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## TELITHROMYCIN (KETEK™) A NEW ANTIMICROBIAL AGENT


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### Introduction

Infections that invade the lower respiratory tract, such as community-acquired pneumonia (CAP) and acute bacterial exacerbations of chronic bronchitis (ABECB), comprise the more serious respiratory tract infections (RTIs). They are associated with considerable morbidity and mortality, particularly in groups such as the very young, the elderly and those with co-morbid illness. Up to 80% of community-acquired RTIs are caused by *Streptococcus pneumoniae, Haemophilus influenzae* or *Moraxella catarrhalis* and are usually treated empirically. In the United States, 2-3 million cases of CAP result in approximately 10 million physician visits, 500,000 hospitalizations, and 45,000 deaths each year.[1] CAP is associated with a mortality rate of approximately 14% among patients who require hospitalization versus a mortality rate of <1% for patients who can be managed in an outpatient setting. There is an urgent need for new agents that are active against resistant respiratory tract pathogens, but also exhibit a low potential to select for resistance or induce cross-resistance to existing antibacterial agents.

Telithromycin (Ketek®, Aventis), the first of a new class of semi-synthetic antibiotics, the ketolides, was FDA-approved in April 2004. Ketolides were designed specifically for the treatment of community-acquired respiratory tract infections (RTI), such as CAP, acute bacterial sinusitis, and ABECB, including those caused by penicillin-resistant and/or macrolide resistant *Streptococcus pneumoniae.* Ketolides are members of the macrolide-lincosamide-streptogramin B ($MLS_B$) family, and consequently execute their antibacterial activity through the inhibition of bacterial protein synthesis. Telithromycin differs from macrolides in a structural modifications that allow the drug to bind more tightly to two distinct regions of ribosomal RNA. This dual binding mechanism enhances the ability of telithromycin to overcome resistance caused by modification of one of the target sites.

This article will overview the emergence of macrolide resistance, and the pharmacology, pharmacokinetics, indications, dosing, clinical trials, and safety profile of telithromycin.

### Macrolide Resistance

The emergence of antibiotic-resistant bacterial strains has increased at an alarming rate among the key bacterial pathogens associated with upper and lower RTIs. The combined percentage of penicillin-intermediate and penicillin-resistant strains of *S. pneumoniae* is now >40% in many regions. Re-

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**Table 1. CAP: Clinical cure rate at post-therapy follow-up (17-24 days) [2,4,11,12]**

| Controlled Studies | Patients (n) | Telithromycin | Comparator |
|---|---|---|---|
| Telithromycin vs. clarithromycin 500 mg BID for 10 days | 318 | 88.3% | 88.5% |
| Telithromycin vs. trovafloxacin* 200 mg QD for 7 to 10 days | 166 | 90.0% | 94.2% |
| Telithromycin vs. amoxicillin 1000 mg TID for 10 days | 301 | 94.6% | 90.1% |
| Telithromycin for 7 days vs. clarithromycin 500 mg BID for 10 days | 307 | 88.8% | 91.8% |

*This study was stopped prematurely after trovafloxacin was restricted for use in hospitalized patients with severe infection.

sistance has severely limited the role of penicillins for the treatment of upper RTIs while combination therapy is often necessary for lower RTIs due to their lack of activity against atypical pathogens (e. g., *Chlamydia pneumoniae*). The resistance and cross-resistance of macrolides, which initially offered an attractive option against a broad spectrum of respiratory pathogens, is increasing among agents within the class.

The most common mechanisms of resistance to $MLS_B$ antimicrobials are: (i) target site modification, (ii) reduced intracellular accumulation due to decreased influx or increased efflux of the drug and (iii) production of inactivation enzymes. Target site modification occurs due to methylation of the 23S rRNA. Methylation is usually governed by the acquisition of *erm* genes, which are responsible for encoding methyltranferases. Ribosomal methylation causes cross-resistance to all $MLS_B$ antibacterials because there is overlap between the binding sites.[5] A conformational change is made in the ribosome due to methylation. This results in decreased affinity for $MLS_B$ antibiotics. Ketolides remain active against strains that harbor the *erm* gene, and, compared with macrolides, telithromycin is less likely to activate inducible *erm* genes.[6] Presence of *erm* does reduce telithromycin's binding affinity; however, to a much less degree as compared to other $MLS_B$ antibiotics. The nature of the side-chain substituting the C11-C12 carbamate residue is responsible for enhancing the in vitro and in vivo activities in comparison with erythromycin. These activities are enhanced due to the pharmacodynamic and pharmacokinetic properties, the intracellular features, and tolerance of the side chain.[7]

