

Telithromycin: The First Ketolide

Thomas File, MD



The treatment of respiratory tract infections (RTIs) continues to be an international challenge; RTIs are associated with considerable morbidity and mortality in both developed and developing countries. Globally, lower RTIs accounted for 4.3 million premature deaths in 1990.¹

A major barrier to the confident prescribing of empiric therapies for RTIs is the increasing resistance worldwide among respiratory tract pathogens to existing antimicrobial agents.^{2,3} Although the clinical impact of penicillin-resistant *Streptococcus pneumoniae* (*S. pneumoniae*) has been controversial in non-meningococcal respiratory infections, the usefulness of penicillin against this pathogen can be reduced by the progressive development of resistance.^{2,6} Even more worrisome is the fact that penicillin-resistant *S. pneumoniae* strains are often resistant to other β -lactams and the macrolides.⁷⁻¹⁰

The macrolide-linosamide-streptogramin (MLS_B) group of antimicrobials are clinically valuable drugs, particularly for the treatment of RTIs, which can be caused by *S. pneumoniae* as well as by "atypical" pathogens like *Mycoplasma pneumoniae*. Resistance of *S. pneumoniae* to these antimicrobials, however, is increasing on an international scale. From 1997 to 1998, non-susceptible rates ranged from 9% in the United Kingdom to 74% in China. Of most recent concern is the emergence, noted in some studies, of occasional resistance to fluoroquinolones. Resistance is associated with the increased use of these agents.¹¹⁻¹³

Telithromycin (Ketek, Aventis) is the first of a new family of semisynthetic anti-

microbials known as the ketolides. Chemically derived from the macrolides, this novel antibiotic has been specifically developed to overcome the problem of increasing resistance to the antimicrobials in the MLS_B group, and is characterized by a broad microbiological spectrum, a unique mechanisms of action, and a favorable resistance profile. Most importantly, it possesses good *in vitro* activity against most of the common respiratory pathogens, including *S. pneumoniae* that are resistant to beta-lactams or macrolides. If, however, the strains resistant to macrolides carry the ermB gene, many of those strains will also be resistant to telithromycin.^{14,15}

CHEMISTRY AND PHARMACOLOGY

Chemically, telithromycin is designated 11,12-dideoxy-3-de [(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribo-hexopyranosyl) oxy] 6-O-methyl-3-oxo-12,11-[oxycarbonyl[4-[4-(3-pyridinyl)-1 H-imidazol-1-yl]butyl]imino]]erythromycin. Its empirical formula is C₄₃H₆₅N₅O₁₀ and its molecular weight is 812.03. Telithromycin is a white to off-white crystalline powder.

Although telithromycin is chemically related to the macrolide clarithromycin and retains some of its favorable properties, such as a good safety profile, this new ketolide is differentiated from the macrolides by several innovative features. These features enable it to overcome most MLS_B resistance, offer a low potential to select for resistance *in vitro*, avoid the induction of cross-resistance to members of the MLS_B group of antimicrobials, and offer a broad spectrum of antimicrobial activity (Figure 1).¹⁶

One of the main chemical differences in telithromycin is the presence of a 3-keto group in place of the neutral sugar C3-cladinose moiety, which was long thought to be important

for the antimicrobial activity of the macrolides. The replacement of the cladinose sugar with a keto group has not caused a loss of activity, but rather has been linked to improved activity against erythromycin-resistant *S. pneumoniae* strains and is associated with the ketolide's inability to induce MLS_B resistance *in vitro*¹⁷⁻¹⁹ (Figures 2 and 3). Also, the presence of a methoxy group at C6 provides excellent stability in an acidic environment, a factor that has important implications for oral bioavailability and for activity in the acidic environment of respiratory tract cells and tissues.²⁰ In addition, an alkyl/arylcarbonate extension at positions C11,12 of the lactone ring increases telithromycin's affinity for ribosomes,²¹ resulting in enhanced antibacterial activity and possibly accounting for its ability to overcome MLS_B resistance.²² This modification of target ribosomal binding sites also has been suggested as a reason for telithromycin's low potential to select for resistance (Figure 4).

PHARMACOKINETIC/ PHARMACODYNAMIC PROFILE

Pharmacokinetics

The pharmacokinetic parameters of telithromycin were reported in a three-period, randomized, crossover study to determine the proportionality of telithromycin phar-

The Ketolide Class

- Ketolides are new medicinal chemical entities that are designed to overcome erythromycin A resistance within gram-positive cocci

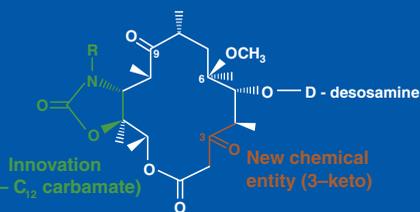


Figure 1. Used with permission from Aventis

Dr. File is Professor of Internal Medicine at Northeastern Ohio Universities College of Medicine in Akron, Ohio.

