

Telithromycin (Ketek[®], Aventis Pharmaceuticals, Inc.)

The first of the ketolide antibiotics

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Telithromycin is the first drug approved in the ketolide class. It is a derivative of erythromycin. Telithromycin was the first drug approved for the treatment of pneumonia caused by multi-drug-resistant strains of *S. pneumoniae*, defined as strains that are resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracyclines and trimethoprim/sulfamethoxazole. Multi-drug-resistant pneumococci have become more common in recent years, leading to treatment failures and increasing uncertainty in the choice of antimicrobials.¹

PHARMACOLOGY/PHARMACOKINETICS

Telithromycin is a ketolide antibiotic, a member of the macrolide-lincosamide-streptogramin B (MLS_B) group of antibiotics, and a derivative of erythromycin.² Like all antimicrobials of this class, telithromycin inhibits bacterial protein synthesis by binding to bacterial ribosomes. The affinity of telithromycin for the specific nucleotides at the binding site within the 50S ribosome is approximately ten times greater than that of erythromycin. In addition, telithromycin interferes with the assembly process of new 50S subunits. *In vitro*, telithromycin exhibits concentration-dependent bactericidal activity against *S. pneumoniae*.

Telithromycin is orally absorbed with an absolute bioavailability of 57%.³ Food has no effect on the rate or extent of absorption. Peak plasma concentrations are attained at approximately one hour after an oral dose. Following multiple-dose administration, the C_{max} is approximately 2.27 mcg/mL; the AUC is 12.5 mcg hr/mL and the terminal elimination half-life is approximately 10 hours. Hepatic metabolism accounts for 37% of elimination, with 13% excreted unchanged in the urine and 7% excreted unchanged in the feces. Telithromycin is 60%-70% protein bound, with a volume of distribution of 2.9 L/kg. The ratio of tissue concentration to plasma concentration twelve hours after administration is 6.33 for the bronchial mucosa, 13.8 for epithelial lining fluid and 180 for alveolar macrophages.

There are no differences in the pharmacokinetic parameters of telithromycin based on gender. In hepatically impaired patients, the pharmacokinetics of telithromycin did not vary significantly from healthy subjects, perhaps due to an increase in renal clearance of the drug in hepatic impairment. The AUC and C_{max} of telithromycin are significantly increased in patients with severe renal impairment. The effect of dialysis on telithromycin is unknown. The manufacturer makes no recommendations regarding dose in patients with severe renal impairment, including those on dialysis. The AUC of telithromycin is in-

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Summary

Indications. Telithromycin is indicated for the treatment of infections caused by susceptible strains of bacteria in the following conditions: acute bacterial exacerbations of chronic bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*; acute bacterial sinusitis caused by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* or *Staphylococcus aureus*; community-acquired pneumonia of mild-to-moderate severity caused by *S. pneumoniae* (including multi-drug-resistant isolates), *H. influenzae*, *M. catarrhalis*, or *S. aureus*.

Monitoring parameters. Patients should be monitored for improvement in the signs and symptoms of infection, such as fever and white blood cell count; signs of hypersensitivity, such as wheezing, rash or swelling; elevated liver function tests, especially in patients with hepatic impairment; severe diarrhea; dizziness; QTc interval prolongation

Dose. The recommended dose of telithromycin is 800 mg (two 400 mg tablets) once daily; may be taken with or without food

Geriatrics. No dose adjustment required for geriatric patients

Pregnancy category. C

Breastfeeding. Telithromycin may be excreted in breast milk.

Renal insufficiency. In patients with creatinine clearance <30 mL/min, including those on dialysis, the dose of telithromycin has not been determined

Hepatic impairment No dose adjustment required for patients with hepatic impairment

Cost. The AWP for two 400 mg tablets is \$11.54. A five-day dose pack is available at an AWP of \$57.69. The AWP for a 7-10 day course of therapy is \$80.78-\$115.40

creased in patients older than 65 years; however, no dose adjustment based on age is necessary.

