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**Department of Vermont Health Access**

***Therapeutic Class Review  
Ketolides***

**Overview/Summary**

Telithromycin is the first member of the ketolide group of antibiotics which is related to the macrolide group of antibiotics. It was developed to target respiratory pathogens resistant to the macrolides.<sup>1</sup> Telithromycin works by binding to two sites on the 50S ribosomal subunit.<sup>2</sup> Compared to the macrolides, structural modifications enable it to bind more tightly to bacterial ribosomes.<sup>1</sup> These modifications result in decreased resistance, an improved pharmacokinetic profile and increased potency.<sup>1</sup> Telithromycin has also been shown to alter the secretion of interleukin-1alpha and tumor necrosis factor-alpha, the significance of which has not been established.<sup>2</sup>

Telithromycin is Food and Drug Administration (FDA) approved to treat community acquired pneumonia due to *Streptococcus pneumoniae*, including multi-drug resistant isolates, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydomphila pneumoniae* and *Mycoplasma pneumoniae*.<sup>3</sup> On January 20, 2006, the FDA issued a public health advisory regarding the risk of liver injury in patients taking telithromycin, and in June of 2006, warnings regarding the risk of acute hepatic failure and severe, potentially fatal liver injury were strengthened in telithromycin's product labeling. The hepatic reactions which have been reported include fulminant hepatitis and hepatic necrosis necessitating liver transplant in some patients. Physicians and patients are urged to monitor for signs and symptoms of hepatitis including but not limited to jaundice, fatigue, malaise, anorexia, nausea, and liver tenderness.<sup>4</sup>

In February of 2007, the labeling of telithromycin was updated to include a boxed warning stating that the use of this medication is contraindicated in patients who have been diagnosed with myasthenia gravis. This warning is due to reports of fatal respiratory failure associated with telithromycin use in this patient population. At the same time, warnings regarding the risk of visual disturbances and loss of consciousness were strengthened. At this time, the FDA removed two of the three previously approved indications for telithromycin- acute bacterial exacerbations of chronic bronchitis and acute bacterial sinusitis.<sup>5</sup>

These safety concerns have prompted the FDA to conclude that the risks of telithromycin outweigh the benefits in the treatment of minor illnesses. In patients with mild to moderate community acquired pneumonia, telithromycin should be reserved as a second-line agent to other antimicrobial agents.<sup>1</sup>

Telithromycin is not available generically at this time.

**Medications**

**Table 1. Medications Included Within Class Review**

<b>Generic Name (Trade name)</b>	<b>Medication Class</b>	<b>Generic Availability</b>
Telithromycin (Ketek <sup>®</sup> )	Ketolide	-

The ketolides have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration-approved indications for the ketolides that are noted in Table 3. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be

initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

**Table 2. Microorganisms Susceptible to the Ketolides<sup>3</sup>**

Organism	Telithromycin
<b>Gram-Positive Aerobes</b>	
<i>Streptococcus pneumoniae</i> *	✓
<b>Gram-Negative Aerobes</b>	
<i>Haemophilus influenzae</i>	
<i>Moraxella catarrhalis</i>	✓
<b>Other Organisms</b>	
<i>Chlamydophila (Chlamydia) pneumoniae</i>	
<i>Mycoplasma pneumoniae</i>	✓

\*Including multi-drug resistant isolates.

**Indications**

**Table 3. Food and Drug Administration (FDA) Approved Indications<sup>3</sup>**

Generic Name	Community Acquired Pneumonia
Telithromycin	✓ (including multi-drug resistant isolates of <i>Streptococcus pneumoniae</i> )

**Pharmacokinetics**

**Table 4. Pharmacokinetics<sup>3</sup>**

Generic Name	Time to Peak Blood Levels (hours)	Protein Binding (%)	Renal Excretion (%)	Serum Half-Life (hours)
Telithromycin	1	60 to 70	13	10

**Clinical Trials**

Overall, telithromycin has demonstrated efficacy in the treatment of community acquired pneumonia. Open-label studies demonstrate efficacy in clinical and bacteriologic response, including the treatment of erythromycin-resistant *Streptococcus pneumoniae* and penicillin-resistant *Streptococcus pneumoniae*.<sup>6,7</sup> No significant differences were observed in clinical or bacteriologic response rates when comparing 10 days of therapy with telithromycin to 10 days of therapy with clarithromycin.<sup>8</sup> Tellier and colleagues compared five and seven day regimens of telithromycin to 10 days of therapy with clarithromycin. No significant differences were observed between groups in clinical and bacteriologic response.<sup>9</sup> When compared to high dose amoxicillin, similar clinical and bacteriologic responses were observed between groups.<sup>10</sup>

