Telithromycin (Ketek™) for the Treatment of Upper and Lower Respiratory Infections

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INTRODUCTION

Community-acquired pneumonia (CAP), acute bacterial sinusitis (ABS), and acute exacerbations of chronic bronchitis (AECB) are some of the most commonly diagnosed infectious diseases in the U.S.1,2 CAP is a lower respiratory tract infection (LRTI) acquired from the community outside of a hospital or a long-term care facility. It is characterized by inflammation of the lungs and is generally preceded by a viral upper respiratory tract infection (URTI).3,4 Each year, CAP is diagnosed in 5.6 million U.S. residents, with 1.1 million people requiring hospitalization.1

Approximately 15% of Americans are affected by ABS annually, and almost 30 million people seek treatment.2,5 ABS is a bacterial URTI occurring in one or more sinuses (i.e., maxillary, ethmoid, or frontal). It is generally preceded by a viral URTI. The prevalence of ABS may be higher, because symptoms associated with it (facial pain, headache, fever, and purulent nasal discharge) often make it difficult to distinguish ABS from allergies or the common cold, for which people do not always seek professional treatment.2 Worsening of bronchitis symptoms, such as an increase in dyspnea, sputum volume, or sputum purulence, accurately characterizes AECB. Almost 14 million Americans have chronic bronchitis, and these individuals experience at least three acute exacerbations each year.5,6

Beta-lactams, macrolides, fluoroquinolones, trimethoprim-sulfamethoxazole, and tetracyclines are the antibacterial agents that are commonly used for the treatment of URTIs and LRTIs.1,7,8,9 Although most of these antibacterial therapies are effective in treating particular strains of bacteria, the need for an oral antibacterial agent that possesses a low potential to induce bacterial resistance and that can retain activity against pathogens that have become resistant to current regimens has sparked the emergence of a new class of antibacterial agents.6,10

Telithromycin (Ketek™, Aventis) is the first member of the ketolides (a new class of antibacterials structurally related to the macrolides) and the newest addition to the macrolide/lincosamide/streptogramin B (MLSb) family of antimicrobial agents.7,11-15 It is a semisynthetic derivative of erythromycin specifically formulated for the treatment of respiratory tract infections, such as ABS, AECB, and mild-to-moderate CAP, in patients 18 years of age or older.10 Like other agents belonging to the MLSb family, telithromycin also exerts its antibacterial activity via inhibition of bacterial protein synthesis.

Resistance to macrolide antimicrobial agents occurs because of a modification to one of the target sites as a result of methylation. Unlike those of the macrolides, telithromycin’s structural modifications allow it to bind more tightly to two distinct regions of the ribosomal RNA, thereby enhancing its potency and enabling this drug to overcome the resistance commonly seen in the MLSb family.12

ETIOLOGY

In most cases, ABS, AECB, and CAP are caused by bacterial infections. Streptococcus pneumoniae and Haemophilus influenzae contribute to 70% of the ABS cases reported. Moraxella catarrhalis, Staphylococcus pyogenes, and staphylococcal infections occur less frequently and are seen more often in patients with chronic or recurrent sinuses.2,5 In patients with AECB, H. influenzae is the most common causative microorganism, but S. pneumoniae and M. catarrhalis are also frequently observed.7 S. pneumoniae accounts for 50% of CAP cases, whereas H. influenzae accounts for 15% of cases. M. catarrhalis, Staphylococcus aureus, S. pyogenes, and atypical or intracellular pathogens such as Chlamydia pneumoniae, Legionella pneumophila, and Mycoplasma pneumoniae are other bacteria involved in CAP.2,3

Seasonal allergies (hay fever), changes in atmospheric pressure (i.e., flying, mountain climbing, swimming), and cigarette tobacco (a pollutant that damages the cilia of the mucous membranes responsible for drainage) are all conditions in which the mucous membranes can become inflamed. Swollen mucous membranes trap bacteria, causing their proliferation, thereby increasing the likelihood of an infection. This swelling prevents normal drainage from sinus openings, leading to pain around the cheek and upper teeth (maxillary sinusitis) or pain over the nose and behind the eyes (ethmoid sinusitis).5

Unlike ABS, CAP causes inflammation of the lungs, with pus or another liquid filling the air sacs within the lungs. Oxygen is unable to penetrate through the lungs to the bloodstream, resulting in symptoms such as shortness of breath
Mean (±SD) Pharmacokinetic Profile of Telithromycin Following Single and Multiple (Seven Days) Once-Daily 800-mg Doses in Healthy Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single Dose (n = 18)</th>
<th>Multiple Dose (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mcg/ml)</td>
<td>1.9 (0.80)</td>
<td>2.27 (0.71)</td>
</tr>
<tr>
<td>C24hr (mcg/ml)</td>
<td>0.03 (0.013)</td>
<td>0.07 (0.051)</td>
</tr>
<tr>
<td>AUC(0–24) (mcg/hour/ml)</td>
<td>8.25 (2.6)</td>
<td>12.5 (5.4)</td>
</tr>
<tr>
<td>Terminal t1/2 (hour)</td>
<td>7.16 (1.3)</td>
<td>9.81 (1.9)</td>
</tr>
</tbody>
</table>

*Median (minimum–maximum) values.

