC 25923	--	26 – 32
Streptococcus pneumoniae ATCC 49619	0.03 – 0.12[b]	25 – 31[c]
Haemophilus influenzae ATCC 49247	4 – 16[d]	11 – 17[e]
Helicobacter pylori ATCC 43504	0.015 – 0.12[f]	--
M. avium ATCC 700898	1 – 4[g]	--

a ATCC is a registered trademark of the American Type Culture Collection.
b This quality control range is applicable only to *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation adjusted Mueller Hinton broth with 2-5% lysed horse

blood.[2,3]
c This quality control range is applicable only to *S. pneumoniae* ATCC 49619 for tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.[3,4]
d This quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM[2,3].
e This quality control limit applies to disk diffusion tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM[3,4].
f These are quality control ranges for the agar dilution methodology[6] and should not be used to control test results obtained using alternative methods.
g When tested at pH 6.8 (if tested at pH 5.0 to 7.4 at 7.4, the acceptable range is 0.5 mcg/mL to 2 mcg/mL)[5].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The following *in vitro* mutagenicity tests have been conducted with clarithromycin:

- *Salmonella*/Mammalian Microsomes Test
- Bacterial Induced Mutation Frequency Test
- *In Vitro* Chromosome Aberration Test
- Rat Hepatocyte DNA Synthesis Assay
- Mouse Lymphoma Assay
- Mouse Dominant Lethal Study
- Mouse Micronucleus Test

All tests had negative results except the *in vitro* chromosome aberration test which was positive in one test and negative in another. In addition, a bacterial reverse-mutation test (Ames test) has been performed on clarithromycin metabolites with negative results.

Impairment of Fertility

Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/ to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were twice the human serum levels.

Testicular atrophy occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose (on a body surface area basis).

13.2 Animal Toxicology and/or Pharmacology

Corneal opacity occurred in dogs at doses 12 times and in monkeys at doses 8 times greater than the maximum human daily dose (on a body surface area basis). Lymphoid depletion occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose (on a body surface area basis).

14 CLINICAL STUDIES

14.1 Mycobacterial Infections

Prophylaxis of Mycobacterial Infections

A randomized, double-blind clinical trial (trial 3) compared clarithromycin 500 mg twice a day to placebo in patients with CDC-defined AIDS and CD_4 counts less than 100 cells/µL. This trial accrued 682 patients from November 1992 to January 1994, with a median CD_4 cell count at entry of 30 cells/mcL. Median duration of BIAXIN was 10.6 months vs. 8.2 months for placebo. More patients in the placebo arm than the BIAXIN arm discontinued prematurely from the trial (75.6% and 67.4%, respectively). However, if premature discontinuations due to *Mycobacterium avium* complex (MAC) or death are excluded, approximately equal percentages of patients on each arm (54.8%) on BIAXIN and 52.5% on placebo) discontinued study drug early for other reasons. The trial was designed to evaluate the following endpoints:

1. MAC bacteremia, defined as at least one positive culture for *Mycobacterium avium* complex bacteria from blood or another normally sterile site
2. Survival
3. Clinically significant disseminated MAC disease, defined as MAC bacteremia accompanied by signs or symptoms of serious MAC infection, including fever, night sweats, weight loss, anemia, or elevations in liver function tests

MAC Bacteremia

In patients randomized to BIAXIN, the risk of MAC bacteremia was reduced by 69% compared to placebo. The difference between groups was statistically significant ($p < 0.001$). On an intent-to-treat basis, the one-year cumulative incidence of MAC bacteremia was 5.0% for patients randomized to BIAXIN and 19.4% for patients randomized to placebo. While only 19 of the 341 patients randomized to BIAXIN developed MAC, 11 of these cases were resistant to BIAXIN. The patients with resistant MAC bacteremia had a median baseline CD_4 count of 10 cells/mm^3 (range 2 cells/mm^3 to 25 cells/mm^3). Information regarding the clinical course and response to treatment of the patients with resistant MAC bacteremia is limited. The 8 patients who received BIAXIN and developed susceptible MAC bacteremia had a median baseline CD_4 count of 25 cells/mm^3 (range 10 cells/mm^3 to 80 cells/mm^3). Comparatively, 53 of the 341 placebo patients developed MAC; none of these isolates were resistant to BIAXIN. The median baseline CD_4 count was 15 cells/mm^3 (range 2 cells/mm^3 to 130 cells/mm^3) for placebo patients that developed MAC.

