

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 065488s002

Name: Azithromycin for Oral Suspension USP, 100 mg/5 mL
and 200 mg/5 mL

Sponsor: Lupin LTD

Approval Date: August 24, 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065488s002

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APPLICATION NUMBER:
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APPROVAL LETTER



ANDA 065488/S-002 and S-003

**CHANGES BEING EFFECTED/
PRIOR APPROVAL SUPPLEMENT
APPROVAL**

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
111 South Calvert Street
Harborplace Tower, 24th Floor
Baltimore, MD 21202
Attention: Sudhir Kaushal
Director, Regulatory Affairs

Dear Sir:

This is in reference to your supplemental abbreviated new drug applications (sANDAs) dated and received July 25, 2016 (S-002) and March 16, 2017 (S-003), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C), regarding your abbreviated new drug application (ANDA) for Azithromycin for Oral Suspension USP, 300 mg (100 mg/5 mL) and 1200 mg (200 mg/5 mL) Bottles.

Reference is also made to any amendments submitted prior to the issuance of this letter.

These supplemental ANDAs, submitted as "Changes Being Effected" and "Prior Approval Supplement," provide for:

S-002 (CBE-0): Revised labeling to be in accordance with the reference listed drug.

S-003 (PAS): The merge of information from tentatively approved ANDA 202793 to approved ANDA 065488.

We have completed our review of these sANDAs, as amended, and they are **approved**.

In addition, we are today changing the therapeutic equivalence (TE) evaluation code for your product in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) from "BX" to "AB."

We remind you that you must comply with the requirements for the approved ANDA described in 21 CFR 314.80-81.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



Priya
Shah

Digitally signed by Priya Shah
Date: 8/24/2017 06:24:18AM
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AZITHROMYCIN FOR ORAL SUSPENSION safely and effectively. See full prescribing information for AZITHROMYCIN FOR ORAL SUSPENSION.

AZITHROMYCIN for oral suspension
Initial U.S. Approval: 1991

RECENT MAJOR CHANGES

Warnings and Precautions, Hypersensitivity (5.1) 2/2016

INDICATIONS AND USAGE

Azithromycin for oral suspension is a macrolide antibacterial drug indicated for mild to moderate infections caused by designated, susceptible bacteria:

- Acute bacterial exacerbations of chronic bronchitis in adults (1.1)
- Acute bacterial sinusitis in adults (1.1)
- Uncomplicated skin and skin structure infections in adults (1.1)
- Urethritis and cervicitis in adults (1.1)
- Genital ulcer disease in men (1.1)
- Acute otitis media in pediatric patients (1.2)
- Community-acquired pneumonia in adults and pediatric patients (1.1, 1.2)
- Pharyngitis/tonsillitis in adults and pediatric patients (1.1, 1.2)

Limitation of Use:

Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors. (1.3)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of azithromycin for oral suspension and other antibacterial drugs, azithromycin for oral suspension should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

DOSAGE AND ADMINISTRATION

• Adult Patients (2.1)

| Infection | Recommended Dose/Duration of Therapy |
|--|--|
| Community-acquired pneumonia (mild severity) Pharyngitis/tonsillitis (second-line therapy) Skin/skin structure (uncomplicated) | 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5. |
| Acute bacterial exacerbations of chronic bronchitis (mild to moderate) | 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5 or 500 mg once daily for 3 days. |
| Acute bacterial sinusitis | 500 mg once daily for 3 days. |
| Genital ulcer disease (chancroid) Non-gonococcal urethritis and cervicitis | One single 1 gram dose. |
| Gonococcal urethritis and cervicitis | One single 2 gram dose. |

• Pediatric Patients (2.2)

| Infection | Recommended Dose/Duration of Therapy |
|--------------------|--|
| Acute otitis media | 30 mg/kg as a single dose or 10 mg/kg once daily for |

| | |
|------------------------------|---|
| | 3 days or 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg/day on Days 2 through 5. |
| Acute bacterial sinusitis | 10 mg/kg once daily for 3 days. |
| Community-acquired pneumonia | 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg once daily on Days 2 through 5. |
| Pharyngitis/tonsillitis | 12 mg/kg once daily for 5 days. |

DOSAGE FORMS AND STRENGTHS

- Azithromycin for oral suspension, 100 mg/5 mL and 200 mg/5 mL (3)

CONTRAINDICATIONS

- Patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug. (4.1)
- Patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin. (4.2)

WARNINGS AND PRECAUTIONS

- Serious (including fatal) allergic and skin reactions: Discontinue azithromycin if reaction occurs. (5.1)
- Hepatotoxicity: Severe, and sometimes fatal, hepatotoxicity has been reported. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur. (5.2)
- Prolongation of QT interval and cases of torsades de pointes have been reported. This risk which can be fatal should be considered in patients with certain cardiovascular disorders including known QT prolongation or history torsades de pointes, those with proarrhythmic conditions, and with other drugs that prolong the QT interval. (5.3)
- *Clostridium difficile*-associated diarrhea: Evaluate patients if diarrhea occurs. (5.4)
- Azithromycin may exacerbate muscle weakness in persons with myasthenia gravis. (5.5)

ADVERSE REACTIONS

Most common adverse reactions are diarrhea (5 to 14%), nausea (3 to 18%), abdominal pain (3 to 7%), or vomiting (2 to 7%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Nelfinavir: Close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted (7.1)
- Warfarin: Use with azithromycin may increase coagulation times; monitor prothrombin time. (7.2)

USE IN SPECIFIC POPULATIONS

- Pediatric use: Safety and effectiveness in the treatment of patients under 6 months of age have not been established. (8.4)
- Geriatric use: Elderly patients may be more susceptible to development of torsades de pointes arrhythmias. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 08/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of azithromycin for oral suspension and other antibacterial drugs, azithromycin for oral suspension should be used only to treat 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.

Azithromycin for oral suspension is a macrolide antibacterial drug indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Recommended dosages and durations of therapy in adult and pediatric patient populations vary in these indications. [see *DOSAGE AND ADMINISTRATION* (2)]

1.1 Adult Patients

- Acute bacterial exacerbations of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.
- Acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.
- Community-acquired pneumonia due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy.
- Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.
- Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*.
- Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.
- Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

1.2 Pediatric Patients

[see *USE IN SPECIFIC POPULATIONS* (8.4) and *CLINICAL STUDIES* (14.2)]

- Acute otitis media (**>6 months of age**) caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*
- Community-acquired pneumonia (**>6 months of age**) due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy.
- Pharyngitis/tonsillitis (**>2 years of age**) caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

1.3 Limitations of Use

Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

- patients with cystic fibrosis,
- patients with nosocomial infections,
- patients with known or suspected bacteremia,
- patients requiring hospitalization,
- elderly or debilitated patients, or
- patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

[see INDICATIONS AND USAGE (1.1) and CLINICAL PHARMACOLOGY (12.3)]

| Infection* | Recommended Dose/Duration of Therapy |
|--|---|
| Community-acquired pneumonia Pharyngitis/tonsillitis (second-line therapy) Skin/skin structure (uncomplicated) | 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5 |
| Acute bacterial exacerbations of chronic obstructive pulmonary disease | 500 mg once daily for 3 days OR 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5 |
| Acute bacterial sinusitis | 500 mg-once daily for 3 days |
| Genital ulcer disease (chancroid) | One single 1 gram dose |
| Non-gonococcal urethritis and cervicitis | One single 1 gram dose |
| Gonococcal urethritis and cervicitis | One single 2 gram dose |
| *DUE TO THE INDICATED ORGANISMS [see INDICATIONS AND USAGE (1.1)] | |

Azithromycin tablets can be taken with or without food.

2.2 Pediatric Patients¹

| Infection* | Recommended Dose/Duration of Therapy |
|--|--|
| Acute otitis media | 30 mg/kg as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg/day on Days 2 through 5. |
| Acute bacterial sinusitis | 10 mg/kg once daily for 3 days. |
| Community-acquired pneumonia | 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg once daily on Days 2 through 5. |
| Pharyngitis/tonsillitis | 12 mg/kg once daily for 5 days. |
| *DUE TO THE INDICATED ORGANISMS [see INDICATIONS AND USAGE (1.2)] | |
| ¹ see dosing tables below for maximum doses evaluated by indication | |

Azithromycin for oral suspension can be taken with or without food.