MICROBIOLOGY/RESISTANCE

The first report of the PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) study assessed the antibiotic susceptibilities of 8,926 clinical isolates obtained from patients with community-acquired respiratory tract infections in 25 countries.⁴ Of the 3,362 isolates of *S. pneumoniae*, 14.2% had intermediate penicillin sus-

ceptibility and 22.1% were penicillin-resistant. Over 99% of the penicillin-resistant *S. pneumoniae* isolates were susceptible to telithromycin.

Telithromycin was second to penicillin in potency vs. 1485 *S. pyogenes* isolates. All *S. pyogenes* isolates were susceptible to penicillin; there were 36 isolates with telithromycin MICs of 4 mcg/mL or greater. All of these isolates were macrolide-resistant via the *ermB* mutation. Telithromycin was active against *H. influenzae* isolates, regardless of beta-lactamase production status. *M. catarrhalis* was highly susceptible to telithromycin.

Doern and Brown reported the antibiotic susceptibilities of 16,727 U.S. clinical isolates of *S. pneumoniae*, *S. pyogenes* and *H. influenzae*.⁵ Among the 10,103 *S. pneumoniae* isolates, 26.4% were resistant to penicillin (MIC ≥ 2 mcg/mL) and 12.5% had intermediate susceptibility (MIC 0.12-1 mcg/mL). Of the penicillin-resistant isolates, 77.7% were also resistant to erythromycin, 77.8% were resistant to azithromycin, 77.5% were resistant to clarithromycin and 0.2% were resistant to telithromycin. Penicillin resistance also correlated to resistance to amoxicillin/clavulanate, cefuroxime, clindamycin, tetracycline and TMP/sulfa. Resistance to fluoroquinolones, namely levofloxacin and gatifloxacin, was slightly higher among penicillin-resistant isolates (1.2% compared to 0.7-0.8% of penicillin-susceptible isolates). Overall, telithromycin was surpassed only by linezolid in the proportion of *S. pneumoniae* isolates that was susceptible (99.7% vs. 99.9%).

The *S. pyogenes* isolates were uniformly susceptible to penicillin; however, 5.4% were resistant to erythromycin. While erythromycin resistance correlated strongly with resistance to azithromycin (96.3%) and clarithromycin (96.7%), all erythromycin-resistant strains were susceptible to telithromycin. The MIC₉₀ for telithromycin increased from 0.03 mcg/mL for erythromycin-susceptible and -intermediate strains to 1 mcg/L for erythromycin-resistant strains.

Among *H. influenzae* isolates, telithromycin had greater activity than clarithromycin, and was equivalent to azithromycin, regardless of whether the isolate was a beta-lactamase producer.

Ubukata et al. reported on the susceptibilities of 215 clinical isolates of *S. pneumoniae*, including a majority with either the *mefA* (30.2%) or the *ermB* (37.7%) MLS_B resistance genes, or both (1.4%).⁶ Isolates with the *mefA* resistance gene had reduced susceptibilities (MIC₉₀ = 1-4 mcg/mL) to erythromycin, roxithromycin (not approved in the United States), clarithromycin and azithromycin, but telithromycin was highly active against these strains. Isolates with the *ermB* resistance gene were highly resistant (MIC₉₀ > 64 mcg/mL) to erythromycin, roxithromycin, clarithromycin and azithromycin, as well as other MLS_B antibiotics, but were still susceptible to telithromycin.

Hammerschlag et al. summarized several studies reporting the activity of telithromycin against isolates of *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae*.⁷ A study of 19 clinical isolates of *C. pneumoniae* found that telithromycin had activity comparable to erythromycin, roxithromycin and azithromycin against the isolates. Among five MLS_B antibiotics tested against 30 clinical isolates of *L. pneumophila*, telithromycin was the second most active, with an MIC₉₀ of 0.03 mcg/mL after 48 hours of incubation and an MIC₉₀ of 0.06 mcg/mL after

96 hours of incubation. Telithromycin was as effective as clarithromycin and erythromycin in reducing bacterial counts of *L. pneumophila* in guinea pig alveolar macrophages. When compared to seven macrolide antibiotics for activity against 25 isolates of *M. pneumoniae*, telithromycin was found to be as active as the most active macrolides: erythromycin, roxithromycin, clarithromycin and azithromycin.