AUC(0–24) = area under concentration vs. time curve; AUC measured from 0 to 24 hours; Cmax = maximum plasma concentration; C24hr = post-dose plasma concentration at 24 hours; SD = standard deviation; terminal t1/2 = terminal plasma half-life; Tmax = time to maximum concentration.

Data from Ketek™ (telithromycin) prescribing information. Kansas City, MO: Aventis.10

PHARMACOKINETICS

General Profile

The dissolution and intestinal permeability of telithromycin are high, thereby enabling this drug to exhibit rapid absorption from the gastrointestinal tract after a once-daily oral dosage of 800 mg, achieving peak serum concentrations (2 mcg/ml) in about one hour. The absolute bioavailability in both young and elderly individuals is 57%.10,13 Because food intake does not affect the rate and extent of absorption, telithromycin can be taken with or without regard to meals. Steady-state plasma levels are reached within two to three days of continued once-daily dosing (800 mg). Following oral administration, the terminal-phase elimination half-life is 10 hours.2,8,10 Maximum plasma concentrations (Cmax), time to maximum concentration (Tmax), terminal plasma half-life, area-under-the-curve (AUC) concentration versus the time curve, and plasma concentrations at 24 hours (C24hr) after the dose are denoted in Table 1.

Following intravenous (IV) infusion, the volume of distribution (Vd) of telithromycin is 2.9 L/kg. Human serum albumin accounts for 60% to 70% of the dose being protein-bound (in vitro).10 An 800-mg oral dose taken once daily for five days achieves high drug levels that concentrate in the bronchial mucosa, the epithelial lining fluid, and the alveolar macrophages, exceeding the minimum inhibitory concentration (MIC) of susceptible pathogens, for 2 to 24 hours after dosing.6,7,10,12

Approximately 70% of the absorbed dose of telithromycin is metabolized. It is estimated that 50% of its metabolism is mediated by the cytochrome P450 isozyme CYP450 3A4, and the remaining 50% is CYP450-independent. Telithromycin is a potent inhibitor of CYP3A4.10,11 Plasma levels indicate that 56.7% of the parent compound is the main compound circulating following exposure. The main metabolite represents 12.6% of the AUC concentration of telithromycin, whereas the three other metabolites represent 3% or less. Multiple pathways of elimination include the fecal route (7% unchanged), renal excretion (13% unchanged in the urine), and hepatic metabolism (37% of the dose).10

Special Populations

In a phase 3 study of geriatric patients with CAP, the pharmacokinetic data revealed a 1.4-fold increase in exposure (AUC) in 20 patients 65 years of age or older with CAP and a 2.0-fold increase in exposure (AUC) in 14 subjects 65 years of age or older when compared with subjects younger than age 65 years in a phase 1 study. However, age alone cannot be the sole indicator for dosage adjustments.

In a single-dose (800 mg) and a multiple-dose (800 mg) study of patients experiencing mild to severe hepatic insufficiency, the Cmax, the AUC concentration, and the terminal plasma half-life of telithromycin were comparable to those measurements obtained in healthy subjects of the same age and sex. In both studies, an increase in renal elimination was evident, indicating that the renal pathway may compensate for hepatically impaired patients whose metabolic clearance is limited. No dosage adjustments are recommended for patients with hepatic impairment.

In a multiple-dose study (400, 600, or 800 mg), 36 subjects with different degrees of renal impairment received oral telithromycin therapy daily for five days. At the steady state (SS), a 1.4-fold increase in the maximum concentration (Cmax,ss) and a 1.9-fold increase in the area under concentration versus the time curve (AUC(0–24)ss) concentration at 800-mg multiple doses were documented in the severely renally impaired patients (with a creatinine clearance below 30 ml/minute), compared with healthy volunteers.