**Table 5. Clinical Trials**

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<b>Community Acquired Pneumonia</b>				
<p>van Rensburg et al<sup>6</sup></p> <p>Telithromycin 800 mg once daily for 7 days</p> <p>All patients received active treatment.</p>	<p>MC, OL, RCT</p> <p>Patients 13 years of age and older with a radiologically confirmed diagnosis of community-acquired pneumonia</p>	<p>N=831</p> <p>24 days</p>	<p>Primary: Clinical response (cure defined as resolution of signs and symptoms of infection), bacteriologic response (eradication of causative pathogen in culturable specimen)</p> <p>Secondary: Not reported</p>	<p>Primary: Clinical cure and bacteriologic eradication were seen in 15 of 16 patients infected with erythromycin-resistant <i>S pneumoniae</i> and/or penicillin-resistant <i>S pneumoniae</i>. The overall clinical cure rate was 89.3% and bacteriologic eradication was observed in 87.6% of patients.</p> <p>Secondary: Not reported</p>
<p>van Rensburg et al<sup>7</sup></p> <p>Telithromycin 800 mg once daily for 5 to 10 days</p> <p>All patients received active treatment.</p>	<p>MA, MC</p> <p>Patients 18 years of age and older with community-acquired pneumonia; MA of 8 phase III studies and 1 phase II study</p>	<p>N=327</p> <p>24 to 28 days</p>	<p>Primary: Clinical response (cure defined as disappearance or return to pre-infection state of all signs and symptoms with improvement in chest X-ray or improvement such that no additional antibiotic is needed), bacteriologic response (eradication of causative bacteria based on cultures</p>	<p>Primary: The clinical cure rate with telithromycin was 91.2%. Thirty-five patients had infections caused by strains resistant to erythromycin and of these, clinical cure was established in 88.6%.</p> <p>Clinical failure was recorded in four patients with penicillin- and/or erythromycin-resistant pneumococci.</p> <p>Thirteen patients had penicillin- and/or erythromycin-resistant pneumococcal bacteremia. Clinical cure was established in 84.6% of resistant isolates compared to 90.2% of all pneumococcal bacteremia.</p> <p>The overall rate of satisfactory bacteriologic outcomes was 90.4%.</p> <p>In patients infected with isolates demonstrating reduced susceptibility to penicillin and/or erythromycin, eradication was achieved in 93.4%.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			<p>or improvement in the patient such that a follow-up culture could not be obtained and was presumed to be eradicated)</p> <p>Secondary: Not reported</p>	
<p>Dunbar et al<sup>8</sup></p> <p>Telithromycin 800 mg once daily and placebo once daily for 10 days</p> <p>vs</p> <p>clarithromycin 500 mg BID for 10 days</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients 18 years of age and older with acute community acquired pneumonia</p>	<p>N=448</p> <p>45 days</p>	<p>Primary: Clinical outcome at the post-therapy test-of-cure visit (17 to 24 days)</p> <p>Secondary: Bacteriological outcome at the post-therapy test-of-cure visit, clinical and bacteriological outcome at the late post-therapy visit (31 to 45 days)</p>	<p>Primary: No significant difference was observed between groups in clinical cure rates at the post-therapy test-of-cure visit (88.3% for telithromycin and 88.5% for clarithromycin).</p> <p>Secondary: Satisfactory bacteriologic outcome was observed in 89.3% of telithromycin patients and 96.4% of clarithromycin patients at the post-therapy test-of-cure visit.</p> <p>Clinical cure rates at the late post-therapy visit were 86.0 and 84.6% in the telithromycin and clarithromycin groups respectively. No significant difference was observed.</p> <p>Satisfactory bacteriologic outcome was observed in 88.5% of patients in both groups at the late post-therapy visit.</p> <p>Both treatments were fairly well tolerated.</p>
<p>Tellier et al<sup>9</sup></p> <p>Telithromycin 800 mg once daily for 5 days</p> <p>vs</p> <p>telithromycin 800 mg</p>	<p>AC, DB, MC, PG, RCT</p> <p>Patients 18 years of age and older with community acquired</p>	<p>N=575</p> <p>36 days</p>	<p>Primary: Clinical outcome at the post-therapy test-of-cure visit (17 to 21 days)</p> <p>Secondary: Bacteriologic</p>	<p>Primary: Equivalent clinical cure rates were observed between groups. Clinical cure rates were 89.3, 88.8 and 91.8% in the telithromycin five day, telithromycin seven day and clarithromycin groups respectively.</p> <p>Secondary: Satisfactory bacteriologic response was observed in 87.7, 80.0 and 83.3% of the telithromycin five day, telithromycin seven day and clarithromycin groups</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
once daily for 7 days  vs  clarithromycin 500 mg BID for 10 days	pneumonia		outcome at post-therapy test-of-cure visit	respectively.  Adverse effects were mostly mild to moderate and affected the gastrointestinal tract.
Carbon et al <sup>11</sup>  Telithromycin 800 mg once daily for 5 to 10 days  vs  comparator antibiotics (amoxicillin 1,000 mg TID, clarithromycin 500 mg BID, or trovafloxacin 200 mg once daily)  Some studies were OL with all patients receiving telithromycin.	MA, RETRO  Patients 18 years of age and older with radiologically confirmed community-acquired pneumonia; the study was not able to detect statistical differences between telithromycin and comparator antibiotics due to the small number of patients treated with comparators	N=2,991  Up to 45 days	Primary: Clinical response (cure defined as disappearance or return to pre-infection state of all signs and symptoms with improvement in chest X-ray or improvement such that no additional antibiotic is needed), bacteriologic response (eradication or clinical improvement such that no follow-up culture could be obtained)  Secondary: Not reported	Primary: In patients with pneumococcal bacteremia treated with telithromycin, clinical cure was achieved in 90.2% in the per protocol population and 80.9% in the bacteremic bacteriologic modified ITT population ( <i>P</i> values not reported).  Clinical cure was established in 78.9% of the per protocol population in the pooled analysis of all comparator antibiotics and in 62.5% of the bacteremic bacteriologic modified ITT population ( <i>P</i> values not reported).  Bacteriologic eradication was established in 93.9% of the per protocol population treated with telithromycin and 84.0% of patients in the bacteremic bacteriologic modified ITT population ( <i>P</i> values not reported).  Bacteriologic eradication was established in 78.9% of the per protocol population in the pooled analysis of all comparator antibiotics and in 66.7% of the bacteremic bacteriologic modified ITT population ( <i>P</i> values not reported).  Secondary: Not reported
Hagberg et al <sup>10</sup>  Telithromycin 800 mg once daily for 10 days	DB, MC, RCT  Patients 18 years of age and older with	N=404  36 days	Primary: Clinical outcome at the post-therapy test-of-cure visit (17 to 24 days)	Primary: The clinical cure rates were 94.6 and 90.1% for telithromycin and amoxicillin, respectively at the post-therapy test-of-cure visit (difference, 4.5; 95% CI, -2.1 to 11.1). No significant difference was observed between groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amoxicillin 1,000 mg TID for 10 days	acute community acquired pneumonia		Secondary: Bacteriologic outcome at post-therapy test-of-cure, clinical and bacteriological outcome at late post-therapy visit (31 to 36 days)	Secondary: Bacteriologic eradication rates were similar at 87.5 and 86.7% for the telithromycin and amoxicillin groups respectively at the test-of-cure visit.  Clinical cure rates at the late post-therapy visit were 92.0 and 85.3% for telithromycin and amoxicillin respectively (difference, 6.7; 95% CI,-1.7 to 15.1). No significant difference was observed.