Survival

A statistically significant survival benefit of BIAXIN compared to placebo was observed (see Figure 3 and Table 13). Since the analysis at 18 months includes patients no longer receiving prophylaxis the survival benefit of BIAXIN may be underestimated.

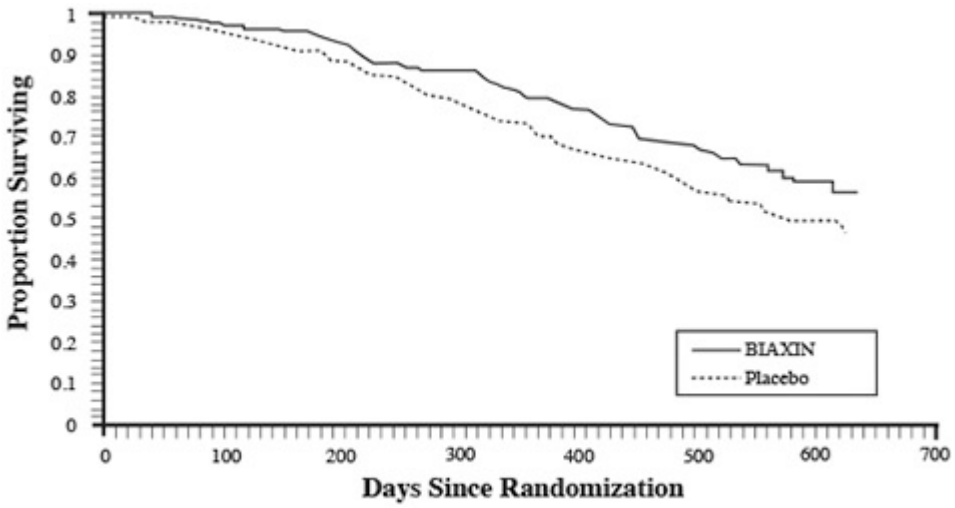

Figure 3. Survival of All Randomized AIDS Patients Over Time in Trial 3

Table 13. Mortality Rates at 18 months in Trial 3

	Mortality Rates		Reduction in Mortality Rates on BIAXIN
	Placebo	BIAXIN	
6 month	9.4%	6.5%	31%
12 month	29.7%	20.5%	31%
18 month	46.4%	37.5%	20%

Clinically Significant Disseminated MAC Disease

In association with the decreased incidence of MAC bacteremia, patients in the group randomized to BIAXIN showed reductions in the signs and symptoms of disseminated MAC disease, including fever, night sweats, weight loss, and anemia.

Treatment of Mycobacterial Infections

Dose-Ranging Monotherapy Trials in Adult AIDS Patients with MAC

Two randomized clinical trials (Trials 1 and 2) compared different dosages of BIAXIN in patients with CDC-defined AIDS and CD_4 counts less than100 cells/mcL. These trials accrued patients from May 1991 to March 1992. Trial 500 was a randomized, double-blind trial; trial 577 was an open-label compassionate use trial. Both trials used 500 mg and 1000 mg twice daily dosing of BIAXIN; trial 1 also had a 2000 mg twice daily BIAXIN group. Trial 1 enrolled 154 adult patients and trial 2 enrolled 469 adult patients. The majority of patients had CD_4 cell counts less than 50 cells/mcL at study entry. The trials were designed to evaluate the following end points:

1. Change in MAC bacteremia or blood cultures negative for *M. avium*.
2. Change in clinical signs and symptoms of MAC infection including one or more of the following: fever, night sweats, weight loss, diarrhea, splenomegaly, and hepatomegaly.

The results for trial 1 are described below. The trial 2 results were similar to the results of trial 1.

MAC Bacteremia

Decreases in MAC bacteremia or negative blood cultures were seen in the majority of patients in all BIAXIN dosage groups. The mean reductions in MAC colony forming units (CFU) from baseline after 4 weeks of therapy in the 1000 mg (n=32) twice daily and 2000 mg (n=26) twice daily regimen was 2.3 Log CFU compared to 1.5 Log CFU in the BIAXIN 500 mg twice daily (n=35) regimen. A separate trial with a four drug regimen[7] (ciprofloxacin, ethambutol, rifampicin, and clofazimine) had a mean reduction of 1.4 Log CFU.

