

Telithromycin in the treatment of acute bacterial sinusitis, acute exacerbations of chronic bronchitis, and community-acquired pneumonia

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Abstract: Acute bacterial sinusitis (ABS), acute exacerbations of chronic bronchitis (AECB), and community-acquired pneumonia (CAP) are common conditions and constitute a substantial socioeconomic burden. The ketolides are a new class of antibacterials with a targeted spectrum of antibacterial activity. In vitro, telithromycin is active against common bacterial pathogens that cause upper and lower respiratory tract infections, including some isolates that are resistant to other antibiotic classes. In 2004, telithromycin was the first ketolide antibiotic approved for clinical use by the US Food and Drug Administration for the treatment of adult outpatients with ABS, AECB, and mild-to-moderate CAP. This review discusses the use of telithromycin in the treatment of these infections, providing an overview of its antibacterial activity, pharmacokinetic and pharmacodynamic properties, clinical efficacy, and tolerability–safety, and concludes that telithromycin is an appropriate option for the treatment of community-acquired ABS, AECB, and mild-to-moderate CAP.

Keywords: telithromycin, respiratory tract infection, ketolide

Introduction

Acute bacterial sinusitis (ABS), acute exacerbations of chronic bronchitis (AECB), and community-acquired pneumonia (CAP) are common conditions and constitute a substantial socioeconomic burden. Lower respiratory tract infections (RTIs), such as CAP and AECB, represent a particular public health concern owing to the morbidity and mortality associated with these infections (Niederman et al 1998, 1999; Bartlett et al 2000).

Bacterial pathogens associated with RTIs include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, and atypical–intracellular organisms such as *Mycoplasma pneumoniae*, *Chlamydia (Chlamydia) pneumoniae*, and *Legionella pneumophila*. Antibacterial treatment of outpatient community-acquired RTIs is usually empiric, since the causative pathogen is rarely identified before initiation of antibacterial therapy. However, the development and spread of antibacterial resistance among respiratory pathogens, in particular *S. pneumoniae*, now represents a key challenge in the management of RTIs (File 2004). Although the clinical impact of bacterial resistance is still under debate, there have been a number of recent cases of treatment failure associated with macrolide use (Rzeszutek et al 2004; Klugman and Lonks 2005).

The ketolides are a new class of antibacterials with a targeted spectrum of antibacterial activity. In vitro, telithromycin is active against common bacterial

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pathogens that cause upper and lower RTIs, including some isolates resistant to other antibiotic classes. In 2004, telithromycin was the first ketolide antibiotic approved for clinical use by the US Food and Drug Administration for the treatment of adult outpatients with ABS, AECB, and mild-to-moderate CAP.

This review discusses the use of telithromycin in the treatment of these infections, providing an overview of its antibacterial activity, pharmacokinetic and pharmacodynamic properties, clinical efficacy, and tolerability–safety.

Chemistry of telithromycin

The ketolide class of antibacterials, of which telithromycin is the first to be approved for clinical use, are semisynthetic derivatives of the 14-membered macrolide, erythromycin. Telithromycin retains the macrolactone ring structure and the D-desosamine sugar attached at position 5 (Figure 1). The defining characteristic of the ketolides is the removal of the neutral sugar, Lcladinose, from the 3 position of the erythronolide ring and the subsequent oxidation of the 3-hydroxyl to a 3-keto functional group (Figure 1). Removal of the Lcladinose moiety improves the acid stability of telithromycin. Furthermore, compounds with the 3-keto group do not trigger the expression of resistance to MLS_B (macrolide–lincosamide–streptogramin_B) antibacterials in strains with inducible *erm* determinants (Bonnefoy et al 1997). This allows telithromycin to remain active against bacterial strains in which MLS_B resistance would be induced (Bonnefoy et al 1997).

The 11, 12-carbamate present in telithromycin (Figure 1) enhances the activity of ketolides (Douthwaite and Champney 2001) and, together with the 6-O-alkyl group, prevents 6–9 or 9–12 cyclization of the compound, which would result in the formation of unstable hemiketal products (commonly formed by erythromycin). Telithromycin also contains heterocyclic aromatic rings spaced from the lactone ring structure via short alkyl or allyl linkages. These structures impart improved ribosomal binding and thereby increase the activity of the compounds against both macrolide-susceptible and macrolide-resistant strains (Mankin et al 2000).

Mechanism of action

Telithromycin inhibits bacterial protein synthesis by interacting close to the peptidyl transferase site of the 50S

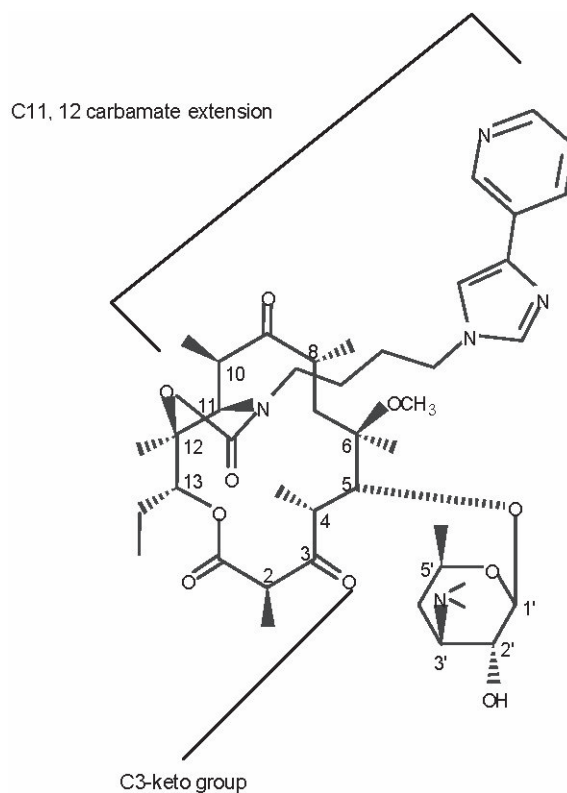


Figure 1 Chemical structure of telithromycin.

ribosomal subunit (Champney and Tober 2001); the main sites of macrolide and ketolide interaction are within domains II and V of the 23S ribosomal RNA (Hansen et al 1999; Xiong et al 1999). Ketolides bind to the ribosome in a 1:1 ratio (Hansen et al 1999), indicating that domains II and V of the 23S rRNA lie in close proximity within the tertiary structure of the rRNA and form a single drug-binding pocket. This structure has been confirmed by crystallographic models of the 50S subunit (Ban et al 2000; Schlunzen et al 2001).

Chemical footprinting experiments have located the main site of ketolide and macrolide interaction at nucleotides A2058 and A2059 in domain V (Hansen et al 1999; Xiong et al 1999). Although both macrolides and ketolides protect these bases from chemical modification, the ketolides display a higher affinity than macrolides for forming interactions with the ribosomes (Bertho et al 1998; Capobianco et al 2000). This increased affinity has been shown to be caused by the additional interaction at A752 in domain II and is mediated by the 11, 12-carbamate side chain and alkyl or allyl linkages (Hansen et al 1999). Base substitutions at position A752 reduce the binding of ketolides, supporting the notion that the adenine base at

A752 is an important secondary contact site for the carbamate ketolides (Novotny et al 2001). This additional contact presumably enables the ketolides to retain activity against bacteria that have base modifications in domain V (Capobianco et al 2000; Douthwaite et al 2000; Bemer-Melchior et al 2000).