CLINICAL TRIALS

Hagberg et al. compared telithromycin 800 mg once daily with amoxicillin 1000 mg three times daily in a randomized, double-blind trial in 404 patients with community-acquired pneumonia (CAP).⁸ The subjects were adult patients with two or more signs and symptoms of CAP, including cough, purulent sputum, auscultatory findings, dyspnea or tachypnea and radiographic findings of bacterial pneumonia. Subjects also had fever, elevated WBC counts or Gram stains showing gram-positive diplococci. Patients were excluded if they were candidates for intravenous antibiotic therapy or ICU admission, or if they were pregnant or could become pregnant, had impaired liver or kidney function, had a history of prolonged QT interval, were immunocompromised or had pulmonary disease that could interfere with assessment of response.

Subjects were randomized to receive either telithromycin 800 mg once daily (n=199) or amoxicillin 1000 mg three times daily (n=205) for ten days. The subjects received a complete physical examination on Day one and had two follow-up visits between days three to five and 11-13, as well as a test-of-cure (TOC) visit between days 17-24 and a late visit between days 31-36. Efficacy was assessed as the clinical outcome at the time of the TOC visit, including cure, defined as improvement or resolution of signs and symptoms and improvement or absence of disease progression on chest x-ray; indeterminate, defined as unavailability of information or need for additional antimicrobial therapy for a condition other than a respiratory infection; or failure, defined as lack of change or worsening of signs and symptoms or chest x-ray, or need for additional antimicrobial therapy. The secondary efficacy measures were bacteriologic outcome at the TOC visit and clinical and bacteriologic outcome at late visit.

At the TOC visit, there was no difference between the telithromycin group and the amoxicillin group in clinical cure rates (94.6% and 90.1%, respectively) among the 301 patients in the per-protocol assessment. A similar result was found at the late visit (92.0% vs. 85.3%). In the modified intent-to-treat analysis, more patients in the telithromycin group had a clinical cure at the final visit (81.4% vs. 72.7%; 8.7% difference, 95% CI 0.1, 17.4). There were two presumed relapses at the final visit among the subjects receiving telithromycin and five presumed relapses at the final visit among the subjects receiving amoxicillin. The bacterial eradication rates at the TOC visit were equivalent for telithromycin and amoxicillin (87.5% and 86.7%, respectively) in the per-protocol assessment.

There were 204 subjects who experienced a treatment-emergent adverse effect (50.5% overall; 55.3% of subjects receiving telithromycin vs. 45.9% of subjects receiving amoxicillin). The most common adverse effects were nausea and diarrhea, fol-

TABLE 1 - SUSCEPTIBILITY OF RESPIRATORY PATHOGENS TO TELITHROMYCIN

Isolate	n	MIC ₅₀ (mcg/mL)	MIC ₉₀ (mcg/mL)	% Resistant	% Susceptible	Ref.
<i>S. pneumoniae</i>	3,362	0.015	0.12		99.9	4
PSSP	2,142	0.008	0.03		100	4
PISP	476	0.015	0.12		100	4
PRSP	744	0.06	0.5		99.6	4
<i>S. pyogenes</i>	1485	0.015	0.015		N/A*	4
<i>H. influenzae</i>	2948	1	2		99.9	4
<i>H. influenzae</i> BL-	2459	1	2		99.9	4
<i>H. influenzae</i> BL+	489	1	2		100	4
<i>M. catarrhalis</i>	1131	0.06	0.12		100	4
<i>S. pneumoniae</i>	10,103	≤0.015	0.5	0.04		5
PSSP	6,183	≤0.015	0.03	0		5
PISP	1,266	0.03	0.5	0		5
PRSP	2,654	0.25	1	0.2		5
ERSP	3,133	0.25	1	0.1		5
<i>S. pyogenes</i>	3,918	0.03	0.03	N/A*		5
ESSPy	3,700	0.03	0.03	N/A*		5
ERSPy	214	0.25	1	N/A*		5
<i>H. influenzae</i>	2,710	2	4	0.6		5
<i>H. influenzae</i> BL-	1,941	2	4	0.6		5
<i>H. influenzae</i> BL+	769	2	4	0.5		5
<i>S. pneumoniae</i> ^a	66	0.016	0.016			6
<i>S. pneumoniae</i> ^b	65	0.063	0.125			6
<i>S. pneumoniae</i> ^c	81	0.063	0.5			6
<i>S. pneumoniae</i> ^d	3	‡	‡			6
<i>C. pneumoniae</i>	19	0.0625	0.25			7
<i>L. pneumophila</i> ^e	30		0.03			7
<i>L. pneumophila</i> ^f	30		0.06			7
<i>M. pneumoniae</i>	25	≤ 0.015	≤ 0.015			7