Drug regimen abbreviations: BID=twice daily, TID=three times daily

Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, DD=double-dummy, ITT=intent-to-treat, MA=meta-analysis, MC=multi-center, OL=open label, PG=parallel group, RCT=randomized controlled trial, RETRO=retrospective

**Special Populations****Table 6. Special Populations<sup>3</sup>**

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Telithromycin	No dosage adjustment required in the elderly population.  Safety and efficacy have not been established in children <18 years of age.	A dose of 600 mg once daily is recommended in patients with creatinine clearance <30 mL/minute and patients needing dialysis; in patients undergoing hemodialysis, the dose should be administered after the dialysis session.	No dosage adjustment is necessary.  In patients with hepatic impairment and severe renal dysfunction (creatinine clearance <30 mL/minute), a dose of 400 mg once daily is recommended.	C	Unknown

**Adverse Drug Events****Table 7. Adverse Drug Events (%)<sup>3</sup>**

Adverse Event	Telithromycin
<b>Cardiovascular</b>	
Arrhythmia	✓
Bradycardia	<0.2
Hypotension	<0.2
Palpitation	✓
<b>Central Nervous System</b>	
Anxiety	<0.2
Confusion	✓
Dizziness	2.8 to 3.7
Fatigue	>0.2<2.0
Hallucinations	✓
Headache	2.0 to 5.5
Insomnia	>0.2<2.0
Loss of consciousness	✓
Paresthesias	<0.2
Somnolence	>0.2<2.0
Vagal syndrome	✓
Vertigo	>0.2<2.0
<b>Dermatologic</b>	
Eczema	<0.2
Erythema multiforme	<0.2
Pruritus	<0.2
Rash	>0.2<2.0
Urticaria	<0.2
<b>Gastrointestinal</b>	
Abdominal distension	>0.2<2.0
Abdominal pain	>0.2<2.0

Adverse Event	Telithromycin
Anorexia	≥0.2<2.0
Constipation	≥0.2<2.0
Diarrhea	10.0 to 10.8
Dry mouth	≥0.2<2.0
Dyspepsia	≥0.2<2.0
Flatulence	≥0.2<2.0
Gastritis	≥0.2<2.0
Gastroenteritis	≥0.2<2.0
Gastrointestinal upset	≥0.2<2.0
Glossitis	≥0.2<2.0
Loose stools	2.1 to 2.3
Nausea	7.0 to 7.9
Oral moniliasis	≥0.2<2.0
Pancreatitis	✓
Stomatitis	≥0.2<2.0
Taste perversion	1.5 to 1.6
Taste loss	✓
Vomiting	2.4 to 2.9
Watery stools	≥0.2<2.0
<b>Genitourinary</b>	
Genital moniliasis	≥0.2<2.0
Vaginitis	≥0.2<2.0
Vaginosis, fungal	≥0.2<2.0
<b>Hematologic</b>	
Eosinophilia	<0.2
Platelets increased	≥0.2<2.0
<b>Hepatic</b>	
Abnormal liver enzymes	≥0.2<2.0
Bilirubin increased	<0.2
Hepatic dysfunction	✓
Hepatic failure	✓
Hepatic necrosis	✓
Hepatitis	0.07
Hepatitis, fulminant	✓
<b>Musculoskeletal</b>	
Arthralgia	✓
Exacerbation of myasthenia gravis	✓
Muscle cramps	✓
Myalgia	✓
<b>Miscellaneous</b>	
Anaphylaxis	✓
Angioedema	✓
Blurred vision	≥0.2<2.0
Difficulty focusing (visual)	≥0.2<2.0
Diplopia	≥0.2<2.0
Facial edema	✓
Flushing	<0.2
Sweating	≥0.2<2.0

✓ Percent not specified.

