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New products

Series editors: Donald Y. M. Leung, MD, PhD, Harold S. Nelson, MD, Stanley J. Szefler, MD, Philip S. Norman, MD, and Andrea Apter, MD, MSc

Telithromycin new product overview

Thomas M. File, Jr, MD, FACP, FIDSA, FCCP

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S361

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Telithromycin new product overview

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Community-acquired respiratory tract infections (CARTIs), including community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute bacterial sinusitis, contribute substantially to health care costs in the United States. Although many prescriptions for antibiotics are written each year for the treatment of CARTIs, most are prescribed on an empiric basis. Concerns about the increasing prevalence of antimicrobial resistance and the changing pattern of pathogens isolated from subjects with CARTIs have raised questions about the empiric treatment paradigm. When choosing appropriate antimicrobial therapy for CARTIs, physicians must consider not only the spectrum of activity of antibiotics but also the potential risk of resistance. Telithromycin is the first member of the ketolide class, a new family of antimicrobials structurally related to the macrolides, to be approved by the US Food and Drug Administration for the treatment of CARTIs. The spectrum of activity of telithromycin includes common typical and atypical causative pathogens associated with community-acquired respiratory tract infections, including antibiotic-resistant strains of *Streptococcus pneumoniae*. Clinical trials have shown that telithromycin is as effective as traditionally used antimicrobial agents in the treatment of mild-to-moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute bacterial sinusitis. (J Allergy Clin Immunol 2005;115:S361-73.)

Key words: Telithromycin, ketolide, community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute bacterial sinusitis, antibiotic resistance

Abbreviations used

ABS:	Acute bacterial sinusitis
AECB:	Acute exacerbations of chronic bronchitis
AM:	Alveolar macrophage
AUC:	Area under the plasma concentration-time curve
C _{max} :	Maximum plasma concentration
CAP:	Community-acquired pneumonia
CARTI:	Community-acquired respiratory tract infection
CYP:	Cytochrome P450
ELF:	Epithelial lining fluid
erm:	Erythromycin resistance methylase
mef:	Macrolide efflux
MIC:	Minimum inhibitory concentration
MLS _B :	Macrolide-lincosamide-streptogramin B
rRNA:	Ribosomal RNA
t _{1/2} :	Elimination half-life
TEAE:	Treatment-emergent adverse event
TOC:	Test of cure

BACKGROUND

Community-acquired respiratory tract infections (CARTIs), which include community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), and acute bacterial sinusitis (ABS), are a common cause of morbidity and mortality in the United States. In addition, CARTIs are associated with substantial health care costs and are among the most frequently cited diagnoses associated with the prescription of antimicrobial agents.¹ The estimated cost of treating CAP was approximately \$10 billion in 2002²; in 1999, expenditures related to the treatment of AECB were estimated at \$1.2 billion for patients 65 years or older and \$419 million for patients younger than 65 years of age.³ In addition, acute and chronic sinusitis accounted for \$3.4 billion in health care costs in 1996⁴ and was ranked as the fifth leading reason for prescribing an antimicrobial agent.¹

Although the majority of CARTIs are viral in origin, bacteriologic causes are common, with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* being the most frequently identified causative agents.⁵⁻¹⁰ Atypical and intracellular pathogens also have been implicated as causative agents in CARTIs, particularly CAP. The diagnosis of a bacterial cause in subjects with symptoms of CARTIs is limited by the difficulties in collecting an adequate sample for pathogen culture, the

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possibility of coinfection with both typical and atypical pathogens, and the fact that cultured bacteria might be part of the individual's normal respiratory flora. In addition, delaying therapy until a causative agent can be identified might compromise the patient's recovery, and therefore CARTIs are most often treated empirically, without a positive identification of the causative pathogen.¹⁰

The effectiveness of empiric antimicrobial therapy in subjects with CARTIs is challenged by the increasing prevalence of antimicrobial resistance among common causative pathogens. For example, *S pneumoniae*, the most commonly isolated pathogen and the largest contributor to both morbidity and mortality in patients with CARTIs, has displayed increasing resistance to traditionally used antimicrobial agents. Over a 5-year period (from 1994-1995 to 1999-2000), the resistance rates of *S pneumoniae* to penicillin and erythromycin increased by 10.6% and 16.1%, respectively.¹¹ Between the years 2000 and 2001, 26.4% of *S pneumoniae* isolates were penicillin resistant, and 31% were resistant to erythromycin.¹² Of particular concern is the development of multidrug resistance among pathogens: 77.7% of penicillin-resistant *S pneumoniae* strains are resistant to macrolides,¹² and almost 9% of *S pneumoniae* isolates display concomitant resistance to penicillin, cefuroxime, erythromycin, and cotrimoxazole.¹³

Surveillance data indicate that the prevalence of macrolide-resistant respiratory pathogens is increasing in the United States, although exact rates vary by geographic region.¹² Approximately 65% of macrolide-resistant pneumococci in the United States have a mechanism of resistance involving efflux pumps¹² that actively remove 14- and 15-membered ring macrolides, lincosamides, or analogues of streptogramin B (MLS_B group). These efflux pumps are encoded by several genes, including macrolide efflux (*mef*) genes in streptococci and macrolide-streptogramin B resistance genes in staphylococci.^{11,14,15} The MLS_B phenotype of resistance, which involves modification of the ribosomal target site through methylation and occurs in bacteria in which erythromycin resistance methylase (*erm*) genes are expressed, accounts for approximately 32% of macrolide-resistant pneumococci in the United States.^{11,16} Resistance caused by target-site modifications on the 23S ribosomal RNA (rRNA) that are not related to *erm* gene expression has also been noted in a few species of bacteria.^{17,18} The clinical relevance of macrolide-resistant *S pneumoniae* might be related to the mechanism of resistance expressed by a particular strain. There have been reports in the literature of treatment failures with macrolides in subjects with pneumococcal pneumonia involving isolates with *erm* and *mef* gene expression, as well as a case of a treatment-emergent macrolide-resistant mutant.¹⁸⁻²¹

