REVIEW ARTICLE

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The Ketolides

A Critical Review

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Abstract

Ketolides are a new class of macrolides designed particularly to combat respiratory tract pathogens that have acquired resistance to macrolides. The ketolides are semi-synthetic derivatives of the 14-membered macrolide erythromycin A, and retain the erythromycin macrolactone ring structure as well as the D-desosamine sugar attached at position 5. The defining characteristic of the

ketolides is the removal of the neutral sugar, L-cladinose from the 3 position of the ring and the subsequent oxidation of the 3-hydroxyl to a 3-keto functional group. The ketolides presently under development additionally contain an 11, 12 cyclic carbamate linkage in place of the two hydroxyl groups of erythromycin A and an arylalkyl or an arylallyl chain, imparting *in vitro* activity equal to or better than the newer macrolides.

Telithromycin is the first member of this new class to be approved for clinical use, while ABT-773 is presently in phase III of development. Ketolides have a mechanism of action very similar to erythromycin A from which they have been derived. They potently inhibit protein synthesis by interacting close to the peptidyl transferase site of the bacterial 50S ribosomal subunit. Ketolides bind to ribosomes with higher affinity than macrolides.

The ketolides exhibit good activity against Gram-positive aerobes and some Gram-negative aerobes, and have excellent activity against drug-resistant *Streptococcus pneumoniae*, including macrolide-resistant (*mef*A and *erm*B strains of *S. pneumoniae*). Ketolides such as telithromycin display excellent pharmacokinetics allowing once daily dose administration and extensive tissue distribution relative to serum. Evidence suggests the ketolides are primarily metabolised in the liver and that elimination is by a combination of biliary, hepatic and urinary excretion. Pharmacodynamically, ketolides display an element of concentration dependent killing unlike macrolides which are considered time dependent killers.

Clinical trial data are only available for telithromycin and have focused on respiratory infections including community-acquired pneumonia, acute exacerbations of chronic bronchitis, sinusitis and streptococcal pharyngitis. Bacteriological and clinical cure rates have been similar to comparators. Limited data suggest very good eradication of macrolide-resistant and penicillin-resistant *S. pneumoniae*. As a class, the macrolides are well tolerated and can be used safely. Limited clinical trial data suggest that ketolides have similar safety profiles to the newer macrolides. Telithromycin interacts with the cytochrome P450 enzyme system (specifically CYP 3A4) in a reversible fashion and limited clinically significant drug interactions occur.

In summary, clinical trials support the clinical efficacy of the ketolides in upper and lower respiratory tract infections caused by typical and atypical pathogens including strains resistant to penicillins and macrolides. Considerations such as local epidemiology, patterns of resistance and ketolide adverse effects, drug interactions and cost relative to existing agents will define the role of these agents. The addition of the ketolides in the era of antibacterial resistance provides clinicians with more options in the treatment of respiratory infections.

Since their discovery macrolide antibiotics such as erythromycin A have played a key role in the treatment of bacterial infections. Macrolides have a broad spectrum of activity covering Gram-positive cocci (such as *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus* species), atypical (such as *Mycoplasma pneumoniae*, *Legionella pneumophila*) and intracellular pathogens (*Chlamydophila [Chlamydia] pneumoniae*), and *Moraxella catarrhalis* and *Haemophilus influenzae* (the newer agents such as azithromycin and clarithromycin). This activity has lead to the widespread use of macrolides for upper and lower respiratory tract infections, and as an alternative for patients allergic to β-lactams.[1] However, the emergence of antibacterial resistance in many bacterial species has prompted the search for newer agents.

In recent studies, antibacterial resistance in key respiratory pathogens has been documented world-

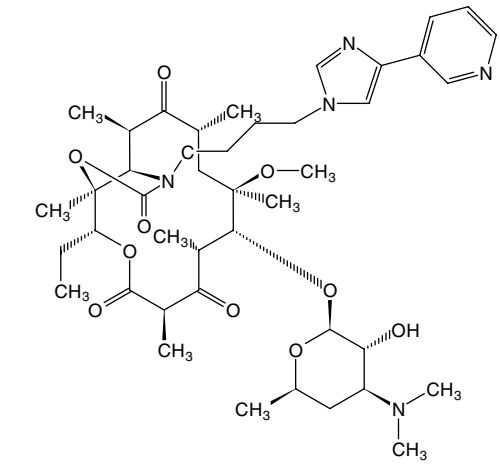
wide.[2] In many cases resistance to macrolides is also accompanied by resistance to β-lactams and other antibacterials such as co-trimoxazole and tetracyclines.[2] The emergence of multi-drug resistant pneumococci in particular has spurred the search for novel agents that either target a new site of action or overcome existing resistance mechanisms.

Ketolides are a new class of semi-synthetic agents derived from erythromycin A and designed to offer activity for the treatment of upper and lower tract respiratory infections, including those caused by resistant strains. The main structural difference between the ketolides and the older macrolides is the lack of the L-cladinose sugar at position 3 of the erythronolide A ring and its replacement with a 3-keto functional group. Presently, telithromycin has been approved for clinical use in several European countries, while ABT-773 is in phase III development. Telithromycin and ABT-773 have excellent activity against various bacterial genera including penicillin- and macrolide-resistant strains.[3-6] In addition, they improve on a number of the pharmacokinetic shortcomings of the macrolide class.[7,8]

This review discusses recent developments concerning the ketolides with a critical analysis of their chemistry, mechanism of action and resistance, *in vitro* and *in vivo* activities, pharmacokinetics and pharmacodynamics, as well as pharmacoeconomic considerations concerning the use of these new agents. The main emphasis is on the agents undergoing clinical trials, but other agents are included for comparison where sufficient data exist.

