# National PBM Drug Monograph
# Telithromycin (Ketek™)
### VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

## Executive Summary

**FDA-approved Indication**: Telithromycin is the first agent in a new class of antibiotics known as the ketolides. It is used for the treatment of acute exacerbation of chronic bronchitis (AECB); acute bacterial sinusitis (ABS); and mild to moderate community-acquired pneumonia (CAP), including those infections caused by multi-drug resistant *Streptococcus pneumoniae*, in patients age 18 and older.

**Spectrum of activity:** The majority of community –acquired respiratory tract infections (CARTIs) are caused by *S. pneumoniae, H. influenzae, and M. catarrhalis*. Telithromycin covers these pathogens including penicillin and /or erythromycin resistant strains. Telithromycin also has activity against atypical pathogens such as *C. pneumonia* and *M. pneumoniae.*

**Efficacy**: There are 10 published trials evaluating telithromycin against a comparator in the treatment of AECB, CAP and ABS. Telithromycin was found to be equivalent to the comparator.

| AECB | CAP | ABS |
|---|---|---|
| Telithromycin 800mg QD x 5 days<br>Cefuroxime 500mg BID x 10 days | Telithromycin 800mg QD x 10 days<br>Amoxicillin 1000mg TID x 10 days | Telithromycin 800mg QD x 5 days<br>Telithromycin 800mg QD x 10 days |
| Telithromycin 800mg QD x 5 days<br>Amox/clav 500mg/125mg TID x 10 days | Telithromycin 800mg QD x 10 days<br>Clarithromycin 500mg BID x 10 days | Telithromycin 800mg QD x 5 days<br>Cefuroxime 250mg BID x 10 days |
| | Telithromycin 800mg QD x 7 -10 days<br>Trovafloxacin 200mg QD x 7-10 days | Telithromycin 800mg QD x 5 days<br>Telithromycin 800mg QD x 10 days<br>Amox/clav 500mg/125mg TID x 10 days |
| | Telithromycin 800mg QD x 5 days<br>Telithromycin 800mg QD x 7 days<br>Clarithromycin 500mg BID x 10 days | Telithromycin 800mg QD x 5 days<br>Moxifloxacin 400mg QD x 10 days |

**Safety:** Commonly reported adverse events during clinical trials include diarrhea, nausea, headache, and dizziness.

During Phase III trials, treatment emergent visual disturbances (difficulty with accommodation) were reported in 1.1% (30/2702) of patients receiving telithromycin compared to 0.28% (6/2139) of patients receiving comparator therapies. The majority of events occurred following the first or second dose (65%). These events lasted several hours and recurred with subsequent dosing in some patients. Females under 40 years of age had the highest incidence of reported events.

Avoid use in patients with myasthenia gravis. There have been 13 patients with exacerbation of myasthenia gravis considered likely to be due to telithromycin and 6 cases possibly related to telithromycin.

Based on the available information, the risk of QTc-interval prolongation and adverse hepatic events appears to be similar to the macrolides.

Telithromycin inhibits the CYP3A4 isoenzyme. Co-administration of telithromycin and pimozide or cisapride is contraindicated; temporary discontinuation of simvastatin, lovastatin, and atorvastatin is recommended. Drugs which cannot be temporarily discontinued may require dosage adjustment.

**Dosing**: The dose of telithromycin is 800mg (400mg tablets x 2) once daily for 5 days for the treatment of AECB, ABS. It should be administered for 7-10days for the treatment of CAP. Telithromycin may be administered without regard to meals.

**Conclusion**: The place in therapy of telithromycin is similar to that of the **appropriate use** of respiratory quinolones. Both are active against organisms commonly responsible for CARTIs, including multi-drug resistant *S. pneumoniae* and the atypical pathogens. Unlike the quinolones, telithromycin is not active against *Klebsiella pneumoniae*. The respiratory quinolones have a broader spectrum of activity, which may potentially increase the risk of developing resistance in nonrespiratory pathogens. Telithromycin and the respiratory quinolones are dosed once daily. The recommended duration of therapy for CAP and ABS is shorter with telithromycin. Factors such as adverse events and drug interactions need to be considered when selecting an antibiotic. The cost of telithromycin is approximately 2.5-4.8 times greater than gatifloxacin/moxifloxacin.

**Recommendation:** In order to keep telithromycin as a viable treatment option against multi-drug resistant *S. pneumoniae*, it is important that it is not misused or overused. Telithromycin should not be added to the National Formulary; however, VISNs should be allowed to add to their VISN formulary.

## INTRODUCTION

Telithromycin was approved on April 2, 2004 for the treatment of acute exacerbation of chronic bronchitis (AECB); acute bacterial sinusitis (ABS); and mild to moderate community-acquired pneumonia (CAP), including those infections caused by multi-drug resistant *Streptococcus pneumoniae*, in patients age 18 and older. Telithromycin is the first agent in a new class of antibiotics known as the ketolides.

**Table 1. FDA-approved indications**

| | |
|---|---|
| Acute exacerbation of chronic bronchitis | *Streptococcus pneumoniae*, Haemophilus influenzae, Moraxella catarrhalis* |
| Acute bacterial sinusitis | *Streptococcus pneumoniae*, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus* |
| Mild-moderate community-acquired pneumonia | *Streptococcus pneumoniae*, Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae, Mycoplasma pneumoniae* |

*Includes multi-drug resistant isolates

## PHARMACOKINETICS

The phamacokinetics in healthy adults are shown in table 2. In a study of 219 patients taking telithromycin 800mg once daily, the mean peak and trough obtained after 3-5 days were 2.9 ± 1.55 and 0.2 ± 0.22mcg/ml respectively. [1]

**Table 2. Pharmacokinetics in healthy adults**

| | |
|---|---|
| Bioavailability | 57% |
| Maximum concentration (Cmax) | 2 ± 0.8 mcg/mL (single dose); 2.27 ± 0.71mcg/ml (multiple dose) |
| Time to maximum concentration (Tmax) | 1hr (0.5-4) (single dose); 1hr (0.5-3) (multiple dose) |
| Half-life (t1/2) | 7.16 ± 1.37hr (single dose); 9.81 ± 1.9hr (multiple dose) |
| Trough concentration ($C_{24}$) | 0.03 ± 0.13mcg/ml (single dose); 0.07 ± 0.051mcg/ml (multiple dose) |
| Area under the curve ($AUC_{0-24}$) | 8.25 ± 2.6 mcg·h/ml (single dose); 12.5 ± 5.4 mcg·h/ml (multiple dose) |
| Volume of distribution (Vd) | 2.9L/kg (after IV dose) |
| Protein binding | 60-70% mainly to albumin |
| Metabolism | 50% CYP3A4 and 50% CYP450 independent<br>There are 4 metabolites; only 1 had antibacterial activity which was 4-10-fold less than the parent compound |
| Elimination | 7% is excreted unchanged in the feces, 13% excreted unchanged in the urine, 37% metabolized by the liver |

Telithromycin distributes well into bronchial mucosa, epithelial lining fluid, and alveolar macrophages with tissue concentrations exceeding plasma concentration.

## MECHANISM OF ACTION

Like the macrolides, telithromycin prevents protein synthesis by inhibiting translation of bacterial mRNA via binding to domains II and V of 23S rRNA of the 50S ribosomal subunit. The primary binding site is domain V, which is also the site susceptible to modification rendering the bacteria resistance to macrolides. Macrolides and ketolides also bind to domain II. Telithromycin differs from macrolides in that it binds more tightly to position A752 in domain II. This allows telithromycin to remain on the ribosome of those bacteria that have had their domain V binding site modified by methylases (*erm* genes).[2-4]

## RESISTANCE

The 2 most common mechanisms of gram-positive bacterial resistance to macrolides are by *mef* -encoded efflux or $MLS_B$ resistance (*erm*-encoded methylation).Telithromycin remains active against strains expressing *mef*-encoded efflux. *Erm*-encoded methylation occurs on domain V of 23S rRNA, which can be constitutive or inducible, prevents proper biding of macrolides or ketolides to domain V. Telithromycin does not induce methylase production; therefore, it remains active against bacterial strains with inducible $MLS_B$ resistance. Constitutively resistant bacteria (*S. aureus* and *S. pyogenes*) are resistant to telithromycin; however, *most S. pneumoniae* strains constitutively expressing the *ermB* gene are susceptible to telithromycin. [2, 3]

## IN VITRO SUSCEPTIBILITY

The following susceptibility break points have been determined for telithromycin.

**Table 3. Telithromycin susceptibility breakpoints**

| | Minimum Inhibitory Concentrations (mcg/mL) | | | Disk Diffusion (zone diameters in mm) | | |
|---|---|---|---|---|---|---|
| | S | I | R | S | I | R |
| *S. aureus** | ≤ 0.25 | | | ≥ 22 | | |
| *S. pneumoniae* | ≤ 1 | 2 | ≥ 4 | ≥ 19 | 16-18 | ≤ 15 |
| *H. influenzae* | ≤ 4 | 8 | ≥ 16 | ≥ 15 | 12-14 | ≤ 11 |

*methicillin and erythromycin susceptible isolates only

There are *in vitro* and clinical data that support the use of telithromycin in respiratory infections due to *Moraxella catarrhalis, Chlamydophila pneumoniae, Mycoplasma pneumoniae.* There are *in vitro* data for the following organisms, but their clinical significance is unknown: *Streptococcus pyogenes* (erythromycin susceptible isolates only), *streptococci* (Lancefield groups C and G), viridans group streptococci, *Prevotella bivia, Prevotella intermedia, peptostreptococcus* spp., *Legionella pneumophila*.[1]

The global surveillance program PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) was established to monitor susceptibility of specific respiratory tract bacterial organisms to telithromycin, macrolides, β-lactams, and quinolones. Data for U.S. isolates are presented; results for international isolates can be found elsewhere. Distribution of resistance in the U.S. varied by geographic region, culture site, and patient age. Readers are asked to refer to the original publications for further information.[5-8]

***Streptococcus pneumoniae***

Among the 10,103 *S. pneumoniae* isolates tested during 2000-2001, 26.4% were resistant to penicillin (MIC≥2mg/L), 12.5% were intermediately susceptible to penicillin (MIC 0.12-1mg/L), 31% were resistant to erythromycin, and 20.3% were resistant to both penicillin and erythromycin. Seventy-two percent of macrolide resistance was due to the *mef*(A) genotype, while 28% exhibited the $MLS_B$ genotype. Penicillin-sensitive *S. pneumoniae* remained susceptible to clindamycin (98%), macrolides (93%), tetracycline (96.8%) and co-trimoxazole (85.2%); however, susceptibility to penicillin-resistant strains was variable ranging as low as 7% with co-trimoxazole to 77% with clindamycin. The susceptibility rate of telithromycin to penicillin-resistant strains was 98.8%. Of the strains that were both penicillin and erythromycin resistant, 98.5% were susceptible to telithromycin, similar to that of gatifloxacin and levofloxacin.[5]

