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Telithromycin

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Contents

Abstract

▲ Telithromycin, the first member of the ketolide antibacterials, has good activity against community-acquired respiratory pathogens, including multiple-drug-resistant strains of *Streptococcus pneumoniae*.

▲ Telithromycin 800mg once daily has been US FDA approved for the treatment of acute bacterial sinusitis (ABS; treatment duration 5 days), acute bacterial exacerbations of chronic bronchitis (AECB; 5 days) and mild-to-moderate community-acquired pneumonia (CAP; 7–10 days).

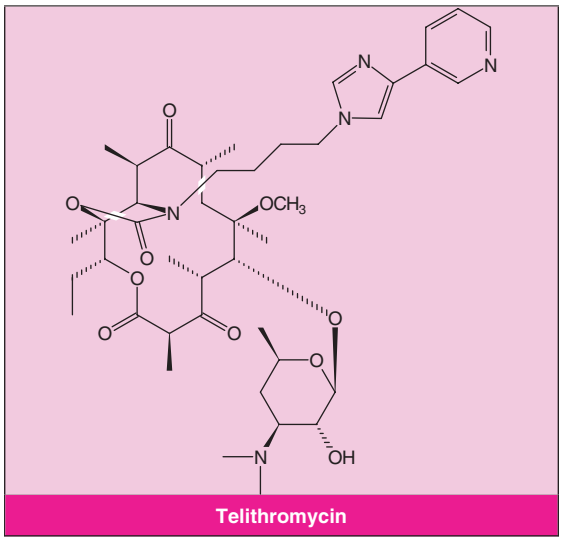
▲ In patients with CAP, telithromycin was as effective as amoxicillin 1000mg three times daily for 10 days, clarithromycin 500mg twice daily for 10 days or trovafloxacin 200mg once daily for 7–10 days.

▲ In patients with AECB, telithromycin was as effective as a 10-day regimen of amoxicillin/clavulanic acid 500/125mg three times daily, cefuroxime axetil 500mg twice daily or clarithromycin 500mg twice daily.

▲ In patients with ABS, telithromycin was as effective as a 10-day course of amoxicillin/clavulanic acid 500/125mg three times daily or cefuroxime axetil 250mg twice daily.

▲ Telithromycin was generally well tolerated and most adverse events were of mild-to-moderate severity and transitory. The most common adverse events with telithromycin were diarrhoea and nausea (10.8% and 7.9% of 2702 patients in clinical trials); these events occurred in 8.6% and 4.6% of 2139 comparator-treated patients.

Features and properties of telithromycin (Ketek®)	
Indications	
Acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, and mild-to-moderate community-acquired pneumonia	
Mechanism of action	
Ketolide antibacterial agent	Inhibition of bacterial ribosome assembly and protein synthesis
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 once daily for 7 days in healthy volunteers)	
Peak plasma concentration	2.27 μg/mL
Time to peak plasma concentration	1 hour
Terminal elimination half-life	9.8 hours
Adverse events	
Most frequent	Mild-to-moderate diarrhoea and nausea



Telithromycin (Ketek®)[1] is the first member of the ketolides (a new family of antibacterials structurally related to the macrolides) to be approved for clinical use. Ketolides are 14-membered-ring agents with a 3-keto group replacing the L-cladinose moiety of the macrolides, and a methoxy group replacing the hydroxy group at position 6. Telithromycin also has a cyclic carbamate linkage at C11/C12.[1,2] These changes confer effects on pharmacokinetic stability, spectrum of activity and potential for development of resistance (see sections 1 and 2).[3] Telithromycin was developed specifically for the treatment of community-acquired respiratory tract infections (RTIs).