### **Contraindications/Precautions**

Telithromycin is contraindicated in patients with myasthenia gravis. Exacerbations have been reported in patients and sometimes occurred within a few hours of the first dose. Reports have included fatal and life-threatening acute respiratory failure with rapid onset and progression.<sup>3</sup>

Telithromycin is contraindicated in patients with previous history of hepatitis and/or jaundice associated with the use of the agent or any macrolide antibiotic.<sup>3</sup>

Telithromycin is contraindicated in patients with history of hypersensitivity to telithromycin or any component of the agent or any macrolide antibiotic.<sup>3</sup>

Concurrent administration of telithromycin with cisapride or pimozide is contraindicated.<sup>3</sup>

Concurrent administration of telithromycin with colchicine in patients with renal or hepatic impairment is contraindicated.<sup>3</sup>

Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients taking telithromycin. Reactions included fulminant hepatitis and hepatic necrosis necessitating liver transplantation. These reactions were observed during or immediately following treatment. In some cases, the liver injury progressed quickly and appeared after several doses of medication. Patients and prescribers should monitor closely for signs and symptoms of hepatitis. If signs or symptoms are observed, telithromycin should be discontinued immediately and the patient should seek medical attention which should include liver function testing. Telithromycin should not be re-administered to any patient with a history of hepatitis and/or jaundice associated with the agent or another macrolide antibiotic. Less severe hepatic dysfunction has also been reported with telithromycin use, which was often reversible.<sup>3</sup>

Telithromycin may prolong the QT interval in some patients, leading to an increased risk for ventricular arrhythmias including torsades de pointes. Avoid the use of telithromycin in patients with congenital QT prolongation and in patients with pro-arrhythmic conditions such as hypokalemia, hypomagnesemia,<sup>3</sup> clinically significant bradycardia and in patients receiving Class IA or Class III antiarrhythmic agents.

Telithromycin may cause visual disturbances, including the ability to accommodate and to release accommodation. Visual disturbances may include blurred vision, difficulty focusing and diplopia. Most events were mild to moderate, though severe cases have been reported.<sup>3</sup>

There have been reports of transient loss of consciousness including some associated with vagal syndrome. Because of the potential for visual disturbances and loss of consciousness, patients should minimize activities such as driving, operating heavy machinery or engaging in hazardous activities while taking telithromycin. If patients experience visual disturbances or loss of consciousness, patients should not drive, operate heavy machinery or engage in hazardous activities.<sup>3</sup>

*Clostridium difficile* associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents. It may range in severity from mild diarrhea to fatal colitis. *C difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C difficile* cause increased morbidity and mortality and may be refractory to antimicrobial therapy, requiring colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary as CDAD may occur over two months after the administration of antibacterial agents. If CDAD is confirmed or suspected, ongoing antibiotic use not directed against *C difficile* should be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C difficile* and surgical intervention should be instituted as indicated.<sup>3</sup>

Prescribing telithromycin in the absence of proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria.<sup>3</sup>

Telithromycin is mainly excreted via the liver and the kidneys. It may be administered without dosage adjustment in patients with hepatic impairment. In the presence of severe renal impairment (creatinine clearance <30 mL/minute), a reduced dosage of telithromycin is recommended.<sup>3</sup>

The black box warning assigned to telithromycin is outlined below.

**Black Box Warning for Ketek<sup>®3</sup>**

<b>WARNING</b>
Ketek <sup>®</sup> is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek <sup>®</sup> .

**Drug Interactions**

**Table 8. Drug Interactions<sup>12</sup>**

<b>Drug</b>	<b>Interaction</b>	<b>Mechanism</b>
Azithromycin, clarithromycin, erythromycin, telithromycin	Antiarrhythmic agents (amiodarone, bretylium, disopyramide, dofetilide, procainamide, quinidine, sotalol)	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. Use certain macrolide agents with caution and avoid the use of telithromycin in patients receiving class IA and class III antiarrhythmics.
Azithromycin, clarithromycin, erythromycin, telithromycin	Digoxin	Coadministration may increase digoxin serum levels and result in toxicity. Monitor digoxin serum levels and symptoms of toxicity and adjust the dose as needed.
Azithromycin, clarithromycin, erythromycin, telithromycin	Dronedarone	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The use of dronedarone is contraindicated in patients taking certain macrolide antibiotics.
Azithromycin, clarithromycin, erythromycin, telithromycin	Nilotinib	Nilotinib plasma concentrations may be increased, increasing the risk of adverse events including life-threatening cardiac arrhythmias (torsades de pointes). Avoid the concomitant use of nilotinib and macrolide antibiotics. If concomitant use cannot be avoided, monitor closely for adverse events and adjust the dose of nilotinib as needed.
Azithromycin, clarithromycin, erythromycin, telithromycin	Pimozide	Increased pimozide plasma concentrations may occur increasing the risk of cardiotoxicity. Coadministration is contraindicated.
Azithromycin, clarithromycin, erythromycin, telithromycin	Quinolones (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin)	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. Sparfloxacin is contraindicated in patients taking medications which increase QT interval (erythromycin). Avoid levofloxacin and use moxifloxacin and gatifloxacin with caution in patients receiving macrolide antibiotics.
Azithromycin, clarithromycin, erythromycin, telithromycin	Tacrolimus	Plasma tacrolimus concentrations may be elevated, increasing the risk of toxicity. Monitor tacrolimus blood levels and symptoms of toxicity and adjust the dose as needed.
Azithromycin, clarithromycin, erythromycin,	Warfarin	The anticoagulant effect of oral anticoagulants may be increased. Monitor anticoagulant parameters and adjust the dose as necessary.

