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Telithromycin

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Contents

Abstract

▲ Telithromycin is the first member of a new family of the macrolide-lincosamide-streptogramin-B (MLS_B) class of antimicrobials, the ketolides. It has a good spectrum of activity against respiratory pathogens, including penicillin- and erythromycin-resistant pneumococci, as well as intracellular and atypical bacteria. Furthermore, it has a low potential to select for resistance or induce cross-resistance among other MLS_B antimicrobials.

▲ At the recommended dosage of 800mg orally once daily, telithromycin reaches maximal plasma concentrations of about 2 mg/L. It penetrates rapidly into bronchopulmonary, tonsillar, sinus and middle ear tissues and/or fluids and achieves high concentrations at sites of infection. It also concentrates within polymorphonuclear neutrophils.

▲ In clinical trials in patients with community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB) or pharyngitis/tonsillitis caused by group A β-haemolytic streptococci, telithromycin 800mg once daily achieved clinical cure rates of 86 to 95%. In acute maxillary sinusitis (AMS), cure rates were 73 to 91%.

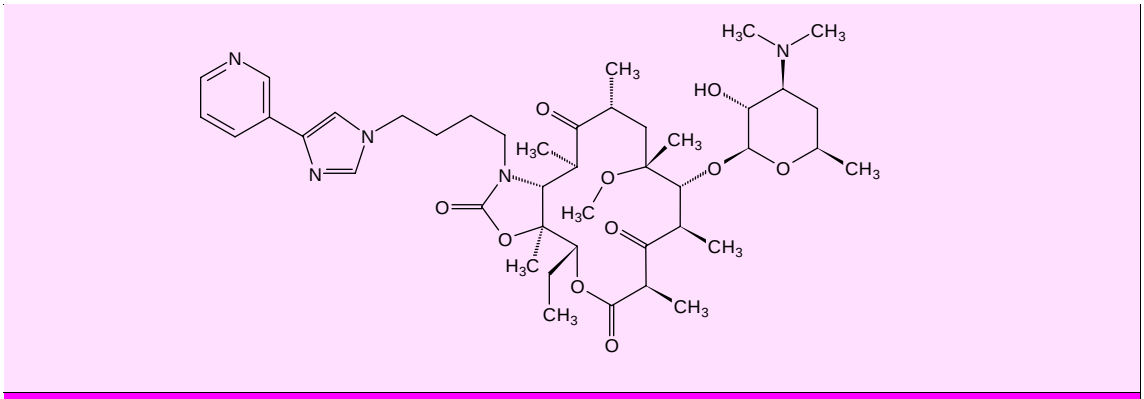
▲ A 7- to 10-day regimen of telithromycin was as effective as a 10-day course of amoxicillin 1000mg 3 times daily, clarithromycin 500mg twice daily or a 7- to 10-day course of trovafloxacin 200mg once daily for treating CAP. A 5-day regimen of telithromycin was as effective as a 10-day regimen of cefuroxime axetil 500mg twice daily or amoxicillin/clavulanic acid 500/125mg 3 times daily in AECB.

▲ A 5-day regimen of telithromycin was as effective as a 10-day regimen of clarithromycin 250mg twice daily or phenoxymethylpenicillin 500mg 3 times daily in pharyngitis/tonsillitis, or a 10-day regimen of amoxicillin/clavulanic acid 500/125mg 3 times daily in patients with AMS.

▲ Telithromycin was well tolerated across all patient populations. Adverse events associated with telithromycin were generally mild to moderate in intensity and seldom led to treatment discontinuation. The most frequent adverse events were diarrhoea (13.3%) and nausea (8.1%). Other adverse events included dizziness and vomiting.

Features and properties of telithromycin (HMR 3647, RU 66647)

Indications	
Treatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute bacterial maxillary sinusitis, pharyngitis/tonsillitis	
Mechanism of action	
Ketolide antibacterial agent	Inhibits bacterial 50S ribosomal protein synthesis and ribosome assembly
Dosage and administration	
Usual dosage in clinical trials	800 mg/day (2 × 400mg tablets)
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (800mg for 7 or 10 days)	
Peak plasma concentration	1.84-2.27 mg/L
Time to peak plasma concentration	1-2h
Terminal elimination half-life	9.81h
Adverse events	
Most frequent	Mild to moderate diarrhoea and nausea, low rate of discontinuation



Telithromycin

Community-acquired respiratory pathogens are becoming increasingly resistant to the β-lactams, erythromycin and the newer macrolides, necessitating the development of alternative antimicrobials. Telithromycin is the first member of a new family of semisynthetic macrolide-lincosamide-streptogramin-B (MLS_B) antimicrobials, the ketolides. Ketolides are 14-membered ring macrolides with a 3-keto structure replacing the L-cladinose moiety of macrolides and a methoxy substituent at C6. In addition, telithromycin possesses a carbamate extension at positions C11/C12. These substitutions confer acid stability and enable telithromycin to overcome the most common forms of macrolide resistance, thereby enhancing activity against erythromycin-resistant strains.[1]

Ketolides have a similar mechanism of action to the macrolides: prevention of bacterial protein synthesis by direct binding to the 50S subunit of bacterial ribosomes and prevention of translation and ribosome assembly.[2] However, they also exhibit important differences in their mode of action which differentiate them from the macrolide class. Telithromycin and the macrolide erythromycin both bind to bacterial ribosomes primarily through interactions with nucleotides in domains II and V of 23S ribosomal RNA. Telithromycin, however, binds 10 times more tightly than erythromycin and 6 times more tightly than clarithromycin to wild-type ribosomes; furthermore, this difference rises to greater than 20 times (versus both macrolides) in ribosomes with domain V modifications that confer MLS_B resistance.[3] This is accounted for by the stronger mode of binding of telithromycin to domain II. These innovative differences in the mechanisms of action result in an extended spectrum of activity for telithromycin covering macrolide-resistant strains.