The antibacterial activity of telithromycin, like that of the macrolides, is due to interaction with the 50S subunit of the bacterial ribosome, and subsequent inhibition of ribosome assembly and protein synthesis.[4] Telithromycin binds to domains II and V of the 23S rRNA of the 50S ribosomal subunit. The increased binding of telithromycin at domain II means activity is retained in the presence of methylase-mediated resistance (*erm* genes) that alter the domain V binding site of telithromycin.[5] Telithromycin binds ten times more tightly than erythromycin and six times more tightly than clarithromycin to wild-type ribosomes (attributed to the C11/C12 linkage).[6] Furthermore, for bacterial ribosomes with domain V modifications conferring MLS_B resistance, telithromycin binds 20 times more tightly than erythromycin or clarithromycin.[7] Thus, *in vitro*, telithromycin is active against multiple-drug-resistant strains of *Streptococcus pneumoniae* (MDRSP) [see section 1]. MDRSP include isolates known as penicillin-resistant *S. pneumoniae*, and are defined as isolates resistant to two or more of the following antimicrobials: penicillin, second-generation cephalosporins (e.g. cefuroxime), macrolides, tetracyclines, or trimethoprim/sulfamethoxazole.[5]

This review focuses on the use of telithromycin in patients with acute bacterial sinusitis (ABS), acute bacterial exacerbations of chronic bronchitis (AECB) or mild-to-moderate community-acquired pneumonia (CAP), indications the US FDA has approved.

1. Antibacterial Activity

This section focuses on the *in vitro* activity of telithromycin against the pathogens associated with community-acquired RTIs for which telithromycin has demonstrated clinical efficacy.

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 that were tested in cell culture). MIC_{50} and MIC_{90} values are the minimum concentrations required to inhibit growth of 50% and 90% of strains, respectively.

The MIC breakpoints indicating susceptibility, intermediate susceptibility and resistance to telithromycin are ≤1, 2 and ≥4 μg/mL for *S. pneumoniae*, and ≤4, 8 and ≥16 μg/mL for *Haemophilus influenzae*.[5] The MIC breakpoint indicating *Staphylococcus aureus* susceptibility to telithromycin is ≤0.25 μg/mL.[5]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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In Vitro Activity

Gram-Positive Bacteria

- Telithromycin showed good activity against *S. pneumoniae*, including MDRSP.[5] Telithromycin MIC_{90} values were low against strains of *S. pneumoniae* that were erythromycin susceptible (MIC_{90} ≤0.008–0.031 μg/mL),[8-20] penicillin resistant (0.25–1.0 μg/mL),[8,9,12,15,18,19,21] and/or erythromycin resistant (0.06–1.0 μg/mL).[8-17,19,21-26]
- The MIC_{90} for telithromycin against 10 103 *S. pneumoniae* isolates collected from the US during the first year (2000–2001) of the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) study was 0.5 μg/mL; 99.7% of isolates were susceptible to telithromycin. Telithromycin MIC_{90} values were in the susceptible range for penicillin- or erythromycin-resistant *S. pneumoniae* (≤1 μg/mL).[27]
- Of the 10 012 *S. pneumoniae* isolates collected from the US during the second year (2001–2) of the PROTEKT study, 3957 (39.5%) exhibited resistance to at least one of the antibacterials tested.[28] Furthermore, of these resistant isolates, approximately 75% were resistant to multiple drugs, with drug resistance to four agents being the most common (30% of MDRSP). However, telithromycin was highly active against MDRSP; >99.5% of isolates exhibiting resistance to two or more antibacterials were susceptible to telithromycin at ≤1 μg/mL.[28]
- Telithromycin has also shown activity against methicillin/oxacillin-susceptible *S. aureus* (MIC_{90} values ≤0.25 μg/mL).[29-31]

Gram-Negative Bacteria

- MIC_{90} values for telithromycin against *H. influenzae* ranged from 2 to 8 μg/mL,[18-20,23,26,29,32-35] with 9 of 11 studies reporting MIC_{90} values of 4 μg/mL (susceptibility),[18-20,23,26,27,29,32,34] including the US results from the first year of the PROTEKT study which collected 2706 isolates.[27] MIC values were unaffected by β-lactamase production or ampicillin resistance.[18,23,26,27,29]
- Telithromycin was highly active against *Moraxella catarrhalis* isolates, with MIC_{90} values ranging from 0.03 to 0.125 μg/mL.[18,19,26,30-32,34,36] Telithromycin retained activity against *M. catarrhalis* isolates irrespective of β-lactamase production (*bro*-1 or *bro*-2 genotype).[18,23]