Of the 10,012 isolates during 2001-2002, 21.2% of isolates were penicillin-resistant, 14.2% were intermediately susceptible to penicillin, 27.9% were resistant to erythromycin, and 17% were resistant to both penicillin and erythromycin. The susceptibility rate of telithromycin to penicillin-intermediate and penicillin-resistant strains was 99.9% and 99.4% respectively. The susceptibility of other antimicrobials to penicillin-resistant strains was variable ranging as low as 8.1% with co-trimoxazole to 98% with gatifloxacin (table 4).[6, 7]

**Table 4. *S. pneumoniae* susceptibility 2001-2002**

| | # Isolates | $MIC_{90}$ (range) | % S to telithromycin | % Susceptible to other antimicrobials tested |
|---|---|---|---|---|
| All isolates | 10,012 | 0.25 (≤0.015- 4) | 99.9% | Levofloxacin (98.8%), gatifloxacin (98.9%), amox/clav (93%), clindamycin (91.5%), TCN (84.9%), cefuroxime (74.1%), macrolides (72%), co-trimoxazole (65.2%) |
| Penicillin-intermediate | 1424 | 0.25 (≤0.015–2) | 99.9% | Amox/clav (99.9%), gatifloxacin (97.9%), levofloxacin (97.8%), clindamycin (86.9%), TCN (77.2%), cefuroxime (67%), macrolides (50.2%), co-trimoxazole (48%) |
| Penicillin-resistant | 2124 | 0.5 (≤0.015- 4) | 99.4% | Levofloxacin (97.8%), gatifloxacin (98.1%), clindamycin (74.7%), amox/clav (67.1%), TCN (52.6%), macrolides (19.6%), co-trimoxazole (8.1%), cefuroxime (0.1%) |
| Penicillin-resistant and erythromycin-resistant | 1709 | 0.5 (≤0.015- 4) | 99.3% | Levofloxacin (97.4%), gatifloxacin (97.7%), clindamycin (68.6%), amox/clav (63.8%), TCN (42.5%), co-trimoxazole (2.5%), cefuroxime (0.2%) |

The susceptibility rate of telithromycin to erythromycin-resistant strains was 99.5%. Susceptibility to telithromycin and other antibiotics, broken down by mechanism of macrolide resistance, is presented in table 5. Of the strains that were both penicillin and erythromycin resistant, 99.3% were susceptible to

telithromycin, similar to gatifloxacin (97.7%) and levofloxacin (97.4%). One percent of isolates (n=100) were resistant to levofloxacin. The susceptibility rate of telithromycin to levofloxacin-resistant strains was 99%.[8]

**Table 5. Susceptibility of macrolide-resistant *S. pneumoniae* 2001-2002**

| Mechanism of macrolide resistance | Isolates n (%) | $MIC_{90}$ (range) | % S to telithromycin | % Susceptible to other antimicrobials tested |
|---|---|---|---|---|
| *mef*(A) | 1881/2793 (68.7%) | 0.5 (≤0.015- 2) | 99.9% | 97.7%-99.5% of isolates susceptible to clindamycin, gatifloxacin, levofloxacin<br>71.4% and 78.8% of isolates susceptible to TCN and amox/clav respectively<br>13%-28.8% of isolates susceptible to co-trimoxazole, PCN, cefuroxime |
| *erm*(B) | 461/2793 (16.8%) | 0.25 (≤0.015–4) | 99.1% | 95.2%-96.5% of isolates susceptible to amox/clav, gatifloxacin, levofloxacin<br>16.1 – 37.5% of isolates susceptible to PCN, cefuroxime, co-trimoxazole<br>Majority of isolates resistant to clindamycin and TCN |
| *mef*(A) + *erm*(B) | 335/2793 (12.2%) | 1.0 (≤0.015- 4) | 98.5% | 98.5% of isolates susceptible to gatifloxacin, levofloxacin<br><10% of isolates susceptible to PCN, cefuroxime, clindamycin, TCN, co-trimoxazole |
| Other | 56/2793 (2.0%) | 1.0 (≤0.015- 2) | 96.4% | 94.6% of isolates susceptible to gatifloxacin, levofloxacin<br>98.2% of isolates susceptible to amox/clav<br>87.5%% of isolates susceptible to TCN<br>67.9-78.6% of isolates susceptible to PCN, co-trimoxazole, cefuroxime |

The $MIC_{90}$ and percent susceptibility of all S. *pneumoniae* isolates to telithromycin over the 2-year period of PROTEKT U.S. are presented in table 6. [5, 6]

**Table 6. Activity of telithromycin against *S. pneumoniae* (PROTEKT U.S.)**

| | # of isolates | $MIC_{90}$ | Range | % Susceptible | % Intermediate | % Resistant |
|---|---|---|---|---|---|---|
| 2000-2001 | 10,103 | 0.5 | ≤0.015-8 | 99.7 | 0.3 | 0.04 |
| 2001-2002 | 10,012 | 0.25 | ≤0.015-4 | 99.9 | 0.1 | 0.02 |

***Haemophilus influenzae***

Among the 2706 *H. influenza* isolates tested during 2000-2001, 28.3% were β-lactamase positive. The *tem-1* and *rob-1* genotypes were seen in 80.5% and 14.4% of the β-lactamase producing isolates respectively. Telithromycin was active against *H. influenzae* regardless of β-lactamase status.[5]

β-lactamase negative strains were susceptible to ampicillin (98%), amoxicillin-clavulanate (99.6%), cefuroxime (96.1%), and tetracycline (99.4%). β-lactamase positive strains were susceptible to amoxicillin-clavulanate (100%), cefuroxime (97.5%), and tetracycline (98.2%). The $MIC_{90}$ for gatifloxacin and moxifloxacin was ≤0.03mg/l and ≤0.06mg/l for levofloxacin (breakpoints had not been established for the fluoroquinolones at the time). Approximately 30% of isolates were intermediately susceptible and 7% are resistant to clarithromycin regardless of β-lactamase status.[5]

During 2001-2002, 27.5% of the isolates were β-lactamase positive. Again, telithromycin was active against *H. influenzae* regardless of β-lactamase status (table 7). There were 13 isolates that were β-lactamase negative yet were resistant to ampicillin. All 13 isolates were susceptible to telithromycin, azithromycin, clarithromycin, cefotaxime, and the quinolones. The number of isolates that were susceptible to amoxicillin/clavulanate, cefuroxime, tetracycline, and cefprozil were 9, 2, 10, and 1 respectively.[6]

**Table 7. *H. influenzae* susceptibility 2001-2002**

| | # isolates | $MIC_{90}$ (range) | % S to telithromycin | % Susceptible to other antimicrobials tested |
|---|---|---|---|---|
| All isolates | 3296 | 4 (≤0.12- >16) | 96.3% | Cefotaxime (100%), Amox/clav (99.8 %), quinolones (99.7%), TCN (99.3%), azithromycin 98.9%, cefuroxime (96.3%), cefprozil (81.3%), clarithromycin (80.2%), ampicillin (71.1%) |
| β-lactamase negative | 2391 | 4 (≤0.12- >16) | 95.9% | Cefotaxime (100%), Amox/clav (99.7 %), quinolones and TCN (99.6%), ampicillin (98.1%), azithromycin 98.8%, cefuroxime (96.5%), cefprozil (89.3%), cefprozil (81.3%), clarithromycin (81.8%) |
| β-lactamase positive | 905 | 4 (≤0.12- >16) | 97.3% | Cefotaxime (100%), Amox/clav and quinolones (99.9%), azithromycin (99.2%), TCN (98.5%), cefuroxime (95.9%), clarithromycin (75.8%), cefprozil (59.9%) |

The $MIC_{90}$ and percent susceptibility of all the *H. influenzae* isolates to telithromycin over the 2-year period of PROTEKT U.S. are presented in table 8.[5, 6]

**Table 8. Activity of telithromycin against *H. influenzae* (PROTEKT U.S.)**

| | # of isolates | $MIC_{90}$ | Range | % Susceptible | % Intermediate | % Resistant |
|---|---|---|---|---|---|---|
| 2000-2001 | 2706 | 4 | ≤0.12 - >32 | 96.3% | 3 | 0.6 |
| 2001-2002 | 3296 | 4 | ≤0.12 - >16 | 96.3% | Not shown | Not shown |

***Streptococcus pyogenes***

The activity of telithromycin was tested in 3918 isolates of *S. pyogenes* during 2000-2001. All isolates were penicillin-sensitive and 5.5% (n=214) were erythromycin-resistant, the majority being of the *mef*(A) genotype. The erythromycin-resistant strains were also resistant to clarithromycin and azithromycin. Nearly 92% of the erythromycin-resistant isolates were susceptible to clindamycin. The $MIC_{90}$ for telithromycin in the erythromycin-sensitive and erythromycin-resistant strains was 0.03mg/l (range ≤ 0.015 – 0.5) and 1mg/l (range ≤ 0.015 ≥ 16) respectively. The data were similar among 4508 isolates of *S. pyogenes* were tested during 2001-2002. There were 12 isolates that were macrolide and clindamycin resistant, suggesting the $MLS_B$ resistance phenotype. The MIC for telithromycin against these isolates was ≥ 4mg/L.[5, 6]

**CLINICAL TRIALS[9-20]**

All 12 studies had an active control arm; none had a placebo arm. In all the AECB, CAP and ABS studies, the primary outcome was to demonstrate equivalency between telithromycin and the comparator for clinical cure rates during the test-of-cure (TOC) visit in the per protocol group. The study by Pullman et al. was an exception because the study was underpowered due to early termination; therefore, only non-inferiority could be determined.[13]

In the tonsillitis/pharyngitis studies the primary outcome was to demonstrate equivalency between telithromycin and the comparator for bacteriologic outcome during the test-of-cure (TOC) visit in the bacteriologically evaluable per protocol group.[19, 20]

In all studies, a matching placebo was used when treatment duration or dosing frequency differed between telithromycin and comparator.

In all the AECB, CAP and ABS studies, telithromycin and the comparator were considered to be equivalent if the lower limit of the 95% confidence interval was ≥ -15% and the upper limit crossed 0. In the tonsillitis/pharyngitis studies, the lower limit of the 95% confidence interval was ≥ -10% and the upper limit crossed 0 (Quinn).[20] In Norrby et al, the lower limit was defined as ≥ -15% with no mention of the upper limit.[19]

The test-of-cure visit and the late-post-therapy assessment generally occurred between days 16-24 and 31-45 respectively.