* - NCCLS breakpoints not determined
PSSP - Penicillin-susceptible *Streptococcus pneumoniae*
PISP - Penicillin-intermediate *Streptococcus pneumoniae*
PRSP - Penicillin-resistant *Streptococcus pneumoniae*
ESSPy - Erythromycin-susceptible *Streptococcus pyogenes*
ERSPy - Erythromycin-susceptible *Streptococcus pyogenes*

BL- - Beta-lactamase-negative
BL+ - Beta-lactamase-positive
^a - No MLS_B resistance gene
^b - With *mefA* gene
^c - With *ermB* gene

^d - With *mefA* and *ermB* genes
‡ - Only MIC reported: 0.25 mcg/mL
^e - After 48 hours' incubation
^f - After 96 hours' incubation

lowed by thrombocytosis, liver enzyme increase, headache, dizziness, abdominal pain and vaginal moniliasis. There was one subject in each group with a serious treatment-emergent adverse effect. The number of subjects in each group that discontinued treatment was similar (eight in the telithromycin group and 10 in the amoxicillin group). There were two deaths in the telithromycin group and one death in the amoxicillin group. The deaths were not considered to be related to the treatment.

Hagberg et al. performed a pooled analysis of three comparative trials and three open trials of telithromycin in patients with mild-to-moderate community-acquired pneumonia.⁹ The analysis included the trial described above. All six trials enrolled subjects with radiologic findings consistent with CAP, and a minimum of two signs and symptoms suggestive of CAP. A total of 503 patients were enrolled. Subjects received 7-10 days of

telithromycin 800 mg once daily PO or one of three comparator drugs: amoxicillin 1000 mg three times daily PO for 10 days, clarithromycin 500 mg twice daily PO for 10 days or trovafloxacin 200 mg daily PO for seven to 10 days. The manner of assessment and the outcome criteria were the same as in the Hagberg 2002 trial.

There was no significant difference between telithromycin and any comparator in clinical cure rate at the TOC visit among the per-protocol population. In the comparative studies, telithromycin produced clinical cures in 88.3% to 94.6% of subjects (91.0% overall), compared with 88.5% to 94.2% for the comparators (90.4% overall). Among the modified intent-to-treat population, the overall clinical cure rate was 82.3% for telithromycin and 80.8% for the comparators. In the open trials, the clinical cure rate ranged from 92.9% to 93.6% (93.1% overall)

among the per-protocol population. Among the modified intent-to-treat population, the overall clinical cure rate was 83.9%.

Bacteriological eradication rates and clinical cure rates for telithromycin were reported in the per-protocol population based on the causative pathogen. The highest eradication and cure rates were for pneumonia caused by *S. pneumoniae* (95.4% eradicated; 94.8% clinically cured), followed by *H. influenzae* (89.5%; 90.5%), *M. catarrhalis* (90.0%; 86.7%) other pathogens (86.0%; 91.2%) and *S. aureus* (78.9%; 78.9%). The overall bacterial eradication rate was 90.5% and the overall clinical cure rate was 91.2%. Patients with antibiotic-resistant strains of *S. pneumoniae* had somewhat lower eradication and cure rates. For penicillin-resistant isolates, the bacteriological eradication rate was 81.3% and the clinical cure rate was also 81.3%. For erythromycin-resistant isolates, the eradication rate and clinical cure rate were both 81.3%. Telithromycin was highly effective against the atypical or intracellular bacteria *C. pneumoniae* (94.1% clinical cure rate), *M. pneumoniae* (96.8%) and *L. pneumophila* (100%). Clinical cure rates were similar among hospitalized and non-hospitalized patients (92.6% and 92.4%, respectively). There were no significant differences between the overall cure rate and the cure rates for patients 65 years and older; patients with pneumococcal bacteremia; and the sickest patients, designated as having a Fine score (a five-point risk stratification scale predecessor to the PORT score) greater than or equal to III. The Fine score categorizes CAP patients by risk of mortality based on demographic variables, comorbidities and abnormal findings on physical examination; a score of III corresponded to a 30-day risk of mortality of 0.9 to 2.8% in a recent validation study.¹⁰