Atypical and Intracellular Organisms

- Telithromycin was active against *Mycoplasma pneumoniae* (MIC_{90} ≤0.015 μg/mL) and *Chlamydophila* (previously *Chlamydia*) *pneumoniae* (MIC_{90} ≤0.25 μg/mL) in a number of *in vitro* studies.[37-41]

Post-Antibiotic Effect

- Telithromycin exhibited a significant and concentration-dependent *in vitro* post-antibiotic effect (PAE; >0.5 hours) against most community-acquired respiratory tract pathogens.[42-45] At 4 and 10 × MIC, telithromycin showed PAEs of 0.8–7.0 and 2.2–8.2 hours against *S. pneumoniae*, *S. aureus*, *H. influenzae* and *M. catarrhalis*.[43]

Resistance Issues

The most common mechanisms of macrolide resistance in gram-positive cocci are *mef*-encoded macrolide/drug efflux or *erm*-encoded ribosomal methylation (MLS_B resistance; i.e. modification of the binding site, thus preventing binding of the drug to the ribosome); *erm* genes can be expressed constitutively or inducibly.[46] Telithromycin does not induce resistance through methylase gene expression in bacteria inducibly resistant to erythromycin because of the 3-keto group in place of the L-cladinose moiety of erythromycin.[47]

- Telithromycin remains active against most erythromycin-resistant strains of *S. pneumoniae* regardless of their expression of *erm* (inducible or constitutive) or *mef* resistance determinants.[11,12,14,17,22-25,48-50]
- Telithromycin selected for resistant mutants less frequently than azithromycin, clarithromycin, erythromycin, roxithromycin, clindamycin or pristinamycin after up to 50 passages of five macrolide-

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susceptible and six macrolide-resistant [containing *mef*(A) or *erm*(B) genes] *S. pneumoniae* strains through sub-inhibitory concentrations.[51] Only three mutants resistant to telithromycin (MIC ≥4 μg/mL) emerged, all of which had MICs ≤8 μg/mL.[51]

2. Pharmacokinetic Properties

Absorption and Distribution

- Telithromycin lacks the L-cladinose moiety common to the macrolides, and has a 3-keto group in its place; this, along with methylation of the 6-hydroxy group, offers improved stability in acidic environments by preventing internal hemiketalisation.[52]
- The absolute bioavailability of single-dose oral telithromycin 800mg was 57% in both young (aged 18–40 years) and elderly (aged 65–85 years) patients.[53] Food or gastric pH do not affect the bioavailability of the drug.[54,55]
- Administration of telithromycin 800mg once daily for 7 days to 15 healthy volunteers produced a mean peak plasma concentration (C_{max}) of 2.27 μg/mL at a median 1 hour post-dose at steady state; steady-state concentrations of telithromycin were reached after 2–3 days of repeated administration; the area under the 24-hour plasma concentration-time curve (AUC_{24}) was 12.5 μg • h/mL.[56]
- Telithromycin 800mg once daily for 5 days produced high concentrations of the drug in bronchopulmonary tissue and fluid.[36,57-59] Concentrations at these sites remained above telithromycin MICs for most pathogens throughout the 24-hour administration period. Bronchopulmonary tissue or fluid to plasma ratios 2–24 hours after the last dose of telithromycin were 55–540 for alveolar macrophages, 8.5–14.41 for epithelial lining fluid and 2.11–12.11 for bronchial mucosa.[59]
- Concentrations of telithromycin in the mucous membrane of the paranasal sinuses in 26 patients undergoing otorhinolaryngological procedures were 4-fold higher than corresponding plasma concentrations 3–6 hours after administration of telithromycin 600mg.[60]
- After a single oral dose of telithromycin 600mg to healthy volunteers with cantharidin-induced skin blisters, the geometric mean blister fluid to plasma AUC_{24} ratio was 1.38, indicating good extracellular exposure (most RTI pathogens are located extracellularly).[61]
- The concentration of telithromycin in white blood cells exceeds that in plasma, and the drug is eliminated more slowly from white blood cells than from plasma. After administration of a single dose of telithromycin 600mg to healthy volunteers, the mean concentration of telithromycin in white blood cells was 44-fold higher than the corresponding mean plasma concentration; this increased to 705-fold 24 hours post-dose.[62] During administration of telithromycin 600mg once daily for 10 days, the mean telithromycin concentration in white blood cells peaked at 72.1 μg/mL 6 hours post-dose on day 5, and was 14.1 μg/mL 24 hours post-dose on day 5; 48 hours after the last dose on day 10, the mean telithromycin concentration in white blood cells was 8.9 μg/mL.[62]
- Telithromycin was preferentially taken up by polymorphonuclear neutrophils, in which concentrations were 197- to 300-fold higher than extracellular concentrations, in two *in vitro* studies.[63,64] In one study, telithromycin accumulated mainly within azurophil granules and was slowly released (80% of the drug was cell associated after 2 hours in fresh medium), suggesting that telithromycin will be effectively delivered to bacteria phagocytosed within these cells. In contrast, the macrolides erythromycin, clarithromycin, azithromycin and roxithromycin did not exhibit cell specificity (they were internalised within different cell types, such as neutrophils, monocytes and lymphocytes) and, except for azithromycin, were released quickly.[63]