The changing pattern of causative pathogens (ie, the increasing occurrence of atypical and intracellular organisms) and the increasing rates of antimicrobial resistance make empiric antibiotic selection for the treatment of CARTIs challenging. Several guidelines for the management of CARTIs have been published to promote

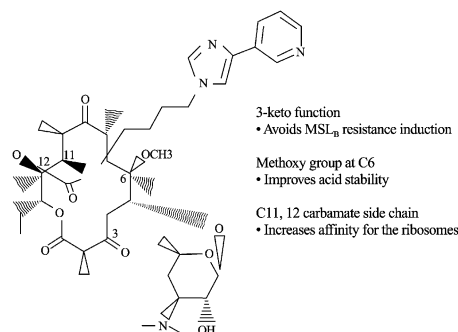


FIG 1. The chemical structure of telithromycin. The keto group results in greater acid stability, and the carbamate side chain increases affinity for the bacterial ribosomes. Reprinted with permission from *Clin Microbiol Infect.* 2001;7(suppl 3):11-7.

judicious antimicrobial prescribing.^{10,22-24} However, even with the availability of treatment guidelines, identifying the appropriate treatment strategy for a specific patient might be daunting.²⁵ Important characteristics to consider when selecting the optimal antimicrobial agent include spectrum of activity and potential for inducing resistance. Thus an antimicrobial with a spectrum of activity targeted to provide coverage against the typical, atypical, and drug-resistant causative pathogens that are most commonly implicated in specific CARTIs and a low potential for inducing resistance would be an appropriate treatment.

Telithromycin is the first member of the ketolide class, a new family of antimicrobials structurally related to the macrolides. It is the first ketolide to be approved by the US Food and Drug Administration with indications for the treatment of mild-to-moderate CAP (including multidrug-resistant isolates of *S pneumoniae*), AECB, and ABS. Telithromycin has a low potential for inducing resistance and has been developed specifically to target the typical (eg, *S pneumoniae*, *H influenzae*, *M catarrhalis*, and *Staphylococcus aureus*) and atypical (eg, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*) causative pathogens that are most frequently identified in CARTIs.

KETOLIDES: UNIQUE CHEMICAL STRUCTURE

Like all ketolides, telithromycin is a semisynthetic derivative of the 14-membered ring macrolide erythromycin (Fig 1). Several modifications have been made to the macrolactone ring that confer improvements in the antimicrobial activity, risk of resistance induction, and pharmacokinetics of the ketolides, including the substitution of the characteristic keto group for the L-cladinose moiety at position C3. In addition, several of the ketolides contain a methoxy group at C6, and telithromycin also has a large *N*-substituted carbamate extension at C11/C12.²⁶ The significance of these structural modifications will be discussed in the context of the mechanisms of action of telithromycin, its activity against

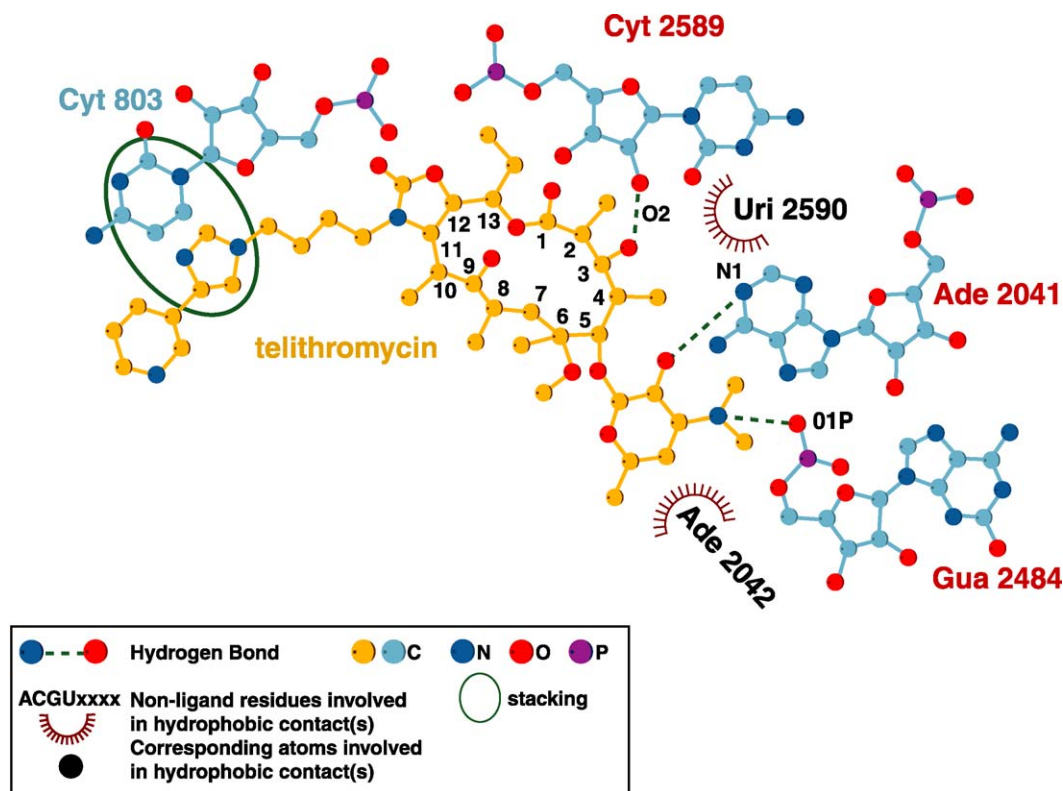


FIG 2. Two-dimensional sketch of telithromycin interactions with *Deinococcus radiodurans* 50S subunit of the 23S rRNA. Reprinted with permission from *J Bacteriol.* 2003;185:4276-9.

