REVIEW ARTICLE

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Benefit-Risk Assessment of Telithromycin in the Treatment of Community-Acquired Pneumonia

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Abstract

The purpose of this review is to assess the benefits and risks associated with the use of the ketolide antibacterial telithromycin, currently licensed for the treatment of adults with mild to moderate community-acquired pneumonia (CAP). Telithromycin is active against both the major (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*) and atypical/intracellular (*Chlamydophila pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae*) CAP pathogens. It is associated with a low potential to select for resistance and has maintained its *in vitro* activity against isolates of respiratory pathogens in countries where it has been in clinical use for several years. In randomized clinical trials, telithromycin has demonstrated efficacy comparable to the established

antibacterial classes (macrolides, fluoroquinolones and β-lactams) in the treatment of CAP.

The safety profile of telithromycin is broadly similar to that of other antibacterials used to treat CAP. The most common adverse events are gastrointestinal adverse effects and headache; these are generally mild to moderate in severity and reversible. Telithromycin appears to be well tolerated by adult patients in all age groups, including those with co-morbid conditions. In common with other antibacterials, telithromycin has the potential to affect the corrected QT interval; the concomitant use of cisapride or pimozide with telithromycin is contraindicated, while telithromycin should be avoided in patients receiving Class IA or Class III antiarrhythmic drugs. Visual disturbances (usually transient) have occurred in a small proportion of patients treated with telithromycin; it is recommended that activities such as driving are minimized during treatment. Telithromycin is contraindicated in patients with myasthenia gravis. Hepatic dysfunction may occur in some patients taking telithromycin; rare cases of acute hepatic failure and severe liver injury, including deaths, have been reported.

As telithromycin is an inhibitor of the cytochrome P450 (CYP) 3A4 system, coadministration of telithromycin with drugs metabolized by this pathway may require dose adjustments (e.g. with benzodiazepines) or a temporary hiatus in the use of the coadministered drug (e.g. HMG-CoA reductase inhibitors) metabolized by CYP3A4. Telithromycin may potentiate the effects of oral anticoagulants; careful monitoring is recommended in patients receiving telithromycin and oral anticoagulants simultaneously.

Although serious and sometimes fatal events have occurred in patients receiving telithromycin therapy, current data indicate that telithromycin offers an acceptable benefit risk ratio in the treatment of mild to moderate CAP.

Telithromycin is the first ketolide antibacterial to have received clinical approval. Originally designed specifically for the treatment of community-acquired respiratory tract infections (RTIs),[1,2] ketolides are semisynthetic derivatives of 14-membered ring macrolides. They have a number of important structural modifications that distinguish them from currently available macrolide antibacterials. The defining feature of ketolides is the substitution of the cladinose sugar at the 3 position of the macrolactone ring with a keto group. This increases acid stability and prevents ketolides from triggering expression of resistance to macrolide, lincosamide, streptogramin$_B$ (collectively known as MLS$_B$) antibacterials in strains with inducible *erm* determinants.[3] The addition of a carbamate side chain at position C11/C12 further improves the stability of telithromycin and differentiates it from the macrolides and other ketolides.[1,4]

Like the macrolides, the antibacterial activity of telithromycin involves inhibition of protein synthesis through binding to the 50S subunit of the bacterial ribosome. Binding occurs principally through domains II and V of the 23S ribosomal RNA of the 50S subunit. Macrolides bind strongly to domain V, but only weakly to domain II, whereas telithromycin, as a result of its structural modifications, binds strongly to both domains.[5,6] Overall, telithromycin binds 6–10 times more tightly than macrolides to bacterial ribosomes.[6]

Telithromycin received EU regulatory approval in 2001, and was first introduced in Germany in October of that year. This review will focus on the benefits and risks of telithromycin in the indication currently approved in North America, i.e., community-acquired pneumonia (CAP) of mild to moderate severity caused by *Streptococcus pneumoniae* (including multidrug-resistant strains), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila* (*Chlamydia*) *pneumoniae* or *Mycoplasma pneumoniae*, in patients ≥18 years of age. The vast majority of information currently available on the

efficacy and safety of telithromycin derives from the phase III/IV programme; therefore, this review should be regarded as a preliminary assessment that may require re-evaluation as more data become available from the routine use of telithromycin in clinical practice.

The primary information pertaining to telithromycin was derived from a search of the PubMed database up to and including September 2007, using the terms 'telithromycin', 'ketolide' and 'HMR 3647'. Additional information came from secondary references and from relevant congress abstract listings. Where no primary publications were available, information on telithromycin safety was obtained directly from the US product label.