Clinical outcomes evaluated with the different dosing regimens of clarithromycin monotherapy are shown in Table 14. The 1000 mg and 2000 mg twice daily doses showed significantly better control of bacteremia during the first four weeks of therapy. No significant differences were seen beyond that point. All of the isolates had MIC less than 8 mcg/mL at pre-treatment. Relapse was almost always accompanied by an increase in MIC.

Table 14. Outcome with the Different Dosing Regimens of BIAXIN

Outcome	BIAXIN 500 mg twice daily	BIAXIN 1000 mg twice daily	BIAXIN 2000 mg twice daily
One or more negative blood cultures at any time during acute therapy	61% (30/49)	59% (29/49)	52% (25/48)
Two or more negative blood cultures during acute therapy sustained through study day 84	25% (12/49)	25% (12/49)	8% (4/48)
Death or discontinuation by day 84	23% (11/49)	37% (18/49)	56% (27/48)
Relapse by day 84	14% (7/49)	12% (6/49)	13% (6/48)
Median time to first negative culture (in days)	54	41	29
Median time to first decrease of at least 1 log CFU (in days)	29	16	15
Median time to first positive culture or study discontinuation following the first negative culture (in days)	43	59	43

Clinically Significant Disseminated MAC Disease

Among patients experiencing night sweats prior to therapy, 84% showed resolution or improvement at some point during the 12 weeks of BIAXIN at 500 mg to 2000 mg twice daily doses. Similarly, 77% of patients reported resolution or improvement in fevers at some point. Response rates for clinical signs of MAC are given in Table 15 below.

The median duration of response, defined as improvement or resolution of clinical signs and symptoms, was 2 weeks to 6 weeks.

Since the trial was not designed to determine the benefit of monotherapy beyond 12 weeks, the duration of response may be underestimated for the 25% to 33% of patients who continued to show clinical response after 12 weeks.

Table 15. Response Rates for Clinical Signs of MAC During 6 Weeks to 12 Weeks of Treatment

Resolution of Fever			Resolution of Night Sweats		
BIAXIN twice daily dose (mg)	% ever afebrile	% afebrile 6 weeks or more	BIAXIN twice daily dose (mg)	% ever resolving	% resolving 6 weeks or more
500	67%	23%	500	85%	42%
1000	67%	12%	1000	70%	33%
2000	62%	22%	2000	72%	36%

Weight Gain Greater Than 3%			Hemoglobin Increase Greater Than 1 gm		
BIAXIN twice daily dose (mg)	% ever gaining	% gaining 6 weeks or more	BIAXIN twice daily dose (mg)	% ever increasing	% increasing 6 weeks or more
500	33%	14%	500	58%	26%
1000	26%	17%	1000	37%	6%
2000	26%	12%	2000	62%	18%

Survival

Median survival time from trial entry (trial 1) was 249 days at the 500 mg twice daily dose compared to 215 days with the 1000 mg twice daily dose. However, during the first 12 weeks of therapy, there were 2 deaths in 53 patients in the 500 mg twice daily group versus 13 deaths in 51 patients in the 1000 mg twice daily group. The reason for this apparent mortality difference is not known. Survival in the two groups was similar beyond 12 weeks. The median survival times for these dosages were similar to recent historical controls with MAC when treated with combination therapies.[7]

Median survival time from entry in trial 2 was 199 days for the 500 mg twice a day dose and 179 days for the 1000 mg twice a day dose. During the first four weeks of therapy, while patients were maintained on their originally assigned dose, there were 11 deaths in 255 patients taking 500 mg twice daily and 18 deaths in 214 patients taking 1000 mg twice daily.

Dosage-Ranging Monotherapy Trials in Pediatric AIDS Patients with MAC

Trial 4 was a pediatric trial of 3.75 mg/kg, 7.5 mg/kg, and 15 mg/kg of BIAXIN twice daily in patients with CDC-defined AIDS and CD_4 counts less than 100 cells/mcL. The trial enrolled 25 patients between the ages of 1 to 20. The trial evaluated the same endpoints as in the adult trials 1 and 2. Results with the 7.5 mg/kg twice daily dose in the pediatric trial were comparable to those for the 500 mg twice daily regimen in the adult trials.