β -lactam- and macrolide-resistant strains, and its low potential for the induction of resistance.

MECHANISMS OF ACTION

The mechanism of antimicrobial activity of telithromycin, as well as all the ketolides, is through inhibition of bacterial protein synthesis at 2 steps. Ketolides interact with the 50S ribosomal subunit near the peptidyl transferase site to inhibit the translation of rRNAs and to prevent the elongation step of protein synthesis.²⁷ Ketolides also interfere with protein synthesis earlier in the process by interacting with partially assembled 50S subunit precursors to block the formation of a functional 50S subunit.²⁷ Telithromycin binds to domains II and V of the 50S subunit on the 23S rRNA (Fig 2).^{28,29}

SIGNIFICANCE OF STRUCTURAL MODIFICATIONS

Keto group

Unlike the MLS_B group of antimicrobial agents, ketolides do not induce the expression of the *erm* gene.^{26,30} The presence of a 3-keto group in place of the L-cladinose moiety allows ketolides, such as telithromycin, to bind to the ribosomal target in the 23S rRNA domain V without causing expression of MLS_B resistance in inducible

strains. Although the exact mechanism for this has not yet been elucidated, *in vitro* studies have demonstrated that ketolides, including telithromycin, either did not induce resistance or induced much less resistance in gram-positive cocci when compared with macrolides, such as erythromycin, azithromycin, and clarithromycin.^{17,31,32} After 3 years of telithromycin use in Germany, the global antibacterial resistance surveillance study did not observe a change in the distribution of telithromycin minimum inhibitory concentrations (MICs).³³

C11/C12 carbamate extension

At the same time that the telithromycin 3-keto group binds to domain V of the 23S rRNA, the large C11/C12 carbamate extension binds to domain II. It is this dual-binding affinity, which is due to the presence of the large C11/C12 carbamate extension, that increases the binding affinity of telithromycin by approximately 10-fold compared with that of erythromycin.²⁸ The resulting improved contact of telithromycin with the rRNA is probably responsible for its activity against macrolide-resistant strains, including isolates with resistance mediated by the *erm* gene.³⁰ Although the binding of telithromycin is reduced by the target-site modifications that occur in macrolide-resistant pathogens expressing *erm* genes, the reduction in affinity is trivial when compared with the 10,000-fold reduction in binding seen when clarithromycin and erythromycin encounter the same mutation.^{34,35}

TABLE I. Comparative pharmacokinetics of the ketolide telithromycin and macrolide antibiotics^{*37}

Parameter	Erythromycin	Azithromycin	Clarithromycin	14-Hydroxy clarithromycin†	Telithromycin
Bioavailability (%)	25	37	55	35	57
C _{max} (mg/L)	0.3-0.9	0.4	2.1-2.4	0.6	1.9-2
t _{max} (h)	3-4	2	2	2-3	1
t _{1/2} (h)	2-3	40-68	3-5	4-7	7.16-13
AUC (mg · h/L)	8	3.4	19	5.7	7.9-8.25

Adapted with permission from *Infect Dis Clin North Am.* 2004;18:621-49.

t_{max}, Time to maximum plasma concentration.

*Mean values after a single 500-mg oral dose (azithromycin or clarithromycin) or 800-mg dose (telithromycin).

†Active metabolite.

The configuration of the telithromycin–domain II interaction suggests a stacking arrangement that would strengthen telithromycin binding, even in the presence of modifications in domain V.³⁴

The C11/C12 carbamate extension also appears to be responsible for the ability of telithromycin to overcome resistance because of an efflux mechanism mediated by *mef* genes. Telithromycin has been shown to retain good activity against streptococci harboring *mef* genes; it is a poor substrate for the efflux pumps that are effective against erythromycin and other macrolides.¹⁷ The clinical effect of this has been observed during clinical trials in which telithromycin achieved high clinical cure and bacterial eradication rates in patients with CARTIs caused by *S pneumoniae* with reduced susceptibility to penicillin and erythromycin, as well as those with high-level resistance to erythromycin.³⁶

C6 methoxy group

Telithromycin, as well as other ketolides, contains a methoxy group at C6, which provides greater acid stability than that of other macrolides, including erythromycin, clarithromycin, and azithromycin. This feature is related to greater gastrointestinal stability.²⁶

PHARMACOKINETICS AND PHARMACODYNAMICS

Absorption and distribution

The pharmacokinetic parameters of telithromycin suggest that it can be administered in once-daily dosing regimens (Table I).³⁷ After oral administration, telithromycin is 57% bioavailable in both young and elderly subjects.³⁸ Bioavailability is not affected by food, and therefore telithromycin can be taken at any time, without regard to meals.³⁹ Maximum serum concentrations are reached 1 hour after a single oral dose of telithromycin, and the elimination half-life (t_{1/2}) ranges from 7.16 to 13 hours.⁴⁰ Telithromycin is 60% to 70% protein bound, which is not modified in elderly subjects or in subjects with hepatic impairment.⁴¹