Drug	Interaction	Mechanism
telithromycin		
Clarithromycin, erythromycin, telithromycin	Benzodiazepines (alprazolam, diazepam, midazolam, triazolam)	Increased sedation may occur. Caution patients about increased or prolonged sedation and adjust the benzodiazepine dose as needed. Benzodiazepines that undergo conjugative metabolism are unlikely to interact.
Clarithromycin, erythromycin, telithromycin	Buspirone	Plasma buspirone concentrations may be increased. Close monitoring is recommended. Azithromycin is unlikely to interact.
Clarithromycin, erythromycin, telithromycin	Cabergoline	Plasma cabergoline concentrations may be increased. Careful monitoring is recommended if coadministration cannot be avoided.
Clarithromycin, erythromycin, telithromycin	Cisapride	Plasma concentrations of cisapride may be increased with potential cardiotoxicity. Concomitant use is contraindicated. Azithromycin may be less likely to interact.
Clarithromycin, erythromycin, telithromycin	Colchicine	Increased colchicine concentrations with toxicity and death may occur. Coadministration of colchicine with clarithromycin or telithromycin in patients with renal or hepatic impairment is contraindicated. In patients with normal renal and hepatic function, administer colchicine with caution at a dose of 0.3 mg twice daily. Use colchicine and erythromycin together with caution at a lower dose of colchicine.
Clarithromycin, erythromycin, telithromycin	Diltiazem	Concentrations of macrolide may be increased, increasing the risk of cardiotoxicity. Until more information is available, avoid concomitant use.
Clarithromycin, erythromycin, telithromycin	Ergot derivatives	Acute ergotism manifested as peripheral ischemia has been reported. Monitor the patient for signs of ergotism. Dose adjustment or discontinuation may be necessary.
Clarithromycin, erythromycin, telithromycin	Everolimus	Plasma levels of everolimus may be elevated. Avoid coadministration and consider alternative antibiotics. Adjust the dose of everolimus as needed.
Clarithromycin, erythromycin, telithromycin	Fesoterodine	Plasma levels of fesoterodine may be elevated. The dose should not exceed 4 mg daily in patients receiving clarithromycin and possibly telithromycin. In patients receiving erythromycin, assess the tolerability of fesoterodine at 4 mg daily before increasing the dose.
Clarithromycin, erythromycin, telithromycin	HMG Co-A reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Severe myopathy or rhabdomyolysis may occur due to elevated HMG Co-A reductase levels. If possible, administer alternative therapy. Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and may be less likely to interact.
Clarithromycin, erythromycin, telithromycin	Opioid analgesics (buprenorphine, codeine, fentanyl, methadone, oxycodone, sufentanil)	Fentanyl plasma concentrations may be elevated. Use caution when administering fentanyl concurrently with macrolide antibiotics. Monitor for signs of opioid toxicity. Adjust the fentanyl dose if needed.
Clarithromycin, erythromycin, telithromycin	Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil)	Phosphodiesterase type 5 inhibitor levels may be elevated increasing the risk of adverse events. Consider lowering the dose of the phosphodiesterase 5 inhibitor. Azithromycin may be a safer alternative.
Clarithromycin,	Protease inhibitors	Amprenavir and tipranavir concentrations may be increased.

Drug	Interaction	Mechanism
erythromycin, telithromycin		Clarithromycin concentrations may be increased by darunavir and tipranavir. No dosage adjustments are needed, but be prepared to make appropriate changes if an interaction is suspected.
Clarithromycin, erythromycin, telithromycin	Quetiapine	Quetiapine levels may be increased, increasing the risk of adverse effects. Close monitoring is recommended and dose reduction of quetiapine may be necessary.
Clarithromycin, erythromycin, telithromycin	Repaglinide	Repaglinide levels may be elevated, increasing the pharmacologic effect and risk of toxicity. Close monitoring is recommended and dose adjustment of repaglinide may be necessary. Azithromycin may be a safer choice.
Clarithromycin, erythromycin, telithromycin	Rifamycins (rifabutin, rifampin, rifapentine)	Antimicrobial effects of macrolides may be decreased. Gastrointestinal and rifamycin adverse effects may be increased. Monitor for increased adverse effects and decrease in response to macrolides. Do not use telithromycin and a rifamycin. Azithromycin may be a safer choice.
Clarithromycin, erythromycin, telithromycin	Verapamil	Increased risk of toxicity exists. Closely monitor cardiac function.
Clarithromycin, telithromycin	Darifenacin	Darifenacin concentrations may be elevated, increasing the risk of adverse events. Darifenacin should not exceed 7.5 mg daily when administered with clarithromycin.
Clarithromycin, telithromycin	Ixabepilone	Ixabepilone plasma concentrations may be increased, increasing the risk of toxicity. Avoid coadministration if possible. If they must be used together consider lowering the Ixabepilone dose to 20 mg/m <sup>2</sup> every three weeks.
Clarithromycin, telithromycin	Lapatinib	Lapatinib concentrations may be elevated, increasing risk of toxicity. Avoid concurrent use if possible. If the agents must be used together, decrease the dose of lapatinib to 500 mg daily. The dose may be increased again one week after discontinuation of the macrolide.
Clarithromycin, telithromycin	Pazopanib	Pazopanib levels may be elevated increasing pharmacologic activity and adverse effects. If coadministration cannot be avoided, decrease the dose of pazopanib to 400 mg daily. Further dose reduction may be necessary.
Clarithromycin, telithromycin	Ranolazine	Ranolazine levels may be elevated, increasing the pharmacologic effect and risk of toxicity. Coadministration is contraindicated.
Clarithromycin, telithromycin	Temsirolimus	Temsirolimus levels may be elevated, increasing the risk of toxicity. If concurrent use cannot be avoided consider lowering the dose of temsirolimus to 12.5 mg/week and monitor levels.
Clarithromycin, telithromycin	Tolvaptan	Tolvaptan levels may be elevated, increasing the pharmacologic activity and risk of adverse effects. Coadministration is contraindicated.