Metabolism and Elimination

- Telithromycin circulates in the plasma mainly (57%) in unchanged form. About 70% (33% presys-

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temic and 37% systemic) of an orally administered dose is metabolised approximately equally by cytochrome P450 (CYP) 3A4 and non-CYP3A4 isoenzymes to form four major metabolites; one of the metabolites, an *N*-oxide pyridine derivative, has antibacterial activity that is one-quarter to one-sixteenth that of telithromycin.[65]

- Of the 57% of the administered dose that reaches the systemic circulation as unchanged drug, 7% is excreted unchanged in the faeces, 13% is excreted unchanged in the urine and 37% is metabolised by the liver.[65]
- At steady state, the elimination half-life ($t_{1/2}$) of telithromycin in healthy volunteers was 9.8 hours, and renal clearance was 12.5 L/h.[56]

Special Patient Populations

- The pharmacokinetics of telithromycin in elderly patients with RTIs and in patients with mild-to-severe hepatic impairment or mild-to-moderate renal impairment were only modestly different to those in young and/or healthy volunteers; dosage adjustments in these patient groups are not considered necessary.[65-68] Similarly, there were no significant differences between males or females in mean C_{max}, AUC and $t_{1/2}$ after single or multiple doses of telithromycin 800mg.[5]
- In patients with severe renal impairment (creatinine clearance <30 mL/min [1.8 L/h]) who received once-daily telithromycin 800mg for 5 days, mean steady-state C_{max} and AUC_{24} were 1.4- and 1.9-fold higher than in healthy volunteers;[68] renal excretion may serve as a compensatory elimination pathway when metabolic clearance is impaired. The dosage of telithromycin in patients with severe renal impairment has not been established.[5]

Drug Interactions

Telithromycin is an inhibitor of the CYP3A4 system; therefore, coadministration of telithromycin with a drug that is primarily metabolised by CYP3A4 isoenzymes (e.g. cisapride, pimozide, simvastatin and midazolam) may increase plasma concentrations of the coadministered drug.[65]