Currently, the recommended dose for patients with severe renal impairment, including patients requiring dialysis, is 600 mg once daily. If the patient is undergoing hemodialysis, telithromycin should be administered after the patient undergoes dialysis on dialysis days.10

TREATMENT OPTIONS

Therapeutic options for the treatment of CAP, ABS, and AECB vary according to the causative organism. If the infection is of viral origin, as in some cases of CAP, the goal is to alleviate signs and symptoms through supportive care (i.e., acetaminophen to reduce fever) because there is no cure. If the cause of infection is bacterial, the clinician’s expertise or preference and antibiotic drug resistance in a particular area are factors that influence the drug of choice. Physicians usually select “empirical therapy”—prescribed according to the suspected cause (bacteria, viruses, or fungi)—because the causative organism is unknown at the start of treatment. After the pathogen is identified, therapy can be tailored to eradicate the specific pathogen.

In the past, beta-lactam antimicrobials were often used for the empirical treatment of community-acquired respiratory infections. In the 1960s, pneumococcal resistance to penicillins emerged, and the spread of penicillin-resistant S. pneumoniae strains has been documented.
With the widespread use of beta-lactams, penicillin-resistant \textit{S. pneumoniae} strains were of more concern than macrolide-resistant \textit{S. pneumoniae} strains. However, since the release of the CAP guidelines, published by the American Thoracic Society in 1993, atypical organisms have steadily become a greater concern. These guidelines recommended empirical treatment with a macrolide as the first-line agent in outpatient CAP. Since then, macrolides have been used widely to treat CAP worldwide. Consequently, the increase in macrolide use has been associated with increasing pneumococcal resistance to this drug class, manifested in the form of macrolide-resistant \textit{S. pneumoniae}.\(^5\) Thus, because \textit{S. pneumoniae} is the major causative organism in CAP, careful considerations should be made in selecting appropriate initial empirical therapy, especially in patients who are more susceptible to pneumococcal infections (i.e., elderly patients and patients with coexisting disease states).\(^5,14,16\)

Drug classes that can be used to treat CAP, ABS, or AECB include the cephalosporins, penicillins, macrolides, ketolides, quinolones, and tetracyclines (Tables 2 and 3).\(^5\) Early treatment with an antibacterial agent is important for (1) decreasing the severity of symptoms; (2) eliminating the causative organism; and (3) preventing permanent mucosal or respiratory damage; chronic illness; and, ultimately, complications.\(^2\)

### MEDICINAL CHEMISTRY AND PHARMACOLOGY

The substitution of a 3-keto function in lieu of the alpha-L-cladinose at position 3 of the erythronolide A ring, along with the addition of an imidazolyl and pyridyl...
ring through a butyl chain in lieu of the C11-12 carbamate, chemically differentiate telithromycin from the macrolide group of antimicrobials.10

The C11-12 linkage allows telithromycin to bind 10 times more tightly than erythromycin and six times more tightly than clarithromycin to wild-type ribosomes.15 Telithromycin binds 10 times more tightly than erythromycin or clarithromycin to bacterial ribosomes with domain V modifications (which show evidence of MLSB resistance). 15 The 3-keto group allows telithromycin to bind to the ribosomal target without causing expression of MLSB resistance in inducible strains. Telithromycin has not been shown to induce resistance to itself.10

These substitutions demonstrate effects on pharmacokinetic stability and spectrum of activity, allowing telithromycin to bind more tightly to two distinct regions on the RNA ribosomal subunit. This dual binding not only augments antibacterial potency but also decreases bacterial resistance caused by alterations to one of the target sites by methylation, as seen in MLSB resistance phenotypes.12

Telithromycin works by inhibiting bacterial protein synthesis by binding to domains II and V of 23S recombinant RNA (rRNA) of the 50S ribosomal subunit.8,10 In the presence of resistance caused by bacterial methylases that alter the domain V binding site of telithromycin, activity is still retained against gram-positive cocci (S. pneumoniae) by binding to domain II. Telithromycin is active against aerobic gram-positive, aerobic gram-negative, and anaerobic bacteria and other microorganisms (Table 4).10

**EFFICACY**

**The Dunbar Study**12

Dunbar et al. conducted a randomized, double-blind, double-dummy, parallel-group study to compare the efficacy and tolerability of telithromycin 800 mg once daily with high-dose clarithromycin (500 mg twice daily) for the treatment of CAP in adults 18 years of age or older. Each regimen was taken for 10 days.

To be eligible for enrollment in this study, patients had to have acute CAP with two or more clinical signs and symptoms associated with CAP as well as a chest film to confirm the presence of an infiltrate. Patients were excluded if they had neoplastic lung disease; progressively fatal disease; corrected QT-interval prolongation syndrome, as documented by the electrocardiogram (ECG); severe hypokalemia; or renal or hepatic impairment. Patients who were pregnant, who were receiving parenteral antibiotic therapy, or who were immunocompromised were also ineligible to enroll.