1. Chemistry

The ketolides are semi-synthetic derivatives of the 14-membered macrolide erythromycin A. They retain the macrolactone ring structure and the D-desosamine sugar attached at position 5.[9] However, a number of important structural changes have been made to improve on both the activity and the pharmacokinetics of earlier compounds. The defining characteristic of the ketolides is the removal of the neutral sugar, L-cladinose from the 3 position of the erythronolide ring and the subsequent oxidation of the 3-hydroxyl to a 3-keto functional group (figure 1). In addition, the ketolides under development contain an 11, 12 cyclic carbamate linkage in place of the two hydroxyl groups of erythromycin A and an arylalkyl or an arylallyl chain linked to the molecule, imparting activity equal to or better than the newer macrolides.[10] This section examines the structure-activity rela-



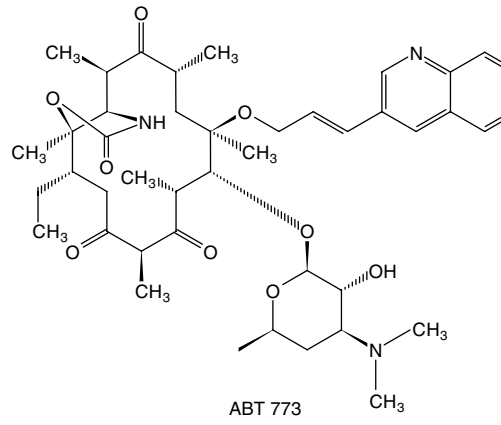


Fig. 1. Chemical structure of the ketolides telithromycin and ABT-773.

tionships of these important developments in the ketolides.

The earliest macrolide antibiotics were found to quickly degrade in an acidic environment, and thus they had an erratic oral absorption and caused increased gastric irritation.[1] One of the advantages of the ketolide molecules is an improved acid stability, which is the result of the removal of the L-cladinose moiety (figure 2). In addition, compounds with the 3-keto group do not trigger the expression of resistance to MLS_B (Macrolide Lincosamide Streptogramin B) antibiotics in strains with inducible *erm* determinants.[11] This allows the ketolides to remain active against bacterial strains in which MLS_B resistance would be induced by 14- and 15-membered macrolides such as azithromycin, clarithromycin and erythromycin.[9,12] One exception is the ketolide TE-802, which induces MLS_B resistance, indicating that the 3-keto alone is not always sufficient to avoid induction and that the arylalkyl side chains probably play a role as well.[13,14] The side chain is of immense importance for the activity of the ketolides. Removal of L-cladinose from erythromycin A causes decreased ribosomal binding, but this can be more than adequately compensated for by the addition of the 11, 12-carbamate extension.[15,16]

The 11, 12-carbamate is present in both telithromycin and ABT-773 (figure 1). It has been shown that this structure improves activity in macrolides and greatly enhances the activity of ketolides.[17] Having a 6-O-alkyl group and an 11, 12-carbamate structure also prevents 6-9 or 9-12 cyclisation within the compound that would result in a hemiketal product commonly formed by erythromycin in acidic media.[18] Carbonate and carbazate linkages have also been used to give compounds antibacterial activity, but they are not as potent (figure 2).[9,19] Also, 11, 12-phosphate and -phosphite linkages have been assessed, but these interfere with the antibacterial activity of the compounds.[20]

Telithromycin and ABT 773 (figure 1) also contain heterocyclic aromatic rings spaced from the lactone ring structure via short alkyl or allyl linkages. These structures impart improved ribosomal binding and thereby increase the activity of the compounds against both macrolide-susceptible and -resistant strains.[16,21] However, these two compounds differ in the nature of the linkages of the side chains to the lactone ring structure. Telithromycin has a butyl imidazolyl pyridinyl side chain attached to the carbamate nitrogen (figure 1). The aromatic nature of the substituent facilitates an interaction with nucleotide A752 in domain II of the 23S rRNA in addition to the main interaction of the drugs in domain V (figure 3). This results in tighter binding to ribosomes[16] and

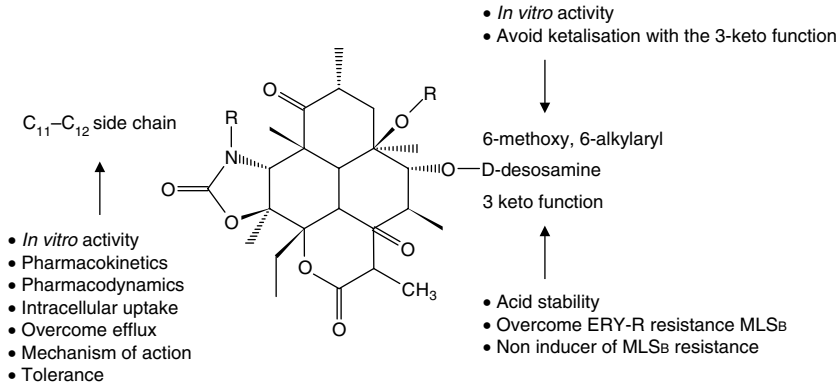


Fig. 2. Structure activity relationship of the ketolides. **ERY-R** = erythromycin resistance; **MLS_B** = Macrolide, Lincosamide, Streptogramin B.

