



Macrolides – Ketolides Therapeutic Class Review (TCR)

December 5, 2013

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FDA-APPROVED INDICATIONS

Drug	Mfg.	AECB	AOM	CAP	Pharyngitis /Tonsillitis	Skin	Sinusitis	Others
azithromycin (Zithromax®) ¹	generic	X	X (> six months old)	X (> six months old)	X (> two years old)	X	X (> six months old)	<ul style="list-style-type: none"> ▪ Non-gonococcal urethritis and cervicitis due to <i>Chlamydia trachomatis</i> ▪ Prevention (taken alone or in combination with rifabutin) and treatment (taken in combination with ethambutol) of disseminated MAC in HIV patients
azithromycin ER suspension (Zmax®) ²	Pfizer	--	--	X (> six months old)	--	--	X (Adults only)	
clarithromycin (Biaxin®) ³	generic	X	X (> six months old)	X (> six months old)	X (> six months old)	X (> six months old)	X (> six months old)	<ul style="list-style-type: none"> ▪ Prevention and treatment of disseminated MAC in HIV patients (> 20 months old) ▪ In combination with other drugs to treat <i>Helicobacter pylori</i>
clarithromycin ER (Biaxin XL®) ⁴	generic	X (Adults only)	--	X (Adults only)	--	--	X (Adults only)	
erythromycin ⁵	generic	--	X	X	X	X	X	<ul style="list-style-type: none"> ▪ Respiratory tract infections ▪ Pertussis ▪ Diphtheria ▪ Legionnaire's disease ▪ PID ▪ Urethritis and cervicitis ▪ Syphilis ▪ Acne vulgaris ▪ Prevent recurrent attacks of rheumatic fever ▪ Gonorrhea ▪ Surgical infection prophylaxis with bowel preparation

FDA-Approved Indications (continued)

Drug	Mfg.	AECB	AOM	CAP	Pharyngitis /Tonsillitis	Skin	Sinusitis	Others
telithromycin (Ketek™) ⁶	Sanofi-Aventis	--	--	X (including MDRSP; Adults only)	--	--	--	<ul style="list-style-type: none"> In 2007, the FDA removed the indications for AECB and sinusitis

Key: AECB = acute exacerbations of chronic bronchitis; AOM = acute otitis media; CAP = community acquired pneumonia; Skin = skin and skin structure infections; MAC = *Mycobacterium avium* complex; HIV = human immunodeficiency virus; PID = pelvic inflammatory disease; MDRSP = Multi-drug resistant *Streptococcus pneumoniae*

OVERVIEW

Erythromycin, the first macrolide, was introduced in 1952. Activity against gram-positive cocci and atypical pathogens made erythromycin a good treatment option for upper and lower respiratory tract infections and soft tissue infections. However, erythromycin does have several limitations, such as variable absorption, short elimination half-life, gastrointestinal irritation, and lack of activity against *Hemophilus influenzae*. Both azithromycin (Zithromax) and clarithromycin (Biaxin) demonstrate better tolerability with more convenient dosing regimens and improved activity against *H. influenzae*.^{7,8}

Telithromycin (Ketek), a ketolide, concentrates inside phagocytes and is effective against intracellular respiratory pathogens. Telithromycin provides effective coverage against many respiratory pathogens in a once daily oral formulation for adults. Serious adverse effects, drug interactions, and having only one indication limit the usefulness of telithromycin.

Joint guidelines from the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) for treatment of community-acquired pneumonia (CAP) published in 2007 recommend macrolides (e.g., erythromycin, clarithromycin, and azithromycin – strong recommendation) or doxycycline (weak recommendation) for adult patients who are otherwise healthy without risk factors for multi-drug resistant *S. pneumoniae*.⁹ For adult outpatients with comorbidities including chronic heart, lung, renal, hepatic disorders, diabetes, alcoholism, malignancies, asplenia, immunosuppression, use of any antibiotic within the last three months, or other risk factors for multi-drug resistant *S. pneumoniae*, first line therapy may include a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin 750 mg) or a beta-lactam plus a macrolide (strong recommendation). Beta-lactam selection may include one of the following: high dose amoxicillin 1 gm three times daily or amoxicillin/clavulanate. Other beta-lactam alternatives include ceftriaxone, cefpodoxime, or cefuroxime. Doxycycline may be used as an alternative to macrolides in combination with a beta-lactam. Antibiotics should be used judiciously with appropriate dosing in an effort to avoid antibiotic resistance.

For children (school-age and adolescents) evaluated in an outpatient setting, macrolide antibiotics should be prescribed when findings are compatible with CAP caused by atypical pathogens.¹⁰

Symptoms of chronic obstructive pulmonary disease (COPD) exacerbation include increased breathlessness, wheezing, chest tightness, increased cough and sputum, change of color and/or tenacity of sputum, and fever. Increased sputum volume and purulence indicates a bacterial cause, as does prior history of chronic sputum production.¹¹ According to the 2011 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, all patients with symptoms of COPD exacerbation should be treated with additional bronchodilators with or without glucocorticosteroids.

Antibiotics should be given to patients with the following three cardinal symptoms: increased dyspnea, increased sputum volume, increased sputum purulence; or to those patients with increased sputum purulence and one other cardinal symptom; or those who require mechanical ventilation.

Current recommendations (2005) from IDSA list erythromycin as an alternative antibiotic for the treatment of skin and skin structure infections including impetigo.¹² Azithromycin and clarithromycin are indicated for skin and skin structure infections. Some strains of *Staphylococcus aureus* and *Streptococcus pyogenes* may be resistant. Updated treatment guidelines for management of skin and skin structure from IDSA are expected in the fall of 2013.