Efflux pumps for erythromycin A have been described for several Gram-positive cocci. The efflux-mediated resistance pattern is encoded by different genes: *mef*(A) or *mef*(E) in streptococci, and *msr*(A) and *msr*(B) in staphylococci.[8] The presence of *mef* confers resistance to macrolides, but lincosamides and streptogrammins remain active. Telithromycin is a poor substrate for efflux pumps, thus, its activity against streptococci harboring *mef* genes is preserved. Production of antibiotic inactivating enzymes plays a minor role in $MLS_B$ resistance. Degradation is caused by hydrolysis of the macrolide lactone ring and modification due to macrolide phosphorylation and lincosamide nucleotidylation. However, only a few strains have been reported to have genes that produce inactivating enzymes.

## Indications

Telithromycin is indicated for the treatment of the following infections caused by susceptible strains of the designated microorganisms in patients 18 years old and above: ABECB due to *S. pneumoniae, H. influenzae,* or *M. catarrhalis*. Acute bacterial sinusitis due to *S. pneumoniae, H. influenzae, M. catarrhalis,* or *S. aureus*; CAP (of mild to moderate severity) due to *S. pneumoniae,* (including

**Table 2. Acute Sinusitis: Clinical cure rate at post-therapy follow-up (17-24 days) [4,13,14]**

| | Patients (n) | | Clinical cure rate | |
|---|---|---|---|---|
| Controlled Studies | Telithromycin | Comparator | Telithromycin (5 day treatment) | Comparator (10 day treatment) |
| Telithromycin vs. amoxicillin/clavulanic acid 500/125 mg TID | 146 | 137 | 75.3% | 74.5% |
| Telithromycin vs. cefuroxime axetil 250 mg BID | 189 | 89 | 85.2% | 82.0% |

multi-drug resistant isolates [MDRSP]), *H. influenzae, M. catarrhalis, C. pneumoniae,* or *Mycoplasma pneumoniae*.[4]

**Pharmacology and Pharmacokinetics**

Ketolides have a mechanism of action similar to erythromycin A, from which they have been derived. Bacterial protein synthesis is inhibited by interacting near the peptidyl transferase site of the 50S ribosomal subunit.[3] Telithromycin differs chemically from macrolides by the lack of α-L-cladinose at position 3 of the erythronolide A ring, resulting in a 3-keto functional group.[4] The main sites of macrolide and ketolide interaction are within domains II and V of the 23S rRNA. However, the ketolides display a higher affinity than macrolides for ribosomal binding sites. By binding at domain II, telithromycin remains bactericidal against gram-positive cocci even in the presence of resistance mediated by methylases (*erm* genes) that alter the domain V binding site of telithromycin.

The ketolides also demonstrate a significant inhibitory effect on the formation of 50S ribosomal subunits. The ketolides were tested against *Staph aureus* where the concentration inhibiting 50% ($IC_{50}$) of the 50S subunit was approximately equivalent to that of the $IC_{50}$ of the inhibition of translation. At higher concentrations, ketolides also inhibit protein synthesis via the 30S ribosomal subunit.[3]

Telithromycin has other potential advantages over macrolides in treating RTIs: it accumulates to a greater extent in bacterial cells and it concentrates in human phagocytes which maintains its activity against intracellular (i.e., atypical) pathogens.[3] The inflammatory response, which causes significant morbidity and mortality during lower RTIs due to *S. pneumoniae* may also be suppressed by ketolides. In vitro and in animal models, ketolides decrease levels of immune mediators and neutrophil recruitment in response to live or heat killed *S. pneumoniae*. PMN-induced phospholipid mediators, such as platelet activating factor, have been shown to induce ciliary slowing and epithelial damage in the airways.