Drug Forecast is a regular department coordinated by Alan Caspi, PharmD, MBA, FASHP, Director of Pharmacy, Lenox Hill Hospital, New York.

Structural Features

- Semisynthetic compounds obtained from erythromycin A
- Removal of L-cladinose (neutral sugar) and oxidation of the obtained 3-hydroxyl (OH) yields a 3-keto group (ketolide)

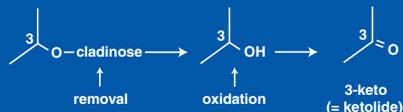


Figure 2.
Used with permission from Aventis

3-Keto Function

- 3-keto function provides the following biological properties:
 - high stability in acidic environment
 - antibacterial activity against *erm*-containing gram-positive cocci
 - inability to induce MLS_B resistance



Figure 3.
Used with permission from Aventis

C₁₁ – C₁₂ Carbamate Residue

- C₁₁ – C₁₂ carbamate provides:
 - reduced impact of efflux mechanism of resistance
 - new mode of action

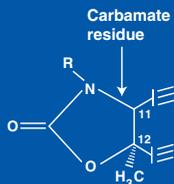


Figure 4.
Used with permission from Aventis

macokinetics after single and multiple dosing in healthy subjects.²³ In each treatment period, subjects received a single oral dose of 400, 800, or 1,600 mg of telithromycin followed four days later by the same dose once daily for seven days. Telithromycin achieved steady state within two to three days of once-daily dosing. A slight accumulation of telithromycin was observed after seven days of therapy, with values of the area under the concentration-time curve (AUC) from 0 to 24 hours approximately 1.5 times higher than those achieved with the single dose.

At a dose of 800 mg daily, telithromycin attained mean maximal and trough plasma concentrations of 2.27 and 0.070 mg per liter, respectively. Elimination was biphasic: initial and terminal half-lives were 2.87 and 9.81 hours for the 800-mg dose. Study medication was generally well-tolerated,

although adverse events tended to be more frequent at the 1,600-mg dose. A once-daily 800-mg dose of telithromycin, therefore, should maintain an effective concentration in plasma for the treatment of RTI involving the key respiratory pathogens.

Distribution

Of particular importance, pharmacokinetic studies have shown that telithromycin given once daily as an oral 800-mg dose successfully penetrates bronchopulmonary tissues and fluids, achieving high and sustained concentrations.^{24,25} Telithromycin concentrations in the epithelial lining fluid (peak of 14.8 mcg/ml) and the bronchial mucosa (peak of 3.88 mcg/ml) exceeded the minimum inhibiting concentrations (MICs) of key respiratory pathogens for 12 to 24 hours after dosing. High concentrations were also reached in the alveolar macrophages, indicating potential activity against intracellular pathogens.

In a related study, telithromycin offered clinical activity against bacterial infections in patients undergoing surgical procedures for otorhinolaryngological problems such as chronic otitis media, chronic paranasal sinusitis, chronic tonsillitis, palliative tonsil hyperplasia, and tonsillar infection.²⁶ Good penetration of telithromycin was shown in the middle ear tissues, the tissues of the paranasal sinuses, and the tonsils. Tissue concentrations three to six hours after a single 600-mg dose of telithromycin were higher than the *in vitro* MICs of telithromycin for strains of *S. pneumoniae* and *M. catarrhalis*.

Metabolism

Telithromycin is primarily metabolized in the liver. RU76363, an alcohol resulting from loss of aryl rings, is the major hepatic metabolite and is present in concentrations of approximately 13% of telithromycin. After oral administration, two-thirds of the telithromycin dose is eliminated renally as metabolites and one-third is eliminated unchanged. In a

seven-day treatment period, approximately 96% is eliminated in the urine within 24 hours of the final dose.²³

PHARMACODYNAMICS

The ultimate goal of antimicrobial chemotherapy for community-acquired RTIs is to optimize the pharmacokinetic and pharmacodynamic parameters that most closely relate to clinical efficacy. For azithromycin, the ketolides, the streptogramins, and the fluoroquinolones, the pharmacodynamic parameter that correlates best with efficacy is concentration above the MIC rather than time above the MIC.^{27,28} For these agents, the aim is to maximize drug concentrations to which the target pathogen is exposed and higher doses and longer dosing intervals can be used. In this case, parameters such as the AUC/MIC ratio or the maximal drug concentration (C_{max})/MIC ratio correlate most closely with clinical efficacy.

SPECTRUM OF ACTIVITY

A group of key pathogens accounts for the majority of cases of community-acquired RTIs. These include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes*. The atypical pathogens *Chlamydia spp.*, *Legionella spp.*, and *Mycoplasma spp.* have also gained recognition in recent years as important causes of community-acquired RTIs, particularly community-acquired pneumonia (CAP).¹¹

Telithromycin has shown a broad spectrum of activity *in vitro* against most usual bacterial strains isolated from upper or lower RTIs.²⁹ Moreover, telithromycin has a more consistent activity than the macrolides against the most frequent respiratory isolates such as penicillin-resistant *S. pneumoniae*, *M. catarrhalis*, *H. influenzae*, and *S. pyogenes* (Table 1).