The following populations were defined as:

| | |
|---|---|
| Clinical per-protocol population (PPc) | All mITT subjects excluding major protocol violators and subjects with an indeterminate response |
| Modified intent-to-treat population (mITT) | Confirmed diagnosis of infection being treated and ≥ 1 dose of study drug |
| Bacteriologically evaluable per-protocol population (PPb) | All PPc population in whom a causative pathogen was isolated from an adequate specimen at pre-therapy/entry |
| Bacteriologic modified intent-to-treat population (bmITT) | All mITT subjects with a pathogen at pre-therapy/entry considered by the investigator to be responsible for infection |

***Acute exacerbation of chronic bronchitis***

There are 2 randomized comparative studies. Aubier compared telithromycin 800mg QD x 5 days to amoxicillin/clavulanate 500/125mg TID x 10days. Zervos compared telithromycin 800mg QD x 5 days to cefuroxime 500mg BID x 10 days.[9, 10]

Patients were diagnosed with AECB if they had increased dyspnea, increased sputum volume, increased sputum purulence, and a negative CXR for acute pulmonary infiltrates. Aubier described that a sputum sample isolating a pathogen was considered adequate if the gram stain showed ≥ 25 PMNs and ≤ 10 epithelial cells.

Clinical cure was defined as disappearance or return to pre-infection state of AECB-related signs and symptoms, or persistence of symptoms as part of the normal clearance of the inflammatory process, but without the need for additional antibiotic therapy. Satisfactory bacterial outcome was defined as eradication of the causative pathogen or presumed eradication (followup culture unobtainable due to clinical improvement) and no additional antimicrobials required.

**Table 9. Patient Characteristics in AECB studies**

| | Aubier | | Zervos | |
|---|---|---|---|---|
| | **Telithromycin** | **Amox/clav** | **Telithromycin** | **Cefuroxime** |
| % ≥ 65y/o | 43.8% | 45.2% | 24.2% | 31.4% |
| %Smoker/ex-smoker | 85.6% | 87% | 84.1% | 81.7% |
| Severity of AECB (mild/moderate/severe) | 6.9%/85%/8.1% | 11.3%/76.9%/11.9% | 24.7%/70.3%/4.9% | 23%/71.7%/4.7% |
| % w/ > 4 episodes of AECB in previous year | 13.1% | 14.8% | 7.7% | 6.3% |

Telithromycin and its comparator were found to be equivalent for clinical cure rates for TOC visits and late post-therapy visits, in both the PPc and mITT populations. (See Appendix 1)

Subgroup analysis in patients > 65y/o, FEV1/FVC < 60%, smokers, frequency of ACEB episodes in the past year, and severe AECB showed that the clinical cure rate for telithromycin was similar to the overall PPc group and between treatment groups.

Satisfactory bacteriologic outcomes were similar between telithromycin and comparators in both the PPb and bmITT groups. Equivalency could not be determined due to small sample size. (See Appendix 1)

Bacterial eradication rates (PPb) for the most common organisms implicated in AECB are presented in table 10 and clinical cure rates for the atypical organisms in table 11.

**Table 10. Bacterial eradication rate by infecting organism (bacteriologic per-protocol population)**

| | Aubier | | Zervos | |
|---|---|---|---|---|
| | **Telithromycin** | **Amox/clav** | **Telithromycin** | **Cefuroxime** |
| *S. pneumoniae* | 10/11 (90.9%) | 4/5 (80%) | 3/3 (100%) | 5/7 (71.4%) |
| *H. influenzae* | 7/14 (50%) | 12/12 (100%) | 8/11 (72.7%) | 3/5 (60%) |
| *M. catarrhalis* | 4/4 (100%) | 7/7 (100%) | 6/6 (100%) | 7/9 (77.8%) |

**Table 11. Clinical cure rates for atypical organisms**

| | Aubier | | Zervos | |
|---|---|---|---|---|
| | Telithromycin | Amox/clav | Telithromycin | Cefuroxime |
| *C. pneumoniae* | 2/2 | 2/2 | 8/9 | 5/8 |
| *M. pneumoniae* | 0/0 | 0/0 | 1/1 | 0/0 |

***Community- Acquired Pneumonia***

There are 4 randomized comparative studies. Hagberg compared telithromycin 800mg QD x 10 days to amoxicillin 1000mg TID x 10 days. Dunbar compared telithromycin 800mg QD x 10 days to clarithromycin 500mg BID x 10 days. Pullman compared telithromycin 800mg QD x 7-10 days to trovafloxacin 200mg QD x 7-10 days. Tellier compared telithromycin 800mg QD for 5 days, 7 days and clarithromycin 500mg BID x 10 days. Inclusion criteria required a CXR indicative of pneumonia, and at least 2 of the following: cough, purulent sputum or change in sputum character, ausculatory findings, dyspnea, tachypnea, fever, elevated WBC, >15% bands.[11-14]

In general, clinical cure was defined as disappearance or improvement in infection related signs and symptoms with no need for additional antibacterial therapy, and CXR findings showing improvement or lack of progression. A satisfactory bacteriological outcome was defined as eradication or presumed eradication of the causative organism. An unsatisfactory outcome included persistence or presumed persistence of the causative organism, appearance of a new organism with worsening clinical /lab signs of infection, reinfection, superinfection, or recurrence.

**Table 12. Patient Characteristics in CAP studies**

| | Hagberg | | Dunbar | | Pullman | | Tellier | | |
|---|---|---|---|---|---|---|---|---|---|
| | TEL | Amox | TEL | Clarithro | TEL | Trova | TEL x 5 | TEL x 7 | Clarithro |
| % ≥ 65y/o | 18.6% | 17.6% | 13.2% | 17% | 19% | 14.4% | 16% | 15.2% | 20.4% |
| %Smoker/ex-smoker | 47.3% | 56.6% | 67.2% | 63.7% | 53% | 69.2% | - | - | - |
| %PSI severity class I and II | 75.4% | 69.7% | 89.7% | 84% | 86% | 91.3% | 81.3% | 81.6% | 79% |
| % w/ unilateral pneumonia on CXR | 96% | 95.6% | 91.9% | 92.8% | 91.8% | 93.1% | 87.2% | 84.3% | 86.7% |
| Bacteremia due to S. pneumoniae | 7% | 6.8% | 2.5% | 0.9% | 3% | 1.9% | 6.4% | 4.2% | 3.3% |
| %Concomitant illnesses (asthma, COPD, DM, CAD) | - | - | 40.2% | 39.6% | 42% | 43% | - | - | - |

Telithromycin and its comparator were found to be equivalent (non-inferior in Pullman et al.) for clinical cure rates in the per protocol group at the TOC visit (See appendix 2). Equivalence was also demonstrated for all secondary clinical outcomes except for late post-therapy cure rates in the mITT group (Hagberg). Non-inferiority was not demonstrated in the late post-therapy cure rate in the per protocol group (Pullman).

Subgroup analysis of high-risk patients (>65y/o, smoker, ex-smoker, PSI score III-V, pneumococcal bacteremia, multilobar pneumonia, pleural effusion) showed that the clinical cure rate for telithromycin was similar to the overall PPc group and between treatment groups.

Satisfactory bacteriologic outcomes were similar between telithromycin and comparators in both the PPb and bmITT groups. Equivalency could not be determined due to small sample size. (See Appendix)

Bacterial eradication rates (PPb) for the most common organisms implicated in CAP are presented in table 13 and clinical cure rates for the atypical organisms in table 14.

**Table 13. Bacterial eradication rate by infecting organism (bacteriologic per-protocol population)**

| | | *S. pneumoniae* | *H. influenzae* | *M. catarrhalis* |
|---|---|---|---|---|
| Hagberg | Telithromycin | 22/23 (95.7%) | 9/12 (75%) | 5/5 (100%) |
| | Amoxicillin | 18/21 (85.7%) | 11/13 (84.6%) | 3/3 (100%) |
| Dunbar | Telithromycin | 16/17 (94.1%) | 14/15 (93.3%) | 2/3 (66.7%) |
| | Clarithromycin | 14/15 (93.3%) | 10/10 (100%) | 2/3 (66.7%) |
| Pullman | Telithromycin | 7/8 (87.5%) | 1/1 (100%) | |
| | Trovafloxacin | 8/8 (100%) | 4/4 (100%) | |
| Tellier | Telithromycin 5 days | 23/24 (95.8%) | 22/25 (88%) | 1/1 (100%) |
| | Telithromycin 7 days | 29/80 (96.7%) | 21/25 (84%) | 4/5 (80%) |
| | Clarithromycin | 23/26 (88.5%) | 15/17 (88.2%) | 3/4 (75%) |

**Table 14. Clinical cure rates for atypical organisms**

| | Hagberg | | Dunbar | | Pullman | | Tellier | | |
|---|---|---|---|---|---|---|---|---|---|
| | TEL | Amox | TEL | Clarithro | TEL | Trova | TEL x 5 | TEL x 7 | Clarithro |
| *C. pneumoniae* | 4/4 | 3/3 | 8/9 | 3/4 | 10/11 | 11/1 | 1/1 | 1/1 | 1/1 |
| *M. pneumoniae* | 9/10 | 7/8 | 6/6 | 6/6 | 4/4 | 5/5 | 3/3 | 3/3 | 2/3 |
| *L. pneumophila* | 0/0 | 2/3 | 1/1 | 0/0 | 0/0 | 0/0 | - | 1/1 | - |

***Acute bacterial sinusitis***

There are 4 randomized comparative studies. Roos compared telithromycin 800mg QD x 5 days to telithromycin 800mg QD x 10 days. Buchanan compared telithromycin 800mg QD x 5 days to cefuroxime 250mg BID x 10 days. Luterman compared telithromycin 800mg QD x 5 days, telithromycin 800mg QD x 10 days, and amoxicillin/clavulanate 500mg/125mg TID x 10 days. Ferguson compared telithromycin 800mg QD x 5 days to moxifloxacin 400mg QD x 10 days. [15-18]

The diagnosis of ABS was based on the presence of the following symptoms (symptoms lasting < 28 days): Purulent nasal discharge; facial pain, pressure, or tightness; toothache or pain on percussion; maxillary pain or tenderness; nasal congestion responding poorly to nasal decongestants (last criterion included in Luterman and Roos) AND a sinus X-ray with the following: presence of air-fluid level and/or total sinus opacity. In 3 studies, the definition also included and/or $\geq$ 6mm mucosal thickening (Luterman); and/or $\geq$ 10mm mucosal thickening (Buchanan and Ferguson). In Roos et al, patients had either a sinus X-ray or CT scan.