Macrolides have a limited role in the management of acute sinusitis. According to the 2007 American Academy of Otolaryngology guidelines on the treatment of adult sinusitis, adults with mild or moderate acute bacterial rhinosinusitis (ABRS) may be observed with watchful waiting. For those with severe ABRS, or the patient worsens or fails to improve with watchful waiting, therapy with amoxicillin should begin.¹³ If treatment failure is observed following seven days of antibiotic therapy, a nonbacterial cause or infection with drug-resistant bacteria should be considered and should prompt a switch to alternate antibiotic therapy and re-evaluation of the patient. Optimal therapy of multidrug-resistant *Streptococcus pneumoniae* and beta-lactamase-producing *Hemophilus influenzae* and *Moraxella catarrhalis* would include high-dose amoxicillin-clavulanate (4 g per day amoxicillin equivalent) or a respiratory fluoroquinolone (levofloxacin, moxifloxacin, or gemifloxacin). These agents would also cover less common pathogens. Patients with penicillin allergy could receive a fluoroquinolone. Updated IDSA guidelines for the management of acute and chronic rhinosinusitis were published in March 2012. The IDSA guidelines recommend that macrolides not be used empirically to treat acute bacterial rhinosinusitis in either children or adults due to high rates of resistance.¹⁴

The 2010 Centers for Disease Control and Prevention (CDC) guidelines for the treatment of sexually transmitted diseases (STDs) list azithromycin as a recommended regimen for the treatment of chancroid, nongonococcal urethritis, cervicitis, and *Chlamydia* infections.¹⁵ A 2012 update to the guideline specifically for uncomplicated gonorrhea, now recommends azithromycin 1 gram orally as a single dose or doxycycline 100 mg orally twice daily for seven days along with ceftriaxone intramuscularly as recommended combination therapy, due to increased resistance to the oral cephalosporin cefixime.¹⁶ Erythromycin base and erythromycin estolate are considered alternative regimens for several infections; however, the gastrointestinal adverse effects of erythromycin may reduce the effectiveness of the therapy if treatment is not completed.

The current CDC guidelines from 2005 (expected to be updated by the end of 2012) recommend erythromycin, azithromycin, or clarithromycin for the post-exposure prophylaxis or treatment of Pertussis.¹⁷

Azithromycin or clarithromycin are the preferred prophylactic agents for *Mycobacterium avium complex* (MAC) according to the 2009 joint guidelines from the CDC, IDSA, and NIH for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents.¹⁸ The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared with azithromycin alone do not warrant a routine recommendation for this regimen.

Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance with clarithromycin being a preferred first agent.¹⁹ Clarithromycin has been studied more extensively than azithromycin in patients with acquired immunodeficiency syndrome (AIDS) and appears to have a more rapid clearance of MAC from the blood. Azithromycin may be used in place of clarithromycin when drug interactions or drug intolerance are a concern. Ethambutol is the recommended second drug for the treatment of MAC. Patients with a history of disseminated MAC disease should receive lifelong secondary prophylaxis (chronic maintenance therapy), unless immune reconstitution occurs as a result of antiretroviral therapy.

Macrolides have been shown to be useful agents in the treatment of upper respiratory bacterial infections including community-acquired pneumonia (CAP), acute sinusitis, and acute otitis media (AOM). Antibiotic resistance may limit the overall effectiveness of the agents in this class as multi-drug resistant bacteria become more prevalent.

PHARMACOLOGY

Macrolide and ketolide antibiotics bind to the 50S ribosomal subunit of susceptible bacteria inhibiting RNA-dependent protein synthesis.²⁰ They may be bacteriostatic or bactericidal, depending on drug concentration and are generally active against, gram positive cocci and bacilli, and, to a lesser extent, gram negative cocci.²¹ Telithromycin (Ketek) exhibits concentration-dependent bactericidal activity against isolates of *Streptococcus pneumoniae*, including multi-drug resistant *S. pneumoniae* (MDRSP). Telithromycin is active against erythromycin- and azithromycin-resistant strains of *S. pneumoniae* and *Streptococcus pyogenes*.^{22,23,24}

Bacterial resistance

Resistance to antibiotics is a public health problem. MDRSP is becoming a more common pathogen in CAP. In a U.S. surveillance study, macrolide use was identified as a risk factor for macrolide-resistant *S. pneumoniae* when macrolides had been used in the six weeks prior to specimen collection.²⁵ Macrolide-resistant isolates of group A streptococci collected in 2002 and 2003 were observed in 6.1 percent of 2,797 pharyngeal isolates.²⁶ In Arizona alone, the resistance rate of macrolide resistant *S. pneumoniae* to macrolides in 562 isolates over a 10 year period was 23.6 percent.²⁷

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-life (hrs)	Metabolites	Excretion (%)
azithromycin (Zithromax) ²⁸	38	68	--	Predominantly bile
azithromycin ER suspension (Zmax) ²⁹	83	59	--	Predominantly bile
clarithromycin (Biaxin)	50 (250 mg)	3 – 4 (250 mg) 5 – 7 (500 mg)	14-OH clarithromycin (active)	Urine: dose dependent 20 (250mg) 30 (500mg) 40 (suspension)
clarithromycin (Biaxin XL) ³⁰	--	--	14-OH clarithromycin (active)	--
erythromycin ³¹	Varies with salt and formulation	1.5 – 2	No active metabolites	Urine: <5 Predominantly bile
telithromycin (Ketek) ³²	57	10	4 metabolites	Urine: 13 Feces: 44

CONTRAINDICATIONS/WARNINGS^{33,34,35,36}

Clostridium difficile-associated diarrhea has been reported with nearly all antibacterials 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 *C. difficile*-associated diarrhea. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. *C. difficile*-associated diarrhea must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since *C. difficile*-associated diarrhea has been reported to occur over two months after the administration of antibacterial agents. If *C. difficile*-associated diarrhea 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.

azithromycin (Zithromax, Zmax)^{37,38}

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any other macrolide or ketolide antibiotic. Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported rarely in patients receiving azithromycin. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, 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 unknown at present. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Azithromycin is safe and effective in the treatment of CAP due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy. 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 nosocomially acquired 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).