Combination Therapy in AIDS Patients with Disseminated MAC

Trial 5 compared the safety and efficacy of BIAXIN in combination with ethambutol versus BIAXIN in combination with ethambutol and clofazimine for the treatment of disseminated MAC (dMAC) infection. This 24-week trial enrolled 106 patients with AIDS and dMAC, with 55 patients randomized to receive BIAXIN and ethambutol, and 51 patients randomized to

receive clarithromycin, ethambutol, and clofazime. Baseline characteristics between treatment arms were similar with the exception of median CFU counts being at least 1 log higher in the BIAXIN, ethambutol, and clofazime arm.

Compared to prior experience with clarithromycin monotherapy, the two-drug regimen of clarithromycin and ethambutol extended the time to microbiologic relapse, largely through suppressing the emergence of clarithromycin resistant strains. However, the addition of clofazimine to the regimen added no additional microbiologic or clinical benefit. Tolerability of both multidrug regimens was comparable with the most common adverse events being gastrointestinal in nature. Patients receiving the clofazimine-containing regimen had reduced survival rates; however, their baseline mycobacterial colony counts were higher. The results of this trial support the addition of ethambutol to clarithromycin for the treatment of initial dMAC infections but do not support adding clofazimine as a third agent.

14.2 Otitis Media

Otitis Media Trial of BIAXIN vs. Oral Cephalosporin

In a controlled clinical trial of pediatric patients with acute otitis media performed in the United States, where significant rates of beta-lactamase producing organisms were found, BIAXIN was compared to an oral cephalosporin. In this trial, strict evaluability criteria were used to determine clinical response. For the 223 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the post-therapy visit was 88% for BIAXIN and 91% for the cephalosporin.

In a smaller number of patients, microbiologic determinations were made at the pre-treatment visit. The presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) are shown in Table 16.

Table 16. Clinical Success Rates of Otitis Media Treatment by Pathogen

Pathogen	Clinical Success Rates	
	BIAXIN	Oral Cephalosporin
S. pneumoniae	13/15 (87%)	4/5
H. influenzae[a]	10/14 (71%)	3/4
M. catarrhalis	4/5	1/1
S. pyogenes	3/3	0/1
All Pathogens Combined	30/37 (81%)	8/11 (73%)

a None of the *H. influenzae* isolated pre-treatment was resistant to BIAXIN; 6% were resistant to the control agent.

Otitis Media Trials of BIAXIN vs. Antimicrobial/Beta-lactamase Inhibitor

In two other controlled clinical trials of acute otitis media performed in the United States, where significant rates of beta-lactamase producing organisms were found, BIAXIN was compared to an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. In these trials, strict evaluability criteria were used to determine the clinical responses. In the 233 patients who were

evaluated for clinical efficacy, the combined clinical success rate (i.e., cure and improvement) at the post-therapy visit was 91% for both BIAXIN and the control.

For the patients who had microbiologic determinations at the pre-treatment visit, the presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) are shown in Table 17.

Table 17. Clinical Success Rates of Acute Otitis Media Treatment by Pathogen

	Clinical Success Rates	
PATHOGEN	**BIAXIN**	**Antimicrobial/Beta-lactamase Inhibitor**
S. pneumoniae	43/51 (84%)	55/56 (98%)
H. influenzae[a]	36/45 (80%)	31/33 (94%)
M. catarrhalis	9/10 (90%)	6/6
S. pyogenes	3/3	5/5
All Pathogens Combined	91/109 (83%)	97/100 (97%)
a Of the *H. influenzae* isolated pre-treatment, 3% were resistant to BIAXIN and 10% were resistant to the control agent.		

14.3 *H. pylori* Eradication to Decrease the Risk of Duodenal Ulcer Recurrence

BIAXIN + Lansoprazole and Amoxicillin

Two U.S. randomized, double-blind clinical trials (trial 6 and trial 7) in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an active ulcer within one year) evaluated the efficacy of BIAXIN 500 mg twice daily in combination with lansoprazole 30 mg twice daily and amoxicillin 1 gm twice daily as 14-day triple therapy for eradication of *H. pylori*.

H. pylori eradication was defined as two negative tests (culture and histology) at 4 weeks to 6 weeks following the end of treatment.