- Coadministration of telithromycin and cisapride resulted in a 95% increase in steady-state cisapride C_{max}, as well as significant increases in the corrected QT (QTc) interval; thus, coadministration of these two drugs is contraindicated.[5] Coadministration of telithromycin and pimozide is also contraindicated because of the potential risk of increased plasma concentrations of pimozide.[5]
- Concomitant administration of telithromycin with simvastatin (an HMG-CoA reductase inhibitor) resulted in 5.3- and 8.9-fold increases in simvastatin C_{max} and AUC. Administration of the two drugs 12 hours apart resulted in 3.4- and 4.0-fold increases in simvastatin C_{max} and AUC. A similar interaction is possible with lovastatin or atorvastatin, but not with pravastatin or fluvastatin. Treatment with simvastatin, lovastatin or atorvastatin should be suspended during telithromycin therapy.[5]
- Similarly, the AUCs of intravenous or oral midazolam (a benzodiazepine) increased 2- and 6-fold, respectively, after coadministration with telithromycin.[65] Caution is recommended when administering telithromycin with benzodiazepines, which are metabolised by CYP3A4 and undergo a high first-pass effect.[5]
- Coadministration of telithromycin with digoxin in healthy volunteers increased the C_{max} and the trough plasma concentration (C_{min}) of digoxin by 73% and 21%; C_{min} of digoxin ranged from 0.74 to 2.17 ng/mL. Although there were no significant changes in ECG parameters and no signs of digoxin toxicity, the monitoring of digoxin adverse effects or plasma concentrations is recommended during coadministration with telithromycin.[5,69]
- The C_{max} and AUC of metoprolol (a CYP2D6 substrate) increased by approximately 38% after coadministration with telithromycin, although the $t_{1/2}$ of metoprolol was not affected. This increase in metoprolol exposure may be of clinical significance in patients being treated with the drug for heart failure; as such, it is recommended that concomitant

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administration of telithromycin and metoprolol in patients with heart failure should be considered with caution.[5]

- Steady-state C_{max} and AUC values of theophylline were increased by approximately 16% and 17% when it was coadministered with telithromycin. However, because coadministration of theophylline with telithromycin may worsen gastrointestinal adverse events, it is recommended that the two drugs be administered 1 hour apart to decrease the likelihood of these events.[5]
- Telithromycin had no clinically significant effect on the pharmacokinetics of paroxetine or low-dose triphasic oral contraceptives containing ethinylestradiol/levonorgestrel.[70,71] Coadministration of ketoconazole, and to a lesser extent itraconazole, modestly increased telithromycin exposure in healthy volunteers; however, there were no clinically significant treatment-related changes in the QTc interval.[72]

3. Therapeutic Efficacy

The therapeutic efficacy of telithromycin 800mg once daily in adults with ABS, AECB or mild-to-moderate CAP has been evaluated in numerous randomised, multicentre trials.[65,73-85] All comparative studies were double-blind.[73-76,80-85] Most of the studies have been fully published,[73,74,76,77,79-81,83-85] whereas three have been presented as abstracts and/or posters.[75,78,82] Some additional data have been taken from an FDA briefing document,[65] including results from one of the noncomparative CAP studies.

The primary endpoint in most studies was clinical outcome (clinical cure was defined as a return to the pre-infection state or improved with post-infectious stigmata) in the per-protocol (PPc) population at the test-of-cure (TOC) visit (day 17–24).[73-76,78-85] In one study,[77] the primary endpoint was the bacteriological eradication rate at the TOC visit (days 17–24). Satisfactory bacteriological outcome was defined as the eradication or presumed eradication of the baseline pathogen at the TOC visit in bacteriologically evaluable per-protocol patients (PPb population). Unless otherwise stated, clinical cure rates presented in this section are from the PPc populations, and bacteriological outcomes are from the PPb populations. However, some studies also reported data from the modified intent-to-treat population (mITT); where possible, these data have been included.

Community-Acquired Pneumonia

The efficacy of telithromycin 800mg for 7–10 days has been evaluated in a total of 1925 patients (PPc population) with a radiologically confirmed diagnosis of CAP in four well controlled, comparative trials[73-76] and four noncomparative studies.[65,77-79]