PEDIATRIC DOSAGE GUIDELINES FOR OTITIS MEDIA, ACUTE BACTERIAL SINUSITIS, AND COMMUNITY-ACQUIRED PNEUMONIA
(Age 6 months and above, [see *USE IN SPECIFIC POPULATIONS (8.4)*])

Based on Body Weight

| OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA: (5-Day Regimen)* | | | | | | | |
|---|---------------|--------------------|---------------------|----------------------|----------------------|--------------------------------------|--------------------------------------|
| Dosing Calculated on 10 mg/kg/day Day 1 and 5 mg/kg/day Days 2 to 5. | | | | | | | |
| Weight | | 100 mg/5 mL | | 200 mg/5 mL | | Total mL per Treatment Course | Total mg per Treatment Course |
| Kg | Lbs. | Day 1 | Days 2 to 5 | Day 1 | Days 2 to 5 | | |
| 5 | 11 | 2.5 mL; (½ tsp) | 1.25 mL; (¼ tsp) | | | 7.5 mL | 150 mg |
| 10 | 22 | 5 mL; (1tsp) | 2.5 mL; (½ tsp) | | | 15 mL | 300 mg |
| 20 | 44 | | | 5 mL; (1 tsp) | 2.5 mL; (½ tsp) | 15 mL | 600 mg |
| 30 | 66 | | | 7.5 mL; (1½ tsp) | 3.75 mL; (¾ tsp) | 22.5 mL | 900 mg |
| 40 | 88 | | | 10 mL; (2 tsp) | 5 mL; (1 tsp) | 30 mL | 1200 mg |
| 50 and above | 110 and above | | | 12.5 mL; (2½ tsp) | 6.25 mL; (1¼ tsp) | 37.5 mL | 1500 mg |

* Effectiveness of the 3-day or 1-day regimen in pediatric patients with community-acquired pneumonia has not been established.

| OTITIS MEDIA AND ACUTE BACTERIAL SINUSITIS: (3-Day Regimen)* | | | | | |
|---|---------------|--------------------|--------------------|--------------------------------------|--------------------------------------|
| Dosing Calculated on 10 mg/kg/day. | | | | | |
| Weight | | 100 mg/5 mL | 200 mg/5 mL | Total mL per Treatment Course | Total mg per Treatment Course |
| Kg | Lbs. | Days 1 to 3 | Days 1 to 3 | | |
| 5 | 11 | 2.5 mL; (1/2 tsp) | | 7.5 mL | 150 mg |
| 10 | 22 | 5 mL; (1 tsp) | | 15 mL | 300 mg |
| 20 | 44 | | 5 mL (1 tsp) | 15 mL | 600 mg |
| 30 | 66 | | 7.5 mL (1½ tsp) | 22.5 mL | 900 mg |
| 40 | 88 | | 10 mL (2 tsp) | 30 mL | 1200 mg |
| 50 and above | 110 and above | | 12.5 mL (2 ½ tsp) | 37.5 mL | 1500 mg |

*Effectiveness of the 5-day or 1-day regimen in pediatric patients with acute bacterial sinusitis has not been established.

| OTITIS MEDIA: (1-Day Regimen) | | | | |
|--|---------------|----------------------|--------------------------------------|--------------------------------------|
| Dosing Calculated on 30 mg/kg as a single dose. | | | | |
| Weight | | 200 mg/5 mL | Total mL per Treatment Course | Total mg per Treatment Course |
| Kg | Lbs. | 1-Day Regimen | | |
| 5 | 11 | 3.75 mL;(3/4 tsp) | 3.75 mL | 150 mg |
| 10 | 22 | 7.5 mL;(1½ tsp) | 7.5 mL | 300 mg |
| 20 | 44 | 15 mL;(3 tsp) | 15 mL | 600 mg |
| 30 | 66 | 22.5 mL;(4½ tsp) | 22.5 mL | 900 mg |
| 40 | 88 | 30 mL;(6 tsp) | 30 mL | 1200 mg |
| 50 and above | 110 and above | 37.5 mL;(7½ tsp) | 37.5 mL | 1500 mg |

The safety of re-dosing azithromycin in pediatric patients who vomit after receiving 30 mg/kg as a single dose has not been established. In clinical studies involving 487 patients with acute otitis media given a single 30 mg/kg dose of azithromycin, 8 patients who vomited within 30 minutes of dosing were re-dosed at the same total dose.

Pharyngitis/Tonsillitis:

The recommended dose of azithromycin for children with pharyngitis/tonsillitis is 12 mg/kg once daily for 5 days. (See chart below.)

PEDIATRIC DOSAGE GUIDELINES FOR PHARYNGITIS/TONSILLITIS (Age 2 years and above, [see USE IN SPECIFIC POPULATIONS (8.4)])

Based on Body Weight

| PHARYNGITIS/TONSILLITIS: (5-Day Regimen) | | | | |
|---|------|-------------------|-------------------------------|-------------------------------|
| Dosing Calculated on 12 mg/kg/day for 5 days. | | | | |
| Weight | | 200 mg/5 mL | Total mL per Treatment Course | Total mg per Treatment Course |
| Kg | Lbs. | Day 1 to 5 | | |
| 8 | 18 | 2.5 mL; (½ tsp) | 12.5 mL | 500 mg |
| 17 | 37 | 5 mL; (1 tsp) | 25 mL | 1000 mg |
| 25 | 55 | 7.5 mL; (1½ tsp) | 37.5 mL | 1500 mg |
| 33 | 73 | 10 mL; (2 tsp) | 50 mL | 2000 mg |
| 40 | 88 | 12.5 mL; (2½ tsp) | 62.5 mL | 2500 mg |

Constituting instructions for azithromycin oral suspension 300, 600, 900, 1200 mg bottles. The table below indicates the volume of water to be used for constitution:

| Amount of water to be added | Total volume after constitution (azithromycin content) | Azithromycin concentration after constitution |
|-----------------------------|--|---|
| 9 mL (300 mg) | 15 mL (300 mg) | 100 mg/5 mL |
| 9 mL (600 mg) | 15 mL (600 mg) | 200 mg/5 mL |
| 12 mL (900 mg) | 22.5 mL (900 mg) | 200 mg/5 mL |
| 15 mL (1200 mg) | 30 mL (1200 mg) | 200 mg/5 mL |

Shake well before each use. Oversized bottle provides shake space. Keep tightly closed.

After mixing, store suspension at 5° to 30°C (41° to 86°F) and use within 10 days. Discard after full dosing is completed.

3 DOSAGE FORMS AND STRENGTHS

Azithromycin for oral suspension after constitution contains a flavored suspension.

Azithromycin for oral suspension is supplied to provide 100 mg/5 mL or 200 mg/5 mL suspension in bottles.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.

4.2 Hepatic Dysfunction

Azithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic

dysfunction associated with prior use of azithromycin.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy. [see *CONTRAINDICATIONS (4.1)*]

Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is presently unknown.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.

5.2 Hepatotoxicity

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

5.3 QT Prolongation

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- patients on drugs known to prolong the QT interval
- 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.

5.4 *Clostridium difficile*-Associated Diarrhea (CDAD)

Clostridium difficile-associated diarrhea has been reported with use of nearly all antibacterial agents, including azithromycin, 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 antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic 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 antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.5 Exacerbation of Myasthenia Gravis

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

5.6 Use in Sexually Transmitted Infections

Azithromycin, at the recommended dose, should not be relied upon to treat syphilis. Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate testing for gonorrhea performed at the time of diagnosis. Appropriate antibacterial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

5.7 Development of Drug-Resistant Bacteria

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious adverse reactions of angioedema and cholestatic jaundice were reported. Approximately 0.7% of the patients (adults and pediatric patients) from the 5-day multiple-dose clinical trials discontinued azithromycin therapy because of treatment-related adverse reactions. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related adverse reactions was 0.6%. In clinical trials in pediatric patients given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related adverse reactions was approximately 1%. Most of the adverse reactions leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. [see *CLINICAL STUDIES (14.2)*]

Adults

Multiple-dose regimens: Overall, the most common treatment-related adverse reactions in adult patients receiving multiple-dose regimens of azithromycin were related to the gastrointestinal system with diarrhea/loose stools (4 to 5%), nausea (3%), and abdominal pain (2 to 3%) being the most frequently reported.

No other adverse reactions occurred in patients on the multiple-dose regimens of azithromycin with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:

Cardiovascular:

Palpitations, chest pain.

Gastrointestinal:

Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.

Genitourinary:

Monilia, vaginitis, and nephritis.

Nervous System:

Dizziness, headache, vertigo, and somnolence.

General:

Fatigue.

Allergic:

Rash, pruritus, photosensitivity, and angioedema.