1. Antimicrobial Activity

This section focuses on the activity of telithromycin against bacterial respiratory pathogens, with a particular emphasis on the more common pathogens associated with community-acquired respiratory tract infections (RTIs).

In this review, *in vitro* antibacterial activity refers to minimum inhibitory concentrations (MICs) determined by broth or agar dilution techniques (except in the case of some intracellular bacteria, which were tested in cell culture). MIC_{50} and MIC_{90} values refer to minimum concentrations required to inhibit the growth of 50 and 90% of strains, respectively. Proposed MIC breakpoints for telithromycin indicating susceptibility, intermediate susceptibility and resistance are ≤1, 2 and ≥ 4 mg/L, respectively, for streptococci, staphylococci and enterococci and ≤2, 4 and ≥8 mg/L for *Haemophilus influenzae*.[4-6] The tentative pharmacokinetic breakpoint predictive of successful clinical outcome is MIC 2 to 4 mg/L.[7]

In Vitro Activity

Gram-Positive Bacteria

Streptococci

• Telithromycin has excellent activity against *Streptococcus pneumoniae*, with reported MIC_{90} values of 0.016 to 0.06 mg/L for erythromycin-susceptible strains.[5,8-10] Telithromycin retains good activity against penicillin-[8,11,12] and erythromycin-[8,12] resistant strains, with MIC_{90}s of 0.25 mg/L[8] and ≤0.12 to 0.5 mg/L, respectively.[5,8,9,11] Its activity against erythromycin-resistant pneumococci includes strains with *erm* (inducible and constitutive) and *mef* resistance determinants.[9,13]

• In contrast, all macrolides, including azithromycin, were inactive against erythromycin-resistant strains (MIC_{90} ≥32 and ≥64 mg/L for clarithromycin and azithromycin, respectively).[14]

• *S. pyogenes* is also highly susceptible to telithromycin with MIC_{90}s ranging from 0.015 to 0.125 mg/L.[15-17] Telithromycin had similar activity to clindamycin (MIC_{90} < 0.06 mg/L) and was more active than azithromycin (MIC_{90} 2 mg/L) or erythromycin (MIC_{90} 0.25 mg/L) against this species.[15] Good activity has also been demonstrated against erythromycin-resistant isolates of *S. pyogenes* with the *erm*A (MIC_{90} 0.06 mg/L) or *mef*A (MIC_{90} 0.5 mg/L) resistance determinants.[18]

Staphylococci

• Methicillin/oxacillin-susceptible *Staphylococcus aureus* (MSSA) was also highly susceptible to telithromycin (MIC_{90} ≤0.12 mg/L),[11] but methicillin/oxacillin-resistant strains (MRSA) were generally resistant (MIC_{50} >16 mg/L).[11,19,20] Telithromycin was >64-fold more active than azithromycin or erythromycin and 2-fold more active than clindamycin against 66 oxacillin-susceptible strains.[20]

• The activity of telithromycin against MRSA is dependent on the pattern of erythromycin resistance. Against 25 isolates of erythromycin-susceptible MRSA, telithromycin MIC_{90} was 0.12 mg/L.[21] The corresponding value for erythromycin-resistant MRSA was ≥128 mg/L.[21] This reduction in activity against erythromycin-resistant MRSA appears to be accounted for by the high proportion of these isolates expressing constitutive mechanisms of resistance to erythromycin,[22] as *S. aureus* isolates with inducible erythromycin resistance remain highly susceptible to telithromycin (MIC_{90} 0.12 mg/L).[23]

Gram-Negative Bacteria

• The MIC_{50} and MIC_{90} of telithromycin against *H. influenzae* were 0.6 and 1.2 mg/L (range 0.08 to 2.5 mg/L), respectively.[13] MIC values were unaffected by β-lactamase production or ampicillin resistance.[12,13] Telithromycin had similar activity to azithromycin and was 4- to 8-fold more active than clarithromycin against *H. influenzae*.[13,24]

• The activity of telithromycin was reduced against 42 cefuroxime-resistant strains of *H. influenzae*, with MIC_{50} and MIC_{90} values of 2 and 16 mg/L, respectively.[24]

• Against *Moraxella catarrhalis* isolates, the majority of which were β-lactamase producers, telithromycin had activity similar to that of azithromycin and clarithromycin[12,25] and levofloxacin[24] (MIC_{90} ≤0.12 mg/L).