A once-daily dose of telithromycin 800 mg achieves high concentrations in both plasma and respiratory tissues and fluids and is maintained at effective levels throughout the 24-hour dosing period. Telithromycin reaches maximal concentration one hour after oral administration. It has an absolute bioavailability of 57% and the rate and extent of absorption are unaffected by food. Steady-state plasma concentrations are reached within 2-3 days. The mean terminal elimination half-life of telithromycin is 10 hours. Total protein binding is approximately 60%-70% and is primarily due to human serum albumin. Protein binding is not changed in elderly subjects or in patients with hepatic impairment. The volume of distribution is approximately 2.9L/kg. Seventy percent of the drug is metabolized, and it is estimated that 50% of telithromycin's metabolism is by CYP 450 3A4 and the remaining 50% is CYP 450-independent. Systemically available telithromycin is eliminated as follows: 7% is excreted unchanged in feces by biliary and/or intestinal secretion; 13% is excreted unchanged in urine by renal excretion; and 37% is

**Table 3. ABECB: Clinical cure rate at post-therapy follow-up (17-24 days) [4,15,16]**

| | Patients (n) | Clinical cure rate | |
|---|---|---|---|
| Controlled Studies | Telithromycin | Telithromycin | Comparator |
| Telithromycin (5 day therapy) vs. cefuroxime axetil 500mg BID (10 day therapy) | 282 | 86.4% | 83.1% |
| Telithromycin (5 day therapy) vs. amoxicillin/ clavulanic acid 500/125 mg TID (10 day therapy) | 227 | 86.1% | 82.1% |
| Telithromycin (5 day therapy) vs. clarithromycin 500mg BID (10 day therapy) | 225 | 85.8% | 89.2% |

metabolized by the liver.

**Clinical Trials**

Telithromycin was studied in four randomized, double-blind, controlled studies and four open-label studies for the treatment of CAP. Patients with mild to moderate CAP who were considered appropriate for oral outpatient treatment were enrolled in these trials. Patients with severe pneumonia were excluded based on any one of the following: intensive care unit (ICU) admission, need for parenteral antibiotics, respiratory rate > 30/minute, hypotension, altered mental status, < 90% oxygen saturation by pulse oximetry, or white blood cell count < 4000/$mm^3$. Total number of clinically evaluable patients in the telithromycin group included 2016 patients. (Table 1)

Telithromycin was studied in two randomized, double-blind, comparative studies for the treatment of acute sinusitis. (Table 2.)

Telithromycin was studied in three randomized, double-blind, controlled studies for the treatment of ABECB. (Table 3)

**Toxicity and Safety**

Common adverse events of telithromycin compared to other antibacterials are listed in Table 4. Most adverse events were gastrointestinal in nature with diarrhea being the most prevalent at 10%. Telithromycin may cause visual disturbances (1.1% of treated patients), particularly in slowing the ability to accommodate and the ability to release accommodation. Females and patients under 40 years old experienced a higher incidence of telithromycin-associated visual adverse events (~2%). Telithromycin also and has the potential to prolong the QT interval (average 3.5 msec). The safe and effective use of telithromycin in children and adolescents < 18 years of age has not been established.

**Dosing and Administration**

Telithromycin is supplied as 400mg oral tablets packaged in bottles of sixty, a Ketek® Pak (10-tablet cards), or as unit dose package of 100. The dose of Ketek® is 800mg (two 400mg tablets) taken orally once every 24 hours. The duration of therapy should be 5 days for acute bacterial exacerbations of chronic bronchitis and for acute bacterial sinusitis. The duration of therapy should be 7-10 days for CAP.

Ketek® may be administered without dosage adjustment in hepatic impairment.
The dose of Ketek® in the presence of severe renal impairment (CrCL<30mL/min), including patients who require dialysis, has not been established.[4]

**Cost**

The average cost, defined as the average price at 3 retail pharmacies, is $69.07 for the Ketek® PAK, while a 10-day course of therapy is expected to cost $126.17.