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

Caution should be exercised when azithromycin ER suspension (Zmax) is administered to patients with glomerular filtration rate (GFR) <10 mL/min. This is due to a higher incidence of gastrointestinal adverse events (8 of 19 subjects) observed in a limited number of subjects with GFR <10 mL/min.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization. In early 2013, the FDA released a warning regarding azithromycin and the risk of

abnormal changes in the electrical activity of the heart that could lead to potentially fatal arrhythmias.³⁹ Postmarketing reviews showed that patients at particular risk are those with known risk factors such as existing QT prolongation, bradycardia, low levels of magnesium or potassium, or who are on anti-arrhythmic agents.

Azithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin. 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.

clarithromycin (Biaxin, Biaxin XL)⁴⁰

Clarithromycin is contraindicated in patients with hypersensitivity to clarithromycin or any other macrolide antibiotic. Clarithromycin is also contraindicated in combination with cisapride, pimozide, astemizole, terfenadine, ergotamine, and dihydroergotamine due to the risk of potentially fatal cardiac arrhythmias including QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Arrhythmias are likely due to inhibition of metabolism of erythromycin and clarithromycin.

For patients with severe renal impairment, with or without coexisting hepatic impairment, decreased clarithromycin dosage or prolonged dosing intervals may be appropriate.

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

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including *torsades de pointes*.

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins), lovastatin or simvastatin, due to the risk of rhabdomyolysis. Treatment with these agents should be discontinued during clarithromycin treatment.

Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects of pregnancy outcome and/or embryo-fetal development in monkeys, rats, mice, and rabbits at doses that produced plasma levels two to 17 times the serum levels achieved in humans treated at the maximum recommended human dose.

erythromycin⁴¹

Erythromycin is contraindicated in patients receiving any of the following drugs: cisapride, pimozide, astemizole, or terfenadine.

Allergic reactions ranging from urticaria to anaphylaxis have occurred with erythromycin. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely.

There have been reports of hepatic function impairment, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin.

Erythromycin may aggravate the weakness of patients with myasthenia gravis.

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. A manufacturer noted one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis; seven neonates (five percent) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. A possible dose-response effect was described with an absolute risk of IHPS of 5.1 percent for infants who took erythromycin for eight to 14 days and 10 percent for infants who took erythromycin for 15-21 days. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal *Chlamydia trachomatis* infections), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents should be informed to contact their physician if vomiting or irritability with feeding occurs.

telithromycin (Ketek)⁴²

Telithromycin is contraindicated in patients with a history of hypersensitivity to telithromycin and/or any components of tablets, or any macrolide antibiotic. Telithromycin is contraindicated in patients with a history of jaundice and/or hepatitis secondary to any macrolide antibiotic. Concurrent administration of cisapride or pimozide with telithromycin is contraindicated.

Telithromycin is contraindicated in patients with myasthenia gravis. Fatal and life-threatening respiratory failure have been reported in patients with myasthenia gravis after receiving telithromycin and even within the first few hours after the first dose.

Telithromycin is a strong CYP3A4 inhibitor, and an interaction may occur while using both drugs at their recommended doses. If coadministration of telithromycin and colchicine is necessary in patients with normal renal and hepatic function, the dose of colchicine should be reduced. Patients should be monitored for clinical symptoms of colchicine toxicity. Concomitant administration of telithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

Acute hepatic failure and severe liver toxicity, including fatal events and life-threatening events requiring liver transplantation, have been reported with telithromycin. Serious events reportedly occur after a few doses of telithromycin and progress very rapidly. If liver injury is suspected, patients should discontinue telithromycin immediately and be evaluated for liver injury (fulminant hepatitis and hepatic necrosis). Elevation of hepatic liver enzymes with hepatitis, both with and without jaundice, has been reported with telithromycin use. Events are generally reversible; however, more serious liver toxicity has been reported.⁴³

Telithromycin also may cause QTc prolongation in patients with risk factors for QTc prolongation (uncorrected hypokalemia or hypomagnesemia, concurrent antiarrhythmics, or severe bradycardia) or those with congenital QTc interval prolongation. Cases of torsades de pointes have been reported following telithromycin.

Visual disturbances including the slowing of ability to accommodate and visual blurring have been reported. Females under 40 years of age appear to have the highest incidence of visual disturbance (2.1 versus zero percent for comparators). Patients should be aware of how this may impact driving and/or operating machinery.

Transient loss of consciousness has been reported with telithromycin. Due to the potential for visual disturbances and loss of consciousness, patients should minimize driving or use of heavy machinery or other hazardous activities while on telithromycin.

DRUG INTERACTIONS

azithromycin (Zithromax, Zmax)⁴⁴

Antacids containing aluminum or magnesium salts reduce the bioavailability of azithromycin.

Use with warfarin can increase coagulation time, monitor prothrombin times.

Coadministration 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 side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.

clarithromycin (Biaxin, Biaxin XL)^{45, 46}

Clarithromycin and erythromycin are substrates and inhibitors of the cytochrome (CYP) P450 3A enzyme family. Clinically significant drug interactions due to inhibition of the 3A family by clarithromycin include disopyramide and quinidine, which can lead to torsades de pointes; ergotamine and dihydroergotamine, which can lead to acute ergot toxicity including vasospasm and ischemia of extremities; triazolam and alprazolam, which can lead to increased pharmacological effect of the benzodiazepines; itraconazole, atazanavir (Reyataz[®]), saquinavir (Invirase[®]) (increased exposure of clarithromycin and antiretroviral), and simvastatin and lovastatin, which may lead to increased risk of myopathy. Concurrent administration of clarithromycin and terfenadine is contraindicated.

When clarithromycin is used in combination with hypoglycemics, including insulin, there is a risk of significant hypoglycemia. Careful monitoring of glucose levels is indicated.