1. Background

1.1 Epidemiology and Aetiology of Community-Acquired Pneumonia (CAP)

CAP is one of the most common infectious diseases treated by primary care physicians. Aside from the considerable economic burden this places on healthcare systems, CAP is associated with significant morbidity and mortality.[7] In the USA, for example, the annual death rate for CAP (approximately 45 000) makes it the leading cause of death from infectious disease and the sixth leading cause of death overall.[7] The bacterial pathogens most commonly responsible for CAP are *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*,[7,8] with the atypical/intracellular bacteria *C. pneumoniae*, *Legionella pneumophila* and *M. pneumoniae* becoming increasingly implicated.[9]

1.2 Management of CAP and the Problem of Resistance

Although bacterial infection is frequently diagnosed in patients with CAP, it is rare that the organism responsible is identified before antibacterial treatment is started. Therefore, initial antibacterial therapy is usually based on knowledge of the most likely causative pathogens and their susceptibility profiles. This empirical approach is under threat from the high levels of antibacterial resistance prevalent among the common pathogens.[10-16] The most pressing issue appears to be the global spread of *S. pneumoniae* strains showing resistance to β-lactams and/or macrolides, as these agents currently provide the mainstay of antibacterial therapy for CAP. Although resistance rates vary around the world, more than 30% of *S. pneumoniae* isolates surveyed in some countries show resistance to penicillin.[16] Macrolide resistance also exceeds 30% in many countries, with even higher rates in certain regions, such as the Far East.[16] The prevalence of multidrug-resistant pneumococcal strains has also risen in recent years.[17] In the USA, rates of penicillin, macrolide and multidrug resistance in *S. pneumoniae* are around 22%, 29% and 31%, respectively.[13]

Although the causes of antibacterial resistance are multifactorial, the increase in macrolide resistance appears to be closely associated with levels of use of this class of antibacterial. Thus, several studies have shown a link between the community use of newer macrolides and increased rates of resistance in *S. pneumoniae*.[18,19] A Canadian study showed that a major risk factor for infection with erythromycin-resistant *S. pneumoniae* was the use of clarithromycin or azithromycin in the previous 3 months.[20] The same study provided evidence that prior azithromycin therapy increased the risk of being infected with *S. pneumoniae* strains resistant to other antibacterials. Although these trends are a cause for concern, the clinical impact of antibacterial resistance is not fully clear. Nonetheless, a number of studies and numerous individual cases of macrolide treatment failure associated with macrolide-resistant *S. pneumoniae* have been described.[19,21]

A range of measures is seen as essential for controlling antibacterial resistance. These include the appropriate use of antibacterials (maximizing therapeutic effectiveness while minimizing toxicity and the development of resistance) and the replacement of older therapies with newer, more effective agents.[22]

1.2.1 Properties of an 'Ideal' Antibacterial Agent

New agents for the empirical treatment of CAP should possess a targeted spectrum of activity against the common causative pathogens (*S. pneumoniae*, *H. influenzae* and *M. catarrhalis*) and relevant atypical/intracellular pathogens such as

C. pneumoniae, *L. pneumophila* and *M. pneumoniae*. Ideally, antibacterials to be used for the treatment of CAP should also have a low potential to induce and select for resistance. Minimal activity against nonrespiratory bacterial flora and pathogens is important in preventing the development of resistance among these organisms ('collateral damage'). The pharmacokinetic/pharmacodynamic (PK/PD) profile of the antibacterial agent is also vitally important in terms of its potential to cause resistance. Agents with PK/PD properties compatible with good penetration at the sites of infection (e.g. epithelial lining fluid and bronchopulmonary tissues) but without the potential to accumulate in non-target tissues should achieve rapid eradication of the infecting organism without collateral damage. An appropriate elimination half-life ($t_{1/2}$) is also important because the use of antibacterials with a long $t_{1/2}$ can lead to prolonged exposure of bacteria to sub-inhibitory drug concentrations, which can increase the risk of resistance selection. One example of this comes from a study comparing resistance in the oral flora of children treated with azithromycin ($t_{1/2}$ 60–70 hours) or clarithromycin ($t_{1/2}$ 3–7 hours); macrolide-resistant isolates were found in 33% of the clarithromycin group compared with 87% of the azithromycin group 6 weeks after treatment.[23] On the other hand, antibacterials a with very short $t_{1/2}$ require multiple daily dose administration regimens, which are associated with poor patient adherence.[24] This often results in incomplete eradication of the infecting bacteria, which in turn increases the risk for resistance development.

In order to maintain high rates of patient adherence to therapy, antibacterials should have a convenient dose administration regimen as well as demonstrating a good tolerability profile. Finally, pharmacoeconomic considerations are becoming increasingly important when it comes to selecting antibacterial therapies.[25,26]

2. Benefit Evaluation

2.1 Spectrum of Activity

Telithromycin is active *in vitro* against common CAP pathogens as well as some important atypical/intracellular organisms.[1,2] This spectrum of activity is similar to that exhibited by newer macrolides such as clarithromycin and azithromycin.[26] Telithromycin also shows significant antibacterial activity against key Gram-negative respiratory tract pathogens, but has minimal activity against Gram-negative nonrespiratory pathogens and commensal bacteria.[27]

An important property of telithromycin is its activity against macrolide-resistant *S. pneumoniae*.[2] One of the main forms of macrolide resistance, mediated by the *erm*B gene, is associated with high-level MLS_B resistance.[28] Telithromycin binds 20 times more strongly than macrolides to ribosomes with domain V modifications that confer MLS_B resistance.[6] As a result, telithromycin is active against MLS_B-resistant *S. pneumoniae*.[29,30] The activity of telithromycin against macrolide-resistant *S. pneumoniae* enables telithromycin to be considered as a useful treatment option for CAP, particularly in the USA and other areas of the world where high rates of macrolide resistance prevail.