**Table 4. Frequency of Treatment-Emergent Adverse Events Reported in Phase III Clinical Studies [4]**

| Adverse Event* | All TEAEs | | Possibly-Related TEAEs | |
|---|---|---|---|---|
| | Telithromycin n= 2702 | Comparator† n= 2139 | Telithromycin n= 2702 | Comparator† n= 2139 |
| Diarrhea | 10.8% | 8.6% | 10.0% | 8.0% |
| Nausea | 7.9% | 4.6% | 7.0% | 4.1% |
| Headache | 5.5% | 5.8% | 2.0% | 2.5% |
| Dizziness | 3.7% | 2.7% | 2.8% | 1.5% |
| Vomiting | 2.9% | 2.2% | 2.4% | 1.4% |
| Loose Stools | 2.3% | 1.5% | 2.1% | 1.4% |
| Dysgeusia | 1.6% | 3.6% | 1.5% | 3.6% |

*Based on a frequency of all and possibly related treatment-emergent adverse events of ≥ 2% in telithromycin or comparator groups.
†Includes comparators from all controlled Phase III studies. TEAE denotes treatment-emergent adverse events.

## Summary

Common pathogens responsible for community-acquired RTIs have become increasingly resistant to antibacterial drugs. Thus, there is a pressing need for new antibiotics with activity against resistant respiratory tract pathogens and a low potential to select for resistance or induce cross-resistance to existing antibiotics. Telithromycin, the first ketolide antibiotic to be FDA approved, has enhanced binding to bacterial rRNA. Through its unique structure, telithromycin retains activity against resistant respiratory pathogens and has shown efficacy in the treatment of RTIs. On the basis of phase III clinical trial experience, telithromycin appears safe and well tolerated across various patient populations, including high-risk groups.[9] Telithromycin represents a promising new agent for the empirical treatment of community-acquired RTIs.

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Vytorin™, a combination product containing the cholesterol-lowering agents ezetimibe and simvastatin was approved in July. It is indicated for adjunctive therapy to diet in patients with primary hypercholesterolemia, mixed hyperlipidemia, and homozygous familial hypercholesterolemia (HoFH). Vytorin™ tablets are available in 4 strengths, each containing 10 mg of ezetimibe and either 10 mg, 20 mg, 40 mg, or 80 mg of simvastatin. The combination of ezetimibe and 10–80 mg of simvastatin achieves LDL reductions of > 51%. The adverse effect profile of Vytorin™ is similar to statin monotherapy, except for an increase in the incidence of hepatic enzyme elevations (3.6% with 80 mg dose). Liver function tests should be monitored at baseline, before titrating to the 80 mg dose, in 12 weeks, and thereafter when clinically indicated.

**New Dosage Forms**

- Extended-release lovastatin will no longer be marketed as Altocor™. Instead, the proprietary name will be Altoprev™.

**Labeling Changes**

- Atorvastatin (Lipitor®) labeling will now include an indication for the prevention of MI, angina, or the risk of coronary revascularization. The new indications apply to patients with normal or only mildly elevated cholesterol levels who have other features indicating increased risk for coronary disease.

Duloxetine (Cymbalta®) was approved in August for the treatment of major depression. Like venlafaxine and clomipramine, Cymbalta® inhibits the reuptake of both serotonin and norepinephrine and is often referred to as a 'dual' inhibitor. It has been shown to be effective for treating symptoms of depression and improving painful physical symptoms (e.g., back pain, shoulder pain) associated with depression. Cymbalta® should be administered at a total dose of 40 mg/day (given as 20 mg BID) to 60 mg/day (given either once a day or as 30 mg BID) without regard to meals. Cymbalta® is a substrate for CYP 1A2 and 2D6; inhibitors of these enzyme systems increase plasma concentrations of Cymbalta®. No dosage adjustments are available. Common adverse reactions include nausea, dry mouth constipation, and decreased appetite. It should be used with caution in patients with hepatic disease; in clinical trials, liver transaminase elevations resulted in the discontinuation of Cymbalta® in 0.3% of patients.

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