Atypical and Intracellular Organisms

• Telithromycin showed excellent activity (MICs ≤0.25 mg/L) against human mycoplasmas other than *Mycoplasma hominis*.[26] It had comparable activity to erythromycin, clarithromycin, azithromycin and levofloxacin against *M. pneumoniae* (MIC_{90} ≤0.015 mg/L).[26,27]

• The activity of telithromycin also extends to intracellular pathogens. Against *Chlamydia pneumoniae* isolates (n = 19) in infected human hepatocyte cells, telithromycin had similar activity to erythromycin and azithromycin (MIC_{90} 0.25 mg/L).[28]

• Against 30 isolates of *Legionella* spp. (including 21 isolates of *L. pneumophila*), telithromycin MIC_{90} was 0.03 mg/L (range ≤0.004 to 0.12 mg/L).[29] Its activity was similar to levofloxacin and higher than that of erythromycin and moxifloxacin.[29] Telithromycin also inhibited the growth of *L. pneumophila* serogroup 1 in guinea-pig alveolar macrophages.[30]

• *Mycobacterium avium*, *M. bovis* BCG, *M. paratuberculosis* and *M. ulcerans* were moderately sus-

ceptible to telithromycin *in vitro* (MICs ≤20 mg/L compared with MICs ≤1.25 mg/L for clarithromycin against the same species). *M. africanum*, *M. bovis*, *M. simiae* and *M. tuberculosis* were resistant to telithromycin (MICs ≥40 mg/L).[31]

Influence of Assay Methodology on Activity

- Broth microdilution, agar dilution, disk diffusion and E-test can all be used reliably to test the susceptibility of both *S. pneumoniae* and *H. influenzae* to telithromycin.[5,32] However, slightly higher MIC values have been reported by E-test.
- Telithromycin MICs against most species and strains tested were minimally affected by an increase of inoculum size from 10^4 to 10^6 colony-forming units (cfu)/ml or by the addition of 20 or 70% serum, although the MIC of *S. pyogenes* increased 4-fold in the presence of 70% serum.[19]
- Choice of media also appears to have a minimal effect on telithromycin susceptibility. For Gram-positive cocci, Mueller–Hinton and Isosensitest agar produced similar results.[33] For *H. influenzae*, the use of media other than *Haemophilus* test medium had little effect on telithromycin MICs.[32]
- Incubation in 5 to 7% CO_2 resulted in a 2-fold increase in telithromycin MICs for *H. influenzae* and a >3-fold increase in azithromycin MICs.[32] CO_2 has also been reported to affect the anti-pneumococcal activity of telithromycin when determined by disk diffusion and E-test experiments.[5] Generally, zone diameters were 4 to 5mm smaller and MICs approximately 1 dilution higher when determined in the presence of CO_2.

Bactericidal Activity

Time-kill studies have demonstrated that telithromycin has dose-dependent bactericidal activity (defined as 99.9% killing and a 3 $\log_{10}$ decrease in cfu/ml) at 2 to 8 × MIC for key respiratory pathogens.

- Against *S. pneumoniae*, telithromycin was bactericidal at 24 hours at 2 × MIC and showed 99% killing of all strains tested after 12 hours. At 4 to 8 × MIC, rapid killing was observed within 6 hours.[8] Telithromycin showed higher bactericidal activity than azithromycin and other macrolides against erythromycin-susceptible pneumococci. At 2 × MIC, telithromycin demonstrated bactericidal activity against erythromycin-resistant *S. pneumoniae* with macrolide MICs ≥64 mg/L.[8] Macrolides, including azithromycin and clarithromycin, showed bactericidal activity only against erythromycin-susceptible strains.
- Complete killing of pneumococci (including penicillin- and erythromycin-resistant strains) was achieved within 1 to 6 hours in *in vitro* dynamic models which simulated the human pharmacokinetic profile achieved after administration of once daily telithromycin 850mg[34] or 800mg.[35]
- Telithromycin was bactericidal at 24 hours at 2 × MIC against some strains of *H. influenzae* and at MIC against *M. catarrhalis*.[36] In general, telithromycin and azithromycin were the most active agents evaluated against these organisms in time-kill experiments.[36,37] At 10 × MIC, telithromycin was bactericidal at 24 hours against *S. aureus* and *S. pyogenes*.[38]
- Telithromycin was bactericidal against *M. pneumoniae*, with a minimal bactericidal concentration (MBC) of ≤0.12 mg/L.[26]
- Telithromycin demonstrated bactericidal activity against *C. pneumoniae*, with an MBC of 0.25 mg/L.[28] At 10 × MIC, time-dependent killing was observed with a maximal bactericidal effect at 72 to 96 hours' exposure.[39] Exposure to 0.5 × MIC after 12 hours' exposure to 10 × MIC increased the killing effect, but not to the degree seen with a static exposure of 10 × MIC for 72 hours.[39]
- Telithromycin also reduced numbers of intracellular *L. pneumophila* in infected guinea-pig alveolar macrophages[30] and slowed regrowth for up to 2 days. Its activity was comparable with that of clarithromycin and erythromycin.[30] Concentration- and time-dependent activity greater than that of erythromycin was demonstrated in *L. pneumophila*-infected human monocyte cell lines. A significant ($p < 0.01$ *vs* control) antimicrobial effect was observed at the lowest concentration of telithromycin evaluated (0.25 × MIC).[40]

Postantibiotic Effects

• Telithromycin exhibited a significant postantibiotic effect (PAE; >0.5 hours) at 4 and 10 × MIC (0.8 to 7 and 1.2 to 8.2 hours, respectively) against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes* and *S. aureus*.[38]