The three comparative trials assessed the tolerability of telithromycin. Overall, the discontinuation rate was 4.9%. Adverse events tended to be mild, with diarrhea (13.1%), nausea (8.0%), vomiting (2.3%) and dizziness (2.1%) reported most commonly. Diarrhea was more common among patients taking telithromycin than among those taking comparator agents. Telithromycin was similar to clarithromycin in its effects on liver enzymes and QTc intervals (percentages not specified).

Two randomized, double-blind studies compared the rates of hospitalization between groups of CAP patients receiving clarithromycin 500 mg twice daily PO with telithromycin 800 mg daily PO for five or seven days or for 10 days.^{11,12} Patients with mild-to-moderate CAP who were 18 years old or older, had positive radiologic findings for CAP and had two or more signs and symptoms of CAP were enrolled in the studies. Assessment and outcomes were structured as in the studies described previously. Hospitalizations for reasons related to CAP were considered in the analysis of hospitalization rates.

There were 581 patients in the telithromycin five or seven days study, with an equal number randomized to receive the five-day therapy, the seven-day therapy and the clarithromycin.¹¹ The clinical cure rates among the per-protocol population at the TOC visit were similar in all three groups: 89.3% for the group receiving five days of telithromycin, 88.8% for the group receiving seven days of telithromycin and 91.8% for those receiving clarithromycin. There was no statistical difference between clarithromycin and either duration of therapy of telithromycin.

The results held up in the modified intent-to-treat population, with clinical cure rates of 82.4%, 82.2% and 81.2%, respectively.

There were 13 hospitalizations among the intent-to-treat population in the clarithromycin group, of which seven were considered to be related to CAP; of nine hospitalizations in the group receiving telithromycin for five days, three were considered to be related to CAP; and in the group receiving seven days of telithromycin, one of four hospitalizations was considered to be related to CAP. The rate of CAP-related hospitalization among the per-protocol population for clarithromycin-treated patients was 3.7 hospitalizations per 100 patients, compared to a combined rate of one per 100 patients in the two telithromycin groups. This difference was statistically significant ($p=0.026$). There were 40.1 CAP-related hospital days per 100 patients in the clarithromycin group compared to 12.1 days in the combined telithromycin groups ($p=0.07$). The numerical results among the modified intent-to-treat population were similar; however, only the difference in the number of hospitalizations between clarithromycin and 7-day telithromycin was statistically significant (7 vs. 1; $p=0.021$).

In the second study, 448 patients age 18 and over were randomized to receive 10 days of telithromycin 800 mg daily PO or 10 days of clarithromycin 500 mg twice daily PO.¹² At the TOC visit, the clinical cure rates among the per-protocol population for clarithromycin and telithromycin were nearly identical (88.3% vs. 88.5%, respectively). In the modified intent-to-treat populations, the findings were similar. The clarithromycin group had a clinical cure rate of 80.7%, compared to 78.9% for the telithromycin group. The results did not differ statistically in either analysis.

Of 14 hospitalizations among the intent-to-treat population in the clarithromycin group, eight were considered to be CAP-related. In the telithromycin group, four of 11 hospitalizations were considered to be CAP-related. The hospitalization rate per 100 patients was 3.6 for clarithromycin and 1.8 for telithromycin (NS). The hospitalization rates among the modified intent-to-treat population were 3.8 and 2.0, respectively. The number of hospital days per 100 patients in the intent-to-treat population was 15.8 in the clarithromycin group and 11.5 in the telithromycin group (NS). There was a numerical advantage for telithromycin compared to clarithromycin in days of intravenous antibiotic therapy (27.2 days per 100 patients vs. 41.5 days per 100 patients, respectively) and in CAP-related hospitalization costs (\$11,321 per 100 patients vs. \$31,503 per 100 patients, respectively), but these results were not statistically significant.