Sinus puncture and aspiration of sinus fluid were performed in all patients (Roos), some patients (Luterman), and U.S. site patients (Buchanan) and the samples were used to determine bacteriologic outcome. In Buchanan, patients at non-U.S. sites underwent sinus endoscopy for specimen collection. In Ferguson, sinus fluid was obtained via sinus endoscopy or deep nasal swab.

Approximately 60% of the patients in Roos et al. and 40% in Luterman had duration of the current episode of less than 7 days, bringing into question whether the cause was of bacterial etiology.

Clinical cure was defined as improvement or return to the pre-infection state of all AMS-related signs and symptoms without a need for subsequent antibiotic treatment and a sinus X-ray that was normal/improved/ not worse. Bacteriologic outcome was designated as satisfactory if the causative pathogen was eradicated on repeat sinus sampling or presumed eradicated when clinical improvement was such that repeat sampling would be unnecessary (with no worsening of sinus X-ray or CT scan).

**Table 15. Patient Characteristics in ABS studies**

| | Roos | | Buchanan | | Luterman | | | Fergusom | |
|---|---|---|---|---|---|---|---|---|---|
| | TEL x 5 d | TEL x 10d | TEL | CEF | TEL x 5d | TEL x 10d | A/C | TEL | MOX |
| % $\geq$ 65y/o | | | 7.9% | 7.8% | | | | 9.4% | 14.1% |
| %Smoker/ ex-smoker | 48.5% | 43.4% | 40.8% | 44.8% | 44.8% | 43.6% | 36.6% | 23.9%/ 25.2% | 16.6%/ 25.2% |
| Sx severity (mild/mod/severe) | 4.8%/ 63%/ 32.3% | 6%/ 66%/ 28% | 5.8%/ 72.1%/ 22.1% | 1.7%/ 71.6%/ 26.7% | 4.5%/ 84.6%/ 10.9% | 6.4%/ 79.9%/ 13.7% | 7.4%/ 76.2%/ 16.3% | 7.5%/ 67.9%/ 24.5% | 7.4%/ 72.4%/ 20.2% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Duration of episode ≥ 7 days* | 37.1% | 43.5% | 89.6% | 98.3% | 60.7%% | 61.8% | 63.4% | 98.7% | 98.2% |
| Antibiotic use in the last year for ABMS (1-3 courses) | 94.9% | 96.1% | 93.6% | 88.2% | 93.8% | 97.5% | 97.4% | 92.1% | 88.9% |

*≥5 days in Ferguson
TEL=telithromycin, CEF=cefuroxime, A/C=amoxicillin/clavulanate; MOX= moxifloxacin

A 5-day course of telithromycin was found to be equivalent to a 10-day course of telithromycin, a 10-day course of amoxicillin-clavulanate, a 10-day course of cefuroxime, and a 10-day course of moxifloxacin at the TOC and late post-therapy evaluations in the both the PPc and mITT populations (only PPc population evaluated in Luterman). (See Appendix 3)

When analyzed by subgroup, clinical outcomes for those with severe AMS, episode > 15 days, and sinus X-ray findings of air-fluid level, total opacity, mucosal thickening, unilateral, bilateral were similar to the overall telithromycin PPc population and between treatment groups. (not assessed in Buchanan)

Satisfactory bacteriologic outcomes (TOC and late post-tx) were similar for both the 5-day and 10-day course of telithromycin (Roos, Luterman) and amoxicillin/clavulanate (Luterman). Equivalency was determined between telithromycin and the comparators cefuroxime and moxifloxacin. (Buchanan, Ferguson) See Appendix 3.

Bacterial eradication rates (PPb) for the most common organisms implicated in ABS are presented in table 16.

**Table 16. Bacterial eradication rate by infecting organism (bacteriologic per-protocol population)**

| | Roos | | Buchanan | | Luterman | | | Ferguson | |
|---|---|---|---|---|---|---|---|---|---|
| | TEL x 5d | TEL x 10d | TEL | CEF | TEL x 5d | TEL x 10d | A/C | TEL | MOX |
| *S. pneumoniae* | 28/30 (93.3%) | 25/28 (89.3%) | 26/29 (89.7%) | 12/12 (100%) | 2/2 | 2/2 | 2/4 | 16/17 (94.1%) | 7/8 |
| *H. influenzae* | 14/14 (100%) | 11/13 (84.6%) | 26/32 (81.3%) | 12/14 (85.7%) | 2/2 | 3/3 | 1/1 | 11/11 (100%) | 14/14 (100%) |
| *M. catarrhalis* | 6/7 (85.7%) | ¾ (75%) | 7/7 (100%) | 6/6 (100%) | - | - | 1/1 | 2/2 | 6/6 |

TEL=telithromycin, CEF=cefuroxime, A/C=amoxicillin/clavulanate; MOX= moxifloxacin

***Tonsillitis/pharyngitis (NOT FDA approved)***

There are 2 randomized comparative studies. Norrby compared telithromycin 800mg QD x 5 days to penicillin V 500mg TID x 10 days. Quinn compared telithromycin 800mg QD x 5 days to clarithromycin 250mg BID x 10 days.[19, 20]

The diagnosis of tonsillitis/pharyngitis included the following: sore throat AND ≥ 1 of the following: fever, erythema or edema of pharynx (or uvula or tonsils in Norrby), or exudate AND positive rapid antigen detection test for strep A antigen or positive throat culture for group A beta-hemolytic strep (in Quinn, both tests had to be positive).

Satisfactory bacteriologic outcome was the primary endpoint and was defined as eradication of the causative pathogen or colonization (new bacterial strain or new serotype of GABHS, but without signs and symptoms of active infection) and no additional antibiotics started. Clinical cure was defined as improvement, disappearance or return to pre-infection state of all infection-related signs and symptoms without need for additional antibiotics.

**Table 17. Patient Characteristics in tonsillitis/pharyngitis**

| | Norrby | | Quinn | |
|---|---|---|---|---|
| | Telithromycin | Penicillin V | Telithromycin | Clarithromycin |
| Fever > 38°C | 31.3% | 29.9% | 15.5%* | 8.2% |
| Cervical lymphadenopathy | 93.4% | 94.9% | 90.5% | 90.5% |

| | | | | |
|---|---|---|---|---|
| Exudates | 82.3% | 78.7% | 64.7% | 65.8% |
| Median age (range) | 32 (15-62) | 33 (15-74) | 29 (13-72) | 29 (13-81) |
| ≥ 65 y/o (n) | - | - | 2 | 3 |

The percent of patients with satisfactory bacteriologic outcomes were equivalent (TOC and late post-tx) between telithromycin and the comparators both in the PPb and mITT populations. (See appendix 4)

Subgroup analysis in patients with cervical lymphadenopathy or pharyngeal exudate showed that the bacterial cure rate for telithromycin was similar to the overall PPb group and to clarithromycin. In patients with fever, the bacterial cure rate was 100% (20/20) for telithromycin and 69% (9/13) for clarithromycin; however, conclusions cannot be drawn due to small sample size. Other factors such as age, sex, smoking status, previous GABHS infection, and prior ENT surgery had no bearing on outcomes in either group. Norrby et al did not present a subgroup analysis.

Rates of clinical cure were similar (TOC and late post-tx) between telithromycin and the comparators in both the PPc and mITT populations.

In a separate publication, Norrby et al assessed relief of symptoms. Using a Kaplan-Meyer curve, there was no difference in time to symptom resolution between telithromycin and penicillin. After 3-5 days of treatment, the total symptom score decreased by 7.5 and 7.0 in the telithromycin and penicillin groups respectively (p=0.042).[21]

***Outcomes for S. pneumoniae resistant or intermediately susceptible isolates***

In a pooled analysis, Fogarty presents clinical and bacteriologic outcomes for patients with *S. pneumoniae* isolates that were resistant to penicillin and or erythromycin in the CAP, AECB and ABS clinical trials. *S. pneumoniae* was isolated in 333/2695 (12.3%) patients who received telithromycin and 90/1190 (7.6%) patients who received a comparator. Of these, 77/333 (23.1%) and 19/90 (21.1%) had reduced susceptibility or resistance to penicillin and or erythromycin. Strains with a penicillin MIC ≥ 2mg/L were defined as resistant and MIC 0.12-1.0mg/L as intermediately susceptible. An erythromycin MIC ≥ 1.0mg/L was defined as resistant.[22]

**Table 18. Outcomes for *S. pneumoniae* resistant or intermediately susceptible isolates**

| | Clinical Cure Rates | | Bacteriologic Eradication Rates | |
|---|---|---|---|---|
| | **Telithromycin (bmITT / PPC)** | **Pooled comparators (bmITT / PPC)** | **Telithromycin (bmITT / PPC)** | **Pooled comparators (bmITT / PPC)** |
| $PEN^S$; $ERY^R$ | 7/8 | 2/2 | 7/8 | 2/2 |
| | 7/8 | 2/2 | 7/8 | 2/2 |
| $PEN^I$; $ERY^R$ | 16/16 | 4/4 | 16/16 | 4/4 |
| | 13/13 | 4/4 | 13/13 | 4/4 |
| $PEN^R$; $ERY^S$ | 11/12 | 2/3 | 12/12 | 2/3 |
| | 9/9 | 2/2 | 9/9 | 2/2 |
| $PEN^R$; $ERY^R$ | 19/24 | 4/6 | 19/24 | 5/6 |
| | 17/22 | 3/5 | 17/22 | 4/5 |
| $PEN^I$; $ERY^S$ | 17/17 | 2/3 | 17/17 | 2/4 |
| | 16/16 | 2/3 | 16/16 | 2/3 |
| Total | 70/77 (90.9%) | 14/18 (77.8%) | 71/77 | 15/19 |
| | 62/68 (91.2%) | 13/16 (81.3%) | 62/68 | 14/16 |

**SAFETY**

Commonly reported adverse events during clinical trials include diarrhea, nausea, headache, and dizziness. See Appendix 5 for adverse events reported by study.

*Visual changes*

During Phase III trials, treatment emergent visual disturbances were reported in 1.1% (30/2702) of patients receiving telithromycin compared to 0.28% (6/2139) of patients receiving comparator therapies. The visual disturbances were described as blurred vision, difficulty focusing, and double-vision when looking quickly between nearby and far away objects. The majority of events occurred following the first or second dose (65%). These events lasted several hours and recurred with subsequent dosing in some patients. Females

under 40 years of age had the highest incidence of reported events. In a Phase IV commitment, Aventis will assess vision-related adverse events reported globally for the first 18 months after U.S. launch.