The combination of BIAXIN plus lansoprazole and amoxicillin as triple therapy was effective in eradication of *H. pylori* (see results in Table 18). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical trial (trial 8) performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) compared the efficacy of BIAXIN in combination with lansoprazole and amoxicillin as triple therapy for 10 days and 14 days. This trial established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *H. pylori* (see results in Table 18).

Table 18. *H. pylori* Eradication Rates-Triple Therapy (BIAXIN/lansoprazole/amoxicillin) Percent of Patients Cured [95% Confidence Interval] (number of patients)

Trial	Duration	Triple Therapy Evaluable Analysis[a]	Triple Therapy Intent-to-Treat Analysis[b]

Trial 6	14 days	92[c] [80-97.7] (n = 48)	86[c] [73.3-93.5] (n = 55)
Trial 7	14 days	86[d] [75.7-93.6] (n = 66)	83[d] [72-90.8] (n = 70)
Trial 8[e]	14 days	85 [77-91] (N = 113)	82 [73.9-88.1] (N = 126)
	10 days	84 [76-89.8] (N = 123)	81 [73.9-87.6] (N = 135)

a Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest (Delta West LTD., Bentley, Australia), histology, and/or culture. Patients were included in the analysis if they completed the trial. Additionally, if patients were dropped out of the trial due to an adverse reaction related to the drug, they were included in the analysis as evaluable failures of therapy.
b Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.
c ($p < 0.05$) versus BIAXIN/lansoprazole and lansoprazole/amoxicillin dual therapy.
d ($p < 0.05$) versus BIAXIN/amoxicillin dual therapy.
e The 95% confidence interval for the difference in eradication rates, 10-day minus 14-day, is (-10.5, 8.1) in the evaluable analysis and (-9.7, 9.1) in the intent-to-treat analysis.

BIAXIN + Omeprazole and Amoxicillin Therapy

Three U.S., randomized, double-blind clinical trials in patients with *H. pylori* infection and duodenal ulcer disease (n = 558) compared BIAXIN plus omeprazole and amoxicillin to BIAXIN plus amoxicillin. Two trials (trials 9 and 10) were conducted in patients with an active duodenal ulcer, and the third trial (trial 11) was conducted in patients with a duodenal ulcer in the past 5 years, but without an ulcer present at the time of enrollment. The dosage regimen in the trials was BIAXIN 500 mg twice a day plus omeprazole 20 mg twice a day plus amoxicillin 1 gram twice a day for 10 days. In trials 9 and 10, patients who took the omeprazole regimen also received an additional 18 days of omeprazole 20 mg once a day. Endpoints studied were eradication of *H. pylori* and duodenal ulcer healing (trials 9 and 10 only). *H. pylori* status was determined by CLOtest®, histology, and culture in all three trials. For a given patient, *H. pylori* was considered eradicated if at least two of these tests were negative, and none was positive. The combination of BIAXIN plus omeprazole and amoxicillin was effective in eradicating *H. pylori* (see results in Table 19).

Table 19. *H. pylori* Eradication Rates: % of Patients Cured [95% Confidence Interval]

	BIAXIN + omeprazole + amoxicillin		**BIAXIN + amoxicillin**	
	Per-Protocol[a]	**Intent-to-Treat[b]**	**Per-Protocol[a]**	**Intent-to-Treat[b]**
Trial 9	[c]77 [64, 86] (n = 64)	69 [57, 79] (n = 80)	43 [31, 56] (n = 67)	37 [27, 48] (n = 84)
Trial 10	[c]78 [67, 88] (n = 65)	73 [61, 82] (n = 77)	41 [29, 54] (n = 68)	36 [26, 47] (n = 84)

Trial 11	[c]90 [80, 96] (n = 69)	83 [74, 91] (n = 84)	33 [24, 44] (n = 93)	32 [23, 42] (n = 99)

a Patients were included in the analysis if they had confirmed duodenal ulcer disease (active ulcer trials 9 and 10; history of ulcer within 5 years, trial 11) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology, and/or culture. Patients were included in the analysis if they completed the trial. Additionally, if patients dropped out of the trial due to an adverse reaction related to the study drug, they were included in the analysis as failures of therapy. The impact of eradication on ulcer recurrence has not been assessed in patients with a past history of ulcer.
b Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodenal ulcer disease. All dropouts were included as failures of therapy.
c $p < 0.05$ versus BIAXIN plus amoxicillin.