Mechanism of resistance

The main factor behind the development of the ketolides was the need for new antibacterials to overcome the problem of macrolide resistance among the common respiratory tract pathogens, particularly *S. pneumoniae*. The most common macrolide resistance mechanisms in Gram-positive bacteria involve drug efflux and target modification (Leclercq and Courvalin 1991; Sutcliffe et al 1996). Efflux resistance in *S. pneumoniae* and *Streptococcus pyogenes* is encoded by the *mef(A)* gene. Target modification involves methylation of the key A2058 nucleotide in the MLS_B antibiotic binding site on the ribosome by methylases encoded by *erm(B)* in *S. pneumoniae*, and *erm(B)* and *erm(TR)* in *S. pyogenes* (Bonnefoy et al 1997; Roberts et al 1999). The L-cladinose moiety present in macrolides contributes to the strong induction of *erm(B)* resistance by these agents. Other less common macrolide resistance mechanisms include mutations in the ribosomal proteins or 23S rRNA (Tait-Kamradt et al 2000).

Telithromycin is active against bacterial strains expressing *mef(A)* resistance (Schito et al 2004; Jenkins et al 2005), most likely because telithromycin is a poor substrate for the macrolide efflux pump (Leclercq 2000). Telithromycin also retains activity against pneumococcal isolates that constitutively express the *erm(B)* resistance gene (Schito et al 2004; Jenkins et al 2005). Furthermore, the lack of an L-cladinose group ensures that telithromycin does not induce *erm* expression and is thereby active against strains inducibly resistant to macrolides (Mauvais and Bonnefoy 2000).

Selection experiments have shown that exposure of pneumococci to telithromycin is less likely to result in development of resistance than exposure to macrolides (Fernandez-Roblas et al 1999; Davies et al 2000; Edlund et al 2000). Typically, exposure to telithromycin resulted in minimal increases in minimum inhibitory concentration (MIC) values, with mutations occurring at lower frequencies than those obtained for macrolides under the same conditions (Davies et al 2000).

In vitro activity

Results from a number of early in vitro studies confirmed that telithromycin possesses potent activity against both common and atypical–intracellular respiratory pathogens (Biedenbach et al 1998; Pankuch, Hoellman, et al 1998; Roblin and Hammerschlag 1998; Bébéar et al 2000). Table 1 summarizes the activity of telithromycin and macrolide antibacterials against key respiratory pathogens collected in the USA (2001–2002) from patients with community-acquired RTIs as part of the PROTEKT US (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin in the United States) longitudinal surveillance study. In this study, telithromycin was more active against *S. pneumoniae*, including both penicillin-resistant and macrolide-resistant strains, than the macrolides (Table 1) (Brown and Rybak 2004). Recently published data from PROTEKT US (2002–2003) demonstrate that MIC₉₀ values for some macrolides against *S. pneumoniae* increased considerably between 2001 and 2002, and 2002 and 2003; the MIC₉₀ for erythromycin changed from 16 µg/mL to 64 µg/mL and the azithromycin MIC₉₀ increased from 32 µg/mL to ≥256 µg/mL. Overall, >99% of isolates were susceptible to telithromycin, and telithromycin susceptibility was unaffected by reduced susceptibility of these isolates to penicillin and/or erythromycin (Brown and Rybak 2004). Telithromycin is also active against Gram-negative respiratory tract bacteria, such as *H. influenzae*, and is not affected by β–lactamase production (Table 1), making it active against ampicillin-resistant strains of these pathogens (Brown and Rybak 2004). Similar results confirming the activity of telithromycin against respiratory pathogens have been demonstrated in the PROTEKT global surveillance study (Kohno et al 2003; Farrell and Felmingham 2004; Reinert, Felmingham, et al 2004).

Telithromycin also shows in vitro activity against less common respiratory pathogens including methicillin (oxacillin)-susceptible *Staphylococcus aureus* (MIC₉₀ ≤0.25 mg/mL) (Barry et al 1998; Boswell, Andrews, Ashby, et al 1998) and atypical–intracellular respiratory pathogens, including *M. pneumoniae* and *C. pneumoniae* (Roblin and Hammerschlag 1998; Bébéar et al 2000). In addition, telithromycin has minimal activity against a range of Gram-negative nonrespiratory pathogens and commensal bacteria, including *Acinetobacter* spp., *Enterobacteriaceae* spp., *Vibrio* spp., *Campylobacter jejuni*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*, and *Pseudomonas aeruginosa* (Felmingham and Farrell 2006).

Table 1 In vitro activities of telithromycin, erythromycin, and azithromycin against key respiratory pathogens collected in the USA as part of the PROTEKT US study 2001–2002^a

Organism	Telithromycin			Erythromycin			Azithromycin		
	MIC ₉₀ ($\mu\text{g/mL}$)	Range ($\mu\text{g/mL}$)	%S	MIC ₉₀ ($\mu\text{g/mL}$)	Range ($\mu\text{g/mL}$)	%S	MIC ₉₀ ($\mu\text{g/mL}$)	Range ($\mu\text{g/mL}$)	%S
<i>Streptococcus pneumoniae</i>									
All (n = 10,012)	0.25	$\leq 0.015\text{--}4$	99.9	16	$\leq 0.06\text{--}>256$	71.9	32	$\leq 0.03\text{--}>256$	71.9
Pen-I (n = 1424) ^b	0.25	$\leq 0.015\text{--}2$	99.9	>256	$\leq 0.06\text{--}>256$	50.1	>256	$\leq 0.03\text{--}>256$	50.2
Pen-R (n = 2124) ^c	0.5	$\leq 0.015\text{--}4$	99.4	>256	$\leq 0.06\text{--}>256$	19.4	>256	$\leq 0.03\text{--}>256$	19.6
Ery-R (n = 2793) ^d	0.5	$\leq 0.015\text{--}4$	99.5	>256	1->256	0	>256	0.5->256	0.1
Pen-R and Ery-R (n = 1709)	1	$\leq 0.015\text{--}4$	99.3	>256	1->256	0	>256	0.5->256	0.2
<i>Haemophilus influenzae</i>									
All (n = 3296)	4	$\leq 0.12\text{--}16$	96.3	ND	ND	ND	2	$\leq 0.12\text{--}>256$	98.9
β -lactamase positive (n = 905)	4	$\leq 0.12\text{--}16$	97.3	ND	ND	ND	2	$\leq 0.12\text{--}128$	99.2
β -lactamase negative (n = 2391)	4	$\leq 0.12\text{--}16$	95.9	ND	ND	ND	2	$\leq 0.12\text{--}>256$	98.8
<i>Streptococcus pyogenes</i> (n = 4508)	0.03	$\leq 0.015\text{--}16$	—	0.12	$\leq 0.06\text{--}>256$	94.0	0.25	$\leq 0.03\text{--}>256$	94.1

^aAdapted from Brown and Rybak (2004).