Single 1-gram dose regimen:

Overall, the most common adverse reactions in patients receiving a single-dose regimen of 1 gram of azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Adverse reactions that occurred in patients on the single 1-gram dosing regimen of azithromycin with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Single 2-gram dose regimen:

Overall, the most common adverse reactions in patients receiving a single 2-gram dose of azithromycin were related to the gastrointestinal system. Adverse reactions that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%). The majority of these complaints were mild in nature.

Pediatric Patients

Single and Multiple-dose regimens: The types of adverse reactions in pediatric patients were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in pediatric patients.

Acute Otitis Media:

For the recommended total dosage regimen of 30 mg/kg, the most frequent adverse reactions ($\geq 1\%$) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea, and rash. [see *DOSAGE AND ADMINISTRATION (2)* and *CLINICAL STUDIES (14.2)*]

The incidence, based on dosing regimen, is described in the table below:

| Dosage Regimen | Diarrhea % | Abdominal Pain % | Vomiting % | Nausea % | Rash % |
|----------------|------------|------------------|------------|----------|--------|
| 1-day | 4.3% | 1.4% | 4.9% | 1.0% | 1.0% |
| 3-day | 2.6% | 1.7% | 2.3% | 0.4% | 0.6% |
| 5-day | 1.8% | 1.2% | 1.1% | 0.5% | 0.4% |

Community-Acquired Pneumonia:

For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2 to 5, the most frequent adverse reactions attributed to treatment were diarrhea/loose stools, abdominal pain, vomiting, nausea, and rash.

The incidence is described in the table below:

| Dosage Regimen | Diarrhea/Loose stools % | Abdominal Pain % | Vomiting % | Nausea % | Rash % |
|----------------|-------------------------|------------------|------------|----------|--------|
| 5-day | 5.8% | 1.9% | 1.9% | 1.9% | 1.6% |

Pharyngitis/Tonsillitis:

For the recommended dosage regimen of 12 mg/kg on Days 1 to 5, the most frequent adverse reactions attributed to treatment were diarrhea, vomiting, abdominal pain, nausea, and headache.

The incidence is described in the table below:

| Dosage Regimen | Diarrhea % | Abdominal Pain % | Vomiting % | Nausea % | Rash % | Headache % |
|----------------|------------|------------------|------------|----------|--------|------------|
| 5-day | 5.4% | 3.4% | 5.6% | 1.8% | 0.7% | 1.1% |

With any of the treatment regimens, no other adverse reactions occurred in pediatric patients treated with azithromycin with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:

Cardiovascular:

Chest pain.

Gastrointestinal:

Dyspepsia, constipation, anorexia, enteritis, flatulence, gastritis, jaundice, loose stools, and oral moniliasis.

Hematologic and Lymphatic:

Anemia and leukopenia.

Nervous System:

Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, and insomnia.

General:

Fever, face edema, fatigue, fungal infection, malaise, and pain.

Allergic:

Rash and allergic reaction.

Respiratory:

Cough, pharyngitis, pleural effusion, and rhinitis.

Skin and Appendages:

Eczema, fungal dermatitis, pruritus, sweating, urticaria, and vesiculobullous rash.

Special Senses:

Conjunctivitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of azithromycin. 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.

Adverse reactions reported with azithromycin during the postmarketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic:

Arthralgia, edema, urticaria, and angioedema.

Cardiovascular:

Arrhythmias including ventricular tachycardia and hypotension. There have been reports of QT prolongation and *torsades de pointes*.

Gastrointestinal:

Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration.

General:

Asthenia, paresthesia, fatigue, malaise, and anaphylaxis.

Genitourinary:

Interstitial nephritis and acute renal failure and vaginitis.

Hematopoietic:

Thrombocytopenia.

Liver/Biliary:

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure. [*see WARNINGS AND PRECAUTIONS (5.2)*]

Nervous System:

Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation, and syncope.

Psychiatric:

Aggressive reaction and anxiety.

Skin/Appendages:

Pruritus serious skin reactions including erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and DRESS.

Special Senses:

Hearing disturbances including hearing loss, deafness and/or tinnitus, and reports of taste/smell perversion and/or loss.

6.3 Laboratory Abnormalities

Adults

Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, neutrophils, and blood glucose; elevated serum creatine phosphokinase, potassium, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils, and eosinophils; with an incidence of less than 1%: leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH, and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline. When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 5000 patients, four patients discontinued therapy because of treatment-related liver enzyme abnormalities and one because of a renal function abnormality.

Pediatric Patients

One, Three, and Five Day Regimens

Laboratory data collected from comparative clinical trials employing two 3-day regimens (30 mg/kg or 60 mg/kg in divided doses over 3 days), or two 5-day regimens (30 mg/kg or 60 mg/kg in divided doses over 5 days) were similar for regimens of azithromycin and all comparators combined, with most clinically significant laboratory abnormalities occurring at incidences of 1 to 5%. Laboratory data for patients receiving 30 mg/kg as a single dose were collected in one single center trial. In that trial, an absolute neutrophil count between 500 to 1500 cells/mm³ was observed in 10/64 patients receiving 30 mg/kg as a single dose, 9/62 patients receiving 30 mg/kg given over 3 days, and 8/63 comparator patients. No patient had an absolute neutrophil count <500 cells/mm³.

In multiple-dose clinical trials involving approximately 4700 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

7 DRUG INTERACTIONS

7.1 Nelfinavir

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. [see *ADVERSE REACTIONS (6)*]

7.2 Warfarin

Spontaneous postmarketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

7.3 Potential Drug-Drug Interactions with Macrolides

Interactions with digoxin or phenytoin have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin or phenytoin are used concomitantly with azithromycin careful monitoring of patients is advised.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These daily doses in rats and mice, based on body surface area, are estimated to be 4 and 2 times, respectively, an adult daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Azithromycin has been reported to be excreted in human breast milk in small amounts. Caution should be exercised when azithromycin is administered to a nursing woman.

8.4 Pediatric Use

[see *CLINICAL PHARMACOLOGY (12.3)*, *INDICATIONS AND USAGE (1.2)*, and *DOSAGE AND ADMINISTRATION (2.2)*]

Safety and effectiveness in the treatment of pediatric patients with acute otitis media, acute bacterial sinusitis and community-acquired pneumonia under 6 months of age have not been established. Use of azithromycin for the treatment of acute bacterial sinusitis and community-acquired pneumonia in pediatric patients (6 months of age or greater) is supported by adequate and well-controlled trials in adults

Pharyngitis/Tonsillitis

Safety and effectiveness in the treatment of pediatric patients with pharyngitis/tonsillitis under 2 years of age have not been established.

8.5 Geriatric Use

In multiple-dose clinical trials of oral azithromycin, 9% of patients were at least 65 years of age (458/4949) and 3% of patients (144/4949) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

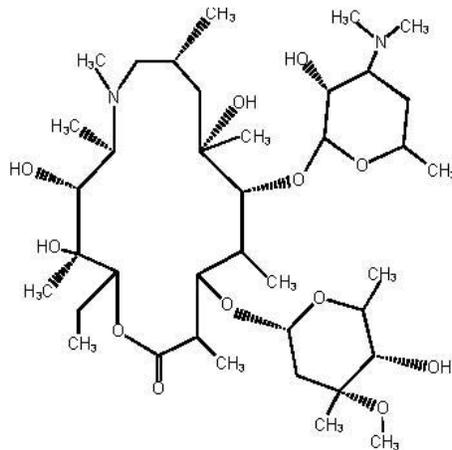
Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients. [see *WARNINGS AND PRECAUTIONS (5.3)*]

10 OVERDOSAGE

Adverse reactions experienced at higher than recommended doses were similar to those seen at normal doses particularly nausea, diarrhea, and vomiting. In the event of overdose, general symptomatic and supportive measures are indicated as required.

11 DESCRIPTION

Azithromycin for oral suspension USP contain the active ingredient azithromycin, a macrolide antibacterial drug, for oral administration. Azithromycin has the chemical name (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)13-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)- β -D-xylohexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00. Azithromycin has the following structural formula:



Azithromycin, as the monohydrate, is a white to almost white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12} \cdot H_2O$ and a molecular weight of 767.00.