- A 7–10 day regimen of telithromycin was as effective as amoxicillin 1000mg three times daily for 10 days (clinical cure rates of 94.6% vs 90.1%),[73] clarithromycin 500mg twice daily for 10 days (88.3% vs 88.5%[74] and 88.8% vs 91.8%[75]) or trovafloxacin 200mg once daily for 7–10 days (90.0% vs 94.2%).[76] In the mITT populations, clinical success rates of 85.9% (171/199) versus 78.5% (161/205) were achieved with telithromycin and high-dose amoxicillin,[73] 78.9% (161/204) versus 80.7% (171/212)[74] and 82.2% (157/191) versus 81.2% (147/181)[65,75] with telithromycin and clarithromycin, and 82.0% (82/100) versus 85.6% (89/104) with telithromycin and trovafloxacin;[76] the between-group differences were not significantly different.[65,73-76]
- Clinical cure rates based on pooled data from the four comparative studies were similar for the telithromycin and comparator treatment regimens. Overall, a total of 499/552 (90.4%) patients in the telithromycin group achieved clinical cure at the TOC visit compared with 490/540 (90.7%) comparator-treated patients (figure 1).[73-76]
- A satisfactory bacteriological outcome was achieved in 80.0–92.9% of patients who received telithromycin compared with 83.3–100% of patients

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who received amoxicillin, clarithromycin or trovafloxacin.[73-76]

- Clinical cure rates by pathogen across the four comparative studies were 93.6% (73/78) for *S. pneumoniae*, 83.0% (39/47) for *H. influenzae*, 85.7% (12/14) for *M. catarrhalis*, 92.0% (23/25) for *C. pneumoniae*, and 95.7% (22/23) for *M. pneumoniae* in telithromycin-treated patients.[5]
- Telithromycin for 7 or 7–10 days was effective in the treatment of patients (n = 1214) with CAP in the four noncomparative studies (clinical cure rates of 89.6–93.6%).[65,77-79] In published studies, a satisfactory bacteriological outcome was reported in 88.9–91.9% of patients (n = 262),[77-79] with pathogen eradication rates of 82.7%[79] and 93.0%.[77]
- Furthermore, telithromycin was effective in patients with CAP caused by MDRSP in controlled and uncontrolled trials; 33 of 36 evaluable patients with CAP due to MDRSP achieved clinical success.[5] Clinical cure rates with telithromycin were high in patients with *S. pneumoniae* resistant to penicillin (86.9% [20/23]), second-generation cephalosporins (90.9% [20/22]), macrolides (89.3% [25/28]), trimethoprim/sulfamethoxazole (88.9% [24/27)] and/or tetracyclines (84.6% [11/13]).[5]

Acute Bacterial Exacerbations of Chronic Bronchitis

Telithromycin 800mg once daily for 5 days has been evaluated in 480 patients (PPc population) with AECB in three well controlled comparative trials.[80-82] A clinical diagnosis of AECB was based on Anthonisen criteria (i.e. increased cough and/or dyspnoea, increased sputum production and increased sputum purulence).

- A 5-day course of once-daily telithromycin was as effective as a 10-day regimen of amoxicillin/clavulanic acid 500/125mg three times daily in treating adult patients with AECB.[80] Clinical cure rates for telithromycin and amoxicillin/clavulanic acid were 86.1% (99/115) and 82.1% (92/112), respectively, and a satisfactory bacteriological outcome was achieved in 69.2% (27/39) and 70.0% (21/30) of patients, respectively; 76.2% versus 81.3% of pathogens were eradicated. Among the mITT population, clinical success rates of 81.3% (130/160) and 78.1% (125/160) were achieved with telithromycin and amoxicillin/clavulanic acid, respectively.[80]