^bPen-I, penicillin-intermediate (MIC 0.12–1 $\mu\text{g/mL}$).

^cPen-R, penicillin-resistant (MIC ≥ 2 $\mu\text{g/mL}$).

^dEry-R, erythromycin-resistant (MIC ≥ 1 $\mu\text{g/mL}$).

Abbreviations: MIC, minimum inhibitory concentration; ND, not determined; S, susceptible.

Pharmacokinetics

Absorption

Following first-pass metabolism of telithromycin by the liver and the gastrointestinal tract, the absolute bioavailability of this agent (which is unaffected by the age of the subject) is ~57% (Perret et al 2002). Neither the rate nor the extent of absorption of telithromycin is affected by food intake, meaning that the drug can be taken without regard to mealtimes (Bhargava, Lenfant, et al 2002). Administration of telithromycin 800 mg once daily for 7 days to healthy volunteers resulted in rapid absorption: the mean peak serum concentration (C_{max}) of 2.27 $\mu\text{g/mL}$ was reached within 1 hour of dosing (Namour et al 2001).

Distribution

Telithromycin is subject to moderate serum protein binding; approximately 60%–70% is protein-bound, mainly to albumin and α_1 -acid glycoprotein. Studies investigating the tissue distribution of telithromycin indicate that the drug penetrates effectively into respiratory tissues and fluids. Dosing of telithromycin 800 mg once daily for 5 days produced high concentrations of the drug in bronchopulmonary tissue and fluid, including alveolar macrophages and epithelial lining fluid (Muller-Serieys et al 2001, 2004; Khair et al 2001). In addition, telithromycin concentrates in other tissues and fluids as shown in Table 2. Drug concentrations at these sites exceeded the peak concentration of the drug in plasma and remained above telithromycin

MICs for key respiratory pathogens throughout the 24-hour administration period.

Metabolism and excretion

Overall, approximately 70% of the administered dose of telithromycin is metabolized (33% pre-systemic and 37% systemic), approximately half of which occurs in the liver via the cytochrome P450 3A4 (CYP3A4) pathway. Of the 57% of administered drug that reaches the systemic circulation unchanged, 13% is excreted unchanged in urine, 7% is excreted unchanged in the feces, and 37% is metabolized by the liver (Sultan et al 1999; Aventis 2003).

Telithromycin has a biphasic half-life, with an overall terminal half-life of ~10 hours and renal clearance of 12.5 L/hour (Namour et al 2001). No dosage adjustment is required in patients with mild-to-moderate renal impairment or in patients with mild, moderate, or severe hepatic impairment.

Pharmacodynamics

Telithromycin exhibits bactericidal activity against *S. pneumoniae*, including isolates resistant to erythromycin (Pankuch, Visalli, et al 1998). Telithromycin also demonstrates limited bactericidal activity against *S. pyogenes*, *H. influenzae*, and *M. catarrhalis* by 24 hours, depending upon the concentration of antibiotic (typically ≥ 4 times the MIC value is required) and the size of the inoculum (Boswell, Andrews, Wise, et al 1998; Pankuch, Hoellman, et al 1998; Pankuch, Visalli, et al 1998; Odenholt

Table 2 Tissue distribution of telithromycin 24 hours after administration of final dose

Target tissue/fluid/cell	Dose regimen	Mean tissue/fluid/ cell to plasma concentration ratio	Reference
Multiple-dose studies			
White blood cells	600 mg once daily for 10 days	1383	Pham Gia et al (1999)
Alveolar macrophages	800 mg once daily for 5 days	2160	Khair et al (2001)
Epithelial lining fluid	800 mg once daily for 5 days	14.41	Khair et al (2001)
Bronchial mucosa	800 mg once daily for 5 days	12.11	Khair et al (2001)
Tonsillar tissue	800 mg once daily for 5 days	13.10	Gehanno et al (2003)
Saliva	800 mg once daily for 10 days	1.60 ^a	Edlund et al (2000)
Sputum	600 mg once daily for 7 days	4.80	Watanuki et al (2001)
Single-dose studies			
Sinus fluid	600 mg dose administered 3–6 hours before tissue collection	4.00	Miyamoto et al (2000)
Middle-ear fluid	600 mg dose administered 3–6 hours before tissue collection	2.40	Miyamoto et al (2000)

^aResults reported as a ratio of AUC_{saliva}/AUC_{plasma}.

Abbreviations: AUC, area under the concentration–time curve.

et al 2001). In vitro pharmacodynamic models that simulate human unbound plasma or epithelial lining fluid concentrations of telithromycin have shown that this agent rapidly eradicates both macrolide-susceptible and macrolide-resistant *S. pneumoniae* (regardless of resistance phenotype) at concentrations likely to be achieved in vivo (Zhan et al 2004, 2005).

An additional consideration when optimizing the dosing schedule of antibiotics is the post-antibiotic effect (PAE), a measure of the agent's continued antibacterial activity after its removal from the medium. Telithromycin has demonstrated PAE values equal to or greater than those of macrolide comparators (Boswell, Andrew, Ashby, et al 1998; Dubois and St-Pierre 2000; Odenholt et al 2001).

In vivo animal models have confirmed that the antibacterial activity of telithromycin is concentration-dependent and that area under the plasma drug concentration–time curve (AUC) divided by the in vitro MIC of the agent against the organism in question (AUC/MIC) is the pharmacodynamic variable most correlated with efficacy (Bermudez et al 2000; Bonnefoy et al 2001). In adult patients with CAP treated with telithromycin 800 mg once daily for 7–10 days, a pharmacodynamic analysis has explored the relationships between predictor variables (including AUC/MIC) and microbiologic outcome for the three major CAP pathogens (*S. pneumoniae*, *H. influenzae*, and *S. aureus*) (Shi, Pfister, et al 2005). Results from this analysis showed that the probability of cure following treatment with telithromycin in adults with CAP was

consistently in the region of 90% across the observed range of AUC/MIC values for each pathogen, providing confirmation that the 800 mg once-daily telithromycin dose exhibits near-maximal antimicrobial activity against *S. pneumoniae*, *H. influenzae*, and *S. aureus* in patients with CAP.

Clinical trials

The clinical efficacy and tolerability of telithromycin 800 mg once daily in adults with ABS, AECB, or mild-to-moderate CAP have been evaluated in 16 multicenter trials (summarized in Table 3).

The trials included analysis of both the intent to treat (ITT) population (mITT = modified intent to treat; any patient enrolled in the study who received at least 1 dose of antibiotic) and the per-protocol (PP) population. In most studies, the primary efficacy endpoint was clinical outcome in the clinically evaluable per-protocol (PPc) population at the test of cure (TOC) visit (Days 17–24). Clinical cure was defined as improvement in signs and symptoms or a return to pre-infection state without the need for additional antimicrobials. The bacteriologic eradication rate at TOC was also recorded for those patients with a causative pathogen isolated at baseline. Satisfactory bacteriologic outcome was defined as the eradication or presumed eradication of the causative pathogen in the bacteriologically evaluable PP or mITT populations (PPb and bmITT populations, respectively).