Gram-Positive Organisms

Results from *in vitro* studies demonstrated that telithromycin was active against 221 pneumococcal strains, including isolates with intermediate levels of resistance to penicillin and erythromycin-resistant isolates. It was also more active than other macrolides, particularly against erythromycin-resistant strains. All strains were inhibited by ≤ 0.5 mcg of telithro-

Comparative *In Vitro* Activity of Telithromycin, Macrolides, and Quinolones Against Respiratory Tract Pathogens

	Range MIC (mg/L)					
	Telithromycin	Erythromycin	Clarithromycin	Azithromycin	Levofloxacin	Ofloxacin
<i>Streptococcus pneumoniae</i> ²⁹⁻³¹						
penicillin susceptible	≤0.01-0.05	≤0.01-0.5	≤0.01-8	≤0.01-16	≤0.12-2	≤0.25-4
penicillin resistant	≤0.01-2	≤0.06-128	≤0.5-256	≤0.5-32	≤0.5-32	<0.5-8
<i>Streptococcus pyogenes</i> ^{29,33}						
	≤0.03-0.125	≤0.06-2	≤0.06-1	≤0.125-8	≤0.5-2	—
<i>Moraxella catarrhalis</i> ^{29,34}						
beta-lactam susceptible	≤0.01-0.06	≤0.01-0.5	≤0.01-0.25	<0.01-0.12	≤0.01.12	≤0.01-0.25
beta-lactam resistant	≤0.01-0.12	≤0.01-0.5	≤0.01-0.25	<0.01-0.12	<0.01-6.12	≤0.01-0.5
<i>Hemophilus influenzae</i> ^{29,34}						
beta-lactam susceptible	≤0.01-16	≤0.01-16	≤0.01-32	≤0.01-8	≤0.01-0.06	≤0.01-0.5
beta-lactam resistant	≤0.03-8	≤0.01-16	≤0.03-32	≤0.06-8	≤0.01-0.5	≤0.01-4
<i>Mycoplasma pneumoniae</i> ^{35,36}						
	≤0.015	≤0.015	≤0.015	≤0.015	≤0.5-1	1

mycin.³⁰ In a related study, telithromycin was active at ≤0.5 mcg against 99% of 584 pneumococcal strains isolated from central and eastern Europe and at ≤0.2 mcg against 100% of these strains, irrespective of the macrolide resistance mechanism.³¹

Comparable results have been reported for *S. pyogenes*. In 599 *S. pyogenes* strains, telithromycin MICs were lower and percent susceptibility rates were higher than those for erythromycin, azithromycin, and clarithromycin.³² All strains except those with ermB were telithromycin-susceptible. This is different than for *S. pneumoniae*, where strains with this resistance are usually susceptible to telithromycin.³³

Gram-Negative and Atypical Organisms

In a comparison, *in vitro* activity study of telithromycin and macrolides, telithromycin was more active than clarithromycin and showed activity comparable to that of azithromycin against *H. influenzae* (MIC₉₀ 4 mcg/ml), whether the strains were beta-lactamase positive or negative. Also, an MIC₉₀ of 0.06 mcg/ml was recorded with telithromycin against *M. catarrhalis*. Like the macrolides, telithromycin is not as active against *H. influenzae* as it is against *S. pneumoniae*.²⁹ In a related study, telithromycin showed a much better range of activity than macrolides against *Neisseria meningitidis*, *Neisseria gonorrhoeae*, saprophytic *Neisseria spp.* isolates, and *M. catarrhalis*, with macrolide MIC₉₀s between eight- and 10-fold higher.³⁴

With respect to telithromycin's activity against atypical organisms, *in vitro* studies carried out in Japan³⁵ and France³⁶

demonstrated the superior activity of telithromycin compared to four of five macrolides, and several quinolones against clinical isolates of human strains of *Mycoplasma spp.* In the Japanese study, against *M. pneumoniae*, telithromycin was less potent than azithromycin, but was more active than the four other macrolides, and minocycline and levofloxacin. In the French study, telithromycin MICs of ≤0.25 mcg/ml were found for all isolates, except for *M. hominis*, whereas levofloxacin was active at concentrations of ≤1 mcg/ml.

CLINICAL EFFICACY STUDIES

At present, 10 large-scale, international phase III clinical trials have been completed, encompassing almost 4,300 patients with a range of RTIs; almost 2,500 were treated with telithromycin and about 1,800 were treated with comparator antibiotics. Telithromycin's efficacy was assessed in RTIs such as CAP, in acute exacerbations of chronic bronchitis (AECB), in acute sinusitis, and in pharyngitis/tonsillitis.