Colchicine is a substrate for CYP450 3A4 enzyme and the efflux transporter, P-glycoprotein (Pgp). Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is an inhibitor of both CYP450 3A4 and Pgp, which may result in a higher exposure to colchicine and digoxin. Patients should be monitored for clinical symptoms of colchicine toxicity. Serum digoxin concentrations should be monitored while patients are receiving clarithromycin concurrently.

Clarithromycin has been shown to interact with carbamazepine, oral anticoagulants, theophylline, and ritonavir (Norvir[®], Kaletra[®]). Consider monitoring carbamazepine levels. Prothrombin times or INR should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants. Serum theophylline concentrations monitoring should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. Ritonavir increases clarithromycin levels significantly; however, dosage adjustments in patients with normal renal function are not necessary. Patients with impaired renal function and taking ritonavir should have clarithromycin dose reduced in the following manner: creatinine clearance (CrCL) 30-60 mL/min – reduce clarithromycin dose by 50 percent; CrCL<30 mL/min – reduce clarithromycin dose by 75 percent.

Bradyarrhythmias, hypotension, and lactic acidosis have been observed in patients receiving concurrent verapamil with clarithromycin.

Interactions that have been reported with erythromycin and/or clarithromycin include alfentanil, bromocriptine, cyclosporine, disopyramide, hexobarbital, phenytoin, pimozide, rifabutin, tacrolimus, methylprednisolone, and valproate.

Clarithromycin tablets and zidovudine doses should be staggered to avoid the decreased absorption of zidovudine. There is no decrease in absorption of zidovudine when administered with clarithromycin suspension.

Coadministration of clarithromycin and erythromycin with sildenafil (Viagra®), tadalafil (Cialis®), or vardenafil (Levitra®) may result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil, and vardenafil dosages should be considered when these drugs are coadministered with clarithromycin.

Concurrent administration of oral midazolam and clarithromycin should be avoided as the midazolam area under the curve (AUC) is increased by seven-fold with coadministration with clarithromycin. Cautious use is warranted with administration of other benzodiazepines metabolized by the CYP3A system, including triazolam and alprazolam.

Tolterodine (Detrol®, Detrol LA®) is metabolized by CYP2D6; however, in a subset of patients devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

erythromycin

Erythromycin has been shown to interact with oral anticoagulants, theophylline, and digoxin. Consider monitoring digoxin levels. Prothrombin times or INR should be carefully monitored while patients are receiving erythromycin and oral anticoagulants. Serum theophylline levels monitoring should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for increases in creatine kinase (CK) and serum transaminases.

telithromycin (Ketek)⁴⁷

Telithromycin has been shown to be a strong inhibitor of the CYP450 3A4 enzyme. Telithromycin is contraindicated with cisapride and pimozide. Concurrent use of telithromycin with atorvastatin (Lipitor®), lovastatin, or simvastatin should be avoided due to the potential for elevated serum levels of the statin and subsequent increased risk of myopathy.

Coadministration telithromycin and drugs metabolized by CYP450 3A4 enzyme, the following drugs may lead to increased levels or prolonged action of these drugs: carbamazepine, hexobarbital, cyclosporine, tacrolimus (Prograf®), and sirolimus (Rapamune®).

Due to enzyme induction by phenytoin, phenobarbital, and carbamazepine, lower telithromycin levels may occur. Patients on rifampin should not receive telithromycin due to enzyme induction by rifampin and expected lower levels of telithromycin.

Monitor digoxin levels with concurrent telithromycin therapy. Increased INR values have been observed with concurrent telithromycin and warfarin administration. Monitoring of the INR is recommended. Heart failure patients on metoprolol may have a greater exposure to metoprolol due to

inhibition of CYP2D6 by telithromycin. Monitoring to determine possible increased effects of metoprolol is recommended.

Coadministration of telithromycin and ergot alkaloid derivatives (such as ergotamine or dihydroergotamine) is not recommended and may result in acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia as it has been reported when macrolide antibiotics were coadministered.

Bradycardias, hypotension, and lactic acidosis have been observed in patients receiving concurrent calcium channel blockers with telithromycin.

In patients treated with metoprolol for heart failure, the increased exposure to metoprolol, a CYP2D6 substrate, may be of clinical importance. Therefore, coadministration of telithromycin and metoprolol in patients with heart failure should be considered with caution.

ADVERSE EFFECTS

Drug	Diarrhea	Nausea	Abdominal pain	Rash	Dizziness	↑ ALT/AST
azithromycin (Zithromax) ^{48,49}	5	3	3	<1	<1	1-2
adults multiple dose	7	5	5	nr	nr	reported
single 1 gram dose						
children						
30 mg/kg x 1 dose	4.3	1	1.4	1	reported	reported
10 mg/kg x 3days	2.6	0.4	1.7	1.6	reported	reported
5 day treatment	1.8-5.8	0.5-1.9	1.2-3.4	0.4-1.6	reported	reported
azithromycin (Zmax) ⁵⁰ adults	12	4	3	<1	<1	<1/<1
children	7-10	4	2-4	5	nr	<1/<1
clarithromycin (Biaxin) ⁵¹ adults	3	3	2	3	reported	<1/<1
children	6	nr	3	3	nr	nr
clarithromycin (Biaxin XL) ⁵²	6	3	nr	nr	reported	<1/<1
erythromycin ⁵³	7.3	7.5	7.5	nr	2.3	nr
telithromycin (Ketek) ⁵⁴	10-10.8	7-7.9	nr	0.2-2	2.8-3.7	1.6 (> 3x ULN)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported. AST = aspartate aminotransferase. ALT = alanine aminotransferase

Abnormal taste has been reported in three percent of adults and seven percent of pediatric patients receiving clarithromycin (Biaxin). With clarithromycin ER (Biaxin XL), abnormal taste was reported in seven percent of adult patients.⁵⁵ Reports of alterations of the sense of smell including smell loss, usually in conjunction with taste perversion or taste loss and tooth discoloration, usually reversible with professional dental cleaning in patient receiving clarithromycin (Biaxin).