Acute bacterial sinusitis

Telithromycin has been evaluated for the treatment of ABS in 4 randomized clinical trials, 3 of which were double-blinded comparative trials (Table 3) (Roos et al 2002; Buchanan et al 2003; Luterman et al 2003; Ferguson et al 2004). A diagnosis of ABS was based on radiologic findings (total sinus opacity and/or air–fluid levels and/or mucosal thickening) accompanied by ≥ 1 clinical symptom (purulent nasal discharge; maxillary tenderness–toothache; maxillary pain on percussion; facial pain, pressure or tightness; or nasal congestion) of < 28 days' duration. Patients with recurrent (> 3 episodes in the previous year) or chronic (symptoms lasting > 28 days) sinusitis were excluded from all 3 studies.

In the first trial by Roos et al (2002), a 5-day course of telithromycin 800 mg once daily was compared with a 10-day course. Both treatment durations were found to result in comparable clinical success rates, with 91.1% cure in the 5-day treatment group (PPc population) vs 91.0% cure in the 10-day treatment group (cure rates in the mITT populations were 82.6% and 87.5% in the 5-day and 10-day groups, respectively). Bacteriologic outcomes were also comparable between treatment groups: a satisfactory bacteriologic outcome was achieved in 92.9% of patients treated for 5 days and in 89.9% of patients who received the 10-day treatment course. These results led the authors to conclude that a 5-day course of telithromycin 800 mg once daily would be effective in the treatment of ABS, and may result in better patient compliance when compared with 10-day treatment courses.

In a second trial (Luterman et al 2003), telithromycin 800 mg for 5 days was compared with telithromycin 800 mg for 10 days and to amoxicillin–clavulanate 500 mg/125 mg 3 times daily for 10 days. Per-protocol clinical cure rates were equivalent for all 3 treatment modalities (75.3% for 5-day telithromycin, 72.9% for 10-day telithromycin, and 74.5% for 10-day amoxicillin–clavulanate). In both the 5-day and 10-day telithromycin treatment groups, a satisfactory bacteriologic outcome was achieved in 6/7 patients, whereas 8/10 comparator-treated patients recorded a satisfactory bacteriologic outcome.

A 5-day course of once-daily telithromycin was also shown to be as clinically effective as a 10-day course of cefuroxime axetil 250 mg twice daily (Buchanan et al 2003). Per-protocol clinical cure rates for telithromycin and cefuroxime axetil were 85.2% and 82.0%, respectively, and 84.0% of telithromycin-treated patients vs 79.6% of comparator-treated patients achieved a satisfactory

bacteriologic outcome (Table 3). The fourth trial (Study 4017; Ferguson et al 2004) demonstrated that a 5-day telithromycin regimen provides equivalent clinical and bacteriologic efficacy to 10 days' treatment with the fluoroquinolone moxifloxacin (400 mg once daily).

Pooled clinical cure rates from 3 of these studies (Studies 3002, 3005, and 3011) were 80.9% (271/355) for patients treated with telithromycin vs 77.4% (175/226) in the comparator-treated group (amoxicillin–clavulanate and cefuroxime axetil) (Roos et al 2005). Clinical cure rates were also comparable between telithromycin and comparator antibacterials for patients in subgroups of special interest, including those with severe infection (as assessed by the investigator) (81.8% [45/55] vs 77.8% [35/45]), patients with radiologic findings of total sinus opacity (85.7% [84/98] vs 76.7% [33/43]), and those with a symptom duration of ≥ 7 days (81.5% [229/281] vs 78.0% [135/173]). Across the 3 studies, clinical cure rates by pathogen in patients who received 5 days of telithromycin treatment were 90.2% (55/61) for *S. pneumoniae*, 87.5% (42/48) for *H. influenzae*, 92.9% (13/14) for *M. catarrhalis*, and 94.7% (18/19) for *S. aureus* (Roos et al 2005).

Acute exacerbations of chronic bronchitis

The efficacy of telithromycin 800 mg once daily for 5 days has been evaluated in a total of 480 patients (PPc population) in 3 double-blind comparator-controlled trials (Aubier et al 2002; Zervos et al 2003; Fogarty, de Wet, et al 2005) (Table 3). Patients eligible for entry into the studies included those with a documented history of chronic bronchitis (characterized by cough and excessive sputum production for ≥ 2 consecutive years) and a clinical diagnosis of AECB based on the presence of increased cough or dyspnea, increased sputum volume, and increased sputum purulence.

Clinical and bacteriologic efficacy

Aubier and colleagues (2002) reported that a 5-day course of telithromycin 800 mg once daily was as effective as a 10-day course of amoxicillin–clavulanate 500 mg/125 mg 3 times daily. Clinical cure rates (PPc population) for telithromycin and amoxicillin–clavulanate were 86.1% and 82.1%, respectively. Among mITT patients, 81.3% of telithromycin-treated patients achieved clinical cure vs 78.1% of comparator-treated patients. Among PPb patients, a satisfactory bacteriologic outcome was recorded for 69.2% of those treated with telithromycin and 70.0% of patients who received amoxicillin–clavulanate. Re-infections at the

late post-therapy visit (Days 31–36) were slightly more common for amoxicillin–clavulanate than telithromycin (9 vs 2).

In the second study, Zervos et al (2003) compared telithromycin 800 mg once daily for 5 days with cefuroxime axetil 500 mg twice daily for 10 days. Both treatments provided equivalent clinical efficacy, with PP cure rates of 86.4% in the telithromycin group and 83.1% in the cefuroxime axetil group. Among mITT patients, 78.0% of telithromycin-treated patients and 72.3% of cefuroxime-treated patients were assessed as clinical cures at the TOC visit. When causative pathogens were identified, a satisfactory bacteriologic outcome was achieved in 76.0% of patients in the telithromycin group vs 78.6% in the cefuroxime axetil group. Relapses or re-infection occurred in a small number of patients in both groups at the late post-therapy visit (10 in the telithromycin group and 8 in the cefuroxime axetil group).

The third study of telithromycin in patients with AECB compared the clinical and bacteriologic efficacy of telithromycin 800 mg once daily for 5 days and clarithromycin 500 mg twice daily for 10 days (Fogarty, de Wet, et al 2005). Clinical cure (PP population) was achieved in 85.8% and 89.2% of telithromycin and clarithromycin recipients, respectively. Among mITT patients, 83.0% of telithromycin-treated patients and 83.7% of clarithromycin-treated patients were assessed as clinical cures. Eradication (presumed or documented) of the causative pathogen occurred in 81.9% of telithromycin patients vs 82.9% of clarithromycin patients.