Telithromycin achieves concentrations in lower respiratory tract infection sites that are higher than the MICs of common respiratory pathogens. At 2 hours after multiple oral doses, the concentration of telithromycin was 3.88 mg/kg in bronchial mucosa, 14.89 mg/L in

epithelial lining fluid (ELF), and 69.32 mg/L in alveolar macrophages (AMs). Corresponding concentrations at 24 hours were 0.78 mg/kg, 0.97 mg/L, and 161.57 mg/L, respectively.⁴² In a separate study concentrations of clarithromycin and azithromycin in ELF and AMs were determined at 4 and 24 hours after multiple oral doses. Clarithromycin concentrations were 34.5 µg/mL at 4 hours and 4.6 µg/mL at 24 hours in ELF and 480 µg/mL at 4 hours and 99.4 µg/mL at 24 hours in AMs. The following corresponding concentrations were achieved with azithromycin: ELF, 1.01 µg/mL and 1.22 µg/mL, and AMs, 42.7 µg/mL and 41.7 µg/mL, respectively.⁴³

High telithromycin concentrations are also achieved in sinus tissue after oral administration. Eight hundred milligrams of telithromycin administered once daily for 3 days reached sinus tissue concentrations of 6.60 mg/kg at 2 hours after dosing, 6.96 mg/kg at 4 hours, and 1.58 mg/kg at 24 hours in adult patients undergoing endoscopic endonasal surgery for nasal polypsis.⁴⁴

Metabolism and elimination

After oral administration, telithromycin undergoes a first-pass effect (metabolism by the liver and intestine) before entering the systemic circulation. Approximately half of the overall metabolism of telithromycin is mediated by the cytochrome P450 (CYP) 3A4 pathway, and the other half is CYP independent. The 57% of an oral dose that reaches the systemic circulation as telithromycin is eliminated by multiple pathways, including gastrointestinal-biliary, renal, and hepatic excretion. The t_{1/2} of telithromycin is about 10 hours after multiple dosing, which permits once-daily dosing.⁴¹

Special populations

In clinical trials the pharmacokinetic profile of telithromycin was not altered in elderly subjects, those with hepatic or mild-to-moderate renal impairment, or subjects with an active infection compared with healthy subjects. The pharmacokinetics of single and repeated oral doses of 800 mg of telithromycin once daily were compared in subjects with hepatic impairment and healthy subjects in 2 open-label, nonrandomized, parallel-group, multicenter studies. Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) for telithromycin were similar in subjects with hepatic impairment and in healthy subjects in the single (C_{max},

TABLE II. MIC_{50/90} of the ketolide telithromycin and macrolide antibiotics⁴⁹

Organism (no. of strains)	Erythromycin MIC _{50/90} (mg/L)	Azithromycin MIC _{50/90} (mg/L)	Clarithromycin MIC _{50/90} (mg/L)	Telithromycin MIC _{50/90} (mg/L)
<i>Streptococcus pneumoniae</i>				
Pen sensitive (100)	0.015/0.03	0.06/0.12	0.015/0.03	0.008/0.008
Ery-resistant, clind-resistant <i>erm</i> (B) genotype (150)	>128/>128	>128/>128	>128/>128	0.06/0.5
Ery-resistant, clind-susceptible <i>mef</i> (E) genotype (50)	4/8	8/8	4/8	0.12/0.25
<i>Streptococcus pyogenes</i>				
Pen, ery, clind, levo sensitive (60)	0.06/0.06	0.12/0.12	0.06/0.06	0.03/0.03
Ery-resistant, clind-susceptible <i>mef</i> (A) genotype (10)	8/8	8/8	16/16	0.06/0.25
Ery-resistant, clind-susceptible <i>erm</i> (A), inducible, genotype (10)	16/32	8/16	16/16	0.12/0.5
<i>Moraxella catarrhalis</i>				
β-lactamase positive, <i>bro-1</i> genotype (428)	0.12/0.25	0.06/0.06	0.12/0.25	0.6/0.12
β-lactamase negative (50)	0.12/0.25	0.06/0.06	0.12/0.5	0.06/0.12
<i>Haemophilus influenzae</i>				
β-lactamase positive (370)	4/8	1/2	4/16	2/4
β-lactamase negative (213)	4/8	1/2	4/16	2/4

pen, Penicillin; ery, erythromycin; clind, clindamycin; levo, levofloxacin.

1.99 vs 2.32 mg/L; AUC_(0-24h), 9.9 vs 9.43 mg · h/L) and repeated-dose studies (day 7 C_{max}, 1.80 vs 1.92 mg/L; AUC_(0-24h), 12.4 vs 13.3 mg · h/L).⁴⁵

The results of 2 separate pharmacokinetic and safety studies involving 76 subjects with varying degrees of renal impairment demonstrated that no dose adjustment was required in subjects with mild-to-moderate renal impairment (creatinine clearance, ≥30 mL/min). In subjects with severe renal impairment (creatinine clearance, <30 mL/min), C_{max} and AUC were increased (1.5- and 2.0-fold, respectively), and thus clinicians might consider adjusting the dosage in these patients.⁴⁶ However, no dose has been established for patients with severe renal impairment at this time.⁴¹ In addition, no significant differences in pharmacokinetic parameters were found between men and women in mean AUC, C_{max}, and t_{1/2} after single and multiple doses of 800 mg of telithromycin once daily in 2 studies, one involving healthy young volunteers (age, 18-40 years) and the other involving 14 healthy elderly volunteers (age, 65-92 years).⁴¹ Furthermore, another study showed that the bioavailability of telithromycin was the same in young (age, 18-40 years) and elderly (age, >65 and ≤85 years) healthy subjects.³⁸ Data from a non-comparative clinical trial involving 240 subjects with radiologically confirmed mild-to-moderate CAP⁴⁷ demonstrated that the pharmacokinetic profile of telithromycin was similar in this population to that previously reported for healthy subjects.⁴⁸