SPECIAL POPULATIONS^{56,57,58,59}

Pediatrics

Safety and efficacy of telithromycin (Ketek) in patients less than 18 years of age have not been established.

Clarithromycin (Biaxin) has been FDA-approved for treatment of children six months of age and older for acute otitis media, CAP, pharyngitis/tonsillitis, skin and skin structure infections, and acute bacterial sinusitis. For the management of MAC, clarithromycin has been studied in children 20 months of age and older. Clarithromycin ER (Biaxin XL) is not indicated for children.

Azithromycin (Zithromax) has been approved for use in children six months of age and older for the treatment of AOM, CAP, and acute sinusitis. Azithromycin has been approved for use in children two years of age and older in the treatment of pharyngitis and tonsillitis. The safety and efficacy of azithromycin in the prevention and treatment of disseminated MAC infections in HIV+ children have not been established. Limited safety data are available for children five months to 18 years of age who were treated for opportunistic infections. Azithromycin ER (Zmax) is approved for the treatment of CAP in children six months of age and older as a single dose treatment. Safety and effectiveness of azithromycin ER (Zmax) in children with acute bacterial sinusitis have not been established.

Pregnancy

Azithromycin and erythromycin are Pregnancy Category B. Clarithromycin, clarithromycin ER, and telithromycin are Pregnancy Category C. Clarithromycin should not be used in pregnancy unless the potential benefit justifies the potential risk to the fetus.

Alaska Native persons

A surveillance study evaluated the antimicrobial resistance in *Helicobacter pylori* isolates from Alaska Native persons during 1999 to 2003.⁶⁰ A total of 964 biopsy specimens were obtained from 687 patients with 51 percent of cultures being positive for *H. pylori*. Metronidazole resistance was noted in 44 percent of isolates. Clarithromycin resistance was observed in 31 percent of isolates and amoxicillin resistance was observed in two percent of isolates. No resistance to tetracyclines was observed in the trial. Females were more likely to have metronidazole resistance ($p < 0.01$) and clarithromycin resistance ($p = 0.05$). These resistance rates were higher than observed in other areas of the US, according to the authors.

DOSAGES^{61,62,63,64}

Drug	AECB Dosage	Duration (Days)	Sinusitis Dosage	Duration (Days)	AOM Dosage	Duration (Days)	CAP Dosage	Duration (Days)
azithromycin (Zithromax) 100, 200 mg/5mL suspension; 250, 500, 600 mg tablet; 1 g powder packet	500 mg for one dose, then 250 mg daily on days 2 – 5 or 500 mg daily for three days	3 – 5	500 mg daily pediatrics: > six months of age: 10 mg/kg for three days	3	pediatrics: > six months of age: 10 mg/kg for one dose, then 5 mg/kg daily on days 2 – 5 or 30 mg/kg for one dose, or 10 mg/kg/day for three days	1 - 5	500 mg for one dose, then 250 mg daily on days 2 – 5 or IV therapy: 500 mg daily IV for ≥ two days then oral 500 mg daily to complete seven to 10 days of therapy pediatrics: > six months of age: 10mg/kg for one dose, then 5 mg/kg daily on days 2 – 5	5 – 10
azithromycin ER suspension (Zmax) 2 g/60 mL suspension	--	--	2 g as one-time dose – take on empty stomach	1	--	--	2 g as one-time dose – take on empty stomach pediatrics: > six months of age: 60mg/kg as one-time dose, up to 2 g maximum. Take on empty stomach	1
clarithromycin (Biaxin) 125, 250 mg/5mL suspension; 250, 500 mg tablet	250 – 500 mg every 12 hours	7 – 14	500 mg every 12 hours pediatrics: > six months of age: 7.5 mg/kg every 12 hours	14	pediatrics: > six months of age: 7.5 mg/kg every 12 hours	10	250 mg every 12 hours pediatrics: > six months of age: 7.5 mg/kg every 12 hours	7 – 14

Dosages (continued)

Drug	AECB Dosage	Duration (Days)	Sinusitis Dosage	Duration (Days)	AOM Dosage	Duration (Days)	CAP Dosage	Duration (Days)
clarithromycin ER (Biaxin XL) 500 mg ER tablet	1,000 mg daily	7	1,000 mg daily	14	--	--	1,000 mg daily	7
erythromycin (many)	--	--	250 – 500 mg (of base or stearate) every six hours or 400 – 800 mg (ethylsuccinate) every six hours pediatrics: 20 – 50 mg/kg/day in divided doses every six to 12 hours	7 – 14	pediatrics: 20 – 50 mg/kg/day in divided doses every six to 12 hours	10	250 – 500 mg (of base or stearate) every six hours or 400 – 800 mg (ethylsuccinate) every six hours pediatrics: 20 – 50 mg/kg/day in divided doses every six to 12 hours	7 – 14
telithromycin (Ketek) 300, 400 mg tablets	--	--	--	--	--	--	800 mg daily	7 – 10

- Azithromycin (Zithromax) oral suspension and azithromycin ER (Zmax) should be given at least one hour before or two hours after a meal. The tablets can be taken with or without food.
- If a patient vomits within five minutes of administration of azithromycin ER (Zmax), the health care provider should consider additional antibiotic treatment since minimal absorption of azithromycin would be expected. Since insufficient data exist on absorption of azithromycin if a patient vomits between five and 60 minutes following administration, alternative therapy should be considered. Neither a second dose of azithromycin ER nor alternative treatment is warranted if vomiting occurs ≥ 60 minutes following administration, in patients with normal gastric emptying. In patients with delayed gastric emptying, alternative therapy should be considered.
- Clarithromycin (Biaxin) tablets and oral suspension may be taken with or without food. Clarithromycin ER (Biaxin XL) should be taken with food. Do not refrigerate clarithromycin suspension.
- Telithromycin (Ketek) may be given without regard for food. Telithromycin (Ketek) dose should be reduced to 600 mg daily for patients with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$). No dosage adjustment is warranted for hepatic impairment unless concurrent renal impairment is also present.