A randomized, double-blind study in 325 adult patients compared telithromycin 800 mg daily PO for five days to amoxicillin/clavulanate 500/125 mg three times daily PO for 10 days in the treatment of acute exacerbations of chronic bronchitis (AECB).¹³ The subjects were 18 years or older with a history of chronic bronchitis and COPD and a clinical diagnosis of AECB; those with pneumonia, acute bronchitis or other pulmonary condition that could confound assessment were excluded, as were those who required hospitalization or intravenous antibiotics or who had hepatic impairment, renal impairment, immune dysfunction or a history of long QT syndrome. The as-

assessment schedule was the same as in the CAP studies. Efficacy was assessed as improvement in AECB signs and symptoms, graded on a 4-point scale from absent to severe. Bacterial eradication was a secondary efficacy measure.

The clinical cure rates among the per-protocol population for telithromycin and amoxicillin/clavulanate at the TOC visit were similar (86.1% vs. 82.1%, respectively). Among the modified intent-to-treat population, the cure rates were 81.3% and 78.1%, respectively. At the late visit (days 31-36), the clinical cure rates were 78.1% and 75.0%, respectively, among the per-protocol population and 73.8% and 71.3%, respectively among the modified intent-to-treat population. There were no statistically significant differences in any comparison of cure rates.

Bacteriological eradication rates at the TOC visit were also similar. Among the per-protocol population, the rates were 69.2% for telithromycin and 70.0% for amoxicillin/clavulanate. The results were similar among the modified intent-to-treat population, at 60.0% and 56.8%, respectively. Only a minority of patients, 105 of the modified intent-to-treat population, had an identified pathogen, however. The most commonly isolated pathogens among the modified intent-to-treat population were *H. influenzae* (20 patients in the telithromycin group; 21 patients in the amoxicillin/clavulanate group), *S. pneumoniae* (12; 8), *M. catarrhalis* (5; 10) and *Haemophilus parainfluenzae* (6; 1). In the telithromycin group, there were five cases of bacterial persistence (*H. influenzae* = 4; *Pseudomonas* spp. = 1) and four cases of presumed persistence (*H. influenzae* = 3; *S. pneumoniae* = 1). In the amoxicillin/clavulanate group, there were four cases of persistence (*Pseudomonas aeruginosa* = 2; *Hafnia alvei* = 1; *S. aureus* = 1), one case of presumed persistence (*S. pneumoniae*) and one case of recurrence (*H. parainfluenzae*).

Both regimens were well-tolerated, although mild-to-moderate adverse reactions were frequent. For telithromycin, 23.8% of patients reported treatment-related adverse reactions, compared to 30.3% for amoxicillin/clavulanate ($p=0.015$). The most commonly reported adverse events in both groups were gastrointestinal. Diarrhea was the only adverse reaction reported by more than 2% of the telithromycin group (3.1%); in the amoxicillin/clavulanate group, diarrhea (10.0%), bronchitis (7.5%), dyspepsia (3.1%) and vomiting (3.1%) were commonly reported. Only one serious adverse reaction was considered to be drug-related; one patient in the amoxicillin/clavulanate group developed a severe gastrointestinal reaction. There was no difference between the groups in safety parameters, including ECG findings.

In a randomized, double-blind trial in 754 adult patients with acute maxillary sinusitis (AMS), amoxicillin/clavulanate 500/125 mg three times daily PO for 10 days was compared to telithromycin 800 mg daily PO for five or 10 days.¹⁴ Subjects included in the trial demonstrated clinical symptoms of AMS for less than 28 days, including purulent nasal discharge, maxillary tenderness or other suggestive pain, or nasal congestion without adequate relief from decongestants, and radiologic findings suggestive of maxillary sinusitis within 48 hours of entry into the trial. Patients were excluded if they had chronic, recurrent or nosocomial sinusitis; suspected nonbacterial infection or documented resistant organisms; anatomical or medical conditions that could confound assessment; progressive fatal illness; long

QT syndrome; hepatic or renal insufficiency; or lactation or pregnancy. Assessments were scheduled as in the previously described trials. Clinical cure at the TOC visit was defined as improvement in AMS signs and symptoms or return to pre-infection state, and improvement or absence of worsening of radiologic findings. Bacteriologic eradication was a secondary outcome.