2.2 Pharmacokinetic and Pharmacodynamic Properties

Peak plasma telithromycin concentrations (C_{max} ≈2μg/mL) are attained approximately 1 hour after administration of a single 800-mg dose, with steady state being reached after 2–3 days of once-daily dose administration.[31,32] The terminal elimination $t_{1/2}$ of telithromycin after once-daily 800-mg dose administration is approximately 10 hours at steady state.[32] The major route of telithromycin elimination occurs via hepatic metabolism, of which approximately 50% is mediated by cytochrome P450 (CYP) 3A4-dependent pathways.[32] Patients with hepatic impairment do not experience significantly increased exposure to the drug, due to the existence of compensatory renal elimination.[33,34] Exposure to telithromycin is not significantly increased in patients with renal impairment.[34] However, a dose-reduction to 600 mg once daily is recommended in patients with severe renal impairment (creatinine clearance [CL_{CR}] <30 mL/min); in patients with hepatic failure and coexisting severe renal impairment, the recommended telithromycin dose is 400 mg once daily.[35]

The steady-state kinetics and short terminal $t_{1/2}$ of telithromycin are properties that ensure that this

drug is compatible with once-daily dose administration. A once-daily dose administration regimen is considered desirable for antibacterial therapies, because this maximizes the likelihood of patient adherence.[36] Furthermore, the comparatively short $t_{1/2}$ of telithromycin prevents prolonged exposure of bacteria to subinhibitory concentrations of the drug, thus reducing the pressure on the pathogens to develop resistance.

Several studies have measured the total drug exposure in patients treated with telithromycin, and mean plasma area under the plasma concentration-time curve from time 0 to 24 hours post-dose (AUC_{24}) values of 10.4–13.4 μg • h/mL have been reported.[37] Good penetration of the antibacterial agent into clinically relevant tissues and fluids is essential to maximize the chances of bacterial eradication. Telithromycin is a concentration-dependent antibacterial; as such, bacteriological efficacy is achieved by maximizing drug exposure at the site of infection.[38] Studies indicate that telithromycin penetrates and accumulates in a range of respiratory tissues and fluids, resulting in concentrations considerably higher than peak plasma concentration.[38] For example, in one study, the mean telithromycin concentrations measured in epithelial lining fluid were shown to exceed those measured in plasma at all time points (the respective telithromycin concentrations in plasma and epithelial lining fluid were 1.86 μg/mL and 14.89 μg/mL at 2 hours after dose administration, 0.23 μg/mL and 3.27 μg/mL at 12 hours and 0.08 μg/mL and 0.97 μg/mL at 24 hours).[39] Importantly, the concentrations of telithromycin achieved in epithelial lining fluid and other bronchopulmonary tissues[39] are equal to or above the telithromycin minimum concentration required to inhibit the growth of 90% of strains (MIC_{90}) values for the common CAP pathogens: *S. pneumoniae*, 0.25–0.5 μg/mL; *H. influenzae*, 2 μg/mL; and *M. catarrhalis*, 0.12 μg/mL.[38,40]

2.3 Potential for Future Resistance

Telithromycin appears to have a low potential for selection of resistant isolates and for induction of resistance among the common respiratory pathogens. This is due to the replacement of the L-cladinose group present in macrolides with a keto group, which ensures that telithromycin does not induce one of the most common forms of resistance to macrolides: *erm*B or MLS_B resistance.[3,41] The unique structure of the ketolides also allows accumulation of these drugs in *S. pneumoniae* strains with efflux (mefA-mediated) resistance, the most common form of macrolide resistance currently prevalent in the USA. In isolates harbouring the mefA gene, competition between ribosomal and Mef-binding sites for the internalized drug is thought to result in a net efflux of non-ketolide antibacterials. However, tight ketolide-ribosomal binding kinetics may reduce the stability of interactions between Mef-binding sites and telithromycin, leading to an accumulation of the drug that exceeds the pump's capacity to expel it from the cell.[42]

In vitro studies have demonstrated that telithromycin possesses bactericidal activity against *S. pneumoniae* (including strains resistant to erythromycin or penicillin), *H. influenzae, M. catarrhalis* and *C. pneumoniae*.[43] Based on the principle that "dead bugs don't mutate",[44] it is thought that antibacterial agents with bactericidal properties have less potential to develop resistance during treatment than bacteriostatic agents such as the macrolides. The minimal activity of telithromycin against Gram-negative nonrespiratory pathogens and commensal bacteria reduces the risk of collateral damage and the potential transfer of resistance genes to opportunistic pathogens associated with serious infections.[27,41]