The patients were randomly assigned, on a 1:1 basis, to receive a 10-day treatment with either oral telithromycin 800 mg once a day in the morning with a placebo in the evening or high-dose clarithromycin 500 mg twice daily.

In terms of efficacy, telithromycin brought about an excellent bacteriological cure rate. The clinical cure rate of...
five-day and 10-day courses of telithromycin with a 10-day course of amoxicillin/clavulanic acid (e.g., Augmentin®,
GlaxoSmithKline).

Eligibility requirements for this study included clinical symptoms of acute maxillary sinusitis for less than 28 days and proof of a maxillary sinus infection confirmed by x-ray examination. Patients were excluded if they had a prolonged QT-interval syndrome, a progressively fatal illness, severe hypokalemia, a history of drug or alcohol abuse, renal or hepatic impairment, a history of chronic or recurrent sinusitis, and cystic fibrosis. Pregnant and lactating women, immunocompromised individuals, and those who had received antibiotic therapy within seven days prior to the study were also excluded.

The patients were randomly assigned, on a 1:1:1 basis, to receive one of these regimens:

- telithromycin 800 mg once in the morning for five days, followed by placebo for five days
- telithromycin 800 mg once in the morning for 10 days
- amoxicillin/clavulanic acid 500/125 mg twice daily for 10 days

Patients in the telithromycin groups also received a placebo at midday and in the evening.

The efficacy variable was the clinical outcome at the time-of-cure (TOC) visit (17–24 days after initiation of therapy) and at the late post-therapy visit (31–45 days after the initiation of therapy). This schedule ensured a more definite measurement of efficacy and identification of early relapses.

In each treatment group, the clinical cure rate was 75%, indicating therapeutic equivalence among the three groups. All three groups of patients achieved a 70% cure rate during the post-therapy visit.

Diarrhea and nausea were the most common adverse drug events (ADEs) reported in each group. The ECG recordings indicated small mean changes in the QT interval that were within the limits of normal variability in each group.2

The Luterman Study2

Luterman and colleagues conducted a randomized, double-blind, three-arm, parallel-group multicenter trial of 754 patients 18 years of age or older who were experiencing clinical symptoms of acute maxillary sinusitis. The goal was to determine the efficacy and tolerability of the telithromycin group of patients was an impressive 88.3%; the rate for the clarithromycin group was 88.5% (Table 5). None of the isolates in this study were resistant to telithromycin, whereas 10.5% of the isolates, including 9.8% of S. pneumoniae were resistant to clarithromycin. Telithromycin exhibited exceptional clinical efficacy in elderly patients, in high-risk patients, and in those with parapneumonic bacteremia. However, a slightly higher incidence of diarrhea was reported with telithromycin than with clarithromycin.

Significant differences in tolerability included taste perversion and headache, which were observed more frequently with clarithromycin; nausea, vomiting, and dizziness occurred more often with telithromycin.12

The Zervos Study7

This multicenter, randomized, controlled, double-blind, parallel-group study

Table 5  Clinical Cure Rates at Post-therapy Check-up (17–24 Days after Start of Treatment)

<table>
<thead>
<tr>
<th>Controlled Study</th>
<th>Patients (No.)</th>
<th>Clinical Cure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketek™</td>
<td>Comparator</td>
</tr>
<tr>
<td>CAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketek™ vs. clarithromycin$h$</td>
<td>162</td>
<td>156</td>
</tr>
<tr>
<td>Ketek™ vs. amoxicillin†</td>
<td>149</td>
<td>152</td>
</tr>
<tr>
<td>Ketek™ vs. clarithromycin‡</td>
<td>161</td>
<td>146</td>
</tr>
<tr>
<td>ABS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketek™ vs. amoxicillin/clavulanic acid§</td>
<td>146</td>
<td>137</td>
</tr>
<tr>
<td>Ketek™ vs. cefuroxime axetil¶</td>
<td>189</td>
<td>89</td>
</tr>
<tr>
<td>AECB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketek™ vs. clarithromycin$h$</td>
<td>225</td>
<td>231</td>
</tr>
<tr>
<td>Ketek™ vs. amoxicillin/clavulanic acid§</td>
<td>115</td>
<td>112</td>
</tr>
<tr>
<td>Ketek™ vs. cefuroxime axetil#</td>
<td>140</td>
<td>142</td>
</tr>
</tbody>
</table>

ABS = acute bacterial sinusitis; AECB = acute exacerbations of chronic bronchitis; CAP = community-acquired pneumonia.