### **Dosage and Administration**

**Table 9. Dosing and Administration<sup>3</sup>**

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Telithromycin	Community acquired pneumonia: Tablet: 800 mg once daily for seven to 10 days	Safety and efficacy have not been established in children <18 years of age.	Tablet: 300 mg 400 mg

**Clinical Guidelines**

The clinical guidelines contained in Table 10 are summarized globally and are not limited to the role of the ketolides. However, the summary of the chronic obstructive pulmonary disease (COPD) guideline focuses only on the treatment of exacerbations which have a bacterial component. The global treatment strategy for COPD is not discussed in this summary.

**Table 10. Clinical Guidelines**

Clinical Guideline	Recommendations
<p>Infectious Diseases Society of America/ American Thoracic Society: <b>Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)</b><sup>13</sup></p>	<p><u>General recommendations</u></p> <ul style="list-style-type: none"> <li>• Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns.</li> <li>• Once the etiology of community acquired pneumonia has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen.</li> </ul> <p><u>Empiric therapy - outpatient treatment</u></p> <ul style="list-style-type: none"> <li>• For previously healthy patients with no risk factors for drug resistant <i>Streptococcus pneumoniae</i> infection, a macrolide (azithromycin, clarithromycin or erythromycin) can be used. Doxycycline may also be an alternate option.</li> <li>• A respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin) is the treatment option in regions with a high rate of macrolide-resistant <i>S pneumoniae</i>, or for patients with comorbidities, such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or use of immunosuppressive drugs. Fluoroquinolones may also be used for patients who have used antimicrobials within the previous three months. Other preferred options for these patients would be the combination of a <math>\beta</math>-lactam (ceftriaxone, cefpodoxime or cefuroxime) plus a macrolide or doxycycline, or amoxicillin/clavulanate.</li> </ul> <p><u>Empiric therapy - inpatient, non-intensive care unit treatment</u></p> <ul style="list-style-type: none"> <li>• A respiratory fluoroquinolone or a combination of a <math>\beta</math>-lactam plus a macrolide is recommended.</li> <li>• Preferred <math>\beta</math>-lactam agents include cefotaxime, ceftriaxone and ampicillin; ertapenem may also be used for selected patients.</li> <li>• A respiratory fluoroquinolone should be used for penicillin allergic patients.</li> </ul> <p><u>Empiric therapy - inpatient, intensive care unit treatment</u></p> <ul style="list-style-type: none"> <li>• A <math>\beta</math>-lactam (cefotaxime, ceftriaxone or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone.</li> <li>• For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.</li> <li>• For <i>Pseudomonas</i> infection, use an antipseudomonal <math>\beta</math>-lactam (piperacillin/tazobactam, cefepime, imipenem or meropenem) plus either ciprofloxacin or levofloxacin.</li> <li>• The antipseudomonal, antipseudomonal <math>\beta</math>-lactams listed above can also be used with either an aminoglycoside and azithromycin or an aminoglycoside and an antipseudomonal fluoroquinolone.</li> <li>• For penicillin-allergic patients, substitute aztreonam for the above <math>\beta</math>-lactam for <i>Pseudomonas</i> infection.</li> </ul>