*QTc-interval*
Like the macrolides, telithromycin can potentially prolong the QTc interval. Telithromycin treatment was associated with mean increase in QTc interval of 1.5ms (Bazett's formula) and 3.8ms (Fredericia'a formula).[28] According to the manufacturer, there were no adverse cardiovascular outcomes that could be attributable to QTc prolongation among the 4780 patients (n=204 with prolonged QTc at baseline) treated with telithromycin in the clinical trials.[1]

A small randomized, double-blind, cross-over study evaluated single and repeat doses of telithromycin, clarithromycin, and placebo on QT-interval in 34 healthy subjects. Eighteen subjects were entered into protocol 1where telithromycin 800mg once daily, clarithromycin 500mg BID and placebo were compared both as a single dose and repeated dose given for 6 days. The remaining 16 subjects were entered into protocol 2 where subjects received single doses of telithromycin 800mg, 1600mg, and 2400mg. For protocol 1 and protocol 2, there were 972 and 448 resting EKGs obtained respectively. No patient had a Bazett's QTc > 450ms (males) >470ms (females). In Protocol 1, there were 8 episodes of EKG changes in 3 subjects who had a Bazett's $\Delta$QTc $\geq$ 60ms compared to baseline. Two of the episodes occurred during administration of telithromycin and 6 during clarithromycin. In Protocol 2, there were 5 episodes of EKG changes in 2 subjects who had Bazett's $\Delta$QTc $\geq$ 60ms. Three episodes were recorded during administration of 1600mg, one with 2400mg and one with placebo.[23]

Telithromycin should be avoided in patients with congenital prolongation of the QTc interval and in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia, hypomagnesemia, clinically significant bradycardia, and patients receiving Class 1A or Class III antiarrhythmic agents.

*Liver function tests*
Increased alanine aminotransferase (ALT) has been reported with telithromycin during the clinical trials. ALT elevation $\geq$ 3x the upper limit of normal was seen in 1.6% and 1.7% of patients treated with telithromycin and comparator respectively. Hepatitis with or without jaundice occurred in 0.7% and was reversible.[1]

As of April 2004, there have been 90 post-marketing reports of hepatic adverse events in 43 patients.[28] The majority of these reports had missing information, making it difficult to assess causality and characterize the pattern of liver injury. Based on the reports that had sufficient ALT and alkaline phosphatase data, a cholestatic, cytolytic and mixed pattern of hepatic injury was seen in 12, 5, and 2 patients respectively. Three patients underwent a liver biopsy. The biopsy results showed liver injury consistent with drug-induced cholestatis, drug-induced hepatocanalicular liver injury, and hepatatocanalicular jaundice.

The method of the Council for International Organizations of Medical Sciences was used to assess causality. Only 14/43 patients had imagining studies and hepatitis serologies and of these, only 5 had any additional data that is commonly used to assess causality.

*Myasthenia gravis*
Avoid use in patients with myasthenia gravis. There have been 13 patients with exacerbation of myasthenia gravis considered likely to be due to telithromycin and 6 cases possibly related to telithromycin. Six patients developed respiratory arrest requiring intubation (1 patient died).

**DRUG INTERACTIONS**
The drug interaction studies have not been published; therefore, the following information was obtained from the product package insert.[1]

*CYP3A4 interactions*
Telithromycin is a strong inhibitor of CYP3A4. The use of telithromycin with cisapride or pimozide is contraindicated. Concomitant administration of simvastatin and telithromycin resulted in an increase in simvastatin plasma concentration. Patients receiving simvastatin, lovastatin, or atorvastatin should

temporarily discontinue use while taking telithromycin. Pravastatin and fluvastatin are not metabolized by CYP3A4 and may be co-administered with telithromycin.

Dosage adjustment of midazolam and other benzodiazepines metabolized by CYP3A4 (eg. triazoloam) may be necessary.

Other drugs that are metabolized by CYP3A4, which cannot be temporarily discontinued, should be used cautiously when co-administered with telithromycin. Dosage adjustment of the drug that is metabolized by CYP3A4 may be necessary.

Telithromycin is also metabolized by CYP3A4. The concurrent administration of other CYP3A4 inhibitors such as ketoconazole and itraconazole increased Cmax and AUC of telithromycin. Interestingly, 240mL of grapefruit juice (a CYP3A4 inhibitor) administered with telithromycin did not affect the pharmacokinetics of telithromycin.

Subtherapeutic levels of telithromycin may occur if administered with drugs that are CYP3A4 inducers (eg. rifampin, phenytoin, carbamazepine, and phenobarbital).

*Other drug interactions*

The AUC and Cmax of metoprolol (a CYP2D6 substrate) were increased by approximately 38% when administered with telithromycin. Half-life of metoprolol was not affected.

The AUC and Cmax were decreased by 20% and 34% respectively when administered with telithromycin due to decreased absorption.

When telithromycin and warfarin were co-administered in healthy subjects, there were no pharmacokinetic or pharmacodynamic interactions on racemic warfarin. There have been post-marketing reports that co-administration of telithromycin and warfarin may potentiate the effects of warfarin. There is also a published case report describing an increased INR from 3.1 to 11 with resultant hemoptysis after 5 days of telithromycin therapy Monitoring prothrombin time or INR is suggested.[24]

Co-administraion of theophylline and telithromycin resulted in a 16% and 17% incrase in steady state Cmax and AUC respectively.

Plasma peak and trough levels of digoxin increased by 73% and 21% respectively when healthy volunteers received digoxin and telithromycin concomitantly. There were no significant EKG changes or signs of digoxin toxicity.

Co-administration of telithromycin and ethinyl estradiol/levonorgestrel containing oral contraceptives resulted in a 50% increase in the AUC of levonorgestrel. The AUC of ethinyl estradiol did not change. Anovulatory effect of ethinyl estradiol/levonorgestrel was not affected.

Absorption of telithromycin is unaffected by antacids or histamine-2 receptor blockers.

**LOOK-ALIKE/SOUND-ALIKE ERROR RISK POTENTIAL**

As part of a pilot program, the VA PBM and Center for Medication Safety queried a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonological similarities, as well as similarities in dosage form, strength and route of administration. By incorporating similarity scores as well as clinical judgment, it was determined that the following drug names may pose as potential sources of drug name confusion.

**Telithromycin (generic name)** Potential name confusion: erythromycin, clarithromycin, azithromycin, dirithromycin

Potential Severity: Minor-Moderate (depending on susceptibility of the organism)

Probability: Occasional

**Ketek (brand name)** Potential name confusion: Keflex, Keftab, K-pek, Kaopek

Potential Severity: Moderate
Probability: Uncommon for Keflex and Keftab (Keflex and Keftab are available as 250mg and 500mg capsules/tablets and are dosed every 6 hours). Remote for K-pek and Kaopek (both are antidiarrheals, K-pek is a suspension and Kaopek is a 2mg tablet containing loperamide)

**DOSE**
Telithromycin may be administered without regard to meals. The dose of telithromycin is 800mg (400mg tablets x 2) once daily for 5 days for the treatment of AECB, ABS. It should be administered for 7-10days for the treatment of CAP.

Dosage adjustment is not necessary in the presence of hepatic impairment. The dose of telithromycin has not been established in patients with SCr < 30mL/min, including those requiring dialysis. Dosage adjustment is not necessary in the elderly.

**PHARMACOECONOMICS**
Non-study costs associated with hospitalizations, outpatient visits, lab tests, and need for additional antibiotics were assessed in the 2 CAP studies (Dunbar and Tellier) that compared telithromycin to clarithromycin. The results of each of these evaluations were published separately.[26, 27] Because each trial was underpowered to show differences in healthcare resource utilization, the data were pooled.[25] The intent-to-treat population was evaluated at the post-therapy test-of-cure visit and the late post-therapy visit. There was a significant difference between telithromycin and clarithromycin for CAP-related hospitalizations. There was no significant difference in the % of patients or events/100 patients for all-cause hospitalizations, CAP-related outpatient visits, CAP-related lab tests, and respiratory tract infection-related additional antibiotics between telithromycin and clarithromycin.

Overall hospitalization costs were calculated by multiplying the total number of CAP-related hospital days per treatment group by the published 2002 American Hospital Association average daily rate for short-term hospitals ($1289.87)

**Table 19. CAP-related hospitalizations**

| | Telithromycin x 5-10 days N=612 | Clarithromycin x 10 days N=411 | Difference [95% CI] |
|---|---|---|---|
| Number (%) of patients | 8 (1.3%) | 14 (3.4%) | -2.1[-4.1, -0.1]* |
| Number of admissions (admissions/100 patients) | 8 (1.3) | 15 (3.6) | -2.3[-4.2, -0.3]* |
| Total length of hospital stay (range) | 70 (1-19) days | 139 (2-21) days | |
| Hospital days/ 100 patients | 11.4 | 33.8 | -23.4 [-43.9, -3.0]* |
| Total hospitalization costs | $90,291 | $179,292 | |
| Hospitalization costs / 100 patients | $14,753 | $43,623 | $30,231[-56,621, -3840] |

*p < 0.05 vs. clarithromycin

**COST**
The cost of telithromycin is compared to the cost of other antibiotics that can be used to treat ABS, CAP and AECB.