Community-Acquired Pneumonia

In an uncontrolled, open-label phase III study, 240 adults (between 18 and 79 years of age) with a confirmed diagnosis of CAP received oral telithromycin 800 mg once daily for seven to 10 days.³⁷ Diagnosis of CAP was based on chest x-ray findings and the presence of two classical CAP symptoms. Despite the fact that 21.5% of patients had relatively severe infections (Fine score≥3), the clinical cure rates were 92.9% in the intent-to-treat

(ITT) population and 79.6% in the per protocol (PP) population. Eradication rates for causative pathogens at the post-therapy visit were 82.7% in the PP population and 85.5% in the ITT population, with particularly high rates of 88.9% for infections caused by *S. pneumoniae*.

Three comparative phase III studies were also carried out to assess telithromycin's efficacy and safety with comparator antimicrobials. A study conducted throughout Europe and South Africa randomized 404 adult patients with a confirmed diagnosis of acute mild to moderate CAP to oral telithromycin 800 mg once daily or oral amoxicillin 1,000 mg three times daily for 10 days.³⁸ Telithromycin proved to be as effective as high-dose amoxicillin (94.6% vs 90.1% clinical cure rates) and these rates were maintained in patients with severe disease, documented pneumococcal bacteremia, and patients with infections caused by atypical organisms. Bacteriological outcomes favored telithromycin in both the ITT population (satisfactory for 79% of telithromycin-treated patients vs. 73% of those on amoxicillin) and in the PP population (satisfactory for 90% vs. 87.5%, respectively, at the post-therapy visit).

Another study, conducted in North and South America and encompassing 448 adult patients with confirmed CAP, demonstrated comparable clinical efficacy between oral telithromycin 800 mg once daily and oral clarithromycin 500 mg twice daily, both for 10 days, with clinical cure rates of 88.3% and 88.5%, respectively.³⁹ Among the pathogens isolated, 87.3% were eradicated by telithro-

continued on page 21

continued from page 16

mycin and 96.4% were eradicated by clarithromycin at the test-of-cure visit in the PP population. In a third study, carried out in Canada, the U.S., and Africa, 228 adult patients with acute CAP were randomized to oral telithromycin 800 mg once daily or oral trovafloxacin 200 mg once daily, for seven to 10 days.⁴⁰ As in the previous studies, telithromycin proved to be equivalent in efficacy to the comparator drug (trovafloxacin) in achieving a clinical cure in adults with CAP (91.1% vs. 94.8% clinical cure rates). Bacteriological eradication rates in the test-of-cure populations were 94.1% in those treated with telithromycin and 100% in those who received trovafloxacin.

In a sub-analysis of the 755 telithromycin-treated patients with CAP in the three multicenter, randomized, double-blind comparator studies and the one multicenter, uncontrolled, open-label study, 35 patients had documented bacteremia at baseline.⁴¹ Thirty of patients were deemed evaluable; 26 of those had bacteremias attributable to *S. pneumoniae*, including three penicillin-resistant (MIC>2 mg/L) and two erythromycin A-resistant (MIC>1 mg/L) strains. The clinical cure rate was 90%, with a rate of 88.5% in those with confirmed pneumococcal bacteremias. The bacteriological efficacy rate was 90% for all pathogens and 88.5% for *S. pneumoniae*. In another sub-analysis of this group of patients, administration of oral telithromycin 800 mg once daily for seven to 10 days was shown to provide excellent clinical cure rates for patients with CAP caused by atypical pathogens including *Chlamydia pneumoniae* (74/81 or 91.4%), *Mycoplasma pneumoniae* (174/190 or 91.6%), *Legionella pneumoniae* (4/4 or 100%), and *Coxiella burnetii* (4/5 or 80%).⁴²

Acute Exacerbation of Chronic Bronchitis

In an international, multicenter study, 324 adult patients with a history of bronchitis and chronic obstructive pulmonary disease (COPD) and presenting with AECB, presumably caused by bacterial infection, were randomly assigned to oral telithromycin 800 mg once daily for five days or amoxicillin/clavulanic acid 500 mg/125 mg three times daily for 10 days. The purpose was to assess the clinical

and bacteriological efficacy and safety of telithromycin compared to amoxicillin/clavulanic acid in the treatment of AECB.⁴³ Telithromycin once daily for five days was as effective as a standard 10-day course of amoxicillin/clavulanic acid, with clinical cure rates of 86.1% versus 82.1%, and bacteriological eradication rates of 69.2% and 70%, respectively, among the PP population at post-therapy. In a second study, carried out in North America, a five-day regimen of oral telithromycin 800 mg once daily was equivalent in clinical efficacy to a 10-day regimen of oral cefuroxime axetil 500 mg twice daily in 495 adult outpatients with AECB. The clinical cure rates were 89.2% and 86.3%, respectively.⁴⁴ Satisfactory bacteriological outcome at the test-of-cure visit was achieved in 87.9% of telithromycin-treated patients and 86% of those on cefuroxime axetil, with identified causative organisms.