Dosages (continued)^{65,66,67,68}

Drug	Prevention of disseminated MAC infections in HIV+ patients		Treatment of disseminated MAC infections in HIV+ patients	
	Adults	Children	Adults	Children
azithromycin (Zithromax)	1,200 mg weekly	--	600 mg daily	--
clarithromycin (Biaxin)	500 mg twice daily	7.5 mg/kg twice daily	500 mg twice daily	7.5 mg/kg twice daily

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved uses for all drugs in this class. Randomized, controlled trials performed in the United States comparing agents in this class within the last five years for the currently approved indications are considered the most relevant in this category. Studies with children were also included in the search. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Numerous clinical trials have been published comparing azithromycin and clarithromycin in both the inpatient and outpatient settings. There is little evidence that one drug is better than others for the approved indications. Due to the more rapid rise in macrolide resistance among *S. pneumoniae* isolates in the United States in the last several years, only studies published since 2000 are included. Nationwide and regional variances in pathogens and susceptibility and resistance rates must be taken into consideration when evaluating studies. Many trials utilize investigator-blinded study designs, especially in the pediatric studies, where double-blind studies with suspension products are difficult. Many short-term clinical trials in outpatients with minor infections lose a significant portion of patients (greater than 25 percent) to a lack of follow-up. Only studies evaluating infections treated as outpatients were included.

Many trials performed with the macrolides and ketolides compare these products to other broad-spectrum antibiotics such as the fluoroquinolones, cephalosporins, and penicillins.

azithromycin (Zithromax) versus clarithromycin (Biaxin)

In a randomized, double-blind, double-dummy multicenter trial, azithromycin and clarithromycin were compared in 322 adults with AECB in the outpatient setting.⁶⁹ Patients were randomized to azithromycin 500 mg once daily for three days or clarithromycin 500 mg twice daily for 10 days. The primary outcome was clinical response on days 21 to 24 in the modified intent-to-treat analysis (n=318). The clinical cure rates were similar, with 85 percent in the azithromycin group and 82 percent in the clarithromycin group (95% CI, -5.9 to 12). No differences in clinical cure rates or bacteriological success rates were identified

when specific pathogens were evaluated. Adverse effects were similar between the groups with the most common being abdominal pain, diarrhea, and nausea. The manufacturer of azithromycin supported the study.

azithromycin ER suspension (Zmax) versus clarithromycin ER (Biaxin XL)

A phase III, multicenter, randomized, double-blind, double-dummy trial compared single-dose azithromycin and clarithromycin ER in 501 adults with mild to moderate CAP.⁷⁰ Azithromycin was given as a single 2 g dose, and clarithromycin ER was given as 1 g daily for seven days. Clinical cure rates at days 14 to 21 were 92.6 (187/202 patients) and 94.7 percent (198/209 patients) for azithromycin and clarithromycin, respectively, in the clinical per protocol population. Pathogen eradication rates were 91.8 percent (123/134 patients) for the azithromycin group and 90.5 percent (153/169 patients) for the clarithromycin ER group. Adverse event rates were similar for both groups, with most reported as mild to moderate in severity.

clarithromycin (Biaxin) versus clarithromycin ER (Biaxin XL)

Clarithromycin and clarithromycin ER were compared in 485 patients with AECB in a double-blind, randomized, parallel-group study.⁷¹ Patients were ambulatory patients with AECB, purulent sputum, and a diagnosis of COPD with a FEV₁ of less than 70 percent of predicted value. Patients were given clarithromycin 500 mg twice daily for seven days or clarithromycin ER 1,000 mg daily for five days. Test of cure visit was scheduled at days 14 to 40. A total of 391 patients completed the follow-up. Clinical cure rates were similar between the groups (both 84 percent; 95% CI, -7.9 to 7.2). Microbiological eradication rates were 87 and 89 percent for clarithromycin ER and clarithromycin groups, respectively. Clarithromycin ER and clarithromycin adverse reaction rates were 13 and 18 percent, respectively; the rate of gastrointestinal complaints and abnormal taste were less in the clarithromycin ER group. Clarithromycin ER had significantly lower rates of abnormal taste (three and eight percent, p=0.012) compared to clarithromycin.

telithromycin (Ketek) versus clarithromycin (Biaxin)

Telithromycin and clarithromycin were compared in 416 adult patients with diagnosed CAP in a randomized, double-blind, double-dummy, parallel-group multicenter clinical trial.⁷² Patients received either telithromycin 800 mg once daily (administered as two 400 mg encapsulated tablets in the morning) and placebo (administered as two encapsulated tablets identical to telithromycin in the evening) or high-dose clarithromycin 500 mg administered as two 250 mg identical encapsulated tablets twice daily for 10 days. Clinical outcome was evaluated post-therapy and days 17 to 24 after the completion of therapy. Clinical cure rates determined on days 31 to 45 were 88.3 percent with telithromycin and 88.5 percent with clarithromycin. Bacterial eradication rates were comparable between treatment groups (telithromycin 87.5 percent; clarithromycin 96.7 percent). Both treatments were fairly well tolerated with mostly mild adverse effects.