Overall, an analysis of pooled data from the 3 studies indicated similar levels of clinical and bacteriologic efficacy for telithromycin and comparator antibacterials (Fogarty, Zervos, et al 2005). Per-protocol clinical cure rates at TOC were 86.0% (413/480) and 85.8% (416/485) for telithromycin and comparators, respectively, and a satisfactory bacteriologic outcome was achieved in 77.2% (105/136) of telithromycin-treated patients and 79.1% (106/134) of comparator-treated patients. Clinical cure rates were also comparable between telithromycin and comparator antibacterials for patients in subgroups of special interest, including those aged ≥ 65 years (85.3% [157/184] vs 83.3% [179/215]), patients with significant airway obstruction (77.1% [64/83] vs 81.4% [79/97]), patients with severe AECB (as assessed by the investigator) (84.4% [38/45] vs 75.0% [36/48]), and patients who smoked (86.8% [190/219] vs 85.4% [169/189]) (Fogarty, Zervos, et al 2005). Across the 3 studies, clinical cure rates by pathogen in

patients who received 5 days of telithromycin treatment were 81.5% (22/27) for *S. pneumoniae*, 73.3% (44/60) for *H. influenzae*, and 93.1% (27/29) for *M. catarrhalis* (Fogarty, Zervos, et al 2005).

Health outcomes

Healthcare resource utilization (including unscheduled AECB-related outpatient visits, emergency room [ER] visits, hospitalizations, and time lost from work) has been documented in one of the AECB clinical trials (comparing telithromycin with clarithromycin) (Fogarty, de Wet, et al 2005). Percentages of patients attending an unscheduled AECB-related ER visit were lower in the telithromycin group compared with the clarithromycin group (0% vs 2.8%, respectively), fewer telithromycin-treated patients were hospitalized owing to AECB (0.4% vs 1.4%, respectively), and fewer employed telithromycin patients reported days lost from work (23% vs 31%, respectively) (Fogarty, de Wet, et al 2005). These differences in healthcare resource use were estimated to contribute to a direct cost saving of approximately US\$146 per patient.

Community-acquired pneumonia

The efficacy of telithromycin 800 mg for 5 or 7–10 days has been evaluated in a total of 9 trials involving adult or adolescent patients with a radiologically confirmed diagnosis of CAP (Hagberg et al 2002; van Rensburg et al 2002; Carbon, Moola, et al 2003; Pullman et al 2003; Mathers Dunbar et al 2004; Tellier, Niederman, et al 2004; Fogarty, Patel, et al 2005; Mouton et al 2005) (Table 3).

Clinical and bacteriologic efficacy

Administration of telithromycin for 7–10 days in 2 open-label studies (van Rensburg et al 2002; Carbon, Moola, et al 2003) resulted in clinical cure rates of 92.9% and 93.6% among PPc patients (cure rates in the mITT populations were 79.6% and 85.8%, respectively). The remaining 2 open-label studies in which the duration of telithromycin treatment was 7 days (Fogarty, Patel, et al 2005) reported PPc clinical cure rates of 89.6% and 93.0%, with corresponding mITT cure rates of 83.1% and 85.4%.

In 3 of the comparative trials, a 7- to 10-day regimen of telithromycin once daily was shown to be as clinically effective (PPc population) as amoxicillin 1000 mg 3-times daily for 10 days (94.6% vs 90.1%) (Hagberg et al 2002), clarithromycin 500 mg twice daily for 10 days (88.3% vs 88.5%) (Mathers Dunbar et al 2004), and trovofloxacin 200 mg once daily for 7–10 days (90.0% vs 94.2%) (Pullman

Table 3 Phase III/IV clinical trials for the treatment of patients with acute bacterial sinusitis, acute exacerbations of chronic bronchitis, or community-acquired pneumonia

Study	Design	Patient age range, years (mITT population)	Total nr patients ^a	Regimen	Length of treatment	Clinical response, n/N (%) ^b	Bacteriologic outcome, n/N (%) ^c
Acute bacterial sinusitis							
3002 (Roos et al 2002)	Randomized	18–66		335 (256) T 800 mg od	5 days	mITT 138/167 (82.6) PP 112/123 (91.1)	80/97 (82.5) 65/70 (92.9)
3005 (Luterman et al 2003)	Randomized, double-blind, parallel-group	16–84	607 (423)	T 800 mg od T 800 mg od T 800 mg od	5 days 10 days	mITT 147/168 (87.5) PP 121/133 (91.0) mITT nd PP 110/146 (75.3)	93/104 (89.4) 62/69 (89.9) nd 6/7 (85.7)
3011 (Buchanan et al 2003)	Randomized, double-blind, parallel-group	14–84	356 (278)	A/C 500/125 mg tid T 800 mg od	10 days 5 days	mITT 102/137 (74.5) PP 193/240 (80.4)	8/10 (80.0) 102/126 (81.0)
4017 (Ferguson et al 2004)	Randomized, double-blind, parallel-group	18–85	322 (272)	CA 250 mg bid T 800 mg od MOX 400 mg od	10 days 5 days 10 days	mITT 161/189 (85.2) PP 84/116 (72.4) PP 73/89 (82.0)	84/100 (84.0) 44/60 (73.3) 39/49 (79.6)
Acute exacerbations of chronic bronchitis							
3003 (Aubier et al 2002)	Randomized, double-blind, parallel-group	18–84	320 (227)	T 800 mg od A/C 500/125 mg tid	5 days 10 days	mITT 128/159 (80.5) PP 118/135 (87.4)	36/41 (87.8) 32/34 (94.1)
3007 (Zervos et al 2003)	Randomized, double-blind, parallel-group	19–97	373 (282)	T 800 mg od CA 500 mg bid	5 days 10 days	mITT 125/163 (76.7) PP 119/137 (86.9)	31/43 (72.1) 31/33 (93.9)

^aNumber of patients in the mITT population, with the number of patients that were clinically evaluable at the end of treatment (PP) in parentheses.

^bProportion of patients clinically cured at the post-therapy test of cure visit.

^cProportion of patients with a satisfactory bacteriologic outcome (presumed or documented eradication of the causative pathogen) at the post-therapy test of cure visit.

Abbreviations: A, amoxicillin; A/C, amoxicillin-clavulanic acid; bid, twice daily; C, clarithromycin; CA, cefuroxime axetil; COMP, comparator; mITT, modified intent to treat; MOX, moxifloxacin; nd, no data presented; od, once daily; PP, per-protocol; T, telithromycin; tid, three-times daily; TR, trovafloxacin.

