

# Telithromycin: a novel agent for the treatment of community-acquired upper respiratory infections

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The ketolides are a new subclass of macrolides, and telithromycin is the first of these agents to be approved. Modifications to the basic macrolide structure result in enhanced activity against penicillin- and erythromycin-resistant respiratory pathogens. It is therefore an option in the treatment of mild to moderate community-acquired respiratory infections, such as pneumonia, acute exacerbations of chronic bronchitis, pharyngitis/tonsillitis, and sinusitis. Telithromycin also offers the advantages of once-daily dosing and a shorter course of therapy in certain infections. Comparative clinical trials, although limited and involving only a small number of resistant organisms, showed the equivalence of telithromycin to existing therapies, although telithromycin generally had a higher frequency of mild to moderate gastrointestinal adverse effects. Further clinical and safety data, especially in patients with resistant organisms, are needed.

**A**ntibiotic resistance to common respiratory pathogens is on the rise. Currently, approximately 30% of *Streptococcus pneumoniae* infections are resistant to penicillin and erythromycin (1). New antibiotics are needed that target resistant organisms while avoiding resistance themselves. Telithromycin (Ketek, Aventis Pharmaceuticals, Bridgewater, NJ) is the first agent of a new subclass of antibiotics, called ketolides, designed to overcome pneumococcal resistance. It was approved by the Food and Drug Administration on April 1, 2004.

Although macrolide resistance can occur by several mechanisms, the majority of cases occur by either macrolide-lincosamide-streptogramin B (MLS<sub>B</sub>) resistance or by efflux pumps. MLS<sub>B</sub> resistance is encoded by erythromycin resistance methylase (*erm*) genes on plasmids or chromosomes, which alter ribosomal structure and therefore decrease their affinity for antibiotics (2, 3). This type of resistance is important because strains containing the *erm* gene display high-level erythromycin resistance (minimum inhibitory concentrations [MICs]  $\geq 64$   $\mu\text{g/mL}$ ). MLS<sub>B</sub> resistance can be either constitutive or inducible (2, 3). Organisms with inducible resistance can develop resistance to other antibiotics in the MLS<sub>B</sub> group upon exposure to erythromycin, clarithromycin, or azithromycin. The substitution of the L-cladinose moiety for a keto group on telithromycin inhibits induction, giving telithromycin activity against organisms with inducible resistance to macrolides (2, 4). In addition, telithromycin is able to bind more completely to bacterial ribosomes, making it effective when MLS<sub>B</sub> antibiotics become ineffective (2–4). However, constitutively resistant organisms are often resistant to telithromycin (3). The macrolide efflux system accounts for 60% of macrolide resistance seen in the USA. It is encoded by the macrolide efflux (*mef*) gene.

Unlike *erm*-mediated resistance, *mef*-mediated resistance confers low- or mid-level erythromycin resistance (MICs 1–32  $\mu\text{g/mL}$ ) (2, 3). It has been shown that ketolides are not affected by these efflux pumps and maintain their antibacterial activity (2, 4).

Telithromycin is a semisynthetic derivative of erythromycin. Modifications to the basic structure of erythromycin account for the enhanced activity of telithromycin against pneumococcus, as well as activity against other respiratory pathogens such as *Haemophilus influenzae* and *Moraxella catarrhalis* (2). Telithromycin has been studied in clinical trials for community-acquired pneumonia (CAP), acute sinusitis, acute bacterial exacerbations of chronic bronchitis, and pharyngitis/tonsillitis.

## INDICATIONS

Telithromycin is approved for once-daily treatment of CAP, acute sinusitis, and acute bacterial exacerbations of chronic bronchitis in patients  $\geq 18$  years of age.

## PHARMACOLOGY

Similar to the macrolides, telithromycin binds to the bacterial 50S ribosomal subunit, inhibiting translation of bacterial mRNA and thereby preventing bacterial protein synthesis. This activity can be either bacteriostatic or bacteriocidal, depending on the sensitivity of the organism (3, 4).