Azithromycin for oral suspension USP is an off white to pinkish powder before constitution. The suspension after constitution contains a cherry flavored suspension that is red in color and is supplied in bottles containing azithromycin monohydrate powder equivalent to 300 mg, 600 mg, 900 mg, or 1200 mg azithromycin per bottle and the following inactive ingredients: hydroxy propyl cellulose; liquid banana flavor; liquid cherry flavor; spectracol FD&C Red #40; sucrose; talc; tribasic sodium phosphate dodecahydrate and xanthan gum. After constitution, each 5 mL of suspension contains 100 mg or 200 mg of azithromycin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Azithromycin is a macrolide antibacterial drug. [see Microbiology (12.4)]

12.2 Pharmacodynamics

Based on animal models of infection, the antibacterial activity of azithromycin appears to correlate with the ratio of area under the concentration-time curve to minimum inhibitory

concentration (AUC/MIC) for certain pathogens (*S. pneumoniae* and *S. aureus*). The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with azithromycin.

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with oral azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

12.3 Pharmacokinetics

Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were $AUC_{0-72}=4.3$ (1.2) mcg·hr/mL; $C_{max}=0.5$ (0.2) mcg/mL; $T_{max}=2.2$ (0.9) hours. Two azithromycin 250 mg tablets are bioequivalent to a single 500 mg tablet.

In a two-way crossover study, 12 adult healthy volunteers (6 males, 6 females) received 1500 mg of azithromycin administered in single daily doses over either 5 days (two 250 mg tablets on day 1, followed by one 250 mg tablet on days 2 to 5) or 3 days (500 mg per day for days 1 to 3). Due to limited serum samples on day 2 (3-day regimen) and days 2 to 4 (5-day regimen), the serum concentration-time profile of each subject was fit to a 3-compartment model and the $AUC_{0-\infty}$ for the fitted concentration profile was comparable between the 5-day and 3-day regimens.

| Pharmacokinetic Parameter [mean (SD)] | 3-Day Regimen | | 5-Day Regimen | |
|--|---------------|-------------|---------------|-------------|
| | Day 1 | Day 3 | Day 1 | Day 5 |
| C_{max} (serum, mcg/mL) | 0.44 (0.22) | 0.54 (0.25) | 0.43 (0.20) | 0.24 (0.06) |
| Serum $AUC_{0-\infty}$ (mcg·hr/mL) | 17.4 (6.2)* | | 14.9 (3.1)* | |
| Serum $T_{1/2}$ | 71.8 hr | | 68.9 hr | |

*Total AUC for the entire 3-day and 5-day regimens.

Absorption

The absolute bioavailability of azithromycin 250 mg capsules is 38%.

In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high fat meal, food was shown to increase C_{max} by 23% but had no effect on AUC.

When azithromycin oral suspension was administered with food to 28 adult healthy male subjects, C_{max} increased by 56% and AUC was unchanged.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL.

The antibacterial activity of azithromycin is pH related and appears to be reduced with decreasing pH, However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Azithromycin has been shown to penetrate into human tissues, including skin, lung, tonsil, and cervix. Extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, very low concentrations were noted in cerebrospinal fluid (less than 0.01 mcg/mL) in the presence of noninflamed meninges.

Metabolism

In vitro and *in vivo* studies to assess the metabolism of azithromycin have not been performed.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and IV doses declined in a polyphasic pattern resulting in a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Specific Populations

Renal Insufficiency:

Azithromycin pharmacokinetics was investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1.0 g dose of azithromycin (4 x 250 mg capsules), mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively, in subjects with mild to moderate renal impairment (GFR 10 to 80 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). The mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively, in subjects with severe renal impairment (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min).

Hepatic Insufficiency:

The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.

Gender:

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

Geriatric Patients:

Pharmacokinetic parameters in older volunteers (65 to 85 years old) were similar to those in young adults (18 to 40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen. [see Geriatric Use (8.5)]

Pediatric Patients:

In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5 in two groups of pediatric patients (aged 1 to 5 years and 5 to 15 years, respectively). The mean pharmacokinetic parameters on day 5 were C_{max} =0.216 mcg/mL, T_{max} =1.9 hr, and AUC_{0-24} =1.822 mcg·hr/mL for the 1 to 5-year-old group and were C_{max} =0.383 mcg/mL, T_{max} =2.4 hr, and AUC_{0-24} =3.109 mcg·hr/mL for the 5 to 15-year-old group.

In another study, 33 pediatric patients received doses of 12 mg/kg/day (maximum daily dose 500 mg) for 5 days, of whom 31 patients were evaluated for azithromycin pharmacokinetics following a low fat breakfast. In this study, azithromycin concentrations were determined over a 24 hr period following the last daily dose. Patients weighing above 41.7 kg received the maximum adult daily dose of 500 mg. Seventeen patients (weighing 41.7 kg or less) received a total dose of 60 mg/kg. The following table shows pharmacokinetic data in the subset of pediatric patients who received a total dose of 60 mg/kg.

| Pharmacokinetic Parameter [mean (SD)] | 5-Day Regimen (12 mg/kg for 5 days) |
|---------------------------------------|-------------------------------------|
| N | 17 |
| C_{max} (mcg/mL) | 0.5 (0.4) |
| T_{max} (hr) | 2.2 (0.8) |
| AUC_{0-24} (mcg·hr/mL) | 3.9 (1.9) |

Single dose pharmacokinetics of azithromycin in pediatric patients given doses of 30 mg/kg have not been studied. [see DOSAGE AND ADMINISTRATION (2)]

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in Table 1 and the effects of other drugs on the pharmacokinetics of azithromycin are shown in Table 2.

Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 1. No dosage adjustment of drugs listed in Table 1 is recommended when co-administered with azithromycin.

Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the C_{max} and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in Table 2. [see DRUG INTERACTIONS (7.3)]

| Table 1. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin | | | | | |
|--|--|---|----|---|---|
| Co-administered Drug | Dose of Co-administered Drug | Dose of Azithromycin | n | Ratio (with/without azithromycin) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00 | |
| | | | | Mean C _{max} | Mean AUC |
| Atorvastatin | 10 mg/day for 8 days | 500 mg/day orally on days 6 to 8 | 12 | 0.83 (0.63 to 1.08) | 1.01 (0.81 to 1.25) |
| Carbamazepine | 200 mg/day for 2 days, then 200 mg twice a day for 18 days | 500 mg/day orally for days 16 to 18 | 7 | 0.97 (0.88 to 1.06) | 0.96 (0.88 to 1.06) |
| Cetirizine | 20 mg/day for 11 days | 500 mg orally on day 7, then 250 mg/day on days 8 to 11 | 14 | 1.03 (0.93 to 1.14) | 1.02 (0.92 to 1.13) |
| Didanosine | 200 mg orally twice a day for 21 days | 1200 mg/day orally on days 8 to 21 | 6 | 1.44 (0.85 to 2.43) | 1.14 (0.83 to 1.57) |
| Efavirenz | 400 mg/day for 7 days | 600 mg orally on day 7 | 14 | 1.04* | 0.95* |
| Fluconazole | 200 mg orally single dose | 1200 mg orally single dose | 18 | 1.04 (0.98 to 1.11) | 1.01 (0.97 to 1.05) |
| Indinavir | 800 mg three times a day for 5 days | 1200 mg orally on day 5 | 18 | 0.96 (0.86 to 1.08) | 0.90 (0.81 to 1.00) |
| Midazolam | 15 mg orally on day 3 | 500 mg/day orally for 3 days | 12 | 1.27 (0.89 to 1.81) | 1.26 (1.01 to 1.56) |
| Nelfinavir | 750 mg three times a day for 11 days | 1,200 mg orally on day 9 | 14 | 0.90 (0.81 to 1.01) | 0.85 (0.78 to 0.93) |
| Sildenafil | 100 mg on days 1 and 4 | 500 mg/day orally for 3 days | 12 | 1.16 (0.86 to 1.57) | 0.92 (0.75 to 1.12) |
| Theophylline | 4 mg/kg IV on days 1, 11, 25 | 500 mg orally on day 7, 250 mg/day on days 8 to 11 | 10 | 1.19 (1.02 to 1.40) | 1.02 (0.86 to 1.22) |
| Theophylline | 300 mg orally twice a day for 15 days | 500 mg orally on day 6, then 250 mg/day on days 7 to 10 | 8 | 1.09 (0.92 to 1.29) | 1.08 (0.89 to 1.31) |
| Triazolam | 0.125 mg on day 2 | 500 mg orally on day 1, then 250 mg/day on day 2 | 12 | 1.06* | 1.02* |
| Trimethoprim/ Sulfamethoxazole | 160 mg/800 mg/day orally for 7 days | 1200 mg orally on day 7 | 12 | 0.85 (0.75 to 0.97)/ 0.90 (0.78 to 1.03) | 0.87 (0.80 to 0.95)/ 0.96 (0.88 to 1.03) |
| Zidovudine | 500 mg/day orally for 21 days | 600 mg/day orally for 14 days | 5 | 1.12 (0.42 to 3.02) | 0.94 (0.52 to 1.70) |
| Zidovudine | 500 mg/day orally for 21 days | 1200 mg/day orally for 14 days | 4 | 1.31 (0.43 to 3.97) | 1.30 (0.69 to 2.43) |