Sinusitis

Two international, multicenter phase III clinical trials were performed to evaluate the efficacy and safety of telithromycin against comparator antimicrobials or as a five- or 10-day regimen for the treatment of adult patients with acute maxillary sinusitis (AMS). In one study, 336 patients with community-acquired AMS were randomized to a five-day course of telithromycin 800 mg once daily or a 10-day course of telithromycin of the same dose.⁴⁵ A pre-therapy sinus tap was conducted for bacteriological assessment. A five-day course was shown to be as effective as a 10-day course of treatment for AMS, with comparable cure rates of 91.1% and 91%. In total, 92% of patients receiving five-day telithromycin and 89.9% of those treated with the 10-day course had a satisfactory bacteriological outcome at the post-therapy visit.

By comparison, 93.3% (28/30) of *S. pneumoniae* were presumed eradicated in the five-day arm and 89.3% (25/28) were presumed eradicated in the 10-day arm. In the second study, in 790 patients with AMS, telithromycin 800 mg daily for five days was as effective clinically as a 10-day course of amoxicillin/clavulanic acid 500/125 mg three times daily or a 10-day regimen of telithromycin 800 mg once daily, with clinical cure rates of 75.8%, 74.6%, and 74.1%, respectively.⁴⁶ Satisfactory bacteriological

outcome in the PP population of the three groups was 85.7% in both telithromycin groups and 75% in those treated with amoxicillin/clavulanic acid.

Pharyngitis/Tonsillitis

Because penicillin is currently the treatment of choice for group A-hemolytic streptococcal (GABHS) pharyngitis/tonsillitis, a multicenter, European phase III trial was carried out to compare the efficacy and safety of oral telithromycin 800 mg once daily for five days, and five days of placebo versus oral penicillin V 500 mg three times daily for 10 days, in 396 adult patients with a presumed diagnosis of GABHS pharyngitis/tonsillitis.⁴⁷ Patients who took telithromycin only five times had clinical cure rates comparable to a standard 10-day course of penicillin comprised of 30 doses (94.8% vs. 94.1%). In the PP population, bacteriological eradication rates at the post-therapy visit were 84.3% in patients treated with telithromycin and 89.1% for those who received penicillin V. In a second study, conducted in North America, 463 adolescent and adult (13–81 years) patients with GABHS pharyngitis/tonsillitis were randomly assigned to oral telithromycin 800 mg once daily for five days or oral clarithromycin 250 mg twice daily for 10 days.⁴⁸ In the 285 patients who were evaluable post-therapy, the five-day telithromycin regimen was equivalent in efficacy to the standard 10-day course of clarithromycin in eradicating GABHS in patients 13 years of age or older with acute pharyngitis/tonsillitis, with clinical cure rates of 92.7% versus 91.7% and bacteriological eradication rates of 91.3% versus 88.1%, respectively.

ADVERSE EVENTS

Telithromycin is generally well-tolerated. Among the 1,899 patients who took part in the controlled phase III clinical trials and were treated with telithromycin 800 mg once daily for five or seven to 10 days, approximately 35%^{38-41, 43-48} experienced adverse events. Adverse reactions that were judged by investigators to be at least possibly drug-related and occurring in more than 1% of all telithromycin-treated patients were diarrhea (12.9%), nausea (7.3%), dizziness (3.0%), vomiting (2.6%), and headache (2.1%). Similarly, in the 240

patients enrolled in the uncontrolled CAP study and who received at least one dose of study medication,³⁷ the most frequent adverse events considered to be possibly drug-related were abnormal liver function tests (11.3%), an event known to be associated with CAP; diarrhea (7.5%); and nausea (4.6%). The majority of adverse events were mild to moderate in both the controlled and uncontrolled studies and rarely led to treatment discontinuation. Most discontinuation in the telithromycin groups resulted from adverse gastrointestinal effects, primarily diarrhea (1%), nausea (1%), and vomiting (1%). Finally, no differences were seen in the occurrence of clinically noteworthy abnormal values between treatment with telithromycin and any of the comparator antimicrobials administered in the controlled studies.^{37-40, 43-48}

DRUG INTERACTIONS

Telithromycin does not form any inhibitor complexes with CYP-450, especially CYB3A4, suggesting that common drug-drug interactions reported with macrolides are unlikely to occur with this new ketolide in humans. The reverse Type 1 interaction between telithromycin and CYP3A4 indicates that the rate of metabolism of telithromycin should be low.⁴⁹ Phase I studies have shown that the risk of increasing plasma concentrations of telithromycin of CYP3A4 is minimal. A potent inhibitor, such as ketoconazole, results in only a 1.5-fold increase in the C_{max} of telithromycin in plasma.⁵⁰

Telithromycin, like clarithromycin, has been shown to increase the plasma concentrations of drugs metabolized by CYP3A4, such as cisapride and simvastatin. Pharmacokinetic interactions for individual drugs metabolized extensively by CYP3A4 cannot be discounted. Caution is advised, as with macrolides, if telithromycin is administered concomitantly with substrates of CYP3A4 that have a narrow therapeutic margin or effects on the QT interval. As with clarithromycin, the use of telithromycin with cisapride or pimozone is contraindicated.