ANTIMICROBIAL SPECTRUM OF ACTIVITY

In vitro, telithromycin has activity against many common gram-positive and gram-negative organisms, as well as atypical and intracellular respiratory pathogens, including MLS_B-resistant strains (Table II).^{35,49} Telithromycin has demonstrated activity against *S pneumoniae* isolates that express either *erm* or *mef* genes,⁵⁰ and it is more active than clarithromycin against erythromycin-susceptible

gram-positive cocci.³⁵ Telithromycin is equally effective against both β-lactamase-negative and β-lactamase-positive strains of *H influenzae* and is active against atypical respiratory pathogens (ie, *Bordetella* species, *Legionella* species, *C pneumoniae*, and *M pneumoniae*).⁵¹⁻⁵³

Telithromycin essentially is inactive against *Enterobacteriaceae* species; nonfermentative, gram-negative bacilli; *Acinetobacter baumannii*; and, constitutively, MLS_B-resistant *S aureus*.³⁵

CLINICAL STUDIES OF TELITHROMYCIN IN SUBJECTS WITH CARTIs

CAP

An estimated 2 to 3 million cases of CAP are diagnosed each year, accounting for approximately 10 million physician visits, 500,000 hospitalizations, and 45,000 deaths.²³ Although antimicrobial resistance among the key bacterial pathogens associated with CAP has been increasing rapidly,¹² the clinical relevance of penicillin-resistant strains in the treatment of CAP has not been clearly demonstrated. Most studies suggest that the current level of β-lactam resistance does not generally result in treatment failures for patients with CAP.⁵⁴ However, since 2000, anecdotal reports and one controlled study have documented failures because of multidrug-resistant *S pneumoniae* in patients treated with an oral macrolide who have subsequently required admission to the hospital with *S pneumoniae*-induced bacteremia.¹⁸⁻²¹ Although the worldwide prevalence of pneumococcal resistance to the newer fluoroquinolones (levofloxacin, gatifloxacin, and moxifloxacin) remains low (<2%), resistance has increased markedly in some areas.^{55,56} Treatment failures have already been reported, most often in patients who have been treated with fluoroquinolones previously.^{57,58} This suggests that drug-resistant *S pneumoniae* can be clinically relevant, increasing the need for new therapeutic options for such infections.⁵⁹

TABLE III. Clinical cure rates for telithromycin and comparator antibiotics in the treatment of CARTIs

Study	Regimen	Clinical cure, % (n/N)	Between-group difference (95% CI)
CAP			
Dunbar et al ⁶⁰	Tel 800 mg qd × 10 d	88.3 (143/162)	−0.2 (−7.8 to 7.5)
Tellier et al ⁶¹	Clar 500 mg bid × 10 d	88.5 (138/156)	
	Tel 800 mg qd × 5 d	89.3 (142/159)	−2.5 (−9.7 to 4.7)*
Pullman et al ⁶²	Tel 800 mg qd × 7 d	88.8 (143/161)	−3.0 (−10.2 to 4.3)*
	Clar 500 mg bid × 10 d	91.8 (134/146)	
Hagberg et al ⁶³	Tel 800 mg qd × 7-10 d	90.0 (72/80)	−4.2 (−13.6 to 5.2)
	Trov 200 mg qd × 7-10 d	94.2 (81/86)	
Hagberg et al ⁶³	Tel 800 mg qd × 10 d	94.6 (141/149)	4.5 (−2.1 to 11.1)
	Amox 1000 mg tid × 10 d	90.1 (137/152)	
AECB			
Zervos et al ⁶⁴	Tel 800 mg qd × 5 d	86.4 (121/140)	3.3 (−5.7 to 12.4)
	Cef 500 mg bid × 10 d	83.1 (118/142)	
Aubier et al ⁶⁵	Tel 800 mg qd × 5 d	86.1 (99/115)	4.0 (−6.4 to 14.3)
	Amox/clav 500/125 mg tid × 10 d	82.1 (92/112)	
Fogarty et al ⁶⁶	Tel 800 mg qd × 5 d	85.8 (193/225)	−3.4 (NA)
	Clar 500 mg bid × 10 d	89.2 (206/231)	
ABS			
Buchanan et al ⁶⁷	Tel 800 mg qd × 5 d	85.2 (161/189)	3.2 (−7.1 to 13.4)
	Cef 250 mg bid × 10 d	82.0 (73/89)	
Luterman et al ⁶⁸	Tel 800 mg qd × 5 d	75.3 (110/146)	0.9 (−9.9 to 11.7)*
	Tel 800 mg qd × 10 d	72.9 (102/140)	−1.6 (−12.2 to 9.5)*
Ferguson et al ⁶⁹	Amox/clav 500/125 mg tid × 10 d	74.5 (102/137)	
	Tel 800 mg qd × 5 d	87.4 (118/135)	0.5 (−8.1 to 9.2)
	Mox 400 mg qd × 10 d	86.9 (119/137)	

Tel, Telithromycin; qd, every day; Clar, clarithromycin; bid, twice daily; Trov, trovafloxacin; Amox, amoxicillin; tid, 3 times daily; Cef, cefuroxime axetil; Amox/clav, amoxicillin/clavulanate; NA, not available; Mox, moxifloxacin.

*Versus clarithromycin.

The safety and efficacy of telithromycin in the treatment of CAP was assessed in 8 trials (4 comparative and 4 noncomparative trials). For this review, the focus will be on the comparative trials. Subjects enrolled were considered appropriate for oral therapy and had a diagnosis of CAP on the basis of radiologic findings and the presence of 2 or more of the following signs and symptoms: cough, production of purulent sputum, Gram-stain findings consistent with a respiratory pathogen, auscultatory findings, dyspnea or tachypnea, fever, and increased total peripheral white blood cell count. Subjects were assessed before study entry, immediately after the end of therapy, and at a posttherapy test-of-cure (TOC) visit 17 to 24 days after study entry. The primary efficacy outcome was the clinical cure rate in the clinically evaluable per protocol (ie, subjects receiving ≥1 dose of study medication with no major protocol violations) population at the TOC visit.