Clinical Guideline	Recommendations
	<p><u>Pathogen-directed therapy</u></p> <ul style="list-style-type: none"> <li>• <i>S pneumonia</i> (penicillin non-resistant)- penicillin G or amoxicillin preferred; alternative agents include macrolides, cephalosporins (oral cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren or parenteral cefuroxime, ceftriaxone or cefotaxime), clindamycin, doxycycline or a respiratory fluoroquinolone.</li> <li>• <i>S pneumonia</i> (penicillin resistant)- agents chosen based on susceptibility; alternative agents include vancomycin, linezolid and high-dose amoxicillin (3 g/day).</li> <li>• <i>Haemophilus influenza</i> (non-β-lactamase producing)- amoxicillin preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin.</li> <li>• <i>H influenza</i> (β-lactamase producing)- second- or third-generation cephalosporin or amoxicillin/clavulanate preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin.</li> <li>• <i>Mycoplasma pneumonia/Chlamydia pneumonia</i>- macrolide, tetracycline preferred; alternative agent is fluoroquinolone.</li> <li>• <i>Legionella</i> species- fluoroquinolone, azithromycin preferred; alternative agent is doxycycline.</li> <li>• <i>Chlamydia psittaci</i>- tetracycline preferred; alternative agent is a macrolide.</li> <li>• <i>Coxiella burnetii</i>- tetracycline preferred; alternative agent is a macrolide.</li> <li>• <i>Francisella tularensis</i>- doxycycline preferred; alternative agents include gentamicin or streptomycin.</li> <li>• <i>Yersinia pestis</i>- streptomycin, gentamicin recommend; alternative agents include doxycycline or fluoroquinolone.</li> <li>• <i>Bacillus anthracis</i> (inhalation)- ciprofloxacin, levofloxacin, doxycycline preferred (usually with a second agent); alternative agents include other fluoroquinolones, rifampin, clindamycin, chloramphenicol or a β-lactam if susceptible.</li> <li>• <i>Enterobacteriaceae</i>- third generation cephalosporin, carbapenem; alternative agents include a β-lactam/β-lactamase inhibitor or a fluoroquinolone.</li> <li>• <i>Pseudomonas aeruginosa</i>- antipseudomonal β-lactam plus ciprofloxacin or levofloxacin or aminoglycoside preferred; alternative agents include aminoglycoside plus ciprofloxacin or levofloxacin.</li> <li>• <i>Burkholderia pseudomallei</i>- carbapenem, ceftazidime preferred; alternative agents include fluoroquinolone or sulfamethoxazole/trimethoprim (SMX/TMP).</li> <li>• <i>Acinetobacter</i> species- carbapenem preferred; alternative agents include cephalosporin and aminoglycoside, ampicillin/sulbactam, colistin.</li> <li>• <i>Staphylococcus aureus</i> (methicillin susceptible)- antistaphylococcal penicillin preferred; alternative agents include cefazolin and clindamycin.</li> <li>• <i>S aureus</i> (methicillin resistant)- vancomycin or linezolid preferred; alternative agent is SMX/TMP.</li> <li>• <i>Bordetella pertussis</i>- macrolide preferred; alternative agent is SMX/TMP.</li> <li>• Anaerobe (aspiration)- β-lactam/β-lactamase inhibitor or clindamycin preferred; alternative agent is carbapenem.</li> <li>• Influenza virus- oseltamivir or zanamivir preferred.</li> <li>• <i>Mycobacterium tuberculosis</i>- isoniazid plus rifampin plus ethambutol plus pyrazinamide preferred.</li> <li>• <i>Coccidioides</i> species- no therapy generally recommended in normal host</li> </ul>

Clinical Guideline	Recommendations
	<p>for uncomplicated infection; if therapy desired, itraconazole or fluconazole preferred; alternative agent is amphotericin B.</p> <ul style="list-style-type: none"> <li>• <i>Histoplasmosis</i>- itraconazole preferred; alternative agent is amphotericin B.</li> <li>• <i>Blastomycosis</i>- itraconazole preferred; alternative agent is amphotericin B.</li> <li>• Suspected H1N1 pandemic influenza should be treated with oseltamivir and antibacterial agents targeting <i>S pneumonia</i> and <i>S aureus</i>.</li> </ul>
<p>American College of Chest Physicians: <b>Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement (2005)</b><sup>14</sup></p>	<ul style="list-style-type: none"> <li>• The oral route for medications is recommended if the patient can tolerate it, and if the availability and activity of the agents are adequate.</li> <li>• Severity of illness, patient age, comorbidities, concomitant medications and ease of administration are all factors that can impact the empiric treatment decision.</li> <li>• The use of a macrolide, doxycycline or fluoroquinolone antibacterial agent is recommended by both the Infectious Disease Society of America and the American Thoracic Society consensus guidelines as appropriate empiric outpatient treatment for low-risk patients.</li> <li>• Amoxicillin/clavulanate and some second generation cephalosporins (cefuroxime, cefpodoxime or cefprozil) are alternatives for low-risk patients.</li> <li>• A patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with a <math>\beta</math>-lactam/macrolide combination or an antipneumococcal fluoroquinolone.</li> <li>• Double therapy with either a <math>\beta</math>-lactam/macrolide combination or a <math>\beta</math>-lactam/antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for intensive care unit admission but have chosen to remain in the home.</li> </ul>
<p>Infectious Diseases Society of America/ American Thoracic Society: <b>Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2004)</b><sup>15</sup></p>	<ul style="list-style-type: none"> <li>• Empiric therapy for hospital-acquired pneumonia, ventilator-associated pneumonia and healthcare-associated pneumonia should include agents from a different class than the patient has recently received.</li> <li>• Judicious use of combination therapy in hospital-acquired pneumonia for a specific pathogen is recommended with consideration of short-duration (five days) aminoglycoside therapy when used in combination with <math>\beta</math>-lactam to treat <i>P aeruginosa</i> pneumonia.</li> <li>• De-escalation of antibiotics should be considered once results are available of lower respiratory tract cultures and patient's clinical response.</li> <li>• For patients with uncomplicated hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia who have received initially appropriate therapy and have had a good clinical response with no evidence of infection with nonfermenting gram-negative bacilli, a shorter duration of antibiotic therapy (seven to eight days) is recommended.</li> <li>• The following initial empiric therapy is recommended for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with early onset of disease, no known risk factors for multidrug-resistant pathogens and any disease severity: ceftriaxone, levofloxacin, moxifloxacin, ciprofloxacin, ampicillin/sulbactam or ertapenem.</li> <li>• The following initial empiric therapy is recommended for hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia in patients with late onset of disease or known risk factors for multidrug-resistant pathogens and all disease severity: antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or <math>\beta</math>-lactam/ <math>\beta</math>-lactamase inhibitor</li> </ul>