Table 3 Continued

Study	Design	Patient age range, years (mITT population)	Total nr patients ^a	Regimen	Length of treatment	Clinical response, n/N (%) ^b	Bacteriologic outcome, n/N (%) ^c
3013 (Fogarty, de Wet, et al 2005)	Randomized, double-blind, parallel-group	18–95	552 (456)	T 800 mg od	5 days	mITT 224/270 (83.0)	nd
				C 500 mg bid	10 days	PP 193/225 (85.8)	59/72 (81.9)
						mITT 236/282 (83.7)	nd
						PP 206/231 (89.2)	63/76 (82.9)
Community-acquired pneumonia							
3000 (Carbon, Moola, et al 2003)	Non-blinded, non-comparative	18–79	240 (197)	T 800 mg od	7–10 days	mITT 191/240 (79.6)	49/67 (73.1)
3009OL (van Rensburg et al 2002)	Non-blinded, n on-comparative	18–89	212 (187)	T 800 mg od	7–10 days	PP 183/197 (92.9)	40/45 (88.9)
3010 (Fogarty, Patel, et al 2005)	Non-blinded, non-comparative	13–92	418 (357)	T 800 mg od	7 days	mITT 182/212 (85.8)	80/98 (81.6)
3012 (Aventis, data on file)	Non-blinded, non-comparative	13–90	538 (473)	T 800 mg od	7 days	PP 175/187 (93.6)	61/68 (89.7)
3001 (Hagberg et al 2002)	Randomized, double-blind, parallel-group	16–88	404 (301)	T 800 mg od	10 days	mITT 357/418 (85.4)	215/255 (84.3)
				A 1000mg tid	10 days	PP 332/357 (93.0)	137/149 (91.9)
3006 (Mathers, Dunbar, et al 2004)	Randomized, double-blind, parallel-group	18–92	416 (318)	T 800 mg od	10 days	mITT 447/538 (83.1)	229/265 (86.4)
				C 500 mg bid	10 days	PP 424/473 (89.6)	161/179 (89.9)
3009 (Pullman et al 2003)	Randomized, double-blind, parallel-group	17–99	204 (166)	T 800 mg od	7–10 days	mITT 171/199 (85.9)	49/62 (79.0)
				TR 200 mg od	7–10 days	PP 141/149 (94.6)	36/40 (90.0)
						mITT 161/205 (78.5)	46/63 (73.0)
						PP 137/152 (90.1)	35/40 (87.5)
						mITT 161/204 (78.9)	36/48 (75.0)
						PP 143/162 (88.3)	25/28 (89.3)
						mITT 171/212 (84.6)	37/45 (82.2)
						PP 138/156 (88.5)	27/28 (96.4)
						mITT 82/100 (82.0)	27/32 (84.4)
						PP 72/80 (90.0)	13/14 (92.9)
						mITT 89/104 (85.6)	30/34 (88.2)
						PP 81/86 (94.2)	22/22 (100)

^aNumber of patients in the mITT population, with the number of patients that were clinically evaluable at the end of treatment (PP) in parentheses.

^bProportion of patients clinically cured at the post-therapy test of cure visit.

^cProportion of patients with a satisfactory bacteriologic outcome (presumed or documented eradication of the causative pathogen) at the post-therapy test of cure visit.

Abbreviations: A, amoxicillin; A/C, amoxicillin-clavulanic acid; bid, twice daily; C, clarithromycin; CA, cefuroxime axetil; COMP, comparators; mITT, modified intent to treat; MOX, moxifloxacin; nd, no data presented; od, once daily; PP, per-protocol; T, telithromycin; tid, three-times daily; TR, trovafloxacin.

Table 3 Continued

Study	Design	Patient age range, years (mITT population)	Total nr patients ^a	Regimen	Length of treatment	Clinical response, n/N (%) ^b	Bacteriologic outcome, n/N (%) ^c
Community-acquired pneumonia							
4003 (Tellier; Niederman, et al 2004)	Randomized, double-blind, parallel-group	15–88	559 (466)	T 800 mg od	5 days	mITT PP	nd 57/65 (87.7)
				T 800 mg od	7 days	mITT PP	nd 52/65 (80.0)
				C 500 mg bid	10 days	mITT PP	nd 45/54 (83.3)
4015 (Mouton et al 2005)	Non-blinded, comparative, parallel-group	nd	482 (438)	T 800 mg od	7–10 days	mITT PP	nd nd
				Pooled COMP	nd	mITT PP	nd nd

^aNumber of patients in the mITT population, with the number of patients that were clinically evaluable at the end of treatment (PP) in parentheses.

^bProportion of patients clinically cured at the post-therapy test of cure visit.

^cProportion of patients with a satisfactory bacteriologic outcome (presumed or documented eradication of the causative pathogen) at the post-therapy test of cure visit.

Abbreviations: A, amoxicillin; A/C, amoxicillin–clavulanic acid; bid, twice daily; C, clarithromycin; CA, cefuroxime axetil; COMP, comparators; mITT, modified intent to treat; MOX, moxifloxacin; nd, no data presented; od, once daily; PP, per-protocol; T, telithromycin; tid, three-times daily; TR, trovafloxacin.

et al 2003). In the mITT populations, telithromycin clinical success rates were 85.9%, 78.9%, and 82.0% vs 78.5%, 84.6%, and 85.6% for amoxicillin, clarithromycin, and trovofloxacin, respectively. The fourth comparative study demonstrated that telithromycin administered once daily for either 5 or 7 days was as effective as clarithromycin 500 mg twice daily for 10 days with PPc clinical cure rates of 89.3%, 88.8%, and 91.8%, respectively (Tellier, Niederman, et al 2004). The corresponding mITT cure rates were 82.4%, 82.2%, and 81.2%.

Across the 8 studies described above, a satisfactory bacteriologic outcome was achieved in 80.0%–92.9% of telithromycin-treated patients at the TOC visit (PP population) (Table 3). Among patients who received a comparator antibacterial, a satisfactory bacteriologic outcome was achieved in 83.3%–100% of patients (amoxicillin, 87.5%; clarithromycin, 96.4% and 83.3%; trovafloxacin, 100%). Pooled analyses of data from the 8 CAP studies have been used to investigate the efficacy of telithromycin in subgroups of patients, including those with infections caused by pneumococci resistant to penicillin and/or erythromycin (van Rensburg et al 2005), patients infected with atypical–intracellular pathogens (Dunbar et al 2005), and patients with pneumococcal bacteremia (Carbon, van Rensburg, et al 2003). Among a total of 37 PP patients infected with *S. pneumoniae* isolates resistant to penicillin and/or erythromycin, 33 (89.2%) achieved clinical cure and eradication of the causative pathogen at TOC (van Rensburg et al 2005). The clinical success rate was also high for telithromycin-treated patients infected with atypical–intracellular pathogens: *C. pneumoniae*, 34/36 (94.4%); *M. pneumoniae*, 36/37 (97.3%); and *L. pneumophila*, 13/13 (100%) (Dunbar et al 2005). Among telithromycin-treated patients with documented pneumococcal bacteremia (n = 82; PP population), clinical cure and bacterial eradication rates were 90.2% (74/82) and 93.9% (77/82), respectively (Carbon, van Rensburg, et al 2003).

Recent data from a randomized, open-label, comparative, international study (Study 4015) suggest that telithromycin may be more effective in treating CAP than a range of commonly prescribed antibiotics, at least in areas where pneumococcal macrolide resistance is high (Mouton et al 2005). The study was conducted in 9 countries with documented erythromycin resistance rates $\geq 30\%$ (Greece, Hong Kong, Hungary, South Africa, South Korea, Spain, Taiwan, Thailand, and Tunisia). Adults with CAP received either telithromycin 800 mg once daily for 7–10 days or a

comparator oral antibiotic usually prescribed locally and/or recommended by local guidelines (β -lactam, macrolide, or fluoroquinolone). The clinical cure rate in the telithromycin group was significantly higher than that in the comparator group (mITT population): 86.0% vs 78.8%, respectively (p = 0.04). The results of this trial are the first to demonstrate superior clinical efficacy of telithromycin over comparators.