Recent results from the PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) global surveillance programme indicate that the *in vitro* activity of telithromycin against clinical isolates of *S. pneumoniae* and other important respiratory pathogens did not diminish between 1999 and 2003, even in countries where telithromycin had been introduced for clinical use.[16,45] Sporadic reports of telithromycin resistance among erythromycin-resistant *S. pneumoniae* isolates have appeared,[46,47] although data from PROTEKT suggest that the global rate of telithromycin resistance among such isolates remains very low (<0.2%).[16] Nevertheless, it should be remembered that resistance has developed to all the antibacterial agents ever brought into clinical use. Although results with telithromycin to date are encour-

Table I. Clinical and bacteriological outcomes in randomized, double-blind, controlled studies of telithromycin 800 mg once daily in patients (pts) with community-acquired pneumonia

Study	Regimen	No. of pts	Clinical cure (%)[a]	Successful bacteriological outcome [n/N (%)][b]
Hagberg et al.[48]	10-d TEL	149	94.6	36/40 (90.0)
	10-d AMX	152	90.1	35/40 (87.5)
Mathers Dunbar et al.[49]	10-d TEL	162	88.3	25/28 (89.3)
	10-d CLA	156	88.5	27/28 (96.4)
Pullman et al.[51]c	7- to 10-d TEL	80	90.0	13/14 (92.9)
	7- to 10-d TVA	86	94.2	22/22 (100.0)
Tellier et al.[50]	5-d TEL	159	89.3	57/65 (87.7)
	7-d TEL	161	88.8	52/65 (80.0)
	10-d CLA	146	91.8	45/54 (83.3)
Mouton et al.[52]	7- to 10-d TEL	219	87.2	NR
	Pooled COMP[d]	219	79.9	NR

a Per-protocol population.

b Bacteriologically evaluable per-protocol population. (n/N is the number of successfully treated pts out of the total number of bacteriologically evaluable pts).

c Study discontinued prematurely owing to concerns over the safety of trovafloxacin.

d Various comparators, according to local practice.

AMX = amoxicillin (1000 mg three times daily); **CLA** = clarithromycin (500 mg twice daily.); **COMP** = comparators; **NR** = not reported; **TEL** = telithromycin (800 mg once daily); **TVA** = trovafloxacin (200 mg once daily).

aging, they must be seen as preliminary, and surveillance programmes should be pursued.

2.4 Clinical Efficacy: Review of Phase III/IV Trials

The phase III controlled studies conducted in patients with mild to moderate CAP compared telithromycin with high-dose amoxicillin 1000 mg three times daily for 10 days,[48] clarithromycin 500 mg twice daily for 10 days[49,50] and trovafloxacin 200 mg once daily for 7–10 days.[51] Clinical response rates observed with telithromycin across these studies ranged from 88.3% to 94.6%; corresponding rates were 90.1% with amoxicillin, 88.5–91.8% with clarithromycin and 94.2% with trovafloxacin (this study was terminated early owing to safety concerns with trovafloxacin) [table I]. In one of these studies,[50] telithromycin was shown to be similarly effective when administered for 5 or 7 days, with both regimens resulting in clinical and bacteriological cure rates comparable to those seen in patients treated with clarithromycin for 10 days (table I). A pooled analysis of data from eight CAP trials (four controlled and four uncontrolled) showed clinical cure rates of 91% for both the telithromycin and comparator groups.[35]

Telithromycin showed high rates of clinical and bacteriological success in the treatment of CAP caused by *S. pneumoniae* (including penicillin- and macrolide-resistant strains), *H. influenzae*, *M. catarrhalis*, *S. aureus* and intracellular/atypical pathogens.[48,50,51,53,54] In an analysis of data from one phase II and eight phase III studies, telithromycin was shown to be effective in 61 CAP patients infected with *S. pneumoniae* nonsusceptible to penicillin and/or erythromycin; clinical cure and bacterial eradication rates in these patients were 91.8% and 93.4%, respectively.[55] The clinical cure rate in patients with CAP caused by multidrug-resistant *S. pneumoniae* was 92%.[35] Telithromycin has also shown effectiveness in patients aged ≥65 years[53] and in those with pneumococcal bacteraemia.[48,50,56]

All of the above-mentioned CAP trials were designed to demonstrate non-inferiority of telithromycin therapy versus the comparator in the treatment of patients with mild to moderate disease. Data from a randomized, open-label, comparative, international study provided the first preliminary evidence that telithromycin may be more effective in treating CAP than a range of commonly prescribed antibacterials, at least in areas where pneumococcal macrolide resistance rates are high.[52] The study was conducted in a group of countries where ery-

thromycin resistance rates were ≥30% (i.e. Greece, Hong Kong, Hungary, South Africa, South Korea, Spain, Taiwan, Thailand and Tunisia). Adults with CAP received either telithromycin 800 mg once daily for 7–10 days or a comparator oral antibacterial usually prescribed locally and/or recommended by local guidelines (mostly β-lactams, macrolides or fluoroquinolones). In the modified intention-to-treat population, clinical cure rates for patients who received telithromycin were significantly higher than those seen in patients who received comparator agents (86.0% versus 78.8%; p = 0.04).[52]