• Against erythromycin-susceptible strains of *S. aureus*, *S. pyogenes* and *S. pneumoniae*, PAEs ranged from 0.5 to 3.8, 0.6 to 10.8 and 0 to 9.5 hours, respectively, at 0.5 to 64 × MIC. Maximum PAEs against erythromycin-resistant strains of these organisms were lower but still significant (3.5, 3.8 and 6.6 hours, respectively).[41]

In Vivo Activity

Animal Models of Infection

• In a murine model of pneumonia caused by β-lactamase-producing *H. influenzae*, oral telithromycin 50 mg/kg (4 doses) was as active as oral azithromycin or ciprofloxacin (both 100 mg/kg) in eradicating bacteria in the lung (3/12 *vs* 5/18 and 3/13 animals). Amoxicillin 25 mg/kg, erythromycin, clarithromycin and pristinamycin (all 100 mg/kg) failed to sterilise the lungs in any animal, but all test agents, except amoxicillin, reduced lung bacterial counts ($p < 0.05$ *vs* untreated animals).[42]

• Telithromycin 50 or 100 mg/kg twice daily for 3 days was more active than azithromycin 100 mg/kg in a mouse model of macrolide-resistant (azithromycin MIC >128 mg/L) pneumococcal infection (survival rates 47 and 71 *vs* 29% at 7 days postinfection).[43] In a rabbit model of pneumococcal pneumonia, telithromycin (dosed to simulate serum concentration profiles achieved with 800mg twice daily in humans) was active against penicillin-resistant strains and strains with erythromycin MICs of 16 mg/L but not against highly erythromycin-resistant strains (MIC >64 mg/L).[44]

• Telithromycin has also demonstrated high therapeutic efficacy in an animal model of infection caused by erythromycin-susceptible *S. pyogenes* [dose required to protect 50% of animals (PD_{50}) 16 mg/kg] and erythromycin-susceptible and inducibly resistant isolates of *S. aureus* (PD_{50} 8 and 4.5 mg/kg).[45]

• Telithromycin 30 mg/kg (2 oral doses) was active in reducing lung bacterial counts in experimental *Legionella* pneumonia in guinea-pigs and was associated with a better survival rate than erythromycin or roxithromycin (89 *vs* 60 *vs* 75%) and a slightly lower survival rate than pefloxacin 7.5 mg/kg (2 doses; 100%).[46] An intraperitoneal telithromycin dosage of 10 mg/kg given once or twice daily for 5 days was associated with 100% survival in a similar model.[30]

Pharmacokinetic Predictors of In Vivo Activity

• Studies in the neutropenic murine thigh infection model suggest that AUC (area under the concentration-time curve)/MIC is the most important pharmacokinetic/pharmacodynamic determinant of *in vivo* activity of telithromycin.[47,48] In this murine model, AUC/MIC is also the best predictor of efficacy for azithromycin; however, the 2 drugs showed differences in their pharmacodynamic characteristics. Telithromycin produced concentration-dependent, whereas azithromycin exhibited time-dependent, killing against *S. pneumoniae*. Maximum killing for telithromycin and azithromycin was 4 to 5.3 and 1.5 to 2.3 $\log_{10}$ cfu/thigh, respectively.[48]

• Results of a preliminary study in 240 patients with community-acquired pneumonia (CAP) suggested that infections caused by pathogens with MICs as high as 2 to 4 mg/L may be successfully treated with telithromycin 800mg once daily.[7]

Resistance Issues

The most clinically important resistance mechanism to the MLS_B group of antimicrobials is target modification via *erm* genes, which encode ribosome methylases (MLS_B resistance). *Erm* genes can be expressed constitutively or inducibly. Both 14- and 15-membered ring macrolides can induce MLS_B resistance. Another common mechanism is active efflux via *mef* genes.[49] Ketolides do not induce methylase gene expression in erythromycin-inducibly resistant strains.[50] Furthermore, their

activity is not affected by inducible MLS_B resistance or efflux mechanisms.[9,13]

• Whereas telithromycin was active against constitutive MLS_B-resistant *S. pneumoniae* (MIC 0.25 mg/L),[9,51] its activity was affected by constitutive MLS_B resistance in *S. pyogenes* (MIC_{90} ≥64 mg/L) and *S. aureus* (MIC_{90} ≥128 mg/L).[18,23,52]

• Telithromycin selected resistant mutants less frequently than did azithromycin, clarithromycin, erythromycin, roxithromycin, clindamycin and pristinamycin after 50 passages of macrolide-susceptible (n = 5) and -resistant (containing *mef*E or *erm*B genes; n = 6) *S. pneumoniae* through subinhibitory concentrations. Only 3 mutants resistant to telithromycin (MIC >1 mg/L) emerged, all of which had MICs ≤8 mg/L. In contrast, 20 to 45 resistant mutants emerged for the other drugs.[53]