Health outcomes

CAP-associated healthcare resource utilization data were collected for telithromycin- and comparator-treated patients enrolled in two of the four comparator-controlled clinical trials (Niederman et al 2004a; Tellier, Chang, et al 2004). The similar design of these studies and the use of a common comparator agent (clarithromycin) allowed data from the two studies to be pooled to investigate whether there were any differences in overall healthcare resource utilization associated with telithromycin for 5, 7, or 10 days vs clarithromycin for 10 days (Niederman et al 2004b). Although the two treatments showed equivalent clinical efficacy, telithromycin treatment (for 5, 7, or 10 days) was associated with significantly fewer CAP-related hospitalizations (1.2 vs 3.6 per 100 patients) and CAP-related days spent in hospital (8.8 vs 33.8 days per 100 patients). Similar differences were noted among subsets of patients with risk factors for morbidity. Among patients aged ≥ 65 years, there were 0 vs 6.6 hospitalizations and 0 vs 64.5 hospital days per 100 patients receiving telithromycin and clarithromycin, respectively. In patients with a Fine score $> II$, there were 2.1 hospitalizations per 100 telithromycin-treated patients vs 9.5 hospitalizations per 100 clarithromycin patients (resulting in 15.6 vs 94.6 hospital days per 100 patients, respectively [Niederman et al 2004b]). Overall, CAP-related hospitalization costs were significantly lower for telithromycin recipients, resulting in an estimated cost saving of US\$302 per patient.

Safety and tolerability

The safety and tolerability of telithromycin have been evaluated in a total of 16 Phase III clinical trials, comprising 14 of the 16 studies presented in Table 3 (Study 4017 and Study 4015 were not included in the analysis) and 2 studies conducted in patients with tonsillitis–pharyngitis. The safety-evaluable population included all patients who received at least 1 dose of study medication and had at least 1 safety assessment following randomization.

Telithromycin 800 mg once daily for up to 10 days was generally well tolerated and most adverse events (AEs) were of mild to moderate intensity. In the 11 comparator-controlled clinical trials, 1348 patients out of a total of 2702 (49.9%) treated with telithromycin reported at least 1 treatment-emergent AE (TEAE) compared with 48.4% (1035/2139) of comparator-treated patients. TEAEs considered by the investigator to be possibly related to study medication were reported in 31.9% (861/2702) of telithromycin-treated patients and 28.3% (606/2139) of comparator-treated patients participating in the 11 trials. The most frequent of these possibly related TEAEs (occurring in >1% of patients in either treatment group) are listed in Table 4. Overall, TEAEs of the gastrointestinal and nervous system were the most commonly reported events possibly related to study medication. Incidences of blurred vision were reported more frequently with telithromycin (30/2702 [1.1%]) than with comparator antibacterials (6/2139 [0.28%]). Fifteen of the 20 cases reported in telithromycin-treated patients were considered by the investigator to be possibly related to study medication. The events were generally mild in intensity and started most frequently within the first 2 days of treatment. All cases resolved without sequelae and no cases were reported as serious AEs. Rates of discontinuation of study medication were similar between telithromycin and comparator agents (4.4% and 4.3%, respectively). Most treatment discontinuations were attributable to gastrointestinal TEAEs, primarily diarrhea (telithromycin 0.9%, comparators 0.6%) and vomiting (telithromycin 0.8%, comparators, 0.5%). Clinically noteworthy elevations in liver enzymes (eg, aspartate aminotransferase and alanine aminotransferase) occurred in similar proportions of telithromycin-treated (1.2% and 1.6%, respectively) and comparator-treated patients (1.3% and 1.7%, respectively). Overall, 1.1% of patients in the controlled Phase III trials reported treatment-emergent visual AEs compared with 0.28% of patients who received comparators (Aventis 2005). Visual disturbances included blurred vision, diplopia, or difficulty focusing. Most of these events were mild to moderate, although severe cases have been reported; all visual AEs were reversible upon cessation of drug treatment (Aventis 2005).

Across all 16 trials, the incidence of death was low (telithromycin, 17/4472 [0.4%]; comparators, 9/2139 [0.4%]) and none of the deaths was considered to be related to study medication. Similarly, the frequency of serious TEAEs considered related to study medication was low and comparable across treatment groups in the controlled

Table 4 Treatment-emergent adverse events (TEAEs) possibly related to study medication reported by >1% of patients in 11 comparator-controlled trials of telithromycin

Possibly related TEAE	Number (%) of patients	
	Telithromycin (n = 2702)	Comparators (n = 2139)
Diarrhea	270 (10.0)	171 (8.0)
Nausea	190 (7.0)	87 (4.1)
Headache	54 (2.0)	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 (1.0)
Dysgeusia	40 (1.5)	76 (3.6)
Total nr of patients with possibly related TEAEs	861 (31.9)	606 (28.3)

trials (telithromycin, 0.3% [9/2702]; comparators, 0.3% [6/2139]).

At therapeutic doses, telithromycin was associated with a small mean increase (1.5 milliseconds) in QTc interval. However, QTc outlier values were uncommon and similar in frequency to those seen with clarithromycin and nonmacrolide antibacterials, and no excess in risk for significant QTc prolongation was noted in telithromycin-treated patients, including those in at-risk populations.

Post-marketing surveillance

The results of a post-marketing surveillance study conducted in Germany (the country in which telithromycin was first introduced in 2001) provide the first broad-ranging evidence of the safety and effectiveness of telithromycin in routine practice (Lorenz and Roscher 2004). Data are available for a total of 34 929 outpatients with community-acquired RTIs treated with telithromycin 800 mg once daily for a median of 5 days (AECB, ABS, or tonsillitis–pharyngitis) or 7 days (CAP). There was a high level of satisfaction with telithromycin therapy, with 95.6% of physicians and 94.1% of patients reported to be satisfied or very satisfied. The overall rate of clinical cure or improvement with telithromycin was 98.4%. Adverse drug reactions were reported by 1.9% of patients and were predominately gastrointestinal in nature. Serious adverse drug reactions were observed in 32 patients (0.1%).

Rare occurrences of allergic reactions, atrial arrhythmias, syncope (usually associated with vagal syndrome), and exacerbations of myasthenia gravis have been reported in the worldwide post-marketing surveillance for telithromycin (Aventis 2005).

Interactions with other drugs

Telithromycin, like the macrolides, is both a substrate and an inhibitor of the CYP3A4 metabolic pathway. A number of specific drug interaction studies have been undertaken in humans to assess the effects of co-administration of telithromycin with CYP3A4 inhibitors, CYP3A4 inducers, and CYP3A4 substrates. In addition, drug interaction studies have been conducted with several other concomitantly prescribed drugs, including paroxetine and metoprolol, theophylline, warfarin, digoxin, class III antiarrhythmic agents, and oral contraceptives. The results of the drug interaction studies are summarized in Table 5.