* -90% Confidence interval not reported

| Table 2. Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs [see DRUG INTERACTIONS (7)] | | | | | |
|--|--------------------------------------|-----------------------------|----|---|------------------------|
| Co-administered Drug | Dose of Co-administered Drug | Dose of Azithromycin | n | Ratio (with/without co-administered drug) of Azithromycin Pharmacokinetic Parameters (90% CI); No Effect = 1.00 | |
| | | | | Mean C _{max} | Mean AUC |
| Efavirenz | 400 mg/day for 7 days | 600 mg orally on day 7 | 14 | 1.22 (1.04 to 1.42) | 0.92* |
| Fluconazole | 200 mg orally single dose | 1,200 mg orally single dose | 18 | 0.82 (0.66 to 1.02) | 1.07 (0.94 to 1.22) |
| Nelfinavir | 750 mg three times a day for 11 days | 1,200 mg orally on day 9 | 14 | 2.36 (1.77 to 3.15) | 2.12 (1.80 to 2.50) |

* -90% Confidence interval not reported

12.4 Microbiology

Mechanism of Action

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and interferes with bacterial protein synthesis. Nucleic acid synthesis is not affected.

Cross Resistance

Azithromycin demonstrates cross resistance with erythromycin resistant Gram positive isolates.

Azithromycin has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical. [see *INDICATIONS AND USAGE (1)*]

Gram-Positive Bacteria

Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Gram-Negative Bacteria

Haemophilus ducreyi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae

Other Bacteria

Chlamydophila pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

The following *in vitro* data are available, but their clinical significance is unknown. Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 4 mcg/ml or less against most ($\geq 90\%$) isolates of the following bacteria; however, the safety and effectiveness of azithromycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

Gram-Positive Bacteria

Beta-hemolytic streptococci (Groups C, F, G)
Viridans group streptococci

Gram-Negative Bacteria

Bordetella pertussis
Legionella pneumophila

Anaerobic Bacteria

Prevotella bivia
Peptostreptococcus species

Other Bacteria

Ureaplasma urealyticum

Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antibacterial drugs used in resident hospitals 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 antibacterial drug product for treatment.

Dilution Techniques

Quantitative methods are used to determine minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized test method ^{1,2,3} (broth or agar). The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antibacterial compounds. The zone size provides an estimate of the susceptibility of bacteria to antibacterial compounds. The zone size should be determined using a standardized method^{2,3}. This procedure uses paper disk impregnated with 15 mcg azithromycin to test the susceptibility of bacteria to azithromycin. The disk diffusion interpretive criteria are provided in Table 3.

| Pathogen | Minimum Inhibitory Concentrations (mcg/mL) | | | Disk Diffusion (zone diameter in mm) | | |
|---|--|---|----|--------------------------------------|----------|-----|
| | S | I | R | S | I | R |
| <i>Haemophilus influenzae</i> ^b | ≤4 | - | - | ≥12 | | |
| <i>Staphylococcus aureus</i> | ≤2 | 4 | ≥8 | ≥18 | 14 to 17 | ≤13 |
| Streptococci including <i>S. pneumoniae</i> | ≤0.5 | 1 | ≥2 | ≥18 | 14 to 17 | ≤13 |

^a Clarithromycin is used for susceptibility testing due to its better solubility

^b Insufficient information is available to determine Intermediate or Resistant interpretive criteria

The ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues. [*see CLINICAL PHARMACOLOGY (12)*]

A report of “Susceptible” indicates that the pathogen is likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentration at the infection site necessary to inhibit growth of the pathogen. A report of “Intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the antibacterial is not likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test ^{1,2,3}. Standard azithromycin powder should provide the following range of MIC values provided in Table 4. For the diffusion technique using the 15 mcg azithromycin disk the criteria provided in Table 4 should be achieved.

Table 4: Acceptable Quality Control Ranges for Susceptibility Testing

| Quality Control Organism | Minimum Inhibitory Concentrations (mcg/mL) | Disk Diffusion (zone diameters in mm) |
|---|--|---------------------------------------|
| <i>Staphylococcus aureus</i> ATCC* 25923 | Not Applicable | 21 to 26 |
| <i>Staphylococcus aureus</i> ATCC 29213 | 0.5 to 2 | Not Applicable |
| <i>Haemophilus Influenzae</i> ATCC 49247 | 1.0 to 4.0 | 13 to 21 |
| <i>Streptococcus pneumoniae</i> ATCC 49619 | 0.06 to 0.25 | 19 to 25 |

*ATCC = American Type Culture Collection

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found in rats given daily doses up to 10 mg/kg (approximately 0.2 times an adult daily dose of 500 mg based on body surface area).

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) in dogs and rats treated with azithromycin at doses which, expressed on the basis of body surface area, are similar to or less than the highest recommended adult human dose. This effect has been shown to be reversible after cessation of azithromycin treatment. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (50 mg/kg/day dose) at the observed maximal plasma concentration of 1.3 mcg/mL (1.6 times the observed C_{max} of 0.821 mcg/mL at the adult dose of 2 g). Similarly, it has been shown in the dog (10 mg/kg/day dose) at the observed maximal serum concentration of 1 mcg/mL (1.2 times the observed C_{max} of 0.821 mcg/mL at the adult dose of 2 g). Phospholipidosis was also observed in neonatal rats dosed for 18 days at 30 mg/kg/day, which is less than the pediatric dose of 60 mg/kg based on the surface area. It was not observed in neonatal rats treated for 10 days at 40 mg/kg/day with mean maximal serum concentrations of 1.86 mcg/mL, approximately 1.5 times the C_{max} of 1.27 mcg/mL at the pediatric dose. Phospholipidosis has been observed in neonatal dogs (10 mg/kg/day) at maximum mean whole blood concentrations of 3.54 mcg/mL, approximately 3 times the pediatric dose C_{max} . The significance of these findings for animals and for humans is unknown.

14 CLINICAL STUDIES

14.1 Adult Patients

Acute Bacterial Exacerbations of Chronic Bronchitis

In a randomized, double-blind controlled clinical trial of acute exacerbation of chronic bronchitis (AECB), azithromycin (500 mg once daily for 3 days) was compared with clarithromycin (500 mg twice daily for 10 days). The primary endpoint of this trial was the clinical cure rate at Days 21 to 24. For the 304 patients analyzed in the modified intent-to-treat analysis at the Days

21 to 24 visit, the clinical cure rate for 3 days of azithromycin was 85% (125/147) compared to 82% (129/157) for 10 days of clarithromycin.

The following outcomes were the clinical cure rates at the Days 21 to 24 visit for the bacteriologically evaluable patients by pathogen:

| Pathogen | Azithromycin (3 Days) | Clarithromycin (10 Days) |
|-----------------------|------------------------------|---------------------------------|
| <i>S. pneumoniae</i> | 29/32 (91%) | 21/27 (78%) |
| <i>H. influenzae</i> | 12/14 (86%) | 14/16 (88%) |
| <i>M. catarrhalis</i> | 11/12 (92%) | 12/15 (80%) |

Acute Bacterial Sinusitis

In a randomized, double-blind, double-dummy controlled clinical trial of acute bacterial sinusitis, azithromycin (500 mg once daily for 3 days) was compared with amoxicillin/clavulanate (500/125 mg three times a day for 10 days). Clinical response assessments were made at Day 10 and Day 28. The primary endpoint of this trial was prospectively defined as the clinical cure rate at Day 28. For the 594 patients analyzed in the modified intent to treat analysis at the Day 10 visit, the clinical cure rate for 3 days of azithromycin was 88% (268/303) compared to 85% (248/291) for 10 days of amoxicillin/clavulanate. For the 586 patients analyzed in the modified intent to treat analysis at the Day 28 visit, the clinical cure rate for 3 days of azithromycin was 71.5% (213/298) compared to 71.5% (206/288), with a 97.5% confidence interval of -8.4 to 8.3, for 10 days of amoxicillin/clavulanate.