Effects on Oral and Faecal Flora

• Administration of telithromycin 800mg once daily (the dosage used in all clinical trials) for 10 days to 10 healthy volunteers did not result in any overgrowth of yeasts or *Clostridium difficile* among the oral and faecal microflora.[54] Quantitative ecological disturbances in the normal microflora were moderate and transient and were similar to those observed amongst a group of 10 healthy volunteers receiving clarithromycin 250mg twice daily. Telithromycin showed a more favourable ecological profile than clarithromycin in terms of the emergence of resistance. Salivary α-haemolytic streptococci remained susceptible to telithromycin (MIC ≤1 mg/L), although MICs increased slightly. In contrast, clarithromycin administration was associated with the rapid emergence of highly resistant isolates (MIC >128 mg/ L). In faeces, emergence of resistant enterococci (*Enterococcus faecalis*; MIC_{90} 32 mg/L) and *Bacteroides* spp. (MIC_{90} >128 mg/L) were noted after telithromycin administration. Highly resistant faecal enterococci, enterobacteriaceae and *Bacteroides* spp. (MICs >128 mg/L) developed during clarithromycin administration.[54]

2. Pharmacokinetic Profile

Absorption and Distribution

• The recommended telithromycin dosage (800mg once daily) produced a peak plasma concentration (C_{max}) of 1.84 to 2.27 mg/L at 1 to 2 hours (t_{max}) at steady state in healthy volunteers. AUC_{0-24} was 8.4 to 12.5 mg/L · h.[55,56]

• Steady-state plasma concentrations were reached after 2 to 3 days of repeated administration. After 7 or 10 days' administration there was a slight accumulation of telithromycin compared with single administration: the accumulation ratio was approximately 1.2 to 1.5.[55,56]

• The pharmacokinetics of telithromycin deviate modestly from dose proportionality and this is mainly observed for AUC: for a 2-fold increase in dose there was an approximately 3-fold increase in AUC, whereas C_{max} was approximately dose proportional.[55]

• The oral absolute bioavailability of telithromycin is 57%.[57] Food does not affect the bioavailability of the drug.[58]

• Telithromycin 600 or 800mg once daily for 5 days produced high concentrations in tonsillar tissue[59] and bronchopulmonary tissues and fluids.[60-62] Concentrations at these sites remained above telithromycin MICs for most respiratory pathogens throughout the 24-hour administration period.

• Concentrations in tonsils were 3-fold higher than concurrent plasma concentrations at 3 hours postdose and 13-fold higher at 24 hours.[59] Bronchopulmonary tissue or fluid : plasma ratios over the 24-hour administration period ranged from 4.8 to 14.4 for epithelial lining fluid, 2.1 to 12.1 for bronchial mucosa and 37.2 to 2159.6 for alveolar macrophages.[60-62] The penetration of telithromycin into respiratory tissues and fluids is shown in figure 1.

• In 26 patients undergoing otorhinolaryngological procedures, concentrations of telithromycin in the mucous membrane of middle ear and paranasal sinuses, respectively, were 2.4- and 4-fold higher

than concurrent plasma concentrations 3 to 6 hours after administration of telithromycin 600mg.[63]

• Telithromycin C_{max}, C_{min} (minimum plasma concentrations) and AUC values in saliva were approximately 1.2- to 1.5-fold, 3- to 5-fold and 1.6- to 1.7-fold higher, respectively, in saliva than in plasma in 10 healthy volunteers who received 800mg once daily for 10 days.[54]

• In 8 healthy young volunteers, the mean C_{max} of telithromycin in cantharidin-induced skin blister fluid was 0.44 mg/L 9 hours after a single oral dose of 600mg. The blister fluid : plasma AUC_{0-24} ratio was 1.38.[64] In white blood cells, telithromycin concentrations were approximately 100-fold higher than corresponding plasma concentrations 2 hours after administration of a 600mg oral dose, indicating good intracellular penetration.[65]

• An *in vitro* study showed that telithromycin was preferentially taken up by polymorphonuclear neutrophils, in which it was concentrated up to 300-fold, rather than by other cell types such as peripheral blood mononuclear cells and cell lines of haematopoietic and nonhaematopoietic origin. The drug was concentrated mainly within azurophil granules, suggesting that telithromycin will be effectively delivered to phagocytosed intracellular bacteria within these cells.[66]

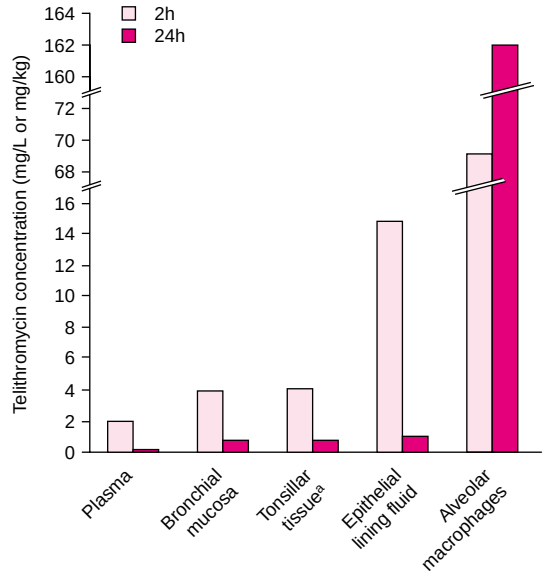


Fig. 1. Penetration of telithromycin into respiratory tissues and fluids. Concentrations of telithromycin at 3 and 24 hours after the fourth dose in tonsillar tissue,[59] and at 2 and 24 hours after the last dose in bronchial mucosa, epithelial lining fluid and alveolar macrophages[62] in patients undergoing tonsillectomy (n = 20)[59] or routine fibreoptic bronchoscopy (n = 19)[62] after receiving once daily oral telithromycin 800mg for 5 days. Telithromycin plasma concentrations reported by Andrews et al.[62] are also included. **a** Tonsillectomy was performed at 3, 12 or 24 hours after the fourth dose; data are presented for the 3- and 24-hour timepoints.