Eight hundred milligrams of telithromycin once daily for 5, 7, or 10 days was found to be comparable with 500 mg of clarithromycin twice daily for 10 days, 200 mg of trovafloxacin once daily for 7 to 10 days, and 1000 mg of amoxicillin 3 times daily for 10 days in the treatment of CAP during 4 randomized, double-blind, parallel-group, multicenter, multinational, clinical trials (Table III).⁶⁰⁻⁶⁹

AECB

More than 6% of US adults have AECB.⁷⁰ Approximately 50% of exacerbations are caused by typical bac-

teria (ie, *S pneumoniae*, *H influenzae*, and *M catarrhalis*). Atypical bacteria (ie, *M pneumoniae* and *C pneumoniae*) are associated with AECB less commonly.⁷ Because patients with stable chronic bronchitis have a high prevalence of bacterial colonization in the lower respiratory tract,⁷¹ the role of antimicrobial therapy in AECB has been controversial. However, evidence suggests that exacerbations might be related to the appearance of new strains of colonized bacteria.⁷² Furthermore, results of a meta-analysis⁷³ and other placebo-controlled studies⁷⁴⁻⁷⁶ have shown that antimicrobial therapy is most beneficial in patients with more severe symptoms (ie, increased dyspnea, sputum volume, and sputum purulence).

In the treatment of subjects with AECB and other respiratory tract infections, the ability to administer antimicrobial therapy for shorter durations (ie, 5 days instead of 7-10 days) and still achieve high rates of clinical cure and bacteriologic eradication can potentially reduce the risk of inducing bacterial resistance and enhance patient adherence. Treatment with short-course (5 days) telithromycin was as efficacious as commonly used antibiotics for a standard duration of 7 to 10 days in 3 phase III randomized, double-blind, multicenter clinical trials in subjects with AECB (Table III).⁶⁴⁻⁶⁶ Adult outpatients were included in the studies if they had a history of chronic bronchitis, chronic obstructive pulmonary disease, and/or symptoms, including increased cough, dyspnea, or both and excessive sputum production or purulence.

The overall telithromycin clinical cure rate in the clinically evaluable per protocol population from these studies was 86% compared with 85.8% for comparator agents. In addition, Zervos et al⁶⁴ found that clinical cure rates for a telithromycin 5-day regimen were comparable with those obtained with a 10-day regimen of cefuroxime axetil, even among subjects with poor prognostic indicators. For example, in subjects aged 65 years or older, cure rates with telithromycin and cefuroxime axetil were 89.5% (34/38) and 76.6% (36/47), respectively. Among smokers, clinical cure rates were 87.8% (65/74) with telithromycin and 85.5% (53/62) with cefuroxime axetil.

ABS

Sinusitis is the fifth most common reason for antimicrobial prescriptions in the United States; in 1985, sinusitis accounted for 5% of all prescriptions written, and by 1992, sinusitis was the cause for 12% of all prescriptions.¹ The most commonly cultured pathogens in subjects with ABS are *S pneumoniae*, *H influenzae*, and *M catarrhalis*.⁷⁷

The efficacy and tolerability of 800 mg of telithromycin once daily for 5 or 10 days in the treatment of ABS were evaluated in 3 randomized, double-blind, multicenter studies (Table III). Depending on the study, the diagnosis of ABS was based on radiologic findings (ie, total sinus opacity, presence of an air-fluid level, and mucosal thickening), sinus puncture, or sinus endoscopy. In addition, the study subjects had symptoms of purulent nasal discharge, maxillary tenderness, and facial pain. Primary efficacy assessment was the clinical cure rate at the TOC visit (days 17-24). The results of these clinical trials have demonstrated that 800 mg of telithromycin administered once daily for 5 or 10 days is as effective as treatment with commonly used antimicrobial agents administered for 10 days in subjects with ABS.^{67-69,78}

Telithromycin's bacteriologic efficacy in CARTIs

A pooled analysis of the bacterial eradication rates achieved with telithromycin during CAP clinical trials demonstrated its *in vivo* activity against common respiratory pathogens, including resistant strains. The overall eradication rates were 95.9% (305/318) for *S pneumoniae* and 89.1% (204/229) for *H influenzae*. Eradication rates for resistant strains of *S pneumoniae* were 88.9% (24/27) for penicillin-resistant isolates and 88% (44/50) for macrolide-resistant isolates.

A recent pooled analysis by Low et al⁷⁹ determined the activity of telithromycin by means of *in vitro* susceptibility testing of key respiratory tract pathogens isolated from subjects with CAP, AECB, and ABS enrolled in telithromycin trials to correlate this with the observed clinical outcomes. In the pooled, bacteriologic, modified intent-to-treat population, treatment with telithromycin for 5 or 7 to 10 days resulted in an overall clinical cure rate of 88.1% (1593/1808) and satisfactory bacteriologic outcome of 89% (1593/1789). The clinical cure and bacterial eradication rates achieved by comparator agents ranged from 76.3% to 90.3% and 80.0% to 95.6%, respectively. In

cases involving infection with key respiratory pathogens, the following clinical cure and bacterial eradication rates were achieved with telithromycin: *S pneumoniae*, 92.7% and 94.3%; *M catarrhalis*, 89.7% and 89.7%; and *H influenzae*, 87.0% and 85.6%, respectively.⁷⁹

ROLE OF TELITHROMYCIN IN CARTIs

Although the symptoms, natural history, and prognoses of CAP, AECB, and ABS differ, empiric treatment strategies for CARTIs with bacterial cause include antimicrobial agents that target the most frequently identified causative pathogens: *S pneumoniae*, *H influenzae*, and *M catarrhalis*. For CAP, treatment strategies must also encompass atypical pathogens, such as *M pneumoniae* and *C pneumoniae*. In all CARTIs the possibility of infection with an antibiotic-resistant pathogen must be considered.