In addition to CAP, the clinical efficacy of telithromycin has been evaluated in randomized controlled trials in acute sinusitis[57-59] and acute exacerbations of chronic bronchitis.[60-62]

2.5 Pharmacoeconomic Data

The high prevalence of CAP and its associated morbidity means that this condition places a considerable burden on overall healthcare spending.[25] Although the costs of antibacterials used in the treatment of CAP and other respiratory tract infections are considerable,[25] they represent a small proportion of the total direct and indirect costs.[63,64] There are only limited pharmacoeconomic data on the use of telithromycin in the treatment of CAP. The results of one study suggested that telithromycin may be associated with fewer CAP-related hospitalizations than clarithromycin 500 mg twice daily,[65] while a pooled analysis of data from two CAP clinical trials indicated that telithromycin treatment for between 5 and 10 days was associated with significantly fewer hospital admissions (1.3 vs 3.6 per 100 patients; p = 0.023) and shorter lengths of hospital stay (11.4 vs 33.8 per 100 patients; p = 0.025) than clarithromycin treatment.[66] The estimated requisite CAP-related hospitalization costs were thereby significantly lower in patients who received telithromycin than in those receiving clarithromycin.

2.6 Benefit Evaluation in Summary

Telithromycin demonstrates good therapeutic outcomes when used to treat CAP and a low propensity to select for resistance. Its spectrum of activity targets both common and atypical pathogens implicated in CAP, including macrolide-resistant *S. pneumoniae*. In addition to this, telithromycin has a negligible effect on important nonrespiratory Gram-negative pathogens and its short, once-daily dosage regimen may aid patient adherence to treatment. Telithromycin exhibits bactericidal activity, and accumulates in a number of relevant respiratory tissues and fluids; together, these properties prevent telithromycin persisting at sub-inhibitory concentrations, thereby narrowing the opportunity for the development of resistance.

In equivalence studies, telithromycin 800 mg once daily for 7−10 days demonstrated non-inferior clinical cure and bacteriological outcomes in patients with CAP when compared with other commonly used antibacterials.[51] Efficacy has also been demonstrated over a 5-day treatment period with the once-daily dose administration regimen.[50] In addition, an international open-label trial provided evidence that telithromycin may be more effective in the treatment of CAP than comparator agents.[52] Telithromycin treatment may reduce indirect costs associated with hospitalization when compared with standard antibacterial regimens.

3. Risk Evaluation: Tolerability and Safety Profile

Most of the data relating to the tolerability and safety of telithromycin derive from the phase III programme in which more than 4000 patients with CAP or other community-acquired RTIs were treated with telithromycin 800 mg once daily for 5–10 days.[67] Spontaneous reporting during the postmarketing use of telithromycin has added to the overall picture of the safety of telithromycin in everyday clinical practice.

3.1 Tolerability and Safety Data from Phase III Trials

3.1.1 Common Adverse Events

The tolerability of telithromycin when compared with other commonly used antibacterials has been investigated in several controlled trials that involved patients with CAP, acute sinusitis, or acute exacerbations of chronic bronchitis. Overall, 2702 patients received telithromycin 800 mg once daily for 5 or 7–10 days and 2139 patients were treated with com-

Table II. Treatment-emergent adverse events (TEAEs) possibly related to study medication reported by >1% of patients (pts) in comparator-controlled phase III trials of telithromycin

Possibly related TEAE	Pts [n (%)]	
	telithromycin (n = 2702)	comparators (n = 2139)
Diarrhoea	270 (10.0)	171 (8.0)
Nausea	190 (7.0)	87 (4.1)
Headache	54 (2.0)	53 (2.5)
Dizziness (excluding vertigo)	75 (2.8)	33 (1.5)
Vomiting	64 (2.4)	30 (1.4)
Loose stools	58 (2.1)	30 (1.4)
Dyspepsia	36 (1.3)	21 (1.0)
Dysgeusia	40 (1.5)	76 (3.6)
Total no. of pts with possibly related TEAEs	**861 (31.9)**	**606 (28.3)**

parator antibacterials. Pooled data from these trials indicate that the most common adverse events considered to be possibly related to telithromycin treatment were diarrhoea (10.0% vs 8.0% with comparators), nausea (7.0% vs 4.1%), headache (2.0% vs 2.5%), dizziness (2.8% vs 1.5%), vomiting (2.4% vs 1.4%), loose stools (2.1% vs 1.4%) and dysgeusia (1.5% vs 3.6%) [table II].[35,68] Adverse events reported during treatment were reported as being predominantly mild or moderate in severity. The rate of discontinuations owing to treatment-emergent adverse events was similar in patients treated with telithromycin (4.4%) and pooled comparators (4.3%).[35,68]