Clinical Guideline	Recommendations
	(piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin or tobramycin) plus linezolid or vancomycin.
Global Initiative for Chronic Obstructive Lung Disease: <b>Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2010)</b> <sup>16</sup>	<p><u>Management of exacerbations of chronic obstructive pulmonary disease (COPD) with a bacterial component</u></p> <ul style="list-style-type: none"> <li>• Predominant bacteria include <i>H influenzae</i>, <i>S pneumoniae</i> and <i>M catarrhalis</i>.</li> <li>• Patients with severe COPD requiring mechanical ventilation may be more frequently infected with <i>P aeruginosa</i>.</li> <li>• Patients with mild exacerbations and no risk for poor outcome may be treated with oral penicillin, ampicillin, amoxicillin, tetracycline or SMX/TMP. Alternative agents include amoxicillin/clavulanate, a macrolide, a second or third generation cephalosporin or a ketolide.</li> <li>• Patients with moderate exacerbations and risk factors for poor outcomes should be treated with amoxicillin/clavulanate. Alternative agents are fluoroquinolones. Parenteral options include <math>\beta</math>-lactam/<math>\beta</math>-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones.</li> <li>• Patients with severe exacerbations with risk factors for <i>P aeruginosa</i> should be treated with high dose oral or parenteral fluoroquinolones or parenteral <math>\beta</math>-lactam with <i>P aeruginosa</i> activity.</li> </ul>

### Conclusions

Telithromycin is Food and Drug Administration (FDA) approved to treat community acquired pneumonia due to *Streptococcus pneumoniae*, including multi-drug resistant isolates, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.<sup>3</sup> On January 20, 2006, the FDA issued a public health advisory regarding the risk of liver injury in patients taking telithromycin, and in June of 2006, warnings regarding the risk of acute hepatic failure and severe, potentially fatal liver injury were strengthened in telithromycin's product labeling.<sup>4</sup> In February of 2007, the labeling of telithromycin was updated to include a boxed warning stating that the use of this medication is contraindicated in patients who have been diagnosed with myasthenia gravis. This warning is due to reports of fatal respiratory failure associated with telithromycin use in patients with myasthenia gravis. At the same time, warnings regarding the risk of visual disturbances and loss of consciousness were strengthened.<sup>5</sup> At this time, the FDA removed two of the three previously approved indications for telithromycin- acute bacterial exacerbations of chronic bronchitis and acute bacterial sinusitis.<sup>5</sup> In patients with mild to moderate community acquired pneumonia, telithromycin should be reserved as a second-line agent to other antimicrobial medications.<sup>1</sup>

Open-label studies demonstrate efficacy in clinical and bacteriologic response, including the treatment of erythromycin-resistant *S pneumoniae* and penicillin-resistant *S pneumoniae*.<sup>6,7</sup> No significant differences were observed in clinical or bacteriologic response rates when comparing 10 days of therapy with either telithromycin or clarithromycin.<sup>8</sup> Tellier and colleagues compared five and seven day regimens of telithromycin compared to 10 days of therapy with clarithromycin. No significant differences were observed between groups in clinical and bacteriologic response.<sup>9</sup> When compared to high dose amoxicillin, similar clinical and bacteriologic responses were observed between groups.<sup>10</sup>

Telithromycin is not available generically at this time.

### Appendix I: Utilization Within This Drug Class for DVHA

There was no utilization for Ketek in the period between January 1, 2011 and June 30, 2011.

### **Recommendations**

In consideration of the FDA approved indication, warnings and contraindications, consensus guideline recommendations, and current utilization of Ketek, the following change (marked in red) is recommended to the current Department of Vermont Health Access (DVHA) approval criteria (below).

#### **Ketek:**

- The member is continuing a course of therapy initiated while an inpatient at a hospital.  
OR
- The diagnosis or indication for the requested medication is community-acquired pneumonia.  
AND
- The member is at least 18 years of age at the time of the request.  
AND
- The member has no contraindication or a history of hypersensitivity or serious adverse event from any macrolide antibiotic.  
AND
- Infection is due to documented *Streptococcus pneumoniae* (including multi-drug resistant [MDRSP\*] *s.pneumoniae*), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*.  
AND
- **The member has had a documented therapeutic failure with all clinically appropriate alternatives.**  
AND
- The member does not have any of the following medical conditions: myasthenia gravis, hepatitis or underlying liver dysfunction, history of arrhythmias (e.g. QTc prolongation, or antiarrhythmic therapy), uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, a history of therapy with Class IA (e.g. quinidine or procainamide) or Class III (e.g. dofetilide) antiarrhythmic medications.

\*MDRSP includes penicillin-resistant *S. pneumoniae* isolates (PRSP) that are resistant to  $\geq 2$  of the following antibiotics: penicillin, 2<sup>nd</sup> generation cephalosporins, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

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