Current guidelines for the outpatient treatment of CAP recommend using a macrolide or doxycycline as first-line therapy in patients without underlying cardiopulmonary disease and not at increased risk for antibiotic-resistant pathogens. In patients with complicating factors, treatment with β -lactams (eg, cefuroxime, high-dose amoxicillin, amoxicillin/clavulanate plus macrolide or doxycycline) or an antipneumococcal fluoroquinolone is recommended.^{23,25,80} Because telithromycin has activity against the most common typical and atypical respiratory tract infections, including penicillin- and macrolide-resistant strains, it could be a potential first-line treatment option, especially for patients at risk for infection with drug-resistant pathogens.

Current guidelines for AECB and ABS offer similar treatment recommendations. Patients who have AECB and no increased risk of resistant pathogens should be treated with amoxicillin, doxycycline (a second-generation cephalosporin), or an advanced macrolide (ie, azithromycin or clarithromycin), whereas patients with ABS should receive amoxicillin with or without clavulanate or a cephalosporin.^{22,24,81} Patients with AECB should be designated as high or low risk on the basis of clinical factors, including possible infection with antibiotic-resistant pathogens.^{24,82} In general, narrow-spectrum antibiotics are acceptable as initial treatment for simple AECB, with broader-spectrum antibiotics reserved for patients at increased risk of treatment failure. However, there are concerns that increased use of broad-spectrum antimicrobials might lead to the emergence of resistant strains.^{24,83} Telithromycin provides coverage for the target pathogens associated with AECB and ABS but has little *in vitro* effect on normal enteric flora (eg, *Escherichia coli*), which should be beneficial in reducing the emergence of resistance. Thus telithromycin provides clinicians with an appropriate treatment option for the management of AECB and ABS.

SAFETY, TOLERABILITY, AND DRUG-DRUG INTERACTIONS

Telithromycin is well tolerated, and its adverse-event profile is similar to that of other antimicrobial agents

commonly used to treat CARTIs. The safety and tolerability of telithromycin were evaluated in 16 phase III clinical trials, including 11 controlled studies that are discussed here. The comparator antimicrobial agents used in these studies included amoxicillin, amoxicillin/clavulanate, cefuroxime axetil, clarithromycin, trovafloxacin, and penicillin V potassium. The majority of treatment-emergent adverse events (TEAEs) observed during these studies were mild to moderate in intensity, with gastrointestinal events being the most commonly reported. TEAEs that were possibly related to treatment are presented in Table IV.⁴¹

The frequency of serious TEAEs was comparable between treatment groups (telithromycin, 2.2% [59/2702]; comparators, 2.9% [61/2139]), and the incidence of possibly related serious TEAEs was low in both treatment groups (telithromycin, 0.3% [9/2702]; comparators, 0.3% [6/2139]). Discontinuation rates were similar in the 2 treatment groups: only 3.2% (86/2702) of subjects given telithromycin discontinued because of a possibly related TEAE compared with 2.5% (60/2139) for the comparator group. During the phase III controlled studies, 16 subjects died, 7 (0.3%) in the telithromycin group (n = 2705) and 9 (0.4%) in the comparator group (n = 2139); none of the deaths were considered treatment related.⁴¹

Postmarketing reports show there have been 8 cases of exacerbations of myasthenia gravis during treatment with telithromycin, and therefore telithromycin is not recommended for patients with this disorder.^{41,84} The mechanisms of these exacerbations and their relationship to treatment with telithromycin have not been elucidated. However, preclinical studies have not shown an effect of telithromycin on neuromuscular junction transmission at concentrations of up to 100 times the therapeutic concentration.⁸⁴

Telithromycin has the potential to prolong the QTc interval of the electrocardiogram in some subjects. Although no incident of cardiovascular morbidity or mortality was attributed to QTc prolongation during telithromycin treatment in subjects evaluated in clinical efficacy trials, it is recommended that telithromycin be avoided in patients with congenital prolongation of the QTc interval; in those with ongoing proarrhythmic conditions, such as uncorrected hypokalemia or clinically significant bradycardia; and in patients receiving group 1A (eg, quinidine and procainamide) or class III (eg, dofetilide) antiarrhythmic agents.⁴¹

Telithromycin might cause mild-to-moderate and transient visual disturbances, such as blurred vision, difficulty focusing, and diplopia. In clinical trials, 1.1% of telithromycin-treated patients experienced visual events compared with 0.28% of patients treated with comparator agents. Most visual events occurred after the first or second dose. In some cases these events resolved while the subject remained on therapy, whereas in other subjects the visual events continued until the full course of treatment with telithromycin was completed. As with all drugs that affect vision, patients initiating treatment with telithro-

TABLE IV. Incidence ($\geq 1.0\%$) of possibly related TEAEs in controlled phase III studies⁴¹

Preferred term	Telithromycin, n (%) (N = 2702)	Comparator, n (%) (N = 2139)
Subjects with possibly related TEAEs	861 (31.9)	606 (28.3)
Diarrhea	270 (10)	171 (8)
Nausea	190 (7)	87 (4.1)
Headache	54 (2)	53 (2.5)
Dizziness (excluding vertigo)	75 (2.8)	33 (1.5)
Vomiting	64 (2.4)	30 (1.4)
Loose stools	58 (2.1)	30 (1.4)
Dyspepsia	36 (1.3)	21 (1)
Dysgeusia	40 (1.5)	76 (3.6)

mycin should be advised of the possible effects that visual disturbances can have on driving a vehicle or operating machinery.⁴¹