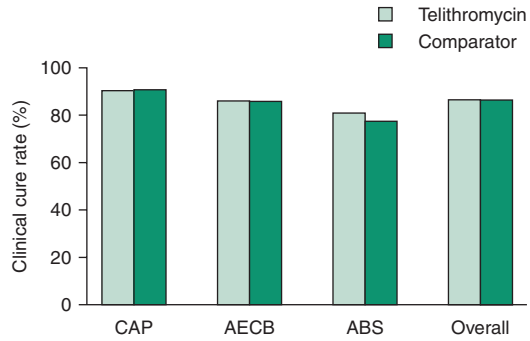

Fig. 1. Therapeutic efficacy of telithromycin. Pooled results from nine randomised, double-blind, active-comparator controlled, multicentre trials in patients with acute bacterial sinusitis (ABS),[84,85] acute bacterial exacerbations of chronic bronchitis (AECB)[80-82] or mild-to-moderate community-acquired pneumonia (CAP)[73-76] who received telithromycin 800mg once daily for 5 (AECB and ABS) or 7–10 (CAP) days or an active comparator. Comparator drugs in CAP trials were amoxicillin 1000mg three times daily for 10 days, clarithromycin (CLA) 500mg twice daily for 10 days or trovafloxacin 200mg once daily for 7–10 days. In AECB trials, comparators were 10-day regimens of amoxicillin/clavulanic acid (AMC) 500/125mg three times daily, cefuroxime axetil (CXM) 500mg twice daily, or CLA 500mg twice daily. In ABS trials, comparators were 10-day regimens of AMC 500/125mg three times daily or CXM 250mg twice daily. Clinical cure was defined as a return to the pre-infection state or improvement with post-infectious stigmata at the test-of-cure visit (day 17–24) in the per-protocol population.

- Similarly, a 5-day regimen of telithromycin was as effective as a 10-day regimen of cefuroxime axetil 500mg twice daily in treating adult patients with AECB.[81] Of the 140 and 142 patients treated with telithromycin or cefuroxime axetil, 86.4% and 83.1%, respectively, achieved clinical cure, and a satisfactory bacteriological outcome was achieved in 76.0% (19/25) and 78.6% (22/28) of patients (78.6% and 75.0% of pathogens were eradicated). Clinical success rates in the telithromycin and cefuroxime axetil mITT populations were 78.0% (142/182) and 72.3% (138/191), respectively.
- A 5-day course of once-daily telithromycin was also as effective as a 10-day course of clarithromycin 500mg twice daily. Clinical cure was

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achieved in 85.8% (193/225) and 89.2% (206/231) of telithromycin and clarithromycin recipients, respectively; bacteriological outcome is yet to be reported.[82]

- Clinical cure rates based on pooled data from the three comparative studies were similar for the telithromycin (86.0%; 413/480) and comparator (85.8%; 416/485) treatment regimens (figure 1).[80-82]
- Clinical cure rates by pathogen in telithromycin-treated patients across the three studies were 81.5% (22/27) for *S. pneumoniae*, 73.3% (44/60) for *H. influenzae* and 93.1% (27/29) for *M. catarrhalis*.[65]

Acute Bacterial Sinusitis

Telithromycin 800mg once daily for 5 days has been compared with an active comparator in two well designed studies[84,85] or with telithromycin 800mg once daily for 10 days in a third study in patients with ABS.[83]

- Five- and 10-day regimens of telithromycin were equally effective in the treatment of adult patients with ABS (confirmed via clinical signs and symptoms and sinus radiograph showing total opacity or air-fluid level) of <1 month's duration.[83] A clinical cure rate of 91% was achieved with the 5- or 10-day regimens, and a satisfactory bacteriological outcome was achieved in 92.9% (65/70) and 89.9% (62/69) of patients, respectively. In the mITT population, clinical success rates of 82.6% (138/167) and 87.5% (147/168) were achieved with the 5- and 10-day regimens, respectively.
- Telithromycin for 5 days was as effective as a 10-day regimen of amoxicillin/clavulanic acid 500/125mg three times daily in patients with ABS of <28 days' duration.[84] Clinical cure rates for telithromycin (75.3%; 110/146) and amoxicillin/clavulanic acid (74.5%; 102/137) were similar. A satisfactory bacteriological outcome was achieved in 6/7 and 8/10 patients, respectively.
- Telithromycin for 5 days was as effective as cefuroxime axetil 250mg twice daily for 10 days in the treatment of patients with ABS.[85] Clinical cure rates for telithromycin and cefuroxime axetil were 85.2% (161/189) and 82.0% (73/89), respectively; the proportion of patients with satisfactory bacteriological outcome was 84.0% (84/100) and 79.6% (39/49), respectively, and eradication rates of 84.8% (112/132) and 82.0% (50/61) were achieved. In the mITT population, clinical cure rates were 80.4% (193/240) for telithromycin and 72.4% (84/116) for cefuroxime axetil.[85]
- Pooled clinical cure rates from the studies comparing telithromycin with amoxicillin/clavulanic acid or cefuroxime axetil were 80.9% (271/335) in the telithromycin group and 77.4% (175/226) in the comparator group (figure 1).[84,85]
- Clinical cure rates by pathogen in telithromycin recipients across the two active comparator studies were 87.1% (27/31) for *S. pneumoniae*, 82.4% (28/34) for *H. influenzae*, 7/7 for *M. catarrhalis* and 8/8 for *S. aureus*.[5]