Among the per-protocol population, clinical cure rates at the TOC visit were 75.3% for the telithromycin five-day group, 72.9% for the telithromycin 10-day group and 74.5% for the amoxicillin/clavulanate group (NS). The clinical cure rates were also statistically similar among the groups at the late visit (69.9%, 67.7% and 70.8%, respectively). The causative organisms were isolated in only a fraction of patients. There were 33 organisms identified from the sinus punctures of 29 patients. The most commonly isolated organisms from the per-protocol population were *S. pneumoniae* and *H. influenzae* (six isolates each). The bacteriologic outcome was satisfactory (defined as documented eradication or presumed eradication based on patient's clinical recovery) at the TOC visit in six of seven per-protocol patients in each of the two telithromycin groups and eight of 10 patients in the amoxicillin/clavulanate group.

Adverse drug reactions were common, occurring in 44% of patients overall, but the reactions were for the most part mild. Reactions occurring in 5% or more of the patients in the five-day telithromycin group were diarrhea (19.3%), nausea (11.9%) and dizziness. The reactions occurring in the 10-day group were similar; diarrhea (20.5%), nausea (9.4%), dizziness (5.1%) and abdominal pain (5.1%) were the most common. In the amoxicillin/clavulanate group, adverse reactions occurring in 5% or more were diarrhea (23.7%), nausea (7.8%) and vaginal candidiasis (5.3%). The number of patients withdrawing from the study because of adverse reactions was similar in the three groups. Overall 41 patients (5.5%) withdrew, 16 in the five-day telithromycin group, 14 in the telithromycin 10-day group and 11 in the amoxicillin/clavulanate group. There were seven patients with a serious treatment-emergent adverse event; four of those events were thought to be drug-related. In the 10-day telithromycin group, one patient developed an allergy to the medication, one developed gastroenteritis and a third developed pseudomembranous colitis. In the amoxicillin/clavulanate group, one patient developed pseudomembranous colitis. There were no patients in any group with clinically significant changes in the QTc interval, and there were no differences among the groups in vital signs or laboratory test results, such as serum transaminases.

ADVERSE EFFECTS

The adverse reactions reported in the clinical trials tended to be mild and not significantly different from the comparator drugs. Gastrointestinal intolerance, primarily diarrhea and nausea, were the most common reactions. The majority of severe adverse reactions in clinical trials were gastrointestinal problems. In the phase III trials of telithromycin, the adverse reactions thought to be treatment-related that occurred in 2% or more of subjects receiving telithromycin were diarrhea (10.0%), nausea (7.0%), dizziness (2.8%), vomiting (2.4%), loose stools (2.1%) and headache (2.0%).³ Infrequently observed adverse reactions in-

clude gastritis, oral candidiasis, stomatitis, increased serum transaminases, dry mouth, abdominal pain, blurred vision, diplopia, difficulty focusing, vaginal candidiasis and rash. In some cases, visual disturbances were severe, and caused patients to discontinue therapy. The visual reactions tended to occur after the first or second dose, lasted for several hours, recurred upon rechallenge, and resolved even as therapy continued, although some disturbances persisted until therapy was complete.