$h$ Clarithromycin dosing = 500 mg twice daily for 10 days.

† Amoxicillin dosing = 1,000 mg three times daily.

‡ Ketek™ duration of therapy = 7 days.

§ Amoxicillin/clavulanic acid dosing = 500/125 mg three times daily.

¶ Cefuroxime axetil dosing = 250 mg twice daily.

# Cefuroxime axetil dosing = 500 mg twice daily.

Note: Comparator drug therapy is indicated for 10 days; telithromycin therapy is indicated for five days in cases of ABS or AECB and is taken for 10 days for CAP.

Data from Ketek™ (telithromycin) prescribing information. Kansas City, MO: Aventis.10
ADVERSE DRUG REACTIONS

Telithromycin 800 mg once daily for up to 10 days was generally well tolerated, with adverse events ranging from mild to moderate in severity and duration. The most common adverse events associated with telithromycin were gastrointestinal in nature and included diarrhea, nausea, and vomiting (Table 6). Visual disturbances included blurred vision, diplopia, or difficulty focusing, which was noted after all doses but was more frequent following the first or second dose. Most of these events were mild to moderate in severity and were temporary in duration; the incidence of visual disturbances was 1.1% with telithromycin and 0.28% with the comparators.10

Telithromycin, like its MLSB group counterparts (i.e., erythromycin and clarithromycin), has the potential to prolong the QT interval. However, clinical trials showed no evidence of QT prolongation, torsades de pointes, or other ventricular arrhythmias.8,10,11

CONTRAINDICATIONS AND PRECAUTIONS

Telithromycin is not intended for patients with a hypersensitivity to the product, its inactive ingredients, or any other macrolide antibiotic. Administration of telithromycin in conjunction with cisapride or pimozide (Orap®, Gate) is contraindicated.

As with other antibacterial agents, pseudomembranous colitis has been reported in some patients receiving telithromycin. Therefore, it is important to consider this infection in patients who have diarrhea after subsequent antibacterial use.

Patients with congenital prolongation of the QT interval, clinically significant bradycardia, and ongoing pro-arrhythmic conditions (i.e., uncorrected hypokalemia or hypomagnesemia) or patients who are taking class 1A or class 3 anti-arrhythmic agents should avoid the concomitant use of telithromycin because it has the potential to prolong the QT interval.10

Because exacerbations of myasthenia gravis have been reported in patients receiving telithromycin, this drug is not recommended as a therapeutic option for these patients unless there are no other alternatives. In such cases, close monitoring for exacerbations of myasthenia gravis is advised.

Concomitant administration of telithromycin with drugs metabolized by CYP3A4 warrants close monitoring and dosage adjustments.13 Patients with heart failure who are receiving metoprol, a CYP2D6 substrate, showed an increase in exposure when it was given concomitantly with telithromycin because it can increase in exposure when it was given concomitantly with telithromycin.

Monitoring is required for patients receiving coadministration of telithromycin and oral anticoagulants because this combination may enhance the prothrombin time and the International Normalized Ratio time.

Therapy with 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins (e.g., simvastatin [Zocor®, Merck®]), should be discontinued in patients receiving telithromycin.10

COST

The cost of a 10-day supply of telithromycin 800 mg once daily is $114.00 (see Table 2).

CONCLUSION

Telithromycin, the first-in-class keto-
lide antibacterial agent to be approved by the U.S. Food and Drug Administration for the treatment of URIs and LRTIs such as CAP, ABS, and AECB, is currently marketed as light-orange, oval, film-coated tablets, each containing 400 mg or 300 mg.10

The duration of therapy for AECB is five days; for ABS, five days; and for CAP, seven to 10 days. As shown in Table 2, the recommended daily dose is 800 mg taken once daily with or without regard to food.8 Dosage modifications are not indicated for patients with severe hepatic insufficiency; however, patients with severe renal impairment or those requiring dialysis should receive a reduced dose of 600 mg once daily.10

Because telithromycin is a potent inhibitor of CYP450 3A4, drugs that are substrates or inducers of CYP3A4 should be monitored and dosage modifications should be made accordingly.10,11

Like most antimicrobial agents, telithromycin is effective in treating a wide range of bacterial pathogens. Moreover, it is a viable option for empirical therapy because of (1) its short course of therapy for patients with ABS and AECB; (2) its convenience of once-daily dosing; (3) its clinical and bacteriological efficacy, which are comparable to other existing antibacterial agents; and (4) its marked activity against typical, atypical, and intracellular pathogens as well as macrolide-susceptible and beta-lactam–susceptible pathogens.2,3,7,12,14

REFERENCES