In addition, co-administration of telithromycin 800 mg once daily with the CYP2D6 substrate paroxetine 30 mg once daily has no significant effect on the pharmacokinetic profile of paroxetine. This lack

of interactions between telithromycin and paroxetine indicates a low potential for clinically relevant pharmacokinetic interactions with other CYP2D6 substrates.⁵¹

A randomized, open-label, two-period, crossover study demonstrated that the bioavailability of telithromycin is unaffected by food. Telithromycin, therefore, can be taken without regard to meals.⁵² Also, the co-administration of telithromycin with the gastric pH-altering agents Zantac or Maalox does not affect the bioavailability of telithromycin.⁵³ With regard to other drug interactions, telithromycin does not affect the pharmacokinetics of warfarin in healthy male adults.⁵⁴ In addition, telithromycin does not increase the risk of ovulation in women of child-bearing age when co-administered with low-dose, triphasic oral contraception.⁵⁵

P&T COMMITTEE CONSIDERATIONS

Telithromycin is presently awaiting FDA approval. This novel antibiotic has an impressive spectrum of antimicrobial activity against *S. pneumoniae*, many strains of which are resistant to macrolides; against *H. influenzae*; *M. catarrhalis*; *S. pyogenes*; *S. aureus*; and the atypical pathogens *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma spp.* The clinical and bacteriological efficacy of telithromycin has been evaluated against gold-standard comparators in a series of phase III clinical trials in North and South America, Europe, and South Africa for the treatment of CAP, AECB, sinusitis, and tonsillitis/pharyngitis.

The results of these studies suggest that telithromycin could prove to be an effective, well-tolerated agent for the treatment of the most commonly encountered community-acquired RTIs. The P&T committee awaits further clinical trial results and FDA approval. ■

REFERENCES

- Murray CJL, Lopez AD (eds). *The global burden of disease. A comprehensive assessment of mortality and disability from disease, injuries and risk factors in 1990 and projected to 2020*. Boston: Harvard University Press; 1996.
- Appelbaum PC. Antimicrobial resistance in *Streptococcus pneumoniae*: An overview. *Clin Infect Dis*. 1992;15:77-83.
- Jacobs MR. Treatment and diagnosis of infections caused by drug-resistant *Streptococcus pneumoniae*. *Clin Infect Dis*. 1992;15:119-127.
- Jones ME, Hickey ML, Diakun DR, et al.

- Resistance surveillance of *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella catarrhalis* isolated in Asia and Europe 1997-1998. *J Antimicrob Chemother* 2000;45:457-466.
- Low E. Trends and significance of antimicrobial resistance in respiratory pathogens. *Curr Opin in Infect Dis*. 2000; 13:145-153.
- File TM. Treating CAP caused by penicillin-resistant *S. pneumoniae*. *J Respir Dis*. 1999;20(12):833-842.
- Doern GV. Trends in antimicrobial susceptibility of bacterial pathogens of the respiratory tract. *Am J Med*. 1995;99(suppl 6B):35-75.
- Doern GV, Brueggemann A, Holley HP and Rauch AM. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: results of a 30-center national surveillance study. *Antimicrob Agents Chemother*. 1996;40:1208-1213.
- Linares J, Alonso T, Perez JL et al. Decreased susceptibility of penicillin-resistant pneumococci to twenty-four β -lactam antibiotics. *J Antimicrob Chemother*. 1992;30:279-288.
- Baquerio F. Pneumococcal resistance to β -lactam antibiotics: A global geographic overview. *Microb Drug Resistance*. 1995;1:115-120.
- Pankuch GA, Jacobs MR and Applebaum PC. Study of comparative antipneumococcal activities of penicillin G, RP59500, erythromycin, sparfloracin, ciprofloxacin, and vancomycin by using time-kill methodology. *Antimicrob Agents Chemother*. 1996;38:2065-2072.
- Ho PL, Que TL, Tseng DN-C et al. Emergence of fluoroquinolone resistance among multiple resistant strains of *S. pneumoniae* in Hong Kong. *Antimicrob Agents Chemother*. 1999; 43:1310-1313.
- Chen DK et al. Decreased susceptibility of *Streptococcus pneumoniae* in fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. *N Engl J Med*. 1999;341:233-239.
- Pankuch GA, Visalli MA, Jacobs MR and Appelbaum PC. Susceptibilities of penicillin and erythromycin-susceptible and -resistant pneumococci to HMR 3647 (RU 66647), a new ketolide, compared with susceptibilities to 17 other agents. *Antimicrob Agents Chemother*. 1998;42:624-630.
- Davies TA, Dewasse BE, Jacobs MR and Appelbaum PC. *In vitro* development of resistance to telithromycin (HMR 3647), four macrolides, clindamycin, and pristinamycin in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 2000;44:414-417.
- Bryskier A. Ketolides: New semisynthetic 14-membered ring macrolides: In Zinner SH, Young LS, Acar JR, Neu HC (eds). *Expanding applications for the new macrolides, azalides, and streptogramins*. New York: Marcel Dekker; 1997:39-53.
- Bonnefoy A, Girard MA, Agouridas C and Chantol JF. Ketolides lack inducibility properties of MLS_B resistance phenotype. *J Antimicrob Chemother* 1997;40:85-90.
- Bonnefoy A, Agouridas C and Chantol JF. HRM 3647: antimicrobial activity of resistance. In: *Proceedings of the 4th International Conference on Macrolides, Azalides, Streptogramins, and Ketolides*. Marcel Dekker, Inc., New York, N.Y. 1998, p. 25.
- Bryskier A, Agouridas C and Chantol JF. Acid stability of new macrolides. *J Chemother*. 1993;5(suppl 1):158-159.
- Roblin RM, Kutlin A, Reznik T and Hammerschlag MR. Activity of grepafloxacin and other fluoroquinolones and newer macrolides against recent clinical isolates of *Chlamydia pneumoniae*. *Int J Antimicrob Agents*. 1999;12:181-184.
- Champney WS and Tobler CL. Inhibition of translation and 50S ribosomal subunit formation in *S. aureus* cell by 11 different ketolide antibiotics. *Curr Microbiol*. 1998;37:418-425.