Efficacy and safety of telithromycin and clarithromycin were compared in 575 adult patients with mild to moderate CAP in a multicenter, double-blind, active-controlled study in Canada.⁷³ Patients were randomized to telithromycin 800 mg once daily for five or seven days or clarithromycin 500 mg twice daily for 10 days. A total of 466 patients completed the study. Clinical cure rates were 89.3 percent (telithromycin five days), 88.8 percent (telithromycin seven days), and 91.8 percent (clarithromycin group). For the identified pathogens, bacteriological eradication rates were similar among the three treatment groups. Eradication of *S. pneumoniae* was 95.8, 96.7, and 88.5 percent for telithromycin five

days, telithromycin seven days, and clarithromycin, respectively. For *H. influenzae*, bacteriological eradication rates were 88, 84, and 88.2 percent for telithromycin five days, telithromycin seven days, and clarithromycin, respectively. Clinical efficacy was demonstrated in both the telithromycin groups for all cases with pneumococcal bacteremia (19/19 cases), atypical pathogens (9/9 cases), and erythromycin-resistant *S. pneumoniae* isolates (5/5 cases). Most common adverse effects were gastrointestinal in nature. Hospitalization rates for patients enrolled in the study were evaluated in a separate analysis.⁷⁴ Hospitalizations occurred in seven patients in the clarithromycin group compared to three patients in the telithromycin five-day group (p=0.283) and one patient in the seven-day group (p=0.021).

SUMMARY

Azithromycin, clarithromycin, and telithromycin are generally active against bacteria susceptible to erythromycin although the newer macrolides have enhanced activity against *H. influenzae*. Telithromycin may be active against some bacteria resistant to erythromycin in the treatment of adults with CAP. However, the risk of serious adverse events and drug interactions limit the usefulness of telithromycin. All erythromycin products have been reported to have a high incidence of gastrointestinal adverse effects. The newer macrolides are given once or twice a day and may have a lower incidence of gastrointestinal adverse effects.

Azithromycin, clarithromycin, and erythromycin have been studied in children for a variety of FDA-approved indications whereas telithromycin (Ketek) and clarithromycin (Biaxin XL) have not been approved for use in pediatric patients. Extended-release formulations of clarithromycin and azithromycin (Zmax) offer less frequent administration; however, comparative clinical trial data are limited.

REFERENCES

- 1 Zithromax [package insert]. New York, NY; Pfizer; February 2013.
- 2 Zmax [package insert]. New York, NY; Pfizer; February 2013.
- 3 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 4 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013
- 5 Clinical Pharmacology. Available at: <http://clinicalpharmacology.com>. Accessed November 8, 2013.
- 6 Ketek [package insert]. Kansas City, MO; Aventis; December 2010.
- 7 Ruuskanen O. Safety and tolerability of azithromycin in pediatric infectious diseases: 2003 update. *Pediatr Infect Dis J*. 2004; 23(2 Suppl):S135-9.
- 8 Blondeau JM. The evolution and role of macrolides in infectious diseases. *Expert Opin Pharmacotherapy*. 2002; 3(8):1131-51.
- 9 Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clin Infect Dis*. 2007; 44(Suppl 2):S27-S72. Available at: http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/CAP%20in%20Adults.pdf. Accessed November 8, 2013.
- 10 Bradley JS, Byington CL, Shah SS, et al. The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011. Available at: <http://cid.oxfordjournals.org/content/early/2011/08/30/cid.cir531.full>. Accessed November 8, 2013.
- 11 The GOLD guidelines. Available at: <http://www.goldcopd.org/guidelines-pocket-guide-to-copd-diagnosis.html>. Accessed November 8, 2013.
- 12 Stevens DL, Bisno AL, Chambers HF, et al for the Infectious Diseases Society of America. Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections. *Clin Infect Dis*. 2005; 41:1373-406. Available at: http://www.idsociety.org/content.aspx?id=4430#skin_and_soft_tissue. Accessed November 8, 2013.
- 13 Rosenfeld RM, Andes D, Bhattacharyya N, Cheung D, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg*. 2007;137(3Suppl):S1-31. Available at: <http://www.entnet.org/qualityimprovement/upload/Adult%20Sinusitis%20Guideline.pdf>. Accessed November 8, 2013.
- 14 Chow AW, Benninger MS, Brook I, et al. IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. *Clin Infect Dis*. 2012; published online 20 March 2012. Available at: <http://cid.oxfordjournals.org/content/early/2012/03/20/cid.cir1043.full>. Accessed November 8, 2013.
- 15 Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR*. 2010; 59(RR-12). Available at: <http://www.cdc.gov/std/treatment/2010/toc.htm>. Accessed November 8, 2013.
- 16 CDC. Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR*. August 10, 2012 / 61(31); 590-594. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm?s_cid=mm6131a3_w. Accessed November 8, 2013.
- 17 CDC. Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of Pertussis. 2005 CDC Guidelines. *MMWR*. 2005; 54(RR-14):1-13. Available at: <http://www.cdc.gov/pertussis/>. Accessed November 8, 2013.