3.1.2 Visual Adverse Events

Telithromycin may cause visual disturbances in some patients. Overall, 1.1% of patients in the controlled phase III trials reported treatment-emergent visual adverse events compared with 0.28% of patients who received comparators. Visual disturbances included blurred vision, diplopia or difficulty focusing. The incidence of visual adverse events was higher (2.1%) in females up to 40 years of age, but similar to the comparators in males over the age of 40 years.[35,69] Most visual disturbances were mild to moderate, although severe cases have been reported in the postmarketing phase; all events were reported as being reversible upon cessation of drug treatment.[35,69]

3.1.3 Cardiac Safety

In common with other major classes of antibacterials, including the fluoroquinolones and macrolides, telithromycin has the potential to prolong the corrected QT (QTc) interval of the electrocardiogram in some patients. QT prolongation may predispose patients to an increased risk of ventricular arrhythmias. However, no significant increase in the QTc interval was observed following repeated 800-mg telithromycin daily dose administration in a study involving 18 healthy adult volunteers (4.2 ± 15.2 milliseconds [mean ± standard deviation]; $p > 0.05$).[70] No cardiovascular morbidity or mortality attributable to QTc prolongation occurred during the telithromycin phase III trial programme involving 4780 patients, including 204 with QTc prolongation at baseline.[35,68] However, it is recommended that telithromycin should be avoided in patients with congenital prolongation of the QTc interval or ongoing proarrhythmic conditions and also in those receiving class Ia or class III antiarrhythmic drugs.[35]

3.1.4 Hepatic Safety

Hepatic dysfunction, including increased liver enzymes and hepatocellular and/or cholestatic hepatitis (with or without jaundice) has been observed with the use of telithromycin. Abnormal liver function tests were usually asymptomatic and reversible in the phase III trial programme, with elevations of ALT levels above three times the upper limit of normal observed in 1.6% and 1.7% of patients treated with telithromycin and comparators, respectively. Hepatitis, with or without jaundice, occurred in 0.07% of patients treated with telithromycin and was reversible.[35] Although the incidence of serious hepatic adverse events appears to be low, postmarketing reports have described rare cases of acute hepatic failure and severe liver injury (in some

cases, fatal) in telithromycin-treated patients.[35,71] The prescribing information for telithromycin indicates that patients should be monitored for the appearance of the signs and symptoms of hepatitis while taking telithromycin and that telithromycin should not be administered to patients with a previous history of hepatitis/jaundice associated with the use of telithromycin or macrolide antibacterials.[35]

3.2 Other Safety Information

Postmarketing experience suggests that telithromycin treatment may cause exacerbations of myasthenia gravis; rare cases of fatal or life-threatening acute respiratory failure have been reported.[72,73] As a result of these reports, a 'black-box' warning was added to the labelling information stating that telithromycin is contraindicated in patients with myasthenia gravis.[35] There have also been rare reports of syncope, usually associated with vagal syndrome.[35] Other postmarketing adverse events of note include rare cases of allergic reaction, such as angioedema and anaphylaxis, in addition to pancreatitis.[35]

Sporadic cases of severe hepatotoxicity in patients treated with telithromycin have recently been reported to the US FDA as part of the MedWatch reporting system.[71,74] A subsequent comprehensive benefit-risk analysis of telithromycin conducted by the FDA in late 2006 led to revisions to the US product labelling alerting patients and physicians to the risk of liver damage associated with the use of telithromycin.[74-76] The revised labelling states that telithromycin treatment should be discontinued and liver function tests performed if signs and symptoms of hepatitis occur (fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly).[35] The new label also narrowed the usage for telithromycin in North America by removing two previously approved indications, acute bacterial sinusitis and acute exacerbations of chronic bronchitis.

According to the European Medicines Agency, sixteen cases of acute liver failure were reported worldwide as of 15 September 2006;[77] twelve of these cases were reported in the US (mostly in 2006),[75] two in France and two in Japan. The latter four cases were described as being unlikely to be related to the use of telithromycin and in the vast majority of all the cases reported, when the relevant information was available, it was not possible to establish a causal relationship between the acute liver failure and the administration of telithromycin.[77]

The incidence of severe hepatotoxicity associated with telithromycin therefore appears to be extremely rare, and similar adverse effects have been reported for both azithromycin[78] and clarithromycin.[79] A recently published analysis of spontaneous reports made to the US FDA Adverse Event Reporting System between January and June 2005 calculated an 82% excess risk of hepatotoxicity in users of telithromycin compared with users of other agents.[80] Interestingly, the increased risk calculated for telithromycin was very similar to that derived for macrolide use (85%). Another interesting finding that emerged from this analysis was the variation in apparent risk of hepatotoxicity by patient age and gender; male patients between the ages of 45 and 64 years showed a higher degree of risk relative to both female patients and to patients <45 or >64 years of age. These findings suggest that the effects of telithromycin on the risk of hepatotoxicity may be modified by demographic and, perhaps, clinical characteristics.