Metabolism and Elimination

• Telithromycin circulates mainly (57%) in unchanged form in the plasma. Four major metabolites of telithromycin have been identified in humans: an alcohol, an acid, an *N*-desmethyldesosamine and an *N*-oxide pyridine derivative.[67]

• At steady state, the terminal elimination half-life ($t_{½z}$) of telithromycin in healthy volunteers was 9.81 hours.[55] Renal clearance was 12.5 L/h.[55]

• On average, 70% of the telithromycin dose is metabolised (33% presystemic and 37% systemic).[68] Among the cytochrome P450 (CYP) isoenzymes, CYP3A4 is the main enzyme involved in the metabolism of telithromycin.[68]

• The absorbed telithromycin is eliminated via various pathways with 7% excreted unchanged in faeces, 13% excreted unchanged in urine and 37% metabolised by the liver.[68]

Influence of Age, Gender and Disease on Pharmacokinetics

• Administration of telithromycin as a single 800mg or repeated 800mg once daily dose (for 10 days) to elderly patients (mean age 73.6 years) produced C_{max} and AUC_{0-24} values of 3.0 or 3.6 mg/L and 11.56 or 17.17 mg/L · h, respectively. The t_{max} in this age group was <1 hour.[69] Concentrations achieved in the elderly are somewhat higher than those observed in young volunteers.

• Renal clearance in elderly patients (7 to 8 L/h) was lower than the range reported for younger age groups and $t_{½z}$ was 14.23 hours after repeated administration, but the accumulation ratio after repeated doses (1.45) was similar to that in younger individuals. Gender did not affect the pharmacokinetics of telithromycin.[69]

• The pharmacokinetics of telithromycin in 12 patients with moderate to severe hepatic impairment (mean Child Pugh score of 9.2, range from 5 to 12) were moderately modified as compared with 12 control healthy volunteers, after administration of a single 800mg dose. Although C_{max} tended to be 20% lower in patients with hepatic impairment, AUC values were similar between patients and healthy controls. There was no correlation between any of the pharmacokinetic parameters and the Child Pugh score.[70]

• The elimination of telithromycin in patients with hepatic impairment tended to be reduced, with a 1.4-fold higher terminal elimination half-life compared with healthy individuals. However, this is not expected to contribute to further accumulation on multiple administration. The observed modest increase in half-lives is a consequence of decreased metabolic clearance of telithromycin in patients with hepatic impairment, which is partially compensated for by a higher rate of renal clearance (50% increase, $p < 0.05$).[70]

• The pharmacokinetic parameters of telithromycin have also been assessed in 240 patients with CAP who participated in a phase III study. Mean C_{max}, C_{min} and AUC were 2.89 mg/L, 0.19 mg/L and 13.9 mg/L · h, respectively, in 220 evaluable patients treated with telithromycin.[7] Analysis of pharmacokinetic data from 1590 patients with RTIs revealed no significant differences on account of sex, age, body size, renal function, smoking status or infection severity.[71]

3. Therapeutic Trials

Telithromycin 800mg once daily has been evaluated in the treatment of RTIs, including CAP, acute exacerbations of chronic bronchitis (AECB), acute maxillary sinusitis (AMS) and pharyngitis/tonsillitis. All comparative studies were randomised, double-blind and multicentre and all studies were published as posters and/or abstracts.

Clinical cure was defined as a return to the pretreatment state or improvement/post-infectious stigmata. For the purposes of this review, clinical success rates cited are those at the test-of-cure (TOC) visit (days 17 to 21) for the per-protocol population. In contrast to other recent studies of antimicrobial efficacy, in which TOC was measured at the end of therapy,[72-74] the TOC visit at 17 to 21 days after treatment initiation allowed capture of early cases of relapse, thus representing a rigorous test of efficacy in line with US Food and Drug Administration (FDA) guidelines. Satisfactory bacteriological outcome was defined as eradication or presumed eradication of the baseline pathogen, or was not defined.

Community-Acquired Pneumonia

The efficacy of telithromycin has been evaluated in a total of 1373 patients with CAP in 6 international, multicentre clinical trials: 3 uncontrolled and 3 randomised, double-blind, comparative studies.

• A 7-day or 7- to 10-day course of telithromycin was an effective treatment for patients with CAP (clinical cure rate 93 to 94%)[75-77] and was as effective as a 7- to 10-day regimen of trovafloxacin 200mg once daily [telithromycin 90% *vs* trovafloxacin 94%; 95% confidence interval (CI) –13.6, 5.2].[68] A 10-day course of telithromycin was as effective as a 10-day regimen of amoxicillin 1000mg 3 times daily [telithromycin 95% *vs* amoxicillin 90% (95% CI –2.1, 11.1); fig. 2a][78] or clarithromycin 500mg twice daily [telithromycin 88% *vs* clarithromycin 89% (95% CI –7.8, 7.5); fig. 2b].[79] Clinical cure rates by pathogen across the 6 CAP studies were 95% (165/174) for *S. pneumoniae*, 90% (95/105) for *H. influenzae*, 87% (26/30) for *M. catarrhalis* and 94 to 100% for atypical/intracellular pathogens in telithromycin-treated patients.[68]