Telithromycin is a competitive inhibitor of the CYP3A4 pathway and, to a lesser extent, the CYP2D6 pathway and thus has the potential for drug-drug interactions with other inhibitors and substrates in this pathway.⁸⁵ Several specific metabolic interaction studies assessed potential drug-drug and drug-food interactions. An abstract presented at a clinical meeting of the American Society of Health-System Pharmacists reported that coadministration of 800 mg of telithromycin and 240 mL of grapefruit juice did not affect telithromycin pharmacokinetics in healthy subjects, even though grapefruit juice is known to enhance the bioavailability of drugs metabolized by the CYP3A4 enzyme system.⁸⁶ When telithromycin was administered with the potent CYP3A4 inhibitors ketoconazole or itraconazole, there was an increased exposure to telithromycin. However, coadministration of each of these agents with telithromycin was safe and well tolerated, with no clinically significant changes in QTc interval observed. Ketoconazole is a stronger inhibitor than telithromycin, and when used alone, it inhibited liver CYP3A4 activity more than telithromycin used alone.⁸⁷ Administration of telithromycin and simvastatin at a 12-hour dosing interval results in a 4-fold increase in plasma concentrations of simvastatin and simvastatin acid. However, this increase is less than that observed when telithromycin and simvastatin are administered concomitantly (simvastatin and simvastatin acid AUC multiplied by a factor of 8.5 and 9.4, respectively) and less than when simvastatin and clarithromycin are administered concomitantly (simvastatin and simvastatin acid AUC multiplied by a factor of 7.9 and 14, respectively).^{88,89} It is recommended that treatment with simvastatin, as well as with lovastatin and atorvastatin, be suspended during treatment with telithromycin. Furthermore, the use of telithromycin with the CYP3A4 substrates cisapride and pimozide is contraindicated.⁴¹ Because the interaction between telithromycin and metoprolol, a CYP2D6 substrate, might be of clinical

TABLE V. Potential for drug-drug interactions⁹⁰

Drug	Effect
Triphasic contraceptives	Telithromycin slightly increases the C_{max} , AUC, and $t_{1/2}$ at steady state of levonorgestrel but does not affect ethinyl estradiol or the reliability of the contraceptive in preventing ovulation. Not clinically significant.
Warfarin*	No clinically significant interaction; consider monitoring prothrombin time (INR). ⁴¹
Simvastatin	Inhibition of CYP3A4 by telithromycin leads to significant increase in C_{max} ($5.3\times$ and AUC $8.9\times$). Avoid concomitant administration.
Cisapride	Steady-state peak plasma concentrations of cisapride were increased by 95% when coadministered with telithromycin, resulting in significant increases in QTc interval. ⁹¹
Itraconazole, ketoconazole	Inhibition of CYP3A4 by these agents leads to slightly increased C_{max} and AUC of telithromycin. Not clinically significant.
Digoxin	Telithromycin results in a moderate increase of $1.7\times C_{min}$ and $1.4\times$ AUC. Monitor and use with caution.
Theophylline	Inhibition of metabolism by telithromycin results in a modest increase in theophylline concentrations. Monitor.
Midazolam	Concomitant administration with telithromycin with intravenous or oral midazolam resulted in 2- and 6-fold increases, respectively, in the AUC of midazolam. Monitor and consider dosage adjustment. ⁴¹
Paroxetine	None
Agents affecting gastric pH (Mg and Al hydroxides, ranitidine)	None

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INR, International normalized ratio; C_{min} , minimum plasma concentration.

*Studies performed in healthy subjects.

importance, the use of telithromycin in subjects being treated with metoprolol for heart failure should be considered with caution.⁴¹ Other potential drug-drug interactions for telithromycin are listed in Table V.^{41,90}

SUMMARY

On the basis of clinical trial data, telithromycin possesses a spectrum of activity against the common typical and atypical respiratory pathogens, including penicillin- and macrolide-resistant strains of *S pneumoniae*. The clinical and bacteriologic efficacy of 800 mg of telithromycin administered once daily to subjects with CARTIs have been confirmed in numerous clinical studies; clinical cure and bacteriologic eradication rates in subjects with CAP, AECS, and ABS after treatment with telithromycin were comparable with those attained with standard 10-day antimicrobial agents that require 2 or 3 times daily administration. In addition, telithromycin is safe and well tolerated, and the most common TEAEs observed during phase III studies were mild to moderate in intensity and were mainly gastrointestinal in nature.

In today's health care environment, the addition of a new treatment option must be considered not only in relation to clinical effectiveness but also to cost effectiveness. The cost of telithromycin is in line with that of comparable agents for the treatment of CAP: a 7- to 10-day regimen of 800 mg of telithromycin once daily ranges from \$79.80 to \$114 versus \$116.20 and \$130.20, respectively, for a 10-day regimen of 875 mg/125 mg of amoxicillin/clavulanate every 12 hours and 500 mg/125 mg of amoxicillin/clavulanate every 8 hours, 250 to 500 mg of clarithromycin twice daily for 10 days costs \$91.40, and a 10-day regimen

of 400 mg of moxifloxacin once daily would total \$96.40. Levofloxacin costs \$104.10 for 500 mg once daily for 10 days and \$97.15 for 750 mg once daily for 5 days. Treatment of AECS and ABS with the recommended 5-day regimen of telithromycin would cost \$57.⁹²

The increasing prevalence of β -lactam- and macrolide-resistant strains of the common causative pathogens associated with CARTIs, as well as the increasing incidence of infection with atypical and intracellular pathogens, have limited the usefulness of many antimicrobial agents traditionally used as first-line empiric treatment. Therefore the availability of telithromycin for the treatment of mild-to-moderate CAP, AECS, and ABS offers clinicians a viable empiric treatment option that should prove especially useful for the treatment of patients who are at greater risk for CARTIs caused by drug-resistant *S pneumoniae*.

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