In an open label, non-comparative study requiring baseline transantral sinus punctures, the following outcomes were the clinical success rates at the Day 7 and Day 28 visits for the modified intent to treat patients administered 500 mg of azithromycin once daily for 3 days with the following pathogens:

Clinical Success Rates of Azithromycin (500 mg per day for 3 Days)

| Pathogen | Day 7 | Day28 |
|-----------------------|--------------|--------------|
| <i>S. pneumoniae</i> | 23/26 (88%) | 21/25 (84%) |
| <i>H. influenzae</i> | 28/32 (87%) | 24/32 (75%) |
| <i>M. catarrhalis</i> | 14/15 (93%) | 13/15 (87%) |

14.2 Pediatric Patients

From the perspective of evaluating pediatric clinical trials, Days 11 to 14 were considered on-therapy evaluations because of the extended half-life of azithromycin. Days 11 to 14 data are provided for clinical guidance. Days 24 to 32 evaluations were considered the primary test of cure endpoint.

Pharyngitis/Tonsillitis

In three double-blind controlled studies, conducted in the United States, azithromycin (12 mg/kg once a day for 5 days) was compared to penicillin V (250 mg three times a day for 10 days) in the treatment of pharyngitis due to documented Group A β -hemolytic *streptococci* (GABHS or *S. pyogenes*). Azithromycin was clinically and microbiologically statistically superior to penicillin at Day 14 and Day 30 with the following clinical success (i.e., cure and improvement) and bacteriologic efficacy rates (for the combined evaluable patient with documented GABHS):

**Three U.S. Streptococcal Pharyngitis Studies
Azithromycin vs. Penicillin V
EFFICACY RESULTS**

| | Day 14 | Day 30 |
|--|---------------|---------------|
| Bacteriologic Eradication: | | |
| Azithromycin | 323/340 (95%) | 255/330 (77%) |
| Penicillin V | 242/332 (73%) | 206/325 (63%) |
| | | |
| Clinical Success (cure plus improvement): | | |
| Azithromycin | 336/343 (98%) | 310/330 (94%) |
| Penicillin V | 284/338 (84%) | 241/325 (74%) |

Approximately 1% of azithromycin-susceptible *S. pyogenes* isolates were resistant to azithromycin following therapy.

Acute Otitis Media

Efficacy using azithromycin given over 5 days (10 mg/kg on Day 1 followed by 5 mg/kg on Days 2 to 5):

Trial 1

In a double-blind, controlled clinical study of acute otitis media performed in the United States, azithromycin (10 mg/kg on Day 1 followed by 5 mg/kg on Days 2 to 5) was compared to amoxicillin/clavulanate potassium (4:1). For the 553 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the Day 11 visit was 88% for azithromycin and 88% for the control agent. For the 521 patients who were evaluated at the Day 30 visit, the clinical success rate was 73% for azithromycin and 71% for the control agent.

Trial 2

In a non-comparative clinical and microbiologic trial performed in the United States, where significant rates of beta-lactamase producing organisms (35%) were found, 131 patients were evaluable for clinical efficacy. The combined clinical success rate (i.e., cure and improvement) at the Day 11 visit was 84% for azithromycin. For the 122 patients who were evaluated at the Day 30 visit, the clinical success rate was 70% for azithromycin.

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. The following clinical success rates were obtained from the evaluable group:

| Pathogen | Day 11 | Day 30 |
|-----------------------|---------------|--------------|
| | Azithromycin | Azithromycin |
| <i>S. pneumoniae</i> | 61/74 (82%) | 40/56 (71%) |
| <i>H. influenzae</i> | 43/54 (80%) | 30/47 (64%) |
| <i>M. catarrhalis</i> | 28/35 (80%) | 19/26 (73%) |
| <i>S. pyogenes</i> | 11/11 (100%) | 7/7 (100%) |
| Overall | 177/217 (82%) | 97/137 (73%) |

Trial 3

In another controlled comparative clinical and microbiologic study of otitis media performed in the United States, azithromycin (10 mg/kg on Day 1 followed by 5 mg/kg on Days 2 to 5) was compared to amoxicillin/clavulanate potassium (4:1). This study utilized two of the same investigators as Protocol 2 (above), and these two investigators enrolled 90% of the patients in Protocol 3. For this reason, Protocol 3 was not considered to be an independent study. Significant rates of beta-lactamase producing organisms (20%) were found. Ninety-two (92) patients were evaluable for clinical and microbiologic efficacy. The combined clinical success rate (i.e., cure and improvement) of those patients with a baseline pathogen at the Day 11 visit was 88% for azithromycin vs. 100% for control; at the Day 30 visit, the clinical success rate was 82% for azithromycin vs. 80% for control.

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. At the Day 11 and Day 30 visits, the following clinical success rates were obtained from the evaluable group:

| Pathogen | Day 11 | | Day 30 | |
|-----------------------|--------------|--------------|--------------|-------------|
| | Azithromycin | Control | Azithromycin | Control |
| <i>S. pneumoniae</i> | 25/29 (86%) | 26/26 (100%) | 22/28 (79%) | 18/22 (82%) |
| <i>H. influenzae</i> | 9/11 (82%) | 9/9 (100%) | 8/10 (80%) | 6/8 (75%) |
| <i>M. catarrhalis</i> | 7/7 (100%) | 5/5 (100%) | 5/5 (100%) | 2/3 (66%) |
| <i>S. pyogenes</i> | 2/2 (100%) | 5/5 (100%) | 2/2 (100%) | 4/4 (100%) |
| Overall | 43/49 (88%) | 45/45 (100%) | 37/45 (82%) | 30/37 (81%) |

Efficacy using azithromycin given over 3 days (10 mg/kg/day):

Trial 4

In a double-blind, controlled, randomized clinical study of acute otitis media in pediatric patients from 6 months to 12 years of age, azithromycin (10 mg/kg per day for 3 days) was compared to amoxicillin/clavulanate potassium (7:1) in divided doses q12h for 10 days. Each patient received active drug and placebo matched for the comparator.

For the 366 patients who were evaluated for clinical efficacy at the Day 12 visit, the clinical success rate (i.e., cure plus improvement) was 83% for azithromycin and 88% for the control agent. For the 362 patients who were evaluated at the Days 24 to 28 visit, the clinical success rate was 74% for azithromycin and 69% for the control agent.

Efficacy using azithromycin 30 mg/kg given as a single dose:

Trial 5

A double-blind, controlled, randomized trial was performed at nine clinical centers. Pediatric patients from 6 months to 12 years of age were randomized 1:1 to treatment with either azithromycin (given at 30 mg/kg as a single dose on Day 1) or amoxicillin/clavulanate potassium (7:1), divided q12h for 10 days. Each child received active drug, and placebo matched for the comparator.

Clinical response (Cure, Improvement, Failure) was evaluated at End of Therapy (Days 12 to 16) and Test of Cure (Days 28 to 32). Safety was evaluated throughout the trial for all treated subjects. For the 321 subjects who were evaluated at End of Treatment, the clinical success rate (cure plus improvement) was 87% for azithromycin, and 88% for the comparator. For the 305 subjects who were evaluated at Test of Cure, the clinical success rate was 75% for both azithromycin and the comparator.

Trial 6

In a non-comparative clinical and microbiological trial, 248 patients from 6 months to 12 years of age with documented acute otitis media were dosed with a single oral dose of azithromycin (30 mg/kg on Day 1).

For the 240 patients who were evaluable for clinical modified Intent-to-Treat (MITT) analysis, the clinical success rate (i.e., cure plus improvement) at Day 10 was 89% and for the 242 patients evaluable at Days 24 to 28, the clinical success rate (cure) was 85%.

| Presumed Bacteriologic Eradication | | |
|---|---------------|----------------------|
| | Day 10 | Days 24 to 28 |
| <i>S. pneumoniae</i> | 70/76 (92%) | 67/76 (88%) |
| <i>H. influenzae</i> | 30/42 (71%) | 28/44 (64%) |
| <i>M. catarrhalis</i> | 10/10 (100%) | 10/10 (100%) |
| Overall | 110/128 (86%) | 105/130 (81%) |

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard -Ninth Edition*. CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement*, CLSI document M100-S23. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition* CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

16 HOW SUPPLIED/STORAGE AND HANDLING

Azithromycin for oral suspension USP appears an off white to pinkish powder before constitution. The suspension after constitution contains a cherry flavored suspension that is red in color. 5 mL of constituted suspension of azithromycin for oral suspension USP, 100 mg/5 mL and 200 mg/5 mL, contain 3.9 mg of sodium. Azithromycin for oral suspension USP is supplied to provide 100 mg/5 mL or 200 mg/5 mL in bottles as follows:

100 mg/5 mL:

Bottle of 300 mg of azithromycin contains 15 mL suspension when constituted with 9 mL of water. Each 5 mL suspension contains azithromycin monohydrate equivalent to 100 mg

azithromycin.