• Telithromycin also demonstrated high efficacy in patients with CAP caused by penicillin- or macrolide-resistant *S. pneumoniae*. 92% (11/12) of pa-

tients who had single-pathogen *S. pneumoniae* with reduced susceptibility to penicillin (MIC ≥ 0.1 mg/L) and 88% (15/17) with erythromycin-resistant (MIC ≥ 1 mg/L) infections achieved clinical cure with telithromycin.[68]

- The efficacy of telithromycin in the treatment of CAP extends to the most vulnerable patients in the community. Analysis of data from 4 clinical studies showed that 90% (27/30) of patients with bacteraemia associated with CAP were successfully treated with telithromycin at the standard oral dosage of 800mg once daily for 7 to 10 days. Among those with pneumococcal bacteraemia, 88.5% (23/26) were clinical successes.[80] In elderly patients (aged ≥65 years) with CAP, the clinical cure rate was 90% (139/154).[81]
- A further analysis showed that among patients with CAP caused by atypical respiratory pathogens, 93% with *C. pneumoniae* (28/30), 96% with *M. pneumoniae* (27/28) and 100% with *L. pneumophila* (4/4) were clinical successes after telithromycin treatment (n = 4 clinical trials).[82]

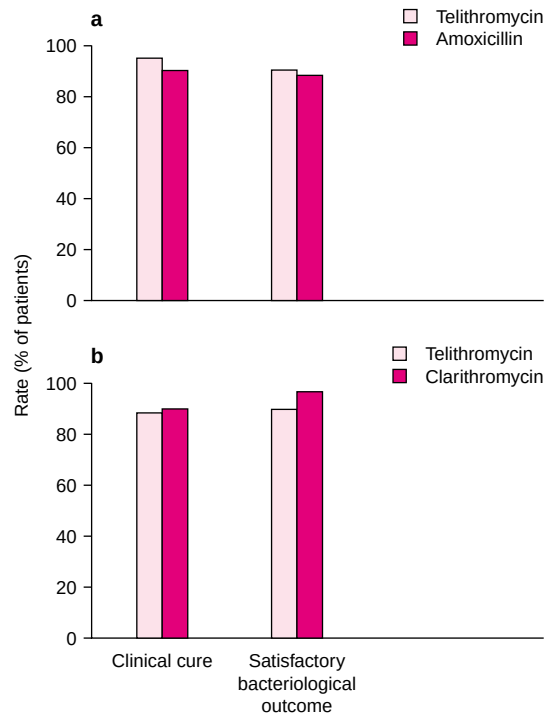


Fig. 2. Clinical and bacteriological outcomes achieved with telithromycin in the treatment of patients with community-acquired pneumonia (CAP). Patients with CAP received (a) a 10-day course of telithromycin 800mg once daily (n = 149) or amoxicillin 1000mg 3 times daily (n = 152)[78] or (b) a 10-day course of telithromycin 800mg once daily (n = 162) or clarithromycin 500mg twice daily (n = 156).[79] Clinical cure was defined as a return to the pretreatment state or improvement/post-infectious stigmata; satisfactory bacteriological outcome was defined as eradication or presumed eradication of the causative organism. Outcomes reported are those at the post-therapy visit (days 17 to 21) in the per-protocol population.

Acute Exacerbations of Chronic Bronchitis

- A 5-day regimen of telithromycin was as effective as a 10-day regimen of cefuroxime axetil 500mg twice daily in treating AECB: 86% (121/140) versus 83% (118/142) of patients achieved clinical cure (95% CI –5.8, 12.4).[68] Satisfactory bacteriological outcome was observed in 76% (19/25) and 79% (22/28) of patients, respectively.[83]
- A 5-day regimen of telithromycin was also as effective as a 10-day regimen of amoxicillin/clavulanic acid 500/125mg 3 times daily in treating AECB in patients with chronic obstructive pulmonary disease. 86% (99/115) versus 82% (92/112) [95% CI –6.4, 14.3] of patients were clinical successes and a satisfactory bacteriological outcome was achieved in 69% (27/39) versus 70% (21/30) of patients (76 versus 81% of pathogens were eradicated).[84]

Acute Maxillary Sinusitis

- A 5-day course of telithromycin was as effective as a 10-day course in treating adults with AMS. Clinical cure was achieved in 91% of patients [112/123 and 121/133, respectively (95% CI –7.7, 7.9)] in both treatment groups and a satisfactory

bacteriological outcome was achieved in 93% (65/70) versus 90% (62/69) of patients.[85]

• These 2 telithromycin regimens were as effective as a 10-day regimen of amoxicillin/clavulanic acid 500/125mg 3 times daily in patients with AMS. Clinical cure rates were almost identical in the 3 treatment groups [73 to 75%; n = 423 evaluable patients (95% CI –9.9, 11.7 for 5-day telithromycin *vs* 10-day amoxicillin/clavulanic acid)].[68]

Pharyngitis/Tonsillitis

• In adults and adolescents with pharyngitis/tonsillitis caused by group A β-haemolytic streptococci (GAS), a 5-day regimen of telithromycin was as effective as a 10-day regimen of clarithromycin 250mg twice daily. Clinical success was achieved in 93 versus 91% of patients (95% CI –5.5, 8.6) and a satisfactory bacteriological outcome in 91% (137/150) versus 88% (119/135) of patients (95% CI –4.5, 11.0).[86]