22. Douthwaite S, Hansen LH and Mauvais P. Macrolide ketolide inhibition of MLS-resistant ribosome is improved by alternative drug interaction with domain II of 23S rRNA. *Mol Microbiol.* 2000;36:183-193.
23. Namour F, Weissels DH, Pascual MH et al. Pharmacokinetics of the new ketolide telithromycin (HMR 3647) administered in ascending single and multiple doses. *Antimicrob Agents Chemother.* 2001;45:170-175.
24. Kadota J, Ishionatsu Y, Iswashita T et al. The ketolide antimicrobial telithromycin (HMR3647) achieves high and sustained concentrations in alveolar macrophages and bronchoalveolar epithelial lining fluid in healthy Japanese volunteers. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2143.
25. Andrews J, Honeybourne D, Khair O et al. Penetration of telithromycin (HMR 3647) into bronchial mucosa (BM), epithelial lining fluid (ELF), and alveolar macrophages (AM) following multiple oral doses. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 658.
26. Miyamoto N, Murakami S, Yajink et al. Pharmacokinetic study of a new ketolide antimicrobial telithromycin (HMR 3647) in otorhinolaryngology. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2144.
27. Munckhof WJ, Borlace G and Turnidge JD. Postantibiotic suppression of growth of erythromycin A-susceptible and -resistant gram-positive bacteria by the ketolides telithromycin (HMR 3647) and HMR 3004. *Antimicrob Agents Chemother.* 2000;44:1749-1753.
28. Drusano GL and Craig WL. Relevance of pharmacokinetics and pharmacodynamics in the selection of antibiotics for respiratory tract infections. *J Chemother.* 1997;9 (Suppl 3):38-44.
29. Dubois J and St Pierre C. *In vitro* study of the minimal inhibitory concentrations (MIC) of telithromycin (HMR 3647), macrolides and quinolones against *Haemophilus*, *Streptococcus*, *Staphylococcus*, and *Moraxella* strains obtained from upper and lower respiratory tract infections and from maxillary sinus aspiration. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2152.
30. Reinert RR, Bryskier A and Lütticken R. *In vitro* activities of the new ketolide antibiotics HMR 3004 and HMR 3647 against *Streptococcus pneumoniae* in Germany. *Antimicrob Agents Chemother.* 1998;42:1509-1511.
31. Appelbaum PC, Hoellman DB, Drukalska L et al. Antipneumococcal activity of telithromycin (HMR 3647) against 584 pneumococci from ten central and eastern European countries. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2154.
32. Appelbaum PC, Kelly LM, Hryniewicz W et al. Activity of telithromycin (HMR 3647) against 599 *S. pyogenes* strains from ten central and eastern European countries. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2153.
33. Nagai K, Davies TA, Applebaum PC, et al. Mechanisms of macrolide resistance in *Streptococcus pneumoniae* and *S. pyogenes* from central and eastern European countries. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 138.
34. Saez-Nieto JA and Vazquez JA. *In vitro* activities of ketolides HMR 3647 and HRM 3004, levofloxacin, and other quinolones and macrolides against *Neisseria spp.* and *Moraxella catarrhalis*. *Antimicrob Agents Chemother.* 1999; 43:983-984.
35. Yamaguchi T, Hirakata Y, Izumikawa K et al. *In vitro* activity of telithromycin (HMR 3647), a new ketolide, against clinical isolates of *Mycoplasma pneumoniae* in Japan. *Antimicrob Agents and Chemother.* 2000;44:1381-1382.
36. Bebear CM, Renaudin H, Bryskier A and Bebear C. Comparative activities of telithromycin (HMR 3647), levofloxacin, and other antimicrobial agents against human mycoplasmas. *Antimicrob Agents and Chemother.* 2000;44:1980-1982.
37. Carbon C, Moola S, Velancsics I et al. Efficacy of telithromycin (HMR 3647), a new once-daily antimicrobial, in the treatment of community-acquired pneumonia. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2245.
38. Hagberg L, Torres A, Van Rensburg DJ et al. Efficacy and tolerability of telithromycin vs. high-dose amoxicillin in the treatment of community-acquired pneumonia. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2244.