Bottles of 15 mL NDC 68180-163-01

200 mg/5 mL:

Bottle of 600 mg of azithromycin contains 15 mL suspension when constituted with 9 mL of water. Each 5 mL suspension contains azithromycin monohydrate equivalent to 200 mg azithromycin.

Bottles of 15 mL NDC 68180-164-01

Bottle of 900 mg of azithromycin contains 22.5 mL suspension when constituted with 12 mL of water. Each 5 mL suspension contains azithromycin monohydrate equivalent to 200 mg azithromycin.

Bottles of 22.5 mL NDC 68180-164-02

Bottle of 1200 mg of azithromycin contains 30 mL suspension when constituted with 15 mL of water. Each 5 mL suspension contains azithromycin monohydrate equivalent to 200 mg azithromycin.

Bottles of 30 mL NDC 68180-164-03

[see DOSAGE AND ADMINISTRATION (2)] for constitution instructions with each bottle type.

Storage: Store dry powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Store constituted suspension between 5° to 30°C (41° to 86°F) and discard when full dosing is completed.

17 PATIENT COUNSELING INFORMATION

General Patient Counseling

Azithromycin for oral suspension can be taken with or without food.

Patients should also be cautioned not to take aluminum-and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Patients should be counseled that antibacterial drugs including azithromycin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When azithromycin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of the 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 azithromycin or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibacterials 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 drug. If this occurs, patients should contact their physician as soon as possible.

See FDA-approved Patient Labeling

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Goa - 403722

India

Revised: August 2016

ID#: 247750

Patient Information

AZITHROMYCIN (ay-ZITH-roe-MYE-sin) FOR ORAL SUSPENSION USP

Rx only

Read this Patient Information leaflet before you start taking azithromycin for oral suspension and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is azithromycin for oral suspension?

Azithromycin for oral suspension is a macrolide antibiotic prescription medicine used in adults 18 years or older to treat certain infections caused by certain germs called bacteria. These bacterial infections include:

- acute worsening of chronic bronchitis
- acute sinus infection
- community-acquired pneumonia
- infected throat or tonsils
- skin infections
- infections of the urethra or cervix
- genital ulcers in men

Azithromycin for oral suspension is also used in children to treat:

- ear infections
- community-acquired pneumonia
- infected throat or tonsils

Azithromycin should not be taken by people who cannot tolerate oral medications because they are very ill or have certain other risk factors including:

- have cystic fibrosis
- have hospital acquired infections
- have known or suspected bacteria in the blood
- need to be in the hospital
- are elderly
- have any medical problems that can lower the ability of the immune system to fight infections

Azithromycin for oral suspension is not for viral infections such as the common cold.

It is not known if azithromycin for oral suspension is safe and effective for genital ulcers in women.

It is not known if azithromycin for oral suspension is safe and effective for children with ear infections, sinus infections, and community-acquired pneumonia under 6 months of age.

It is not known if azithromycin for oral suspension is safe and effective for infected throat or

tonsils in children under 2 years of age.

Who should not take azithromycin for oral suspension?

Do not take azithromycin for oral suspension if you:

- have had a severe allergic reaction to certain antibiotics known as macrolides or ketolides including azithromycin and erythromycin.
- have a history of cholestatic jaundice or hepatic dysfunction that happened with the use of azithromycin.

What should I tell my healthcare provider before taking azithromycin for oral suspension?

Before you take azithromycin for oral suspension, tell your healthcare provider if you:

- have pneumonia
- have cystic fibrosis
- have known or suspected bacteremia (bacterial infection in the blood)
- have liver or kidney problems
- have an irregular heartbeat, especially a problem called “QT prolongation”
- have a problem that causes muscle weakness (myasthenia gravis)
- have any other medical problems
- are pregnant or plan to become pregnant. It is not known if azithromycin for oral suspension will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Azithromycin has been reported to pass into breast milk. Talk to your healthcare provider about the best way to feed your baby while you take azithromycin for oral suspension.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Azithromycin for oral suspension and other medicines may affect each other causing side effects. Azithromycin for oral suspension may affect the way other medicines work, and other medicines may affect how azithromycin for oral suspension works.

Especially tell your healthcare provider if you take:

- nelfinavir
- a blood thinner (warfarin)
- digoxin
- phenytoin
- an antacid that contains aluminum or magnesium

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take azithromycin for oral suspension?

- Take azithromycin for oral suspension exactly as your healthcare provider tells you to take it.
- Azithromycin for oral suspension can be taken with or without food.
- If you take azithromycin for oral suspension, shake the bottle well just before you take it.

- Do not skip any doses of azithromycin for oral suspension or stop taking it, even if you begin to feel better, until you finish your prescribed treatment unless you have a serious allergic reaction or your healthcare provider tells you to stop taking azithromycin for oral suspension. **“See What are the possible side effects of azithromycin for oral suspension?”** If you skip doses, or do not complete the total course of azithromycin for oral suspension your treatment may not work as well and your infection may be harder to treat. Taking all of your azithromycin doses will help lower the chance that the bacteria will become resistant to azithromycin for oral suspension.
- If the bacteria becomes resistant to azithromycin, azithromycin and other antibiotic medicines may not work for you in the future.
- If you take too much azithromycin for oral suspension, call your healthcare provider or get medical help right away.

What are the possible side effects of azithromycin for oral suspension?

Azithromycin for oral suspension can cause serious side effects, including:

- **Serious allergic reactions.** Allergic reactions can happen in people taking azithromycin the active ingredient in azithromycin for oral suspension, even after only 1 dose. Stop taking azithromycin for oral suspension and get emergency medical help right away if you have any of the following symptoms of a severe allergic reaction:
 - trouble breathing or swallowing
 - swelling of the lips, tongue, face
 - throat tightness, hoarseness
 - rapid heartbeat
 - faintness
 - skin rash (hives)
 - new onset of fever and swollen lymph nodes

Stop taking azithromycin for oral suspension at the first sign of a skin rash and call your healthcare provider.

Skin rash may be a sign of a more serious reaction to azithromycin for oral suspension.

- **Liver damage (hepatotoxicity).** Hepatotoxicity can happen in people who take azithromycin for oral suspension. Call your healthcare provider right away if you have unexplained symptoms such as:
 - nausea or vomiting
 - stomach pain
 - fever
 - weakness
 - abdominal pain or tenderness
 - itching
 - unusual tiredness
 - loss of appetite
 - change in the color of your bowel movements
 - dark colored urine
 - yellowing of your skin or of the whites of your eyes

Stop taking azithromycin for oral suspension and tell your healthcare provider right away if you have yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to azithromycin for oral suspension (a liver problem).

- **Serious heart rhythm changes (QT prolongation and torsades de pointes).**
Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you feel faint and dizzy. Azithromycin for oral suspension may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this happening are higher in people:
 - who are elderly
 - with a family history of prolonged QT interval
 - with low blood potassium
 - who take certain medicines to control heart rhythm (antiarrhythmics)
- **Worsening of myasthenia gravis (a problem that causes muscle weakness).**
Certain antibiotics like azithromycin for oral suspension may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.
- **Diarrhea.** Tell your healthcare provider right away if you have watery diarrhea, diarrhea that does not go away, or bloody stools. You may experience cramping and a fever. This could happen after you have finished your azithromycin for oral suspension.

The most common side effects of azithromycin for oral suspension include:

- nausea
- stomach pain
- vomiting

These are not all the possible side effects of azithromycin. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store azithromycin for oral suspension?

- Store azithromycin oral suspension at 5° to 30°C (41° to 86°F).
- Keep azithromycin oral suspension in a tightly closed container.
- Safely throw away any medicine that is out of date or no longer needed.

Keep azithromycin for oral suspension and all medicines out of the reach of children.

General information about the safe and effective use of azithromycin for oral suspension.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use azithromycin for oral suspension for a condition for which it was

not prescribed. Do not give azithromycin for oral suspension to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about azithromycin for oral suspension. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about azithromycin for oral suspension that is written for health professionals.

For more information go to www.lupinpharmaceuticals.com or call 1-800-399-2561.

What are the ingredients in azithromycin for oral suspension?