Because telithromycin is structurally related to the macrolide antibiotics, consideration must be given to the potential for QTc interval prolongation. In a small study performed to evaluate this effect, 18 healthy subjects received single doses and six-day courses of telithromycin 800 mg daily PO, clarithromycin 500 mg twice daily PO, or placebo.¹⁵ A second group of 16 subjects received single oral doses of telithromycin 800 mg, 1600 mg, 2400 mg, or placebo, with a one-week washout period between doses. No group receiving telithromycin or clarithromycin experienced a significant increase in the mean QT interval compared to placebo. Among individuals, however, four subjects had a QT interval change of 30 ms or greater: one following each single dose of clarithromycin and telithromycin 800 mg, two after single doses of telithromycin 800 mg and one after repeated doses of telithromycin. The increases in QT interval ranged from 30 to 42 ms, and the QT interval did not exceed 450 ms among male subject or 470 ms among female subjects. While the effects on the QT interval in this study were not pronounced, the possibility of a greater effect in an individual patient cannot be excluded.

DRUG INTERACTIONS

Telithromycin inhibits the CYP450 3A4 enzyme. Drugs that are metabolized by the 3A4 system may have increased plasma levels and prolonged systemic exposure if administered concurrently with telithromycin. Telithromycin is contraindicated in patients taking cisapride or pimozide, and simvastatin, lovastatin and atorvastatin should be discontinued while telithromycin is administered. Patients taking digoxin should be monitored for increasing serum levels and signs of digoxin toxicity while taking telithromycin. Midazolam and other benzodiazepines may have increased blood levels when taken concurrently with telithromycin; patients taking the drugs together should be monitored and the dose of benzodiazepine adjusted if necessary. Telithromycin should not be taken at the same time as rifampin, a 3A4-inducing drug, as the efficacy of telithromycin may be decreased. Similarly, the antiepileptic drugs phenytoin, carbamazepine and phenobarbital may reduce serum levels of telithromycin and result in therapeutic failure. Telithromycin should be used with caution in patients taking metoprolol and in patients taking drugs that are known to have interactions with the macrolide antibiotics, such as cyclosporine, tacrolimus, sirolimus and ergot alkaloids, although interactions between these drugs and telithromycin have not been reported.

COST, DOSE AND HOW SUPPLIED

Telithromycin is available as 400 mg tablets in 60-tablet bottles and 100-tablet unit dose packages. The AWP for two tablets is

\$11.54. A five-day dose pack is available with an AWP of \$57.69. The five-day pack is appropriate for the treatment of acute bacterial exacerbations of chronic bronchitis or for acute bacterial sinusitis. The recommended duration of treatment for CAP is seven to 10 days, with an AWP of \$80.78-\$115.40.

The AWP of telithromycin is similar that of other drugs used to treat respiratory tract infections. A five-day course of azithromycin (the Z-Pack[®]) has an AWP of \$49.43, amoxicillin/clavulanate 875/125 has an AWP of \$85.81-\$122.59 for a 7-10 day course, levofloxacin 500 mg has an AWP of \$77.61-\$110.88 for a 7-10 day course and clarithromycin 250 mg has an AWP of \$67.76-\$96.80 for a seven to 10 day course.

CONCLUSION

Telithromycin is an attractive option for the treatment of respiratory tract infections. It offers the convenience of once-daily dosing and has excellent activity against pneumococci with high-level macrolide resistance. Its drug interactions and adverse effect profile, including QTc prolongation, are similar to those of clarithromycin. The University of Wisconsin Hospital's Antimicrobial Use Subcommittee has recommended that telithromycin be added to the UWHC formulary and clarithromycin be deleted. Telithromycin may be used as an alternative to fluoroquinolones where macrolide-resistant pneumococci are suspected as infectious agents, thereby decreasing overall exposure to the broad-spectrum activity of the fluoroquinolones. The use of telithromycin in inpatients is expected to be small because of the current lack of a parenteral dosage form.

The Wisconsin Antibiotic Resistance Network (WARN) will issue a statement about the use of telithromycin advocating its use mild to moderate community-acquired pneumonia, bacterial sinusitis and acute exacerbations of chronic bronchitis in patients who may be at risk for infection with a multiple-drug-resistant microorganism, such as those recently treated with antibiotics. Because the ketolides have a narrower antimicrobial spectrum, they are less likely to disrupt a patient's naturally-occurring microbial flora than a respiratory quinolone, and so they may be preferable to quinolones in many respiratory infections. However, WARN does not consider ketolides to be first-line therapy under most circumstances because of the potential for the development of microbial resistance with overuse of new antibiotics. ●

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