BIAXIN + Omeprazole Therapy

Four randomized, double-blind, multi-center trials (trials 12, 13, 14, and 15) evaluated BIAXIN 500 mg three times a day plus omeprazole 40 mg once a day for 14 days, followed by omeprazole 20 mg once a day (trials 12, 13, and 15) or by omeprazole 40 mg once a day (trial 14) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Trials 12 and 13 were conducted in the U.S. and Canada and enrolled 242 and 256 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 219 patients in trial 12 and 228 patients in trial 13. These trials compared the combination regimen to omeprazole and BIAXIN monotherapies. Trials 14 and 15were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in trial 14 and 208 patients in trial 15. These trials compared the combination regimen to omeprazole monotherapy. The results for the efficacy analyses for these trials are described in Tables 20, 21, and 22.

Duodenal Ulcer Healing

The combination of BIAXIN and omeprazole was as effective as omeprazole alone for healing duodenal ulcer (see Table 20).

Table 20. End-of-Treatment Ulcer Healing Rates Percent of Patients Healed (n/N)

Trial	**BIAXIN + Omeprazole**	**Omeprazole**	**BIAXIN**
U.S. Trials			
Trial 13	94% (58/62)[a]	88% (60/68)	71% (49/69)
Trial 12	88% (56/64)[a]	85% (55/65)	64% (44/69)
Non-U.S. Trials			
Trial 15	99% (84/85)	95% (82/86)	N/A
Trial 14[b]	100% (64/64)	99% (71/72)	N/A

a $p < 0.05$ for BIAXIN + omeprazole versus BIAXIN monotherapy.
b In trial 14 patients received omeprazole 40 mg daily for days 15 to 28.

Eradication of H. pylori Associated with Duodenal Ulcer

The combination of BIAXIN and omeprazole was effective in eradicating *H. pylori* (see Table 21). *H. pylori* eradication was defined as no positive test (culture or histology) at 4 weeks following the end of treatment, and two negative tests were required to be considered eradicated. In the per-protocol analysis, the following patients were excluded: dropouts, patients with major protocol violations, patients with missing *H. pylori* tests post-treatment, and patients that were not assessed for *H. pylori* eradication at 4 weeks after the end of treatment because they were found to have an unhealed ulcer at the end of treatment.

Table 21. *H. pylori* Eradication Rates (Per-Protocol Analysis) at 4 to 6 weeks Percent of Patients Cured (n/N)

Trial	BIAXIN + Omeprazole	Omeprazole	BIAXIN
U.S. Trials			
Trial 13	64% (39/61)[a,b]	0% (0/59)	39% (17/44)
Trial 12	74% (39/53)[a,b]	0% (0/54)	31% (13/42)
Non-U.S. Trials			
Trial 15	74% (64/86)[b]	1% (1/90)	N/A
Trial 14	83% (50/60)[b]	1% (1/74)	N/A
a Statistically significantly higher than BIAXIN monotherapy ($p < 0.05$). b Statistically significantly higher than omeprazole monotherapy ($p < 0.05$).			

Duodenal Ulcer Recurrence

Ulcer recurrence at 6-months and at 12 months following the end of treatment was assessed for patients in whom ulcers were healed post-treatment (see the results in Table 22). Thus, in patients with duodenal ulcer associated with *H. pylori* infection, eradication of *H. pylori* reduced ulcer recurrence.

Table 22. Duodenal Ulcer Recurrence at 6 months and 12 months in Patients with Healed Ulcers

	***H. pylori* Negative at 4-6 Weeks**	***H. pylori* Positive at 4-6 Weeks**
U.S. Trials Recurrence at 6 Months		
Trial 100		
BIAXIN + Omeprazole	6% (2/34)	56% (9/16)
Omeprazole	(0/0)	71% (35/49)
BIAXIN	12% (2/17)	32% (7/22)
Trial 067		
BIAXIN + Omeprazole	38% (11/29)	50% (6/12)
Omeprazole	(0/0)	67% (31/46)