Active ingredient: azithromycin monohydrate

Inactive ingredients: hydroxy propyl cellulose; liquid banana flavor; liquid cherry flavor; spectracol FD&C Red #40; sucrose; talc, tribasic sodium phosphate dodecahydrate and xanthan gum.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Goa - 403722

India

Revised: August 2016

ID#: 247751

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 065488s002

LABELING REVIEW

SUPPLEMENT LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

| | |
|--|---|
| Date of this Review | 11/3/2016 |
| Review Cycle Number | 1 |
| ANDA(s) and Supplement Number(s) | 065488/S-002 |
| Applicant Name | Lupin Limited |
| Proprietary Name, Established Name, and Strength(s) | Azithromycin for Oral Suspension USP, 100 mg/5 mL and 200 mg/5 mL |
| Current Received Date | 7/25/2016 |
| Previous Received Date(s) of Proposed Supplement | NA |
| Labeling Reviewer | Soon Oh |
| Labeling Team Leader | Betty Turner |

Review Conclusion

- ACCEPTABLE - No Comments.
- ACCEPTABLE - Include Post approval comments.
- Minor Deficiency/ECD - Refer to Labeling Deficiencies and Comments for the Letter to Applicant
- On Policy Alert List

For labeling supplement(s):

This Change Being Effected supplemental abbreviated new drug application provides for revised package insert labeling to be in accord with the Reference Listed Drug (RLD), ZITHROMAX®, NDA 050710/S-043 approved May 23, 2016.

We have completed the review of this supplemental application. It is approved, effective on the date of this letter. However, please make the following revisions to the labeling and submit them in your next Annual Report, provided the changes are described in full.

PATIENT INFORMATION LEAFLET

Revise your proposed pronunciation of the non-proprietary name to conform to the phonetic pronunciation in the current USP Dictionary of USAN and International Drug Names as follows: (ay zith" roe mye' sin)

For combined supplement(s):

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| | | |
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1. ANDA REGULATORY INFORMATION:

| | |
|--|----|
| Type of Supplement: CBE | |
| Are there any pending issues in <u>DLR's SharePoint Drug Facts</u> ? | NO |
| If Yes, please explain: | |

| | |
|---|----|
| Is the drug product listed in the Policy Alert Tracker on <u>DLRS SharePoint</u>? If Yes, please explain: | NO |
| Reason for Submission: This Changes Being Effected supplemental abbreviated new drug application provides for revised package insert labeling to be in accord with the Reference Listed Drug (RLD), ZITHROMAX®, NDA 050710/S-043 approved May 23, 2016. | |
| Is this supplement combined with another discipline? | NO |
| Is this product an OTC product? | NO |
| Is this ANDA the RLD? | NO |

2. MATERIAL ANALYSIS

The results for each material reviewed in this section provide the basis for the labeling comments to the Applicant and other review disciplines.

2.1.1 MATERIALS REVIEWED

Tables 1 and 2 provide a summary of recommendations for each material analyzed in this review.

| Table 1: Review Summary of Container Label and Carton Labeling | | | | |
|---|----------------------------------|-----------------------|-----------------------|----------------------|
| | Package Size | Draft or Final | Recommendation | Received Date |
| Container | | | | |
| Blister | | | | |
| Carton | | | | |
| Other | | | | |
| Table 2 Review Summary of Prescribing Information and Patient Labeling | | | | |
| | Revision Date and/or Code | Draft or Final | Recommendation | Received Date |
| Prescribing Information | Revised: 08/2016 | Final | Satisfactory | 7/25/2016 |
| Medication Guide | | | | |
| Patient Information | Revised: August 2016 | Final | Satisfactory | 7/25/2016 |

2.1.2 MODEL LABELING

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 3.

| Table 3: Review Model Labeling for Prescribing Information and Patient Labeling (Check all that apply) | | | | | |
|---|--|-----------------------|-----------|--------------------------|-----------|
| NDA/Original or Supplement: | NDA 050710/S-043 | Approval Date: | 5/23/2016 | Proprietary Name: | ZITHROMAX |
| Description of Original or Supplement: | This "Changes Being Effected" supplemental new drug application provides for an update to the labels regarding the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. | | | | |
| <input type="checkbox"/> BPCA TEMPLATE | | | | | |
| <input type="checkbox"/> OTHER (Describe) | | | | | |

For OTC products
Please provide PDP of
NDA

Reviewer Assessment:

Is the NDA listed in the discontinued section of the Orange Book? **NO**
If yes, then comment below regarding the current model labeling.

Comment:

2.1.3 PATENTS AND EXCLUSIVITIES

Are there any remaining unexpired patents or marketing exclusivities for Model Labeling? **YES**

If YES go to the table 4 and assessments below.

Table 4 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

| Table 4: Impact of Model Labeling Patents on ANDA Labeling | | | | | |
|--|-------------------|-----------------|----------------------------|----------------------|--|
| Patent Number | Patent Expiration | Patent Use Code | Patent Use Code Definition | Patent Certification | Labeling Impact ("Carve-out" or "None" or "Not addressed by firm") |
| 6268489 | Jul 31, 2018 | | | IV | None |

Table 5 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

| Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling | | | | |
|---|------------------------|-----------------------------|-----------------------|--|
| Exclusivity Code | Exclusivity Expiration | Exclusivity Code Definition | Exclusivity Statement | Labeling Impact ("Carve-out" or "None" or "Not addressed by firm") |
| NA | | | | |

Reviewer Assessment:

Are there any recently expired patents or exclusivities? **NO**
If yes, did these patents or exclusivities have any labeling impact? **N/A**

Comment:

2.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 6.

Table 6: USP and PF Search Results

| | Date Searched | Monograph? YES or NO | Monograph Title (NA if no monograph) | Copy of pertinent information from USP or PF |
|------------|---------------|----------------------|--------------------------------------|---|
| <u>USP</u> | 11/3/2016 | YES | Azithromycin for Oral Suspension | Packaging and Storage: Preserve in tight containers pH (791) For a solid packaged in single-unit containers: 9.0–11.0, in the suspension constituted as directed in the labeling For a solid packaged in multiple-unit containers: 8.5–11.0, in the suspension constituted as directed in the labeling |
| <u>PF</u> | 11/3/2016 | YES | Azithromycin for Oral Suspension | NA |

Reviewer Assessment:

Are there any updates needed to the labeling based on the USP monograph? **NO**

Comment:

2.1.5 HISTORY OF ANDA

We evaluated previously approved and pending supplements (Table 7) to determine if actions are needed for the current review.

Table 7: History of ANDA

Last approved labels and labeling addressed the following:

| Original or Supplement | Approval Date | What post approval changes requested and were the changes addressed? |
|------------------------|---------------|--|
| S-000 | 5/15/2015 | None |

Are there any Pending Supplements for this ANDA that impact labeling? **NO**

| Supplement | Submission Date | Labeling Impact |
|------------|-----------------|-----------------|
| | | |

3. ASSESSMENT OF CURRENT SUPPLEMENT'S LABELING

3.1.1 CONTAINER AND CARTON LABELS

Reviewer Assessment:

Were container or carton labels submitted in this supplement? **NO**

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Comment:

3.1.2 MODEL CONTAINER LABELS

Please provide the reference listed drug labels if applicant submits container, blister, carton, etc.

Model container/carton/blister labels [Source:]

3.1.3 RX PRESCRIBING INFORMATION AND PATIENT LABELING

Reviewer Assessment:

Was labeling submitted in this supplement? **YES**

Are the labeling contained in the submission the same as the review model labeling (not including allowable differences under 21 CFR 314.94(a)(8))? **YES**

Is the Prescribing Information shared by other ANDAs? **NO** (If yes please list ANDA numbers).

Comment:

3.1.4 DESCRIPTION, HOW SUPPLIED, MANUFACTURING BY STATEMENT sections [for OTC products, please include the inactives in table 8; package sizes being marketed in table 9; and drug product manufacturing/distributing statement in table 10.]

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or OTC labeling? **NO**

Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED section or OTC package sizes? **NO**

Are there changes to the manufacturing/distributing statements? **NO**

If yes, then comment below in Tables 8, 9, and 10.

Table 8: Comparison of DESCRIPTION Section

| Previously Approved | Currently Proposed | Assessment |
|---------------------|--------------------|------------|
| | | |

Table 9: Comparison of HOW SUPPLIED Section

| Previously Approved | Currently Proposed | Assessment |
|---------------------|--------------------|------------|
| | | |

Table 10: Manufactured by Statement

| Previously Approved | Currently Proposed | Assessment |
|---------------------|--------------------|------------|
| | | |

4. SPECIAL CONSIDERATIONS [PLEASE INCLUDE OTHER INFORMATION THAT MAY PERTAIN TO YOUR DRUG PRODUCT APPLICATION.]

NA



Betty
Turner

Digitally signed by Betty Turner
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Soon
Oh

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