Telithromycin maintains the same 14-membered lactone ring structure as erythromycin, with some key modifications made to improve upon the pharmacokinetics and the activity of earlier macrolides (Figure). Replacement of the L-cladinose moiety with a keto group at position 3 improves the acid stability of telithromycin. An 11,12-carbamate side-chain enhances the interaction of telithromycin with bacterial ribosomes, enabling it to retain activity against bacteria that exhibit MLS<sub>B</sub> resistance (3–5).

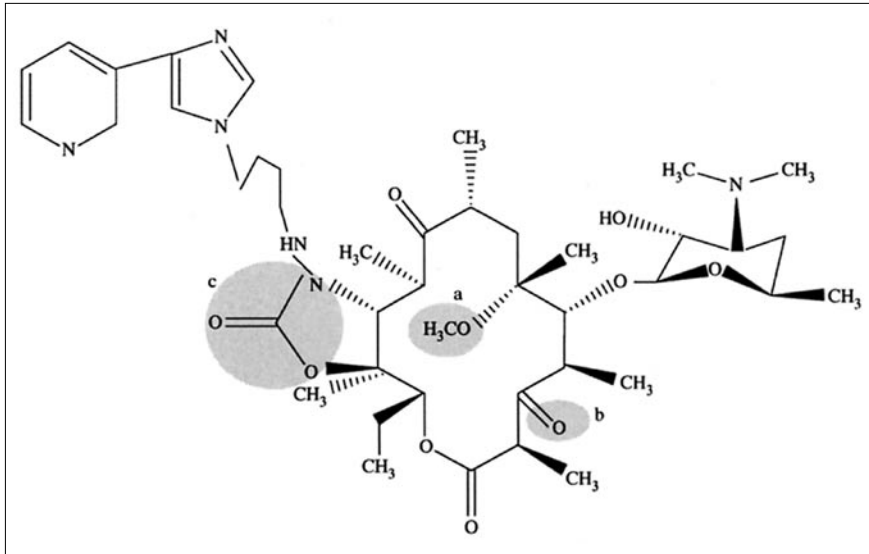
## PHARMACOKINETICS

The single-dose and steady-state pharmacokinetics of telithromycin have been described in healthy volunteers (2, 3).

The oral bioavailability of telithromycin is 57%, with most of the drug lost to first-pass metabolism (3). Absorption is rapid, reaching maximum concentrations within 1 hour of dosing, and

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**Figure.** Chemical structure of telithromycin: (a) the methoxy-group at C6 improves acid stability and prevents internal hemiketalization; (b) 3-keto-function avoids MLS<sub>B</sub> resistance induction and improves ribosome binding; (c) C11,12 carbamate side-chain increases affinity for the ribosomes and improves interaction with MLS<sub>B</sub>-resistant ribosomes. Reprinted from reference 5 by permission of Oxford University Press.

food does not affect absorption. The half-life of telithromycin is 7.2 hours. Telithromycin does not exhibit dose-proportional pharmacokinetics despite lack of drug accumulation after dose-doubling (6).

Telithromycin has excellent penetration into respiratory tract tissues. Concentrations of telithromycin in epithelial lining fluid and alveolar macrophages have exceeded the MICs of common respiratory pathogens. Epithelial lining fluid is the proposed site of infection for extracellular organisms in lower respiratory tract infections, and alveolar macrophages may act as a transporter for antibiotics to the lung (2, 3). Protein binding for telithromycin is reported as 60% to 70%; however, the degree of binding is mild and should not have a clinically significant effect (2).

Telithromycin is metabolized to 4 major metabolites, with only 1 metabolite demonstrating minimal antibacterial activity (3). Metabolism is mediated by the cytochrome P450 (CYP) 3A4 pathway.

Seventy-five percent of telithromycin is eliminated via feces. Only a small amount of drug is excreted unchanged in the urine (2, 3).

No dosage adjustments are required in elderly patients, patients with renal dysfunction, or patients with hepatic dysfunction. Data concerning patients with both renal and hepatic dysfunction are not available (2).

## SPECTRUM OF ACTIVITY

### Gram-positive bacteria

Telithromycin demonstrates good in vitro activity against most gram-positive aerobic bacteria. It is more potent than erythromycin against both erythromycin-sensitive and erythromycin-resistant *S. pneumoniae*. Reported MIC<sub>90</sub> values for 169 erythromycin-sensitive isolates for *S. pneumoniae* were 0.06, 0.125, and 0.25 µg/mL for telithromycin, azithromycin, and clarithromycin, respectively (2, 4). In pneumococci with known macrolide resistance, telithromycin retained its in vitro activity with MIC<sub>90</sub> values of ≤0.12 µg/mL (4). For penicillin-susceptible, -interme-

diante, and -resistant strains of *S. pneumoniae*, MICs were ≤0.12 to 0.5 µg/mL (2).

With regard to erythromycin-sensitive isolates of *S. pyogenes*, telithromycin demonstrates similar activity to that of erythromycin and clarithromycin. Against erythromycin-resistant isolates, telithromycin again exhibits enhanced activity compared with the macrolides. However, MICs vary depending on the mechanism of erythromycin resistance (inducible vs constitutive) (2, 4).

Similar to the macrolides, telithromycin has activity against methicillin-sensitive *Staphylococcus aureus* but lacks activity against methicillin-resistant strains. The activity of telithromycin against enterococci is better than that of the macrolides; however, like the macrolides, it is not recommended for use in any clinically significant infections (2, 4).

### Gram-negative bacteria

Telithromycin displays in vitro activity against several community-acquired gram-negative pathogens, including *H. influenzae* and *M. catarrhalis*. However, its activity against *H. influenzae* is variable. Some studies report telithromycin MICs as one dilution higher than those for azithromycin and one to two dilutions lower than for clarithromycin. The activity of telithromycin against *M. catarrhalis* is similar to that of the macrolides (2, 4). Against other gram-negative organisms, including the Enterobacteriaceae and *Pseudomonas aeruginosa*, telithromycin has poor activity (2).

### Atypical bacteria

Telithromycin has excellent in vitro activity against atypical pathogens, including *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* sp. Low MIC values have been reported for all (2, 4).

### RESISTANCE

Currently, limited data are available on telithromycin resistance. Davies et al demonstrated telithromycin resistance in vitro by exposing macrolide-sensitive and -resistant isolates to daily sub-MICs (7). Compared with other agents studied, telithromycin rarely induced resistance.

### CLINICAL TRIALS

Clinical trials of telithromycin have been conducted for a variety of upper and lower respiratory tract infections. Trials analyzed both the modified intent-to-treat (mITT) population, which included enrolled patients who received at least 1 dose of drug, and the per-protocol (PP) population. Some of the data have been published only in abstract form and presented at scientific meetings and, therefore, information may be incomplete.

### CAP

One open-label and 3 comparative trials have been conducted with telithromycin in the treatment of CAP. Carbon et al studied 240 patients between the ages of 18 and 79 years in whom CAP

had been diagnosed (8). Patients with multiple comorbidities were excluded from the study, and most of the patients were <65 years and had mild to moderate disease. In this multicenter, open-label trial, patients were given telithromycin (800 mg) for 7 to 10 days, as determined by the individual investigator; results were not categorized by number of days of therapy. The clinical cure rate was 93% for the PP group and 80% for the mITT group—a rate similar to that of other currently available drugs. The pathogen eradication rate was 83% for the PP group and 85% for the mITT group. Few resistant organisms were identified. Most common adverse events were mild, including elevated liver function tests, diarrhea, nausea, and vomiting, and led to trial discontinuation in 5% of patients studied.

Hagberg et al studied 404 adult (aged ≥18 years) patients with CAP in a randomized, multicenter, double-blind trial (9, 10). Again, the patients were relatively young with mild to moderate disease. Patients received 10-day treatment with telithromycin (800 mg once a day) or amoxicillin (1000 mg 3 times a day). The clinical cure rate was 95% for telithromycin and 90% for amoxicillin in the PP group and 86% for telithromycin and 78% for amoxicillin in the mITT group. In patients with *H. influenzae*, amoxicillin was clinically effective in 9 of 9 cases, while telithromycin was effective in 4 of 6 cases. The pathogen eradication rate was 90% for telithromycin and 88% for amoxicillin in the PP group and 79% for telithromycin and 73% for amoxicillin in the mITT group. Few resistant organisms were identified. Adverse gastrointestinal effects were the most common adverse events in both groups; nausea and diarrhea occurred more frequently in the telithromycin group than in the amoxicillin group.

Tellier et al studied 416 adult patients with CAP in a randomized, multicenter, double-blind trial (11). Patients received 10-day treatment with telithromycin (800 mg once a day) or clarithromycin (500 mg twice a day). In both treatment groups, 88% of the PP patients were clinically cured. Among the mITT patients, 79% of those receiving telithromycin and 81% of those receiving clarithromycin were clinically cured. The pathogen eradication rate in the PP population was 89% for telithromycin and 96% for clarithromycin. The *H. influenzae* eradication rate was 78% for telithromycin and 100% for clarithromycin. Nausea and diarrhea occurred more frequently in the telithromycin group than in the clarithromycin group.

Pullman et al studied 204 adult patients with CAP in a randomized, multicenter, double-blind trial (12). Patients received 7- to 10-day treatment with telithromycin (800 mg once a day) or trovafloxacin (200 mg once a day). The mean duration of treatment for both groups was 9 days. The clinical cure rate was as follows: PP, 90% for telithromycin and 94% for trovafloxacin; mITT, 82% for telithromycin and 85% for trovafloxacin. The pathogen eradication rate was as follows: PP, 93% for telithromycin and 100% for trovafloxacin; mITT, 84% for telithromycin and 88% for trovafloxacin. No resistant strains were isolated. Equivalence of the 2 drugs was not demonstrated since the trial was prematurely discontinued because of trovafloxacin toxicity. Mild gastrointestinal adverse events were the most common side effect in both groups; diarrhea occurred more frequently in the telithromycin group.

## Acute sinusitis

A comparative duration trial and a comparative trial have been conducted for telithromycin in the treatment of acute sinusitis. Roos et al studied 335 patients (aged 18–65 years) with acute sinusitis (13). Patients with recurrent or chronic sinusitis were excluded. In this randomized, multicenter, double-blind trial, patients received 5- or 10-day treatment with telithromycin (800 mg once daily). The clinical cure rate was as follows: PP, 91% for both 5-day and 10-day treatment; mITT, 83% for 5-day treatment and 88% for 10-day treatment. The pathogen eradication rates for 5-day and 10-day treatments, respectively, were 93% and 90% in the PP group vs 82% and 89% in the mITT group. A sinus puncture was performed on all patients to identify the pathogen; few resistant strains were identified. Pathogen eradication rates, compliance rates, and adverse effects were similar between the 5-day treatment group and the 10-day treatment group.

Tellier et al studied adult patients with acute sinusitis in a randomized, multicenter, double-blind trial (14). Patients received 5- or 10-day treatment with telithromycin (800 mg once daily) or 10-day treatment with amoxicillin/clavulanic acid (500/125 mg 3 times a day). In PP patients, the clinical cure rate was 75% for 5-day telithromycin, 73% for 10-day telithromycin, and 74% for amoxicillin/clavulanic acid; the bacterial eradication rate was 87% for 5- and 10-day telithromycin and 75% for amoxicillin/clavulanic acid. There was a high frequency of adverse effects, including diarrhea and nausea.

## Acute bacterial exacerbations of chronic bronchitis

Two randomized, multicenter, double-blind trials have been published to evaluate the use of telithromycin in acute bacterial exacerbations of chronic bronchitis. Zervos et al studied 373 adult patients with acute bacterial exacerbations of chronic bronchitis (15). The patient population was young, with a median age of 50 to 57 years. Patients were given 5 days of telithromycin (800 mg once a day) or 10 days of ciprofloxacin (500 mg twice a day). The clinical cure rate in the PP patients was 86% for telithromycin and 83% for ciprofloxacin; in the mITT patients, 78% for telithromycin and 72% for ciprofloxacin. The pathogen eradication rate in the PP population was 76% for telithromycin and 79% for ciprofloxacin. The abbreviated regimen did not result in a higher rate of relapse or reinfection a month after treatment. Nausea and gastrointestinal pain were more common in the telithromycin group than in the ciprofloxacin group.

Aubier et al studied 320 adult patients with acute bacterial exacerbations of chronic bronchitis (16). Study subjects were somewhat older than in other studies, with a median age of 61 to 66 years. Patients were given 5 days of telithromycin (800 mg once daily) or 10 days of amoxicillin/clavulanic acid (500/125 mg 3 times a day). The clinical cure rate was as follows: PP, 86% for telithromycin and 82% for amoxicillin/clavulanic acid; mITT, 81% for telithromycin and 78% for amoxicillin/clavulanic acid. The pathogen eradication rate in the PP group was 69% for telithromycin and 70% for amoxicillin/clavulanic acid; in the mITT group, it was 60% for telithromycin and 57% for amoxicillin/clavulanic acid. The *H. influenzae* eradication rate was 50% for telithromycin vs 100% for amoxicillin/clavulanic acid. As with other studies, the most common side effects were mild to moderate gastrointestinal effects. The discontinuation rate

**Table 1. Reported drug interactions for telithromycin**

Drug(s)	Mechanism of action	Result	Comments
Itraconazole, ketoconazole	CYP3A4 inhibition	↑ AUC and C <sub>max</sub> of telithromycin	Not clinically significant
Cisapride	CYP3A4 substrate	↑ AUC and C <sub>max</sub> of cisapride resulting in QTc prolongation	Contraindicated
Simvastatin	CYP3A4 substrate	↑ AUC and C <sub>max</sub> of simvastatin	Caution*
Midazolam	CYP3A4 substrate	↑ AUC and C <sub>max</sub> of midazolam resulting in excess sedation	Monitor and adjust dose if necessary
Digoxin	Not stated	↑ AUC and C <sub>max</sub> of digoxin	Monitor for digoxin toxicity
Theophylline	Inhibition of metabolism	↑ AUC and C <sub>max</sub> of theophylline	Separate administration time by at least 1 hour

\*Concomitant use of simvastatin, lovastatin, or atorvastatin with telithromycin should be avoided.

AUC indicates area under the curve; C<sub>max</sub>, maximum concentration.

due to adverse effects was higher in the amoxicillin/clavulanic acid group than in the telithromycin group.

### Pharyngitis/tonsillitis

Two multicenter, randomized, double-blind trials have been published to evaluate the use of telithromycin in the treatment of pharyngitis/tonsillitis. Norrby et al studied 395 patients aged 15 to 65 years (median age 32–33 years) who had pharyngitis/tonsillitis caused by group A hemolytic streptococci (GABHS) (17). Patients were given 5 days of telithromycin (800 mg once daily) or 10 days of penicillin (500 mg 3 times a day). The clinical cure rate was as follows: PP, 84% for telithromycin and 89% for penicillin; mITT, 80% for telithromycin and 79% for penicillin. The pathogen eradication rate was as follows: PP, 85% for telithromycin and 89% for penicillin; mITT, 80% for telithromycin and 79% for penicillin. The clinical cure rate for macrolide-resistant GABHS was 6 of 6 for telithromycin and 8 of 9 for penicillin. A small number of resistant organisms were identified. Compliance rates for the 5- and 10-day regimens were similar. There was a greater incidence of nausea and diarrhea in the telithromycin group, but study discontinuation rates were similar in the 2 groups.

Quinn et al studied 463 patients ≥13 years (median age 29 years) who had pharyngitis/tonsillitis caused by GABHS (18). Patients were given 5 days of telithromycin (800 mg once a day) or 10 days of clarithromycin (250 mg twice a day). The clinical cure rate was as follows: PP, 93% for telithromycin and 91% for clarithromycin; mITT, 83% for both groups. The pathogen eradication rate was as follows: PP, 91% for telithromycin and 88% for clarithromycin; mITT, 81% for telithromycin and 78% for clarithromycin. The clinical cure rate for macrolide-resistant GABHS was 4 of 5 for telithromycin and 0 of 4 for clarithromycin. The incidence of diarrhea, nausea, and vomiting was higher in the telithromycin group, and similarly the discontinuation rate was 2 times higher for telithromycin than for clarithromycin. Compliance rates were similar for the regimens.

### ADVERSE EFFECTS

The most common adverse effects reported in clinical trials for telithromycin involve the gastrointestinal system. Diarrhea

(14%), nausea (9%), and vomiting (2%) were mild to moderate in severity, with few patients discontinuing therapy secondary to intolerance (2). However, in the comparative trials, gastrointestinal effects were higher with telithromycin compared with the other antibiotics except amoxicillin/clavulanic acid.

Although rare, visual disturbances occurred more often with telithromycin than with other antibiotics during clinical trials (1.1% vs 0.28%). Effects were mild and reversible and included blurred vision, difficulty focusing, and diplopia. Women under the age of 40 years had the highest incidence of these treatment-emergent visual adverse events (19).

Elevations in transaminases have been reported in patients receiving telithromycin. This abnormality seemed to be more pronounced in the CAP trials than in trials for other indications. However, overall elevations in transaminases were similar to those with other agents (2–4).

During clinical trials, there was a small increase in the QTc interval in patients treated with telithromycin compared with other antibiotics. The effects appeared to be concentration dependent and enhanced by concomitant administration with CYP3A4 inhibitors and in patients with decreased clearance. However, there have been no reports of QTc prolongation beyond 500 msec (2, 3). Caution is advised when using telithromycin concurrently with other agents that can alter the QTc interval. Additional safety data are required to fully analyze how telithromycin affects cardiac risk.

### DOSING AND ADMINISTRATION

For the treatment of community-acquired upper respiratory infections, the dose of oral telithromycin is 800 mg daily. No dosage adjustment is required in patients with renal or hepatic dysfunction. Dosing in patients with both renal and hepatic dysfunction has not been studied.

### PREGNANCY CATEGORY

Telithromycin is classified in pregnancy risk category C. There are no adequate and well-controlled studies in pregnant women. Animal data suggest no evidence of direct teratogenic effects (20).

**Table 2. Cost of common oral antibiotics used in the treatment of upper respiratory infections**

Medication	Typical dose per day	Cost per day*
Amoxicillin	1000 mg 3 times daily	\$0.54
Amoxicillin/clavulanic acid (generic)	500/125 mg 3 times daily	\$6.04
Cefuroxime axetil (generic)	500 mg twice daily	\$4.68
Clarithromycin	500 mg twice daily	\$7.98
Levofloxacin	500 mg daily	\$7.06
Penicillin	500 mg 3 times daily	\$0.35
Telithromycin	800 mg daily	\$8.92

\*Cost data are based on Baylor University Medical Center pharmacy acquisition cost.

## DRUG INTERACTIONS

Preliminary studies have shown drug interactions with several CYP3A4 inhibitors (Table 1) (2–4). It is recommended that treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) be suspended during treatment with telithromycin because of an increased risk of myopathy.

In vitro, telithromycin competitively inhibits CYP2D6, but it has not shown a clinical reaction with paroxetine, a CYP2D6 substrate. The drug also has no interactions with warfarin, antacids, and ranitidine.

## ECONOMIC ISSUES

The costs of commonly used antibiotics in the treatment of community-acquired upper respiratory infections are shown in Table 2. While the cost of telithromycin is higher than that of conventional therapy, the benefit of increased patient compliance due to once-a-day dosing and a shorter course of therapy may justify the cost. However, it is important to note that a full dose requires the patient to take two 400-mg tablets.

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