BIAXIN	18% (2/11)	52% (14/27)
Non-U.S. Trials Recurrence at 6 Months		
Trial 058		
BIAXIN + Omeprazole	6% (3/53)	24% (4/17)
Omeprazole	0% (0/3)	55% (39/71)
Trial 812b		
BIAXIN + Omeprazole	5% (2/42)	0% (0/7)
Omeprazole	0% (0/1)	54% (32/59)
Non-U.S. Trials Recurrence at 12-Months in Trial 14		
BIAXIN + Omeprazole	3% (1/40)	0% (0/6)
Omeprazole	0% (0/1)	67% (29/43)

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16 HOW SUPPLIED/STORAGE AND HANDLING

BIAXIN Filmtab (clarithromycin tablets, USP) is supplied as yellow oval film-coated tablets in the following packaging sizes:

250 mg tablets: (imprinted in blue with the “a” logo and KT)

Bottles of 60 (**NDC** 0074-3368-60) and unit dose strip packages of 100 (**NDC** 0074-3368-11).

Store BIAXIN Filmtab 250 mg at controlled room temperature 15° to 30°C (59° to 86°F) in a well-closed container. Protect from light.

500 mg tablets: (debossed with the “a” logo on one side and KL on the opposite side)

Bottles of 60 (**NDC** 0074-2586-60) and unit dose strip packages of 100 (**NDC** 0074-2586-11).

Store BIAXIN Filmtab 500 mg at controlled room temperature 20° to 25°C (68° to 77°F) in a well-closed container.

BIAXIN XL Filmtab (clarithromycin extended-release tablets) is supplied as yellow oval film-coated tablets in the following packaging sizes:

500 mg tablets: (debossed with the “a” logo and KJ)

Bottles of 60 (**NDC** 0074-3165-60), unit dose strip packages of 100 (**NDC** 0074-3165-11), and BIAXIN XL PAC carton of 4 blister packages 14 tablets each (**NDC** 0074-3165-41).

Store BIAXIN XL Filmtab at 20° to 25°C (68° to 77°F). Excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

BIAXIN Granules (clarithromycin for oral suspension, USP) is supplied as white to off-white granules in the following strengths and sizes:

Total Volume After Constitution	Clarithromycin Concentration After Constitution	Clarithromycin Contents Per Bottle	NDC
50 mL	125 mg/5 mL	1250 mg	0074-3163-50
100 mL	125 mg/5 mL	2500 mg	0074-3163-13
50 mL	250 mg/5 mL	2500 mg	0074-3188-50
100 mL	250 mg/5 mL	5000 mg	0074-3188-13

Store BIAXIN Granules below 25°C (77°F) in a well-closed container. Do not refrigerate the reconstituted BIAXIN granules.

17 PATIENT COUNSELING INFORMATION

Provide the following instructions or information about BIAXIN to patients:

- Counsel patients that antibacterial drugs including BIAXIN (clarithromycin) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When BIAXIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be

taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by BIAXIN or other antibacterial drugs in the future.

- Advise patients that diarrhea is a common problem caused by antibacterials including BIAXIN (clarithromycin) which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial. If this occurs, instruct patients to contact their healthcare provider as soon as possible.
- Advise patients that BIAXIN (clarithromycin) may interact with some drugs; therefore, advise patients to report to their healthcare provider the use of any other medications.
- Advise patients that BIAXIN (clarithromycin) Filmtab and oral suspension can be taken with or without food and can be taken with milk; however, BIAXIN XL Filmtab (clarithromycin extended-release tablets) should be taken with food. Do not refrigerate the suspension.
- There are no data on the effect of BIAXIN (clarithromycin) on the ability to drive or use machines. However, counsel patients regarding the potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication. The potential for these adverse reactions should be taken into account before patients drive or use machines.
- Advise patients that if pregnancy occurs while taking this drug, there is a potential hazard to the fetus *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)]*.
- Advise patients who have coronary artery disease to continue medications and lifestyle modifications for their coronary artery disease because BIAXIN may be associated with increased risk for mortality years after the end of BIAXIN treatment.

Filmtab®—Film-sealed tablets is a registered trademark of AbbVie Inc.

BIAXIN Filmtab 250 mg and 500 mg and BIAXIN XL Filmtab 500 mg

Mfd. by AbbVie LTD, Barceloneta, PR 00617

BIAXIN Granules, 125 mg/5 mL and 250 mg/5 mL

Mfd. by AbbVie Inc., North Chicago, IL 60064

For AbbVie Inc., North Chicago, IL 60064, U.S.A.

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