CYP3A4 inhibitors

The azole antifungals ketoconazole and itraconazole both strongly inhibit hepatic CYP3A4. However, although both ketoconazole and itraconazole moderately increased telithromycin C_{max} and AUC (Shi, Montay, et al 2005), the extent of these increases is considered unlikely to be clinically relevant. Grapefruit juice (components of which inhibit intestinal, but not hepatic, CYP3A4) had no effect on telithromycin pharmacokinetics during co-administration (Shi, Montay, et al 2005).

Rifampicin and other CYP3A4 inducers

Rifampicin (a potent inducer of hepatic metabolic enzymes, including CYP3A4) has been shown to reduce serum levels of clarithromycin (Kolars et al 1992). Similarly, concomitant administration of telithromycin with rifampicin reduced telithromycin exposure by approximately 80% (Aventis 2005). Co-administration of the two drugs is therefore not recommended.

CYP3A4 substrates

Administration of telithromycin with the CYP3A4 substrates cisapride and pimozide is contraindicated owing to the potential for prolongation of the cardiac QTc interval if exposure to cisapride or pimozide is increased. Following oral co-administration with the benzodiazepine midazolam, the plasma level of oral midazolam was increased 6-fold (Aventis 2005); patients receiving oral midazolam and telithromycin concomitantly should therefore be monitored, and a reduction in the midazolam dose should be considered if necessary. In a study with healthy volunteers, C_{max} and AUC of simvastatin increased 5.3-fold and 8.9-fold, respectively, during co-administration with telithromycin (Aventis 2005). In a second study in healthy patients in which simvastatin and telithromycin were administered 12

hours apart, there was much lower increase in simvastatin C_{max} and AUC (3.4-fold and 4.0-fold, respectively) (Aventis 2005). Nevertheless, it is recommended that co-administration of telithromycin with simvastatin, lovastatin, or atorvastatin should be avoided; if telithromycin is prescribed, therapy with any of these statins should be suspended during the course of treatment. Pravastatin and fluvastatin are not extensively metabolized by CYP3A4; therefore, telithromycin is not expected to interact with these agents.

Other drug interactions

In line with previous drug interaction studies involving macrolides, telithromycin has been shown to exert moderate effects on the pharmacokinetics of theophylline. The increased exposure to theophylline when co-administered with telithromycin may increase the incidence of gastrointestinal side-effects, and it is recommended that the two drugs be given 1 hour apart (Bhargava, Leroy, et al 2002). Although telithromycin has been observed to increase digoxin levels, no significant changes in electrocardiogram parameters occurred and there were no signs of digoxin toxicity (Montay et al 2002). However, as suggested for macrolides, digoxin side-effects or serum levels should be monitored during concomitant administration with telithromycin. Post-marketing reports suggest that telithromycin could potentiate the effects of oral anticoagulants when the two drugs are co-administered. Consideration should therefore be given to monitoring prothrombin times/International Normalized Ratio (INR) while patients are receiving telithromycin and oral anticoagulants simultaneously (similar interactions between warfarin and macrolides have been reported).

No clinically significant interactions have been observed between telithromycin and antacids containing aluminum or magnesium. In addition, telithromycin does not influence the anti-ovulatory effects of oral contraceptives containing ethinylestradiol or levonorgestrel (Scholtz et al 2000).

Conclusions

The ketolide antibacterial telithromycin demonstrates potent activity against key common RTI pathogens, including *S. pneumoniae* isolates resistant to other antibiotics and atypical–intracellular organisms, and has a low potential to select for or induce resistance. In European countries where telithromycin has been available for clinical use since 2001–2002, antibiotic surveillance data indicate that telithromycin has retained in vitro activity against the common respiratory pathogens, including penicillin-resistant or macrolide-

Table 5 Interactions between telithromycin and commonly prescribed drugs^a

Drug	Interaction	Comments/recommendations
CYP3A4 inhibitors		
Ketoconazole	Increase in TEL exposure: C_{max} by 51%; AUC by 95%	No clinically significant interaction
Itraconazole	Moderate increase in TEL exposure: C_{max} by 22%; AUC by 54%	No clinically significant interaction
CYP3A4 inducers		
Rifampicin	Reduction in TEL exposure: C_{max} by 79%; AUC by 86%	Co-administration not recommended
CYP3A4 substrates		
Cisapride/pimozide	Not tested: potential for TEL to increase pimozide exposure	Use of TEL contraindicated with cisapride and pimozide
Midazolam	6-fold increase in midazolam exposure (AUC)	Midazolam dose adjustment may be necessary
Statins (simvastatin, lovastatin, atorvastatin)	Simvastatin exposure increased 5.3-fold (C_{max})/8.9-fold (AUC). Lovastatin and atorvastatin not tested	Suspension of simvastatin, lovastatin, or atorvastatin therapy recommended if TEL is prescribed
CYP2D6 substrates		
Metoprolol	Moderate increase in exposure to metoprolol: ~38% on C_{max} and AUC, but no effect on elimination half-life of metoprolol	Co-administration in patients with heart failure should be considered with caution
Others		
Theophylline	Moderate increase in exposure to theophylline: ~17% on C_{max} and AUC	To reduce GI side-effects of theophylline, drugs should be administered 1 hour apart
Digoxin	Moderate increase in exposure to digoxin (plasma peak and trough levels increased by 73% and 21%, respectively) but no changes in ECG or signs of digoxin toxicity	Monitor digoxin side-effects or serum levels
Warfarin	No significant effects on racemic warfarin. Post-marketing reports suggest TEL may increase exposure to oral anticoagulants	Consider monitoring prothrombin times/INR
Antacids or other agents containing multivalent cations	No interactions	
Oral contraceptives	Anti-ovulatory effects of oral contraceptives containing ethinylestradiol or levonorgestrel unaffected by TEL	

^aAdapted from Ciervo and Shi (2005).

Abbreviations: AUC, area under the concentration–time curve; C_{max} , peak plasma concentration; CYP, cytochrome P450; ECG, electrocardiogram; GI, gastrointestinal; INR, international normalized ratio; TEL, telithromycin.

resistant strains of *S. pneumoniae* (>99% susceptible) (Reinert, Felmingham, et al 2004; Reinert, Rodloff, et al 2004). Clinical data support these in vitro findings, with results of randomized controlled studies showing telithromycin 800 mg once daily to be as effective as current standards of care for the treatment of ABS, AECB, and CAP. Telithromycin displays pharmacokinetic parameters allowing for once-daily dosing; in addition, it can be administered in short-duration therapy for most RTI indications, which may encourage good patient compliance. In clinical trials, treatment with telithromycin was well tolerated, with AEs being typically mild to moderate in

intensity, transient in nature, and occurring at rates comparable with those seen with other first-line treatment options. Assessment of additional healthcare resource utilization in patients with CAP and AECB also indicates that telithromycin may be associated with reduced rates of hospitalization compared with standard first-line treatment options, suggesting the potential for significant cost savings with wider use.

In summary, based on clinical experience to date, telithromycin is an appropriate option for the treatment of community-acquired ABS, AECB, and mild to moderate CAP.

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