4. Tolerability

- Telithromycin 800mg once daily for up to 10 days was generally well tolerated, and most adverse events were mild to moderate in severity and transitory; gastrointestinal events were the most common adverse events associated with telithromycin treatment.[65]
- The safety profile of telithromycin was evaluated in all phase III clinical trials. In controlled phase III trials, 49.9% of patients treated with telithromycin (n = 2702) experienced at least one treatment-emergent adverse event compared with 48.4% of those treated with a comparator (n = 2139); adverse events possibly related to treatment occurred in 31.9% of telithromycin recipients compared with 28.3% of comparator recipients (comparators were amoxicillin, amoxicillin/clavulanic acid, cefuroxime axetil, clarithromycin, phenoxymethylpenicillin [penicillin VK] and trovafloxacin).[65]
- The most common treatment-related adverse events in patients who received telithromycin or a comparator were diarrhoea (10.8% vs 8.6%), nausea

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(7.9% vs 4.6%), headache (5.5% vs 5.8%), dizziness (3.7% vs 2.7%), vomiting (2.9% vs 2.2%), loose stools (2.3% vs 1.5%) and dysgeusia (1.6% vs 3.6%) [statistical analysis not reported].[5] The majority of adverse events were mild to moderate in severity; 4.4% of telithromycin recipients discontinued treatment because of adverse events compared with 4.3% of comparator-treated patients, with most discontinuations attributable to gastrointestinal adverse events, primarily diarrhoea (0.9% vs 0.7%) and nausea (0.7% vs 0.5%).[5,65]

- Telithromycin may cause visual disturbances in some patients, particularly in slowing the ability to accommodate and the ability to release accommodation.[5] In clinical trials, visual disturbances included blurred vision, difficulty focusing and diplopia, and occurred more frequently with telithromycin (1.1%) than with the comparators (0.28%). Most events were mild to moderate in severity, and all were transitory.[5]
- Telithromycin has the potential to prolong the QTc interval in some patients. However, there was no cardiovascular morbidity or mortality attributable to QTc prolongation in 4780 patients in clinical trials, including 204 patients with a prolonged QTc at baseline.[5]
- Telithromycin has been associated with exacerbations of myasthenia gravis and is not recommended in patients with myasthenia gravis unless other therapeutic options are unavailable. If no other therapeutic options are available, patients with myasthenia gravis receiving telithromycin should be monitored closely.[5] Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has also been reported with telithromycin use; however, these events are generally reversible.[5]

5. Dosage and Administration

In the US, the recommended dosage of telithromycin in patients with mild-to-moderate CAP is 800mg once daily for 7–10 days; in patients with AECB or ABS, the recommended dosage is 800mg once daily for 5 days.[5]

The use of telithromycin in pregnant women has not been studied; therefore, telithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In addition, because telithromycin may be excreted in human breast milk, caution should be used when the drug is administered to a nursing woman.[5]

6. Telithromycin: Current Status

Telithromycin has recently been approved by the FDA for the treatment of adult patients with ABS, AECB, or mild-to-moderate CAP. It has demonstrated good efficacy in these indications in controlled trials and is generally well tolerated, with most adverse events being of mild-to-moderate intensity and transitory.

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