**Acute bacterial sinusitis**

| | FSS Cost per unit | Days of therapy | Cost of therapy |
|---|---|---|---|
| Telithromycin 800mg (2x 400mg) QD | $3.29 | 5 days | $ 32.90 |
| **Mild disease with no recent antibiotic use in past 4-6 weeks** | | | |
| Amoxicillin/clavulanate 500mg q8h | $1.18 (500mg) | 10 days | $35.40 |
| or 875mg q12h | $1.55 (875mg) | | $31.00 |
| Amoxicillin/clavulanate XR 2000mg/125mg (2 x 1000/62.5mg) BID* | $1.63 (XR) | | $65.20 |
| Amoxicillin 500mg q8h or 875mg q12h | 0.06 (500mg) | 10 days | $1.80 or $5.20 |
| Amoxicillin 1gm q8h* | 0.26 (875mg) | | $3.60 |
| Cefpodoxime 200mg BID | $2.76 | 10 days | $55.20 |
| Cefuroxime axetil 250mg BID | 0.35 | 10 days | $7.00 |
| Cefdinir 300mg BID or 600mg QD | $2.50 | 10 days | $50.00 |
| **Mild disease with no recent antibiotic use in past 4-6 weeks and beta-lactam allergic** | | | |

| | | | |
|---|---|---|---|
| TMP/SMX DS BID | $0.06 | 10 days | $1.20 |
| Doxycycline 100mg BID | $0.04-0.14 | 10 days | $0.08-2.80 |
| Clarithromycin 500mg BID | $1.50 | 7-14 days | $ 21-42 |
| Clarithromycin XL 500mg (2 tablets) QD | $1.50 | 7 days | $21 |
| Azithromycin 500mg QD | $8.40 | 3 days | $25.20 |
| **Mild disease with recent antibiotic use (4-6 weeks) or moderate disease** | | | |
| Gatifloxacin 400mg QD | $1.35 | 10 days | $13.50 |
| Moxifloxacin 400mg QD | $1.55 | 10 days | $15.50 |
| Amoxicillin/clavulanate XR 2000mg/125mg (2 x 1000/62.5mg) BID | $1.63 | 10 days | $65.20 |

Recommendations from Sinus and Allergy Health Partnership. Antimicrobial treatment Guidelines for Acute Bacterial Rhinosinusitis. Otolaryngol Head Neck Surg 2004; 130: 1-45.
*higher dose used in areas with high prevalence of penicillin-resistant *S. pneumoniae*

## Initial Empiric Therapy for Community Acquired Pneumonia (outpatient treatment)

| | FSS Cost per unit | Days of therapy | Cost of therapy |
|---|---|---|---|
| Telithromycin 800mg (2x 400mg) QD | $3.29 | 7-10 days | $46.06-65.80 |
| **Previously healthy and no recent antibiotic use** | | | |
| Erythromycin | | | |
| Clarithromycin 250mg BID | $1.50 | 7-14 days | $ 21-42 |
| Clarithromycin XL 1gm (2 x 500mgtablets) QD | $1.50 | 7 days | $21 |
| Azithromycin 500mg QD day 1 then 250mg QD days 2-5 | $4.20 | 5 days | $25.20 |
| Doxycycline 100mg BID | $0.04-0.14 | 7-14 days | $0.56-3.92 |
| **Previously healthy AND antibiotic use within last 3 months** | | | |
| Gatifloxacin 400mg QD | $1.35 | 7-14 days | $9.45-18.90 |
| Moxifloxacin 400mg QD | $1.55 | 7-14 days | $10.85-21.70 |
| Azithromycin or clarithromycin + amoxicillin 1gm TID | | 5/7-10 days<br>7/7-10 days | $27.72-28.80 (azi+amx)<br>$23.52-24.60(clar+amx) |
| Azithromycin or clarithromycin + Amoxicillin/clavulanate XR 2000/125mg (2 x 1000/62.5mg) BID | | 5/7-10 days<br>7/7-10 days | $70.84-90.4 (azi+a/c)<br>$66.64-86.20 (clar+a/c) |
| **Co-morbidities (COPD, diabetes, renal failure, CHF, malignancy) and no recent antibiotic use** | | | |
| Azithromycin or clarithromycin | As above | | |
| Gatifloxacin or moxifloxacin 400mg QD | As above | | |
| **Co-morbidities (COPD, diabetes, renal failure, CHF, malignancy) AND antibiotic use within last 3 months** | | | |
| Gatifloxacin or moxifloxacin 400mg QD | As above | | |
| Azithromycin or clarithromycin + amoxicillin 1gm TID or Amoxicillin/clavulanate XR 2000/125mg (2 x 1000/62.5mg) BID or cefpodoxime 200mg BID or cefuroxime 250-500mg BID | | | $27.72-28.80 (azi+amx)<br>$23.52-24.60(clar+amx)<br>$70.84-90.4 (azi +a/c)<br>$66.64-86.20 (clar+a/c)<br>$80.40 (azi+cefpodox)<br>$76.20 (clar+cefpodox)<br>$32.2-38.60 (azi+cefurox)<br>$29-34.40 (clar+cefurox) |

Recommendations from Update of Practice Guidelines for the Management of Community-Acquired Pneumonia in Immunocompetent Adults. Clin Infect Dis 2003; 37: 1405-33.
Drug dosages and duration of therapy from Clin Infect Dis 2003; 37: 1405-33, product package insert, and The Sanford Guide to Antimicrobial Therapy

## Antibiotics on the VA National Formulary that can be used to treat AECB

| | FSS Cost per unit | Days of therapy | Cost of therapy |
|---|---|---|---|
| Telithromycin 800mg (2x 400mg) QD* | $3.29 | 5 days | $ 32.90 |
| Amoxicillin 500mg q 8h or 875mg q12h | 0.06 (500mg)<br>0.26 (875mg) | 10 days | $1.80<br>$5.20 |
| Doxycycline 100mg BID | $0.04-0.14 | 10 days | $0.40-1.40 |
| TMP/SMX DS BID | $0.06 | 10 days | $1.20 |
| Amoxicillin/clavulanate 875/125mg q12h or 500mg/125mg q8h | $1.55<br>$1.18 (generic) | 10 days | $31.00<br>$35.40 |
| Azithromycin 500mg QD day 1 then 250mg QD days 2-5 **or** 500mg QD | $4.20<br>$8.40 | 5 days<br>3 | $25.20<br>$25.20 |
| Clarithromycin 250-500mg (depending on | $1.50 | 7-14 days | $21.00-42.00 |

| | | | |
|---|---|---|---|
| organism) BID or XL 1gm (2x500mg) QD | (Flat priced) | 7 days (XL) | $21.00 |
| Gatifloxacin 400mg QD | $1.35 | 5 days | $6.75 |
| Cefaclor XR 500mg q12h | $1.91 (XR) | 7 days | $13.37 |
| Cefuroxime 250-500mg q12h | $0.35-0.67 (generic) | 10 days | $7.00-13.40 |
| Cefpodoxime 200mg q12h | $2.76 | 10 days | $55.20 |

*Telithromycin is listed in the table for comparative purposes. Formulary status of telithromycin has not been determined at this time
Dosage and duration of therapy obtained from product package insert or The Sanford Guide to Antimicrobial Therapy

## REFERENCES


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28. FDA transcripts

**Prepared by Deborah Khachikian, Pharm.D.**
**October 2004**

## Appendix 1. Acute Exacerbation of Chronic Bronchitis

| Study | Study dates/ countries | Dose | Clinical Cure | Bacterial outcomes |
|---|---|---|---|---|
| Zervos 2003<br>R, DB, PR | May 1998 – July 1999<br>USA, Canada | Telithromycin 800mg qd x 5 days<br>Cefuroxime 500mg BID x 10 days | **Telithromycin** / **Cefuroxime**<br>**PPc**<br>TOC 121/140 (86.4%) / 118/142 (83.1%)<br>Late post-tx 103/131 (78.6%) / 104/136 (76.5%)<br>TOC= test of cure days 17-24; late post-tx days 31-45<br>All results support equivalency of telithromycin | **Telithromycin** / **Cefuroxime**<br>**PPb**<br>TOC 19/25 (76%) / 18/27 (66.7%)<br>Late post-tx 19/25 (76%) / 18/27 (66.7%)<br>TOC= test of cure days 17-24; late post-tx days 31-45<br>Equivalency not determined due to small sample size |
| Aubier 2002<br>R, DB, PR | March 1998 - May 1999<br>Argentina, Belgium, France, Germany, Ireland, S. Africa, Australia, U.K. | Telithromycin 800mg qd x 5 days<br>Amox/clav 500mg/125mg TID x 10 days | **Telithromycin** / **Amox/clav**<br>**PPc**<br>TOC 99/115 (86.1%) / 92/112 (82.1%)<br>Late post-tx 82/105 (78.1%) / 81/108 (75%)<br>**mITT**<br>TOC 130/160 (81.3%) / 125/160 (78.1%)<br>Late post-tx 118/160 (73.8%) / 114/160 (71.3%)<br>TOC= test of cure days 17-21; late post-tx days 31-36<br>All results support equivalency of telithromycin | **Telithromycin** / **Amox/clav**<br>**PPb**<br>Satisfactory 27/39 (69.2%) / 21/30 (70%)<br>Eradication 32/42 (76.2%) / 26/32 (81.3%)<br>**bmITT**<br>Satisfactory 30/50 (60%) / 25/44 (56.8%)<br>Eradication 36/48 (75%) / 35/43 (81.4%)<br>All values are from TOC days 17-21<br>Equivalency not determined |