• In adults with pharyngitis/tonsillitis caused by GAS, a 5-day regimen of telithromycin was as effective as a 10-day regimen of phenoxymethylpenicillin 500mg 3 times daily, each regimen achieving clinical cure in >94% of patients. A satisfactory bacteriological outcome was achieved in 84% (97/115) versus 89% (106/119) of patients (95% CI –14.2, 4.8) and >85% of pretreatment pathogens were eradicated in each group.[87]

Pooled Eradication Rates

• Analysis of eradication rates of typical respiratory pathogens from 10 clinical trials showed that 105/111 *S. pneumoniae* (95%), 65/82 *H. influenzae* (79%), 24/26 *M. catarrhalis* (92%), 218/247 *S. pyogenes* (88%), 12/14 *H. parainfluenzae* (86%) and 12/12 *S. aureus* (100%) infections were eradicated after telithromycin treatment.[4]

• Clinical cure and bacteriological eradication rates were similar amongst patients with infections caused by penicillin- (MIC ≥2 mg/L) and/or macrolide-resistant (MIC ≥1.0 mg/L) *S. pneumoniae* (as sole pathogen or part of a mixed infection) to the overall rates for all *S. pneumoniae* infections across the phase III clinical programme. Amongst telithromycin-treated patients, eradication and clinical cure rates for resistant isolates of *S. pneumoniae* were both 53/57 (93%). Corresponding values for the comparator-treated patients were 7/10 (70%; clinical cure) and 8/10 (80%; eradication).[88]

4. Tolerability

• Most adverse events in patients receiving telithromycin 800mg once daily for up to 10 days were mild to moderate in intensity and treatment discontinuation because of treatment-related adverse events was uncommon (4%). In 8 comparator-controlled studies, the incidence and profile of adverse events was similar for telithromycin and comparators.[68,78,79,86,87,89]

• The most frequent treatment-related events reported by telithromycin-treated patients (n = 2045) in 9 controlled phase III studies were diarrhoea (13.3%), nausea (8.1%), dizziness (3.6%) and vomiting (2.8%).[68] The overall incidence of diarrhoea was slightly higher in the telithromycin group than for pooled comparators (13.3 *vs* 9.4%), although within the range observed for individual comparators [7.3% (clarithromycin) to 18% (amoxicillin/clavulanic acid)]. Furthermore, the majority of cases of diarrhoea were mild (69%) or moderate (25%) in severity and resulting treatment discontinuations (0.9% of all telithromycin-treated patients) were similar to pooled comparators (0.8%) and lower than for amoxicillin/clavulanic acid (2.4%).[90]

• In double-blind, comparative studies, there was no significant difference in QT effects for telithromycin versus clarithromycin or non-macrolide comparators, and no increase in the incidence of cardiovascular adverse events.[68]

• Consistent with this observation, single (800 to 2400mg) or repeated once daily (800mg) doses of telithromycin did not have any effect on the QT interval in healthy volunteers (n = 34) in a double-blind, placebo-controlled, crossover study.[91]

5. Drug Interactions

• Although it is a competitive inhibitor of CYP3A4, telithromycin did not form inhibitory complexes with CYP in hepatic microsomes *in vitro* since it is metabolised partially by this isoenzyme.[92] Ketoconazole and itraconazole (strong CYP3A4 inhibitors) have been shown to increase telithromycin AUC by 2 and 1.5 times, respectively.[93]

• As with macrolides, concomitant administration of telithromycin with drugs that are metabolised by CYP3A4 results in increased plasma concentrations of the latter, including cisapride, simvastatin and midazolam.[93]

• Coadministration of telithromycin with the CYP2D6 inhibitor paroxetine had no significant effect on the pharmacokinetic parameters of paroxetine.[94]

• Telithromycin 800mg once daily for 7 days did not affect the pharmacokinetics or pharmacodynamic action of warfarin 25mg when the 2 drugs were given concurrently to 24 healthy volunteers.[95]

• Similarly, telithromycin (800mg once daily on days 3 to 12 of the menstrual cycle) did not compromise the efficacy of low dose triphasic contraceptives containing ethinylestradiol/levonorgestrel in preventing ovulation in 38 women of childbearing potential. The pharmacokinetics of ethinylestradiol were not affected by concurrent telithromycin administration. Although plasma concentrations of levonorgestrel increased, this was not considered likely to affect contraceptive efficacy.[96]

• Coadministration of the gastric pH altering agents ranitidine or aluminium hydroxide/magnesium hydroxide had no effect on the bioavailability of telithromycin.[97]

6. Telithromycin: Current Status

Telithromycin, the first member of a new MLS_B antimicrobial family called ketolides, is currently awaiting registration in the US and Europe for the treatment of CAP, AECB, AMS and pharyngitis/tonsillitis. An adult intravenous and a paediatric formulation of telithromycin are also in development. The convenience of the short, once daily dosage regimen (5 days for AECB, AMS and pharyngitis/tonsillitis, and 7 to 10 days for CAP) and its activity against resistant pathogens (particularly penicillin- and/or macrolide-resistant pneumococci) make it a promising new empirical therapy for community-acquired RTIs.

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