3.3 Use of Telithromycin in Special Populations

3.3.1 Elderly Patients and Patients with Co-morbidities

Available data indicate that telithromycin is tolerated equally well in adults and older patients (>65 years of age), with the frequency of adverse events reported to be similar in both age groups.[43] Adverse event rates were also similar in patients with underlying diseases (e.g. cardiovascular disease, diabetes mellitus) or risk factors (e.g. renal insufficiency, liver disease) and in healthy subjects or patients with no underlying disease or risk factors.[43]

3.3.2 Pharmacokinetics and Dose Regimens

Pharmacokinetic studies indicate that the dosage of telithromycin need not be adjusted in patients with mild to moderate renal impairment (CL_{CR} ≥30 mL/min),[81] nor in the elderly on the basis of

age alone.[82] Telithromycin exposure was increased in patients with severe renal impairment compared with healthy subjects,[81] and hence a reduced dose of 600 mg once daily is recommended for patients with severe renal impairment (CL_{CR} <30 mL/min), including those receiving dialysis. No dosage adjustment is required in patients with hepatic impairment providing renal function is not severely impaired.[35] However, the telithromycin dosage should be reduced to 400 mg once daily in patients with hepatic failure and coexisting severe renal impairment.[35]

3.4 Drug-Drug Interactions

3.4.1 Telithromycin Metabolism

Approximately one-half of the metabolism of telithromycin occurs via the hepatic CYP3A4 pathway[32] and therefore the potential exists for interactions between telithromycin and other agents metabolized via CYP3A4. *In vitro* studies have shown that telithromycin, like the macrolides, is both a substrate and an inhibitor of CYP3A4.[32] The interaction between telithromycin and CYP3A4 is similar to that observed for clarithromycin, but far weaker than that seen with older macrolides such as erythromycin.[32,83] Accordingly, the potential for telithromycin to interact with drugs metabolized via CYP3A4 *in vivo* appears similar to that of clarithromycin but lower than that of erythromycin. Telithromycin also demonstrates competitive inhibition of CYP2D6 *in vitro*,[32] raising the possibility of interactions between telithromycin and drugs metabolized by this route.

3.4.2 Possible Drug Interactions

A number of controlled pharmacokinetic studies have investigated the potential for interactions between telithromycin and several commonly used drugs. These studies have been reviewed extensively by Shi et al.[32]

Cytochrome P450 (CYP) 3A4 Substrates

As with macrolides,[84] the concomitant use of telithromycin is contraindicated with cisapride or pimozide owing to the potential for prolongation of the cardiac QTc interval if exposure to cisapride or pimozide is increased.[35,69]

The metabolism of some HMG CoA reductase inhibitors ('statins') is dependent on CYP3A4.[85] A controlled study using healthy volunteers found that coadministration of telithromycin with simvastatin led to increased exposure to simvastatin (C_{max} 5.3-fold; AUC_{24} 8.9-fold).[35] However, a second study in healthy patients demonstrated that the magnitude of this interaction could be reduced by more than 50% if the drugs were administered 12 hours apart.[86] Although not formally tested, it may be expected that similar interactions will occur with atorvastatin and lovastatin, both of which are metabolized via CYP3A4. There is also documentation of increases in statin exposure during concomitant administration with macrolides.[87,88] Thus, coadministration of telithromycin with simvastatin, lovastatin or atorvastatin should be avoided and, if telithromycin is prescribed, therapy with any of these statins should be suspended during the course of treatment.[35] It should also be noted that telithromycin is unlikely to interact significantly with pravastatin, fluvastatin or rosuvastatin, since the metabolism of these statins does not involve CYP3A4.[85]

A number of commonly used benzodiazepines, such as midazolam, are also metabolized via CYP3A4. In a study with healthy volunteers, coadministration of telithromycin increased the plasma level of oral midazolam 6-fold.[35] Similar interactions have been documented for macrolides and benzodiazepines metabolized via CYP3A4.[26] The recommendation for patients receiving oral midazolam and telithromycin concomitantly is that patients should be monitored and a reduction in the midazolam dose considered if necessary.[35] The same precautions would apply to other benzodiazepines metabolized by CYP3A4, but temazepam, nitrazepam and lorazepam, which are not metabolized via CYP3A4, would not be expected to interact significantly with telithromycin.

Inducers of CYP3A4

Rifampicin is a potent inducer of CYP3A4 expression in the liver[89] and therefore has the potential to reduce levels of drugs metabolized by this pathway. When rifampicin was administered concomitantly with telithromycin to healthy volunteers, telithromycin exposure was reduced by approxi-

mately 80%.[32] As a result, coadministration of these two drugs is not recommended.[35] A number of other known CYP3A4 inducers that have the potential to interact with telithromycin have not been tested, including carbamazepine, phenobarbital and phenytoin. In the absence of published information on the interaction of these agents with telithromycin, it would be prudent to avoid concomitant administration of telithromycin with these or any other agents known to cause significant increases in expression of CYP3A4 in the liver.