## Appendix 2. Community Acquired Pneumonia

<table>
<tr><th>Study</th><th>Study dates/ countries</th><th>Dose</th><th>Clinical Cure</th><th>Bacterial outcomes</th></tr>
<tr>
<td>Hagberg 2002<br>R, DB, PR</td>
<td>February 1998 – March 1999<br>Argentina, Australia, Austria, Finland, France, Germany, Hungary, New Zealand, S. Africa, Spain Sweden, U.K., Uruguay</td>
<td>Telithromycin 800mg qd x 10 days<br>Amoxicillin 1000mg TID x 10 days</td>
<td>
<table>
<tr><th></th><th>Telithromycin</th><th>Amoxicillin</th></tr>
<tr><td>PPc</td><td></td><td></td></tr>
<tr><td>TOC</td><td>141/149 (94.6%)</td><td>137/152 (90.1%)</td></tr>
<tr><td>Late post-tx</td><td>115/125 (92%)</td><td>116/136 (85.3%)</td></tr>
<tr><td>mITT</td><td></td><td></td></tr>
<tr><td>TOC</td><td>171/199 (85.9%)</td><td>161/205 (78.5%)</td></tr>
<tr><td>Late post-tx</td><td>162/199 (81.4%)</td><td>149/205 (72.7%)</td></tr>
</table>
TOC= test of cure days 17-24; late post-tx days 31-36<br>All results support equivalency of telithromycin except for late post-tx in the mITT group where patients treated with telithromycin had a higher rate of cure
</td>
<td>
<table>
<tr><th></th><th>Telithromycin</th><th>Amoxicillin</th></tr>
<tr><td>PPb</td><td></td><td></td></tr>
<tr><td>Satisfactory</td><td>36/40 (90%)</td><td>35/40 (87.5%)</td></tr>
<tr><td>Eradication</td><td>42/48 (87.5%)</td><td>39/45 (86.7%)</td></tr>
<tr><td>bmITT</td><td></td><td></td></tr>
<tr><td>Satisfactory</td><td>49/62 (79%)</td><td>46/63% (73%)</td></tr>
<tr><td>Eradication</td><td>57/65 (87.7%)</td><td>52/61 (85.2%)</td></tr>
</table>
All values are from TOC days 17-24<br>Results were considered similar; equivalency not determined
</td>
</tr>
<tr>
<td>Dunbar 2004<br>R, DB, DD, PR</td>
<td>May 1998 – Sept. 1999<br>USA, Canada, Argentina, Chile</td>
<td>Telithromycin 800mg qd x 10 days<br>Clarithromycin 500mg BID x 10 days</td>
<td>
<table>
<tr><th></th><th>Telithromycin</th><th>Clarithromycin</th></tr>
<tr><td>PPc</td><td></td><td></td></tr>
<tr><td>TOC</td><td>143/162 (88.3%)</td><td>138/156 (88.5%)</td></tr>
<tr><td>Late post-tx</td><td>129/150 (86%)</td><td>121/143 (84.6%)</td></tr>
<tr><td>mITT</td><td></td><td></td></tr>
<tr><td>TOC</td><td>161/204 (78.9%)</td><td>171/212 (80.7%)</td></tr>
<tr><td>Late post-tx</td><td>156/204 (76.5%)</td><td>159/212 (75%)</td></tr>
</table>
TOC= test of cure days 17-24; late post-tx days 31-45<br>All results support equivalency of telithromycin
</td>
<td>
<table>
<tr><th></th><th>Telithromycin</th><th>Clarithromycin</th></tr>
<tr><td>PPb</td><td></td><td></td></tr>
<tr><td>Satisfactory (TOC)</td><td>25/28 (89.3%)</td><td>27/28 (96.4%)</td></tr>
<tr><td>Satisfactory (late post-tx)</td><td>23/26 (88.5%)</td><td>23/26 (88.5%)</td></tr>
<tr><td>Eradication (TOC)</td><td>28/32 (87.5%)</td><td>29/30 (96.7%)</td></tr>
<tr><td>bmITT</td><td></td><td></td></tr>
<tr><td>Satisfactory (TOC)</td><td>36/48 (75%)</td><td>37/45 (82.2%)</td></tr>
<tr><td>Satisfactory (late post-tx)</td><td>35/48 (72.9%)</td><td>34/45 (75.6%)</td></tr>
</table>
TOC= test of cure days 17-24; late post-tx days 31-45<br>Results were considered similar; equivalency not determined
</td>
</tr>
<tr>
<td>Pullman 2003<br>R, DB, PR</td>
<td>October 1998 – July 1999<br>USA, Canada, S. Africa</td>
<td>Telithromycin 800mg qd x 7 -10 days<br>Trovafloxacin 200mg qd x 7-10 days</td>
<td>
<table>
<tr><th></th><th>Telithromycin</th><th>Trovafloxacin</th></tr>
<tr><td>PPc</td><td></td><td></td></tr>
<tr><td>TOC</td><td>72/80 (90%)</td><td>81/86 (94.2%)</td></tr>
<tr><td>Late post-tx</td><td>59/68 (86.8%)</td><td>71/76 (93.4%)</td></tr>
<tr><td>mITT</td><td></td><td></td></tr>
<tr><td>TOC</td><td>82/100 (82%)</td><td>89/104 (85.6%)</td></tr>
<tr><td>Late post-tx</td><td>80/100 (80%)</td><td>86/104 (82.7%)</td></tr>
</table>
TOC= test of cure days 17-24; late post-tx days 31-45<br>All results support non-inferiority of telithromycin except for late post-tx in the PPc group where patients treated with telithromycin had a higher rate of cure
</td>
<td>
<table>
<tr><th></th><th>Telithromycin</th><th>Trovafloxacin</th></tr>
<tr><td>PPb</td><td></td><td></td></tr>
<tr><td>Satisfactory (TOC)</td><td>13/14 (92.9%)</td><td>22/22 (100%)</td></tr>
<tr><td>Satisfactory (late post-tx)</td><td>11/12 (91.7%)</td><td>18/19 (94.7%)</td></tr>
<tr><td>Eradication (TOC)</td><td>18/19 (94.7%)</td><td>32/32 (100%)</td></tr>
<tr><td>Eradication (late post-tx)</td><td>14/15 (93.3%)</td><td>25/29 (86.2%</td></tr>
<tr><td>bmITT</td><td></td><td></td></tr>
<tr><td>Satisfactory (TOC)</td><td>27/32 (84.4%)</td><td>30/34 (88.2%)</td></tr>
<tr><td>Satisfactory (late post-tx)</td><td>26/32 (81.2%)</td><td>27/34 (79.4%)</td></tr>
</table>
TOC= test of cure days 17-24; late post-tx days 31-45
</td>
</tr>
<tr>
<td>Tellier 2004<br>R, DB, PR</td>
<td>December 1999-April 2001<br>Argentina, Brazil, Canada, Chile, Germany, S. Africa, Spain, UK, USA</td>
<td>Telithromycin 800mg qd x 5 days<br>Telithromycin 800mg qd x 7 days<br>Clarithromycin 500mg BID x 10 days</td>
<td>
<table>
<tr><th></th><th>TEL x 5 days</th><th>TEL x 7 days</th><th>Clarithromycin</th></tr>
<tr><td>PPc<br>TOC</td><td>142/159 (89.3%)</td><td>143/161 (88.8%)</td><td>134/146 (91.8%)</td></tr>
<tr><td>mITT<br>TOC</td><td>154/187 (82.4%)</td><td>157/191 (82.2%)</td><td>147/181 (81.2%)</td></tr>
</table>
TOC= test of cure days 17-21; late post-tx days 31-36<br>All results support equivalency of telithromycin
</td>
<td>
<table>
<tr><th></th><th>TEL x 5 days</th><th>TEL x 7 days</th><th>Clarithro</th></tr>
<tr><td>PPb</td><td></td><td></td><td></td></tr>
<tr><td>Satisfactory (TOC)</td><td>57/65 (87.7%)</td><td>52/65 (80%)</td><td>45/54 (83.3%)</td></tr>
<tr><td>Eradication (TOC)</td><td>74/82 (90.2%)</td><td>83/95 (87.4%)</td><td>67/77 (87%)</td></tr>
</table>
TOC= test of cure days 17-21<br>Equivalency not determined
</td>
</tr>
</table>

## Appendix 3. Acute Bacterial Sinusitis

| Study | Study dates/ countries | Dose | Clinical Cure | Bacterial outcomes |
|---|---|---|---|---|
| Roos<br>2002<br>R, DB, PR | April 1998- April 1999<br>Austria, Croatia, Czech Rep., Denmark, Finland, France, Germany, Greece, Sweden | Telithromycin 800mg qd x 5 days<br>Telithromycin 800mg qd x 10 days | **TEL x 5 days** / **TEL x 10 days**<br>**PPc**<br>TOC: 112/123 (91.1%) / 121/133 (91%)<br>Late post-tx: 96/108 (88.9%) / 107/120 (89.2%)<br>**mITT**<br>TOC: 138/167 (82.6%) / 147/168 (87.5%)<br>Late post-tx: 135/167 (80.8%) / 145/168 (86.3%)<br>TOC= test of cure days 17-21; late post-tx days 31-36<br>All results support equivalency of telithromycin | **TEL x 5 days** / **TEL x 10 days**<br>**PPb**<br>Satisfactory (TOC): 65/70 (92.9%) / 62/69 (89.9%)<br>Satisfactory (late post-tx): 54/60 (90%) / 53/61 (86.9%)<br>Eradication (TOC): 78/86 (90.7%) / 84/92 (87.5%)<br>**bmITT**<br>Satisfactory (TOC): 80/97 (82.5%) / 93/104 (89.4%)<br>Satisfactory (late post-tx): 77/97 (79.4%) / 91/104 (87.5%)<br>Eradication (TOC): 95/103 (92.2%) / 119/128 (93%)<br>TOC= test of cure days 17-21; late post-tx days 31-36<br>Equivalency not determined |
| Buchanan<br>2003<br>R, DB, PR | April – November 2000<br>Argentina, France, S. Africa, USA | Telithromycin 800mg qd x 5 days<br>Cefuroxime 250mg BID x 10 days | **Telithromycin** / **Cefuroxime**<br>**PPc**<br>TOC: 161/189 (85.2%) / 73/89 (82%)<br>Late post-tx: 139/174 (79.9%) / 64/82 (78%)<br>**mITT**<br>TOC: 193/240 (80.4%) / 84/116 (72.4%)<br>Late post-tx: 178/240 (74.2%) / 77/116 (66.4%)<br>TOC= test of cure days 16-24; late post-tx days 31-45<br>All results support equivalency of telithromycin | **Telithromycin** / **Cefuroxime**<br>**PPb**<br>Satisfactory (TOC): 84/100 (84%) / 39/49 (79.6%)<br>Satisfactory (late post-tx): 73/92 (79.3%) / 34/46 (73.9%)<br>Eradication (TOC): 112/132 (84.8%) / 50/61 (82%)<br>**bmITT**<br>Satisfactory (TOC): 102/126 (81%) / 44/60 (73.3%)<br>Satisfactory (late post-tx): 98/126 (77.8%) / 41/60 (68.3%)<br>TOC= test of cure days 16-24; late post-tx days 31-45<br>All results support equivalency of telithromycin |
| Luterman<br>2003<br>R, DB, PR | July 1998 – June 1999<br>USA, Canada, S. Africa, Argentina, Chile | Telithromycin 800mg qd x 5 days<br>Telithromycin 800mg qd x 10 days<br>Amox/clav 500mg/125mg TID x 10 days | **TEL x 5 days** / **TEL x 10 days** / **Amox/clav**<br>**PPc**<br>TOC: 110/146 (75.3%) / 102/140 (72.9%) / 102/137 (74.5%)<br>**PPc**<br>Late post-tx: 95/136 (69.9%) / 90/133 (67.7%) / 92/130 (70.8%)<br>Relapse (n): 5 / 5 / 3<br>TOC= test of cure days 17-24; late post-tx days 31-45<br>All results support equivalency of telithromycin | **TEL x 5 days** / **TEL x 10 days** / **Amox/clav**<br>**PPb**<br>Satisfactory (TOC): 6/7 (85.7%) / 6/7 (85.7%) / 8/10 (80%)<br>Satisfactory (late post-tx): 5/7 (71.4%) / 5/7 (71.4%) / 5/7 (71.4%)<br>TOC= test of cure days 17-24; late post-tx days 31-45<br>Equivalency not determined |
| Ferguson<br>2004<br>R, DB, PR | December 2002 – September 2003<br><br>USA | Telithromycin 800mg qd x 5 days<br>Moxifloxacin 400mg qd x 10 days | **Telithromycin** / **Moxifloxacin**<br>**PPc**<br>TOC: 118/135 (87.4%) / 119/137 (86.9%)<br>Late post-tx: 101/129 (78.3%) / 104/132 (78.8%)<br>**mITT**<br>TOC: 128/159 (80.5%) / 125/163 (76.7%)<br>Late post-tx: 108/159 (67.9%) / 111/163 (68.1%)<br>TOC= test of cure days 17-24; late post-tx days 31-36<br>All results support equivalency of telithromycin | **Telithromycin** / **Moxifloxacin**<br>**PPb**<br>Satisfactory (TOC): 32/34 (94.1%) / 31/33 (93.9%)<br>**bmITT**<br>Satisfactory (TOC): 36/41 (87.8%) / 31/43 (72.1%)<br>TOC= test of cure days 17-24<br>All results support equivalency of telithromycin |