- 18 Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009; 58(RR04):1-198. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0826a1.htm?s_cid=rr58e0826a1_e. Accessed November 8, 2013.
- 19 Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009; 58(RR04):1-198. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0826a1.htm?s_cid=rr58e0826a1_e. Accessed November 8, 2013.
- 20 Ketek [package insert]. Kansas City, MO; Sanofi-Aventis; December 2010.
- 21 Clinical Pharmacology. Available at: <http://clinicalpharmacology.com>. Accessed November 8, 2013.
- 22 Barry AL, Fuchs PC, Brown SD. Relative potency of telithromycin, azithromycin and erythromycin against recent clinical isolates of gram-positive cocci. Eur J Clin Microbiol Infect Dis. 2001; 20(7):494-7.
- 23 Schite GC, Felmingham D. Susceptibility of Streptococcus pneumoniae to penicillin, azithromycin and telithromycin (PROTEKT 1999-2003). Int J Antimicrob Agents. 2005; 26(6):479-85.
- 24 van Rensburg DJ, Fogarty C, Kohno S, et al. Efficacy of telithromycin in community-acquired pneumonia caused by pneumococci with reduced susceptibility to penicillin and/or erythromycin. Chemotherapy. 2005; 51(4):186-92.
- 25 Beekmann SE, Diekema DJ, Heilmann KP, et al. Macrolide use identified as risk factor for macrolide-resistant Streptococcus pneumoniae in a 17-center case-control study. Eur J Clin Microbiol Infect Dis. 2006; 25(5):335-9.
- 26 Green MD, Beall B, Marcon MJ, et al. Multicentre surveillance of the prevalence and molecular epidemiology of macrolide resistance among pharyngeal isolates of group A streptococci in the USA. J Antimicrob Chemother. 2006; 57(6):1240-3.
- 27 Bowers JR, Driebe EM, Nibecker JL, et al. Dominance of multidrug resistance CC271 clones in macrolide resistance streptococcus pneumoniae in Arizona. BMC Microbiol. 2012;12:12.
- 28 Zithromax [package insert]. New York, NY; Pfizer; February 2013.
- 29 Zmax [package insert]. New York, NY; Pfizer; February 2013.
- 30 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 31 Clinical Pharmacology. Available at: <http://clinicalpharmacology.com>. Accessed November 8, 2013.
- 32 Ketek [package insert]. Kansas City, MO; Sanofi-Aventis; December 2010.
- 33 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013
- 34 Zithromax [package insert]. New York, NY; Pfizer; February 2013.
- 35 Clinical Pharmacology. Available at: <http://clinicalpharmacology.com>. Accessed November 8, 2013.
- 36 Ketek [package insert]. Kansas City, MO; Sanofi-Aventis; December 2010.
- 37 Zithromax [package insert]. New York, NY; Pfizer; February 2013.
- 38 Zmax [package insert]. New York, NY; Pfizer; February 2013.
- 39 Azithromycin information. Available at: <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm343281.htm>. Accessed Nov 19, 2013.
- 40 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 41 Erythromycin. Available at: <http://online.factsandcomparisons.com>. Accessed November 8, 2013.
- 42 Ketek [package insert]. Kansas City, MO; Sanofi-Aventis; December 2010.
- 43 Clay KD, Hanson JS, Pope SD, et al. Brief Communication: Severe hepatotoxicity of telithromycin: Three case reports and literature review. Ann Int Med. 2006; 144:415-420.
- 44 Zithromax [package insert]. New York, NY; Pfizer; February 2013.
- 45 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 46 FDA safety notice. Available at: <http://www.fda.gov/safety/medwatch/safetyinformation/ucm258816.htm>. Accessed 19 NOV 2013.
- 47 Ketek [package insert]. Kansas City, MO; Sanofi-Aventis; December 2010.
- 48 Zithromax [package insert]. New York, NY; Pfizer; February 2013.
- 49 Clinical Pharmacology. Available at: <http://clinicalpharmacology.com>. Accessed November 8, 2013.
- 50 Zmax [package insert]. New York, NY; Pfizer; February 2013.
- 51 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 52 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 53 Clinical Pharmacology. Available at: <http://clinicalpharmacology.com>. Accessed November 8, 2013.
- 54 Ketek [package insert]. Kansas City, MO; Sanofi-Aventis; December 2010.
- 55 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 56 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 57 Zithromax [package insert]. New York, NY; Pfizer; February 2013.
- 58 Clinical Pharmacology. Available at: <http://clinicalpharmacology.com>. Accessed November 8, 2013.
- 59 Ketek [package insert]. Kansas City, MO; Sanofi-Aventis; December 2010.
- 60 Bruce MG, Bruden DL, McMahon BJ, et al. Alaska sentinel surveillance for antimicrobial resistance in Helicobacter pylori isolates from Alaska native persons, 1999-2003. Helicobacter. 2006; 11(6):581-8.
- 61 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 62 Zithromax [package insert]. New York, NY; Pfizer; February 2013.
- 63 Clinical Pharmacology. Available at: <http://clinicalpharmacology.com>. Accessed November 8, 2013.
- 64 Ketek [package insert]. Kansas City, MO; Sanofi-Aventis; December 2010.
- 65 Biaxin / Biaxin XL [package insert]. Chicago, IL; AbbVie; September 2013.
- 66 Zithromax [package insert]. New York, NY; Pfizer; February 2013.
- 67 Clinical Pharmacology. Available at: <http://clinicalpharmacology.com>. Accessed November 8, 2013.
- 68 Ketek [package insert]. Kansas City, MO; Sanofi-Aventis; December 2010.
- 69 Swanson RN, Lainez-Ventosilla A, De Salvo MC, et al. Once-daily azithromycin for 3 days compared with clarithromycin for 10 days for acute exacerbation of chronic bronchitis: a multicenter, double-blind, randomized study. Treat Respir Med. 2005; 4(1):31-9.

-
- 70 Drehobl MA, De Salvo MC, Lewis DE, et al. Single-dose azithromycin microspheres vs. clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. *Chest*. 2005; 128(4):2230-7.
- 71 Gotfried M, Notario G, Spiller J, et al. Comparative efficacy of once daily, 5-day short-course therapy with clarithromycin extended-release versus twice daily, 7-day therapy with clarithromycin immediate-release in acute bacterial exacerbation of chronic bronchitis. *Curr Med Res Opin*. 2005; 21(2):245-54.
- 72 Mathers Dunbar L, Hassman J, Tellier G. Efficacy and tolerability of once-daily oral telithromycin compared with clarithromycin for the treatment of community-acquired pneumonia in adults. *Clin Ther*. 2004; 26(1):48-62.
- 73 Tellier G, Niederman MS, Nusrat R, et al. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. *J Antimicrob Chemother*. 2004; 54(2):515-23.
- 74 Tellier G, Chang JR, Asche CV, et al. Comparison of hospitalization rates in patients with community-acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days. *Curr Med Res Opin*. 2004; 20(5):739-47.

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