Inhibitors of CYP3A4

Any drug that significantly inhibits CYP3A4 has the potential to increase exposure to telithromycin if given concomitantly. The antifungals ketoconazole and itraconazole are strong inhibitors of hepatic CYP3A4 and their potential to interact with telithromycin has been investigated.[90,91] Although ketoconazole and, to a lesser extent, itraconazole both increased telithromycin exposure, the level of increased exposure was moderate (1.2- to 2-fold) and not associated with any clinically significant effects, indicating that telithromycin could be administered with either of these azole drugs, if necessary. Certain components of grapefruit juice can affect the metabolism of some drugs via inhibition of intestinal CYP3A4.[92] However, grapefruit juice was shown to have no effect on telithromycin pharmacokinetics during coadministration.[90]

CYP2D6 Substrates

Although CYP2D6 appears to be a relatively minor route of telithromycin metabolism, the potential has been investigated for interaction between telithromycin and drugs metabolized by this pathway. Telithromycin was shown to moderately increase exposure to metoprolol (1.4-fold for both C_{max} and AUC_{24}).[32] Although this interaction was small, it may be clinically relevant in patients with heart failure; consequently, it is recommended that concomitant administration of telithromycin with metoprolol be considered with caution in these patients.[35] A recent study has indicated that telithromycin does not interact significantly with the antidepressant paroxetine.[32]

Others

Studies have demonstrated that telithromycin, like some macrolides, moderately affects the pharmacokinetics of theophylline.[26,32] There is a possibility that in some patients the increased exposure to theophylline may increase the incidence of gastrointestinal adverse effects. Therefore, it is recommended that if concomitant administration is necessary, the two drugs be administered 1 hour apart.[35]

Interactions between antibacterials and the anticoagulant warfarin have been reported previously.[26,93,94] In a study conducted in healthy subjects, telithromycin was shown not to affect the pharmacokinetics of racemic warfarin significantly.[32] However, postmarketing reports and an isolated published case study suggest that telithromycin could potentiate the effects of oral anticoagulants in some individuals.[95] If patients are receiving telithromycin and oral anticoagulants simultaneously, it is recommended that monitoring prothrombin times/international normalized ratio be considered.[35]

Moderate increases in exposure to digoxin (C_{max} 1.7-fold; AUC_{24h} 1.4-fold) during concomitant administration with telithromycin have been observed in controlled interaction studies; however, there were no clinically significant changes in electrocardiogram parameters and no signs of digoxin toxicity.[32] It is recommended that digoxin serum levels or adverse effects be monitored during concomitant administration of telithromycin and digoxin.[35]

3.5 Risk Evaluation in Summary

Telithromycin demonstrated good tolerability in controlled clinical trials, with an overall safety profile similar to that of other classes of antibacterial. The most commonly reported, possibly drug-related adverse events were mild to moderate gastrointestinal adverse effects, headache, dizziness and dysgeusia. Visual disturbances (generally transient) were also recorded in a small number of patients. Telithromycin is well tolerated by patients in all age groups and in patients with additional morbidities. However, in common with other antibacterials, telithromycin treatment can result in hepatic dysfunction. Indeed, postmarketing reports have shown that serious liver damage can occur. Physicians should therefore be vigilant for the signs and symptoms of hepatitis and extreme caution should be exercised in patients with a history of hepatitis or jaundice. As with the fluoroquinolones and macrolides, telithro-

mycin has the potential to affect the QTc interval and is therefore not recommended for use in patients with congenital arrhythmia.

Telithromycin is metabolized predominantly via the CYP3A4 pathway. Coadministration of telithromycin with substrates, inhibitors and inducers of this metabolic route has been shown to have little or no effect on the uptake of either drug, although monitoring and some special measures are recommended for a small number of drug combinations. As with macrolides, the coadministration of cisapride or pimozide with telithromycin is contraindicated because of the possibility of QTc interval prolongation if exposure to these drugs is increased.

4. Conclusions

The ketolide antibacterial telithromycin shows potent *in vitro* activity against the bacterial pathogens implicated in CAP, including strains resistant to macrolides and other antibacterials. It is also active against atypical/intracellular CAP pathogens. Surveillance studies indicate that telithromycin has a low potential to induce resistance. Randomized controlled non-inferiority trials have shown that telithromycin 800 mg once daily is as effective as other commonly used antibacterials in the treatment of CAP. The pharmacokinetic properties of telithromycin allow for once-daily dose administration, which should promote good patient adherence. Adverse events reported in the controlled clinical trials were typically mild to moderate in intensity, transient in nature and occurred at rates comparable with those seen with other first-line antibacterial treatment options. Postmarketing reports indicate that telithromycin treatment may rarely be associated with hepatotoxicity, with severe cases having been reported. Telithromycin should be discontinued and liver function tests performed if signs and symptoms of hepatitis occur.

Telithromycin is contraindicated in patients with myasthenia gravis, patients with a previous history of hepatitis and/or jaundice associated with the use of antibacterials, patients with a history of hypersensitivity to telithromycin or macrolide antibacterials, and in patients currently receiving cisapride or pimozide.

Based on the clinical and safety experience to date, telithromycin appears to demonstrate an acceptable overall benefit-risk ratio for adults with mild to moderate CAP. In particular, telithromycin could be considered as a replacement for existing recommended options for the treatment of pneumococcal disease in areas with a high prevalence of resistant *S. pneumoniae*.

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