## Appendix 4. Tonsillitis/Pharyngitis

| Study | Study dates/ countries | Dose | Clinical Cure | Bacterial outcomes |
|---|---|---|---|---|
| Norrby 2002 R, DB, PR | October 1998 – July 1999 Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, New Zealand, South Africa, Switzerland, U.K. | Telithromycin 800mg qd x 5 days Penicillin V 500mg TID x 10 days | **Telithromycin** / **Penicillin V**<br>**PPc**<br>TOC 97/115 (84.3%) / 106/119 (89.1%)<br>Late post-tx 89/108 (82.4%) / 94/111 (84.7%)<br>**mITT**<br>TOC 110/138 (79.7%) / 119/150 (79.3%)<br>Late post-tx 103/138 (74.6%) / 109/150 (72.7%)<br>TOC= test of cure days 16-20; late post-tx days 38-45<br>All results support equivalency of telithromycin | **Telithromycin** / **Penicillin V**<br>**PPb**<br>Satisfactory (TOC) 97/115 (84.3%) / 106/119 (89.1%)<br>Satisfactory (late post-tx) 89/108 (82.4%) / 94/111 (84.7%)<br>Eradication (TOC) 98/115 (85.2%) / 106/119 (89.1%)<br>Eradication (late post-tx) 93/108 (86.1%) / 96/111 (86.5%)<br>**bmITT**<br>Satisfactory (TOC) 110/138 (79.7%) / 119/150 (79.3%)<br>Satisfactory (late post-tx) 103/138 (74.6%) / 109/150 (72.7%)<br>Eradication (TOC) 111/138 (80.4%) / 119/150 (79.3%)<br>Eradication (late post-tx) 107/138 (77.5%) / 111/150 (74%)<br>TOC= test of cure days 16-20; late post-tx days 38-45<br>Equivalency met for all satisfactory bacterial outcomes<br>Equivalency not determined for eradication rates |
| Quinn 2003 R, DB, PR | October 1998 – June 1999 USA, Canada | Telithromycin 800mg qd x 5 days Clarithromycin 250mg BID x 10 days | **Telithromycin** / **Clarithromycin**<br>**PPc**<br>TOC 139/150 (92.7%) / 123/135 (91.1%)<br>Late post-tx 120/134 (89.6%) / 103/118 (87.3%)<br>**mITT**<br>TOC 16-23d 193/232 (83.2%) / 192/231 (83.1%)<br>Late post-tx 31-45d 178/232 (76.7%) / 170/231 (73.6%)<br>TOC= test of cure days 16-23; late post-tx days 31-45<br>All results support equivalency of telithromycin | **Telithromycin** / **Clarithromycin**<br>**PPb**<br>Satisfactory (TOC) 137/150 (91.3%) / 119/135 (88.1%)<br>Satisfactory (late post-tx) 112/136 (82.4%) / 98/120 (81.7%)<br>**bmITT**<br>Satisfactory (TOC) 152/187 (81.3%) / 134/173 (77.5%)<br>Satisfactory (late post-tx) 133/187 (71.1%) / 116/173 (67.1%)<br>TOC= test of cure days 16-23; late post-tx days 31-45<br>Equivalency met for all satisfactory bacterial outcomes |

**APPENDIX 5. TREATMENT-EMERGENCT ADVERSE EVENTS REPORTED IN CONTROLLED CLINICAL STUDIES**

| | Zervos | | Aubier | | Hagberg | | Dunbar | | Pullman | | Tellier | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TEL | CEF | TEL | A/C | TEL | AMX | TEL | CLA | TEL | TRV | TEL x5d | TEL x7d | CLA |
| n | 180 | 186 | 160 | 160 | 199 | 205 | 221 | 222 | 108 | 109 | 193 | 195 | 187 |
| %pts. w/ TEAE | - | - | 23.8% | 36.9%* | 55.3% | 45.9% | 57% | 49.1% | - | - | 43% | 46.2% | 44.9% |
| TEAE possibly related to study drug | 30% | 32.3% | 13.1% | 25% | 33.7% | 41.2% | 38.5% | 27.9% | 47.2% | 33% | 24.4% | 21% | 21.9% |
| Discontinued due to TEAE | 3.3% | 1.6% | 1.9% | 10% | 4% | 4.9% | 3.6% | 2.7% | - | - | 4.7% | 3.1% | 5.3% |
| Serious AE | - | - | 4.4% | 3.8% | - | - | 5% | 6.3% | 1.9% | 1.8% | 4.7% | 2.6% | 5.9% |
| Serious AE possibly related to study drug | 0 | 0 | 0 | 0.6% | 0.5% | 0.5% | 0.9% | 0 | 0 | 0 | 0 | 0 | 0.5% |
| Nausea | 8.9%* | 3.2% | | | 8% | 2.9% | 8.6% | 4.9% | | | 3.1% | 3.6% | 2.1% |
| Diarrhea | 12.8% | 11.8% | 3.1% | 10% | 11.6% | 7.3% | 12.7% | 7.2% | 18.5%* | 6.4% | 6.2% | 6.7% | 5.3% |
| Dizziness | 3.3% | 1.6% | - | - | 2.5% | 1.5% | 4.1% | 1.8% | - | - | | | |
| Vomiting | 2.8% | 1.6% | 0.6% | 3.1% | 1.5% | 2% | 3.6% | 1.4% | - | - | | | |
| Abdominal pain | - | - | - | - | 2% | 2% | - | - | - | - | 2.6% | 1.0% | 0.5% |
| Vaginal candidiasis | - | - | - | - | 2% | 0 | - | - | - | - | | | |
| ↑ ALT | - | - | - | - | 4.1% | 2.4% | - | - | - | - | 2.1% | 1.0% | 1.6% |
| GI pain | 2.8%* | 0 | 0.6% | 3.1% | 2% | 0 | - | - | - | - | | | |
| Rash | - | - | - | - | 0.5% | 2% | - | - | - | - | | | |
| Bronchitis | - | - | 1.3% | 7.5% | - | - | - | - | - | - | | | |
| Headache | 2.8% | 4.8% | - | - | 4% | 4.4% | 4.1% | 5.4% | - | - | 0.5% | 2.3% | 0.5% |
| Taste perversion | 0.6% | 2.7% | - | - | 3.6% | 7.2% | - | - | - | - | | | |

TEL=telithromycin; CEF=cefuroxime; A/C= amoxicillin/clavulanate; AMX= amoxicillin; CLA= clarithromycin; TRV= trovafloxacin; PCN= penicillin
Events occurring ≥ 2% (Zervos, Aubier, Hagberg, Tellier, Roos, Buchanan, Ferguson, Norrby); events occurring ≥ 3% (Dunbar); events occurring ≥ 5% (Luterman); not stated (Pullman, Quinn)

**Appendix 5 continued on next page**

**APPENDIX 5 CONTINUED**

| | Roos | | Buchanan | | Luterman | | | Ferguson | | Norrby | | Quinn | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TEL x5d | TEL x10d | TEL | CEF | TEL x 5d | TELx 10d | A/C | TEL | MOX | TEL | PCN | TEL | CLA |
| n | 166 | 167 | 252 | 121 | 244 | 254 | 245 | 173 | 176 | 198 | 196 | 229 | 228 |
| %pts. w/ TEAE | 34.2% | 30.1% | 36.1% | 31.4% | - | - | - | 34.7% | 27.8% | 35.4% | 35.2% | 67.2% | 57.5% |
| TEAE possibly related to study drug | - | - | 22.2% | 16.5% | 42.2% | 46.9% | 42.9% | 24.3% | 21% | 28.8% | 20.9% | 43.2% | 26.3% |
| Discontinued due to TEAE | 3.6% | 9.6% | 2% | 1.7% | 6.6% | 5.5% | 4.5% | 2.9% | 3.4% | 4.5% | 4.1% | 5.7% | 2.5% |
| Serious AE | 0 | 0 | 4.4% | 3.3% | - | - | - | 5.2% | 2.3% | 1% | 1.5% | 1.3% | 0.9% |
| Serious AE possibly related to study drug | 0 | 0 | - | - | 0 | 1.2% | 0.4% | | | 0 | 0 | 0.9% | 0 |
| Nausea | 4.8% | 2.4% | 6.7% | 4.1% | 11.9% | 9.4% | 7.8% | 5.8% | 4.5% | 7.1%* | 1.0% | 10.5%* | 3.9% |
| Diarrhea | 9.6% | 13.3% | 6% | 5% | 19.3% | 20.5% | 23.7% | 8.1% | 1.7% | 13.1%* | 3.1% | 16.6%* | 7.5% |
| Dizziness | 0.6% | 2.4% | 2.8% | 0 | 5.3% | 5.1% | 2% | - | - | 3% | 1% | - | - |
| Vomiting | - | - | 2% | 2.5% | - | - | - | - | - | 2% | 3.1% | 5.2%* | 0 |
| Abdominal pain | - | - | - | - | 3.3% | 5.1% | 2.4% | - | - | 0.5% | 2.6% | - | - |
| Vaginal candidiasis | 3% | 1.8% | - | - | 1.6% | 3.1% | 5.3%* | - | - | - | 2.6%* | - | - |
| ↑ ALT | 2.4% | 0.6% | - | - | - | - | - | - | - | 0.5% | 3.6%* | - | - |
| GI pain | 1.8% | 4.8% | - | - | - | - | - | - | - | 2.5% | | - | - |
| Rash | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Bronchitis | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Headache | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Taste perversion | - | - | - | - | - | - | - | - | - | - | - | - | - |

TEL=telithromycin; CEF=cefuroxime; A/C= amoxicillin/clavulanate; AMX= amoxicillin; CLA= clarithromycin; TRV= trovafloxacin; PCN= penicillin
Events occurring ≥ 2% (Zervos, Aubier, Hagberg, Tellier, Roos, Buchanan, Ferguson, Norrby); events occurring ≥ 3% (Dunbar); events occurring ≥ 5% (Luterman); not stated (Pullman, Quinn)