39. Tellier G, Hassman J, Leroy B et al. Oral telithromycin (HMR 3647) 800 mg daily is well tolerated and as effective as oral clarithromycin 500 mg twice daily in community-acquired pneumonia in adults. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2227.
40. Pullman J, Champlin J, Leroy B and Sidarous E. Oral telithromycin (HMR 3647) 800 mg once daily for 7-10 days is well tolerated and as effective as oral trovafloxacin 200 mg once daily for 7-10 days in community-acquired pneumonia. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2330.
41. Leroy B and Rangaraju M. Efficacy of telithromycin (HMR 3647) in the treatment of bacteremia associated with community-acquired pneumonia. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2223.
42. Leroy B and Rangaraju M. Efficacy of telithromycin (HMR 3647), a new once-daily ketolide, in community-acquired pneumonia caused by atypical pathogens. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2225.
43. Aubier M, Aldons PM, Leak A et al. Efficacy and tolerability of a 5-day course of a new ketolide antimicrobial, telithromycin (HMR 3647) for the treatment of acute exacerbations of chronic bronchitis in patients with COPD. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2241.
44. DeAbate CA, Heyda A, Leroy B et al. Oral telithromycin (HMR 3647) 800 mg once daily for 5 days is well tolerated as cefuroxime axetil 500 mg twice daily for 10 days in adults with acute exacerbations of chronic bronchitis. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2228.
45. Roos K, Brunswig-Pitschner C, Kostrica R et al. Efficacy and tolerability of a 5-day course of a new ketolide antimicrobial telithromycin (HMR 3647) for the treatment of acute sinusitis. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2243.
46. Tellier G, Lasko B, Leroy B et al. Oral telithromycin (HMR 3647) 800 mg once daily for 5 days and 10 days is well tolerated and as effective as amoxicillin/clavulanic acid 500/125 mg three times daily for 10 days in acute maxillary sinusitis (AMS) in adults. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2226.
47. Norrby SR, Rabie W, Bacart P et al. Efficacy of 5 days' telithromycin (HMR 3647) vs. 10 days penicillin V in the treatment of pharyngitis in adults. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2242.
48. Quinn J, Ziter P, Leroy B et al. Oral telithromycin (HMR 3647) 800 mg once daily for 5 days is well tolerated and as effective as oral clarithromycin 250 mg twice daily for 10 days in group A-hemolytic streptococcal (GABHs) pharyngitis/tonsillitis. In: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. 17-20 September 2000. Abstract 2229.
49. Labbe G, Flor M, Lenfant B, HMR 3647, a new ketolide antimicrobial does not inhibit cytochrome P450 activity *in vitro*. (Abstract) *J Antimicrob Chemother* 1999;44(Suppl A): 61.
50. Personal communications. Aventis Pharmaceuticals, January 2001.
51. Lippert C, Leese PT, Sultan. Telithromycin (HMR 3647) does not interact with the CYP2D6 substrate paroxetine. (Abstract). 2001. 11th ECCMID.
52. Lenfant B, Perret C, Pascual MH. The bioavailability of HMR, a new once-daily ketolide antimicrobial, is unaffected by food (Abstract). *J Antimicrob Chemother.* 1999; July;44 (Suppl A) 255.
53. Lippert C, Leese P, Sultan E. Effect of gastric pH on the availability of telithromycin (HMR 3647). 2001. 11th ECCMID.
54. Scholtz HE, Pretorius SG, Wessels DH et al. HMR 3647, a new ketolide antimicrobial, does not affect the pharmacodynamics or pharmacokinetics of warfarin in healthy adult males. (Poster). 5th Int Conf Macrolides, Azalides, Streptogramins, Ketolides, Oxazolidinones. 2000. 14 Abstract 9.30.
55. Scholtz HE, Sultan E, Wessels D et al. HMR 3647, a new ketolide antimicrobial, does not affect the reliability of low-dose triphasic oral contraceptives. In: Program and Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco. September 1999. Abstract 10.