



## Ketek® Monograph<sup>1-2</sup>

**Brand Name:** Ketek®

**Generic Name:** Telithromycin

**Manufacturer:** Aventis Pharmaceuticals

**Year introduced:** 2004

### Mechanisms of Action:

The mechanism of telithromycin is similar to macrolide antibiotics. Telithromycin binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit; this action results in inhibition of RNA-dependent protein synthesis. The binding of telithromycin to bacterial 23S ribosomal RNA is 10-times greater than that of erythromycin and 6-times greater than clarithromycin.

### FDA-Approved Indications:

(Indication is for patients 18 years and older)

Community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including penicillin-resistant *Streptococcus pneumoniae*), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydomphila pneumoniae*, or *Mycoplasma pneumoniae*

### Contraindications:

- Telithromycin is contraindicated in patients with a history of hypersensitivity to telithromycin and/or any components of Ketek tablets, or any macrolide antibiotic.
- Telithromycin is contraindicated in patients with a history of hepatitis and/or jaundice associated with the use of Ketek tablets, or any macrolide antibiotic.
- Concomitant administration of telithromycin with cisapride or pimozide is contraindicated.
- Telithromycin is contraindicated in patients with myasthenia gravis.

### Pharmacokinetics:

Following oral administration, telithromycin reached maximal concentration at about 1 hour (0.5 - 4 hours). It has an absolute bioavailability of 57%. Steady-state plasma concentrations are reached within 2 to 3 days of once daily dosing with telithromycin 800 mg. Following oral dosing, the mean terminal elimination half-life of telithromycin is 10 hours. Approximately 50% of telithromycin metabolism is mediated by CYP 450 3A4 and the remaining 50% is CYP 450-independent. Elimination of telithromycin reaching the systemic circulation occurs via several pathways. Approximately 7% is excreted unchanged in the feces, 13% excreted unchanged in the urine, and 37% is hepatically metabolized. Elimination from white blood cells occurs more slowly than from plasma.

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### Adverse Effects:

- In the clinical studies, most discontinuations in the telithromycin group were due to treatment-emergent adverse events in the gastrointestinal system, primarily diarrhea, and nausea. Other common side effects were headache, dizziness, vomiting, loose stools, and dysgeusia.
- Abnormal liver function tests were observed in 1.6%, and 1.7% of patients and were reversible.
- Ketek may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported. There have been post-marketing adverse event reports of syncope usually associated with vagal syndrome.
- There have been postmarketing reports of severe, and in some cases fatal, hepatotoxicity in patients treated with Ketek. The cases included fulminant hepatitis, hepatic necrosis, and hepatic failure. These hepatic reactions were observed during or immediately after treatment, and in some cases, liver injury progressed rapidly and occurred after administration of only a few doses of Ketek. In some cases, severe reactions have been associated with serious underlying diseases or concomitant medications.

### Drug Interactions:

- The use of telithromycin is contraindicated with cisapride and pimozide. Steady-state peak plasma concentrations of cisapride were increased by 95% in clinical studies.
- Itraconazole and ketoconazole increase serum concentrations of telithromycin.
- Simvastatin, lovastatin or atorvastatin levels were increased due to CYP 3A4 inhibition by telithromycin.
- Monitoring of digoxin side effects or serum levels should be considered during concomitant administration of digoxin and telithromycin.
- Patients should be monitored with concomitant administration of midazolam.
- Concomitant administration of other CYP 3A4 inducers such as rifampin, phenytoin, carbamazepine, phenobarbital or bosentan is likely to result in subtherapeutic levels of telithromycin and loss of effect.
- To minimize the risk for additive QT prolongation effects, concomitant administration of telithromycin with Class IA antiarrhythmics (disopyramide, quinidine, procainamide) and Class III antiarrhythmics (amiodarone, dofetilide, ibutilide, sotalol) is not recommended.
- Telithromycin should not be administered with ergot alkaloids. Although no specific drug interaction studies have been performed with telithromycin, drug interactions have been reported with macrolide antibiotics. Concomitant administration of ergot alkaloids with macrolides resulted in acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.
- Telithromycin can increase the AUC and C<sub>max</sub> of theophylline. Additionally, coadministration may worsen gastrointestinal adverse effects such as nausea and vomiting, especially in female patients. It is recommended that telithromycin and theophylline be taken 1 hour apart to decrease the likelihood of GI adverse effects.
- Concurrent administration of sunitinib with strong inhibitors of cytochrome P450 3A4 such as telithromycin results in increased concentrations of sunitinib and its primary active metabolite. Whenever possible selection of an alternative concomitant medication with no or minimal enzyme inhibition potential is recommended; otherwise, a reduction in the dose of sunitinib is recommended

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### Precaution/Warnings:

- Pseudomembranous colitis has been reported with telithromycin, and may range from mild to life threatening.
- Telithromycin has the potential to prolong the QTc interval and may lead to an increased risk for ventricular arrhythmias, including torsades de pointes.
- Prescribing telithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- Telithromycin may cause visual disturbance including blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported.
- Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has been reported with the use of telithromycin. These events were generally reversible, though acute hepatic failure and severe liver injury, in some cases fatal, have been reported.
- Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients treated with telithromycin. These hepatic reactions included fulminant hepatitis and hepatic necrosis leading to liver transplant, and were observed during or immediately after treatment.
- Exacerbations of myasthenia gravis have been reported and sometimes occurred within a few hours of the first dose of telithromycin.
- There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of telithromycin.

### Pregnancy/Lactation:

- Pregnancy Category C
- Whether telithromycin is excreted in human breast milk is not known. Because many drugs are excreted in human milk, telithromycin should be used cautiously during breastfeeding.

### Usual Dosage:

- Acute bacterial exacerbation of chronic bronchitis and acute bacterial sinusitis: 800 mg once every 24 hours for 5 days
- Community-acquired pneumonia: 800 mg once every 24 hours for 7 days

### Availability:

Ketek is available as 300- and 400-mg tablets.



## Clinical Studies:

Title & Author	Study Design	Results
<p>Efficacy and tolerability of once daily oral telithromycin compared with clarithromycin for the treatment of community-acquired pneumonia in adults</p> <p>Dunbar LM, et al.<sup>3</sup> (2004)</p>	<p>This is a randomized, double-blind, parallel-group trial conducted at 54 centers with 493 patients enrolled.</p> <p>Patients aged <math>\geq 18</math> years with acute community-acquired pneumonia were randomized to receive 10 days oral telithromycin 800 mg once daily or clarithromycin 500 mg twice daily.</p>	<p><b>Primary endpoint:</b></p> <ul style="list-style-type: none"> <li>Clinical cure rate</li> <li>Microbiological cure rate</li> </ul> <p><b>Efficacy: telithromycin = clarithromycin</b></p> <ul style="list-style-type: none"> <li>Clinical cure rates were comparable between treatment groups, 88.3% (143/162) in the telithromycin group and 88.5% (138/156) in the clarithromycin group.</li> <li>Bacterial eradication rates were comparable between treatment groups (87.5% for telithromycin vs. 96.7% for clarithromycin).</li> </ul> <p><b>Safety: telithromycin = clarithromycin</b></p> <ul style="list-style-type: none"> <li>Both treatments were fairly well tolerated; adverse events were experienced in 57.0% of the patients treated with telithromycin and 49.1% of those treated with clarithromycin; most of these adverse events were assessed as mild.</li> </ul>
<p>Efficacy and tolerability of 5 day, once-daily telithromycin compared with 10-day, twice daily clarithromycin for the treatment of group A beta-hemolytic streptococcal tonsillitis/pharyngitis: a multicenter, randomized, double-blind, parallel-group study</p> <p>Quinn J, et al.<sup>4</sup> 2003</p>	<p>This is a multicenter randomized, double-blind, parallel-group study with 526 patients enrolled.</p> <p>Patients aged <math>\geq 13</math> years with a diagnosis of Group A Strep tonsillitis/pharyngitis were randomized to receive either twice daily clarithromycin 250 mg for 10 days or once daily telithromycin 800 mg for 5 days (follow by 5 days placebo).</p>	<p><b>Endpoints:</b></p> <ul style="list-style-type: none"> <li>Clinical cure rate</li> <li>Microbiological cure rate (bacteria eradication rate)</li> </ul> <p><b>Efficacy: telithromycin = clarithromycin</b></p> <ul style="list-style-type: none"> <li>Microbiologic and clinical cures were similar for the 2 treatment groups.</li> <li>Clinical cure rate was achieved in 92.7% of telithromycin recipients and 91.1% clarithromycin-treated patients (difference 1.6%; 95% CI -5.5 to 8.6).</li> <li>Bacterial eradication was achieved in 91.3% of telithromycin-treated patients and 88.1% of clarithromycin recipients (difference, 32%;95% CI, -4.5 to 11).</li> </ul> <p><b>Safety: telithromycin <math>\leq</math> clarithromycin</b></p> <ul style="list-style-type: none"> <li>Treatment-related adverse events occurred more frequently in the telithromycin group than the clarithromycin group (67.2% vs.57.5%, respectively).</li> <li>Diarrhea, nausea and vomiting were more common with telithromycin than with clarithromycin (p = 0.004, 0.01, and 0.001, respectively).</li> <li>Adverse events were generally mild.</li> </ul>
<p>Oral telithromycin 800 mg once daily for 5 days versus cefuroxime axetil 500 mg twice daily for 10 days in adults with acute exacerbations of chronic bronchitis.</p> <p>Zervos MJ, et al.<sup>5</sup> 2003</p>	<p>This is a multicenter, randomized, double-blind, parallel-group trial involving 376 patients with acute exacerbations of chronic bronchitis (AECB).</p> <p>Patients were randomized to a 5-day regimen of 800 mg telithromycin once daily or 10-day regimen of 500 mg cefuroxime axetil twice daily.</p>	<p><b>Endpoints:</b></p> <ul style="list-style-type: none"> <li>Clinical cure rate</li> <li>Microbiological cure rate (bacteria eradication rate)</li> </ul> <p><b>Efficacy: telithromycin = cefuroxime axetil</b></p> <ul style="list-style-type: none"> <li>In clinically evaluable patients (n = 282), post-therapy clinical cure rates were 86.4% with telithromycin and 83.1% with cefuroxime axetil. (p value was not reported)</li> <li>In bacteriologically evaluable patients (n = 53), eradication or presumed eradication of the pathogen was achieved in 76.0% and 78.6% of telithromycin and cefuroxime axetil patients, respectively. (p value was not reported)</li> </ul> <p><b>Safety: telithromycin <math>\geq</math> cefuroxime axetil</b></p> <ul style="list-style-type: none"> <li>Adverse events were mostly mild; the most common were diarrhea</li> </ul>

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Title & Author	Study Design	Results
		(12.8% vs. 11.8%) and nausea (8.9% vs. 3.2%) in telithromycin and cefuroxime axetil patients, respectively.
<p>Telithromycin is as effective as amoxicillin/clavulanate in acute exacerbations of chronic bronchitis.</p> <p>Aubier M, et al.<sup>6</sup> 2002</p>	<p>This is a randomized, double-blind study with 325 adult patients with AECB and a history of chronic obstructive pulmonary disease (COPD).</p> <p>Patients received either telithromycin 800 mg once daily (qd) for 5 days (followed by placebo for 5 days) or amoxicillin/clavulanate 500/125 mg three times daily (tid) for 10 days.</p>	<p><b>Endpoints:</b></p> <ul style="list-style-type: none"> <li>Clinical cure rate</li> <li>Microbiological cure rate (bacteria eradication rate)</li> </ul> <p><b>Efficacy: telithromycin = amoxicillin/clavulanate</b></p> <ul style="list-style-type: none"> <li>Clinical cure rates for telithromycin post-therapy (Days 17-21, test-of-cure) and late post-therapy (Days 31-36) were 86.1% and 78.1%, respectively; 82.1% and 75.0% for amoxicillin/clavulanate. (p value was not reported)</li> <li>Bacteriologic outcome was satisfactory for 69.2% of telithromycin recipients vs. 70.0% for amoxicillin/clavulanate recipients. (p value was not reported)</li> </ul> <p><b>Safety: telithromycin ≥ amoxicillin/clavulanate</b></p> <ul style="list-style-type: none"> <li>Both treatments were generally well tolerated, although the frequency of drug-related adverse events was almost two-fold higher for amoxicillin/clavulanate (25.0% vs. 13.1%).</li> </ul>
<p>Comparison of hospitalization rates in patients with community-acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days.</p> <p>Tellier G, et al.<sup>7</sup> 2004</p>	<p>This is a randomized, double-blind, parallel group, multinational study enrolled 575 patients with community-acquired pneumonia (CAP).</p> <p>Patients received telithromycin 800 mg once daily for 5 (n = 193) or 7 (n = 195) days, or clarithromycin 500 mg once daily for 10 days (n = 187).</p>	<p><b>Endpoints:</b></p> <ul style="list-style-type: none"> <li>The primary efficacy endpoint was clinical cure on day 17-24.</li> <li>Frequency of CAP-related hospitalizations, physician visits/tests/procedures, and additional respiratory tract infection-related antibacterial use were compared</li> </ul> <p><b>Efficacy: telithromycin ≥ clarithromycin</b></p> <ul style="list-style-type: none"> <li>Clinical cure rates were similar in patients who received clarithromycin for 10 days and telithromycin for 5 or 7 days: 91.8% (134/146), 89.3% (142/159), and 88.8% (143/161), respectively.</li> <li>There were 7 CAP-related hospital admissions among clarithromycin patients vs 3 (p = 0.283) and 1 (p = 0.021) admissions among 5- and 7-day telithromycin patients, respectively.</li> <li>The number of hospital days/100 patients was 40.1 for clarithromycin vs 17.1 and 7.2 for 5- and 7-day telithromycin, respectively.</li> </ul> <p><b>Safety: telithromycin = clarithromycin</b></p> <p>Treatment related adverse events were similar for both telithromycin (44.6% total) and clarithromycin (44.9%) treatment.</p>
<p>Comparison of hospitalization rates in patients with community-acquired pneumonia treated with 10 days of telithromycin or clarithromycin.</p> <p>Niederman MS.<sup>8</sup> 2004</p>	<p>This is a randomized, double-blind, multinational study enrolled 448 out patient (≥ 18 years old).</p> <p>Patients received telithromycin 800 mg once daily (n = 224) or clarithromycin 500 mg twice daily (n = 224) for 10 days.</p>	<p><b>Endpoints:</b></p> <ul style="list-style-type: none"> <li>Frequency of CAP-related hospitalizations, physician visits/tests/procedures, and additional respiratory tract infection-related antibacterial use were compared by treatment group (intent to treat population) up to the late post-therapy visit (Days 31-36).</li> </ul> <p><b>Efficacy: telithromycin = clarithromycin</b></p> <ul style="list-style-type: none"> <li>There were 4 CAP-related hospitalizations (1.8 events/100 patients) among patients treated with telithromycin vs 8 (3.6 events/100 patients) among clarithromycin patients (p = 0.281).</li> <li>The total number of CAP-related hospital days for telithromycin and clarithromycin patients was 23 vs 64 days (10.3 vs 28.6 days/100 patients), respectively (p = 0.177).</li> </ul>

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## Conclusion:

Telithromycin is a broad-spectrum antibiotic and the only product available in a family called the 'ketolides.' Chemically, ketolides resemble macrolides; however, pharmacologically, telithromycin exhibits greater affinity to bacterial RNA than macrolides. The advantage of telithromycin over macrolides is the extended spectrum of activity against erythromycin- and penicillin-resistant *Streptococcus pneumoniae*. Similar to macrolides, telithromycin metabolizes through CYP450; therefore, drug interactions are major safety concerns.

Telithromycin has been studied in multiple types of respiratory tract infections. In clinical trials, telithromycin demonstrated equivalent efficacy and similar safety as clarithromycin, amoxicillin/clavulanate, and cefuroxime in both upper and lower respiratory infections. However, due to compelling safety concerns regarding cases of severe liver injury involving several deaths, telithromycin is no longer indicated for chronic bronchitis and acute sinusitis. Consequently, telithromycin should be reserved only for patients with community-acquired pneumonia due to *Streptococcus pneumoniae* that is resistant to other antibiotics. Because determining the clinical advantage of telithromycin over existing antibiotics is difficult, the cost of telithromycin should be evaluated for the decision of PDL status.

## REFERENCES

1. Clinical Pharmacology. [Accessed 2009 December]. Available from: URL: <http://www.clinicalpharmacology-ip.com/Default.aspx>.
2. Ketek [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2007.
3. Dunbar LM, 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;26:48-62.
4. Quinn J, Rouff GE, Ziter PS et al. Efficacy and tolerability of 5 day, once-daily telithromycin compared with 10-day, twice daily clarithromycin for the treatment of group A beta-hemolytic streptococcal tonsillitis/pharyngitis: a multicenter, randomized, double-blind, parallel-group study. *Clin Ther* 2003;25:422-43.
5. Zervos MJ, Heyder AM, Leroy B et al. Oral telithromycin 800 mg once daily for 5 days versus cefuroxime axetil 500 mg twice daily for 10 days in adults with acute exacerbations of chronic bronchitis. *J Int Med Research* 2003 31(3):157-69.
6. Aubier M, Aldons PM, Leak A et al. Telithromycin is as effective as amoxicillin/clavulanate in acute exacerbations of chronic bronchitis. *Respiratory Medicine* 2002;96(11):862-71.
7. Tellier G, Niederman MS, Nusrat R. 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 Research & Opinion* 2004;20(5):739-47.
8. Niederman MS, Chang JR, Stewart J. et al. Comparison of hospitalization rates in patients with community-acquired pneumonia treated with 10 days of telithromycin or clarithromycin. *Current Curr Med Research & Opinion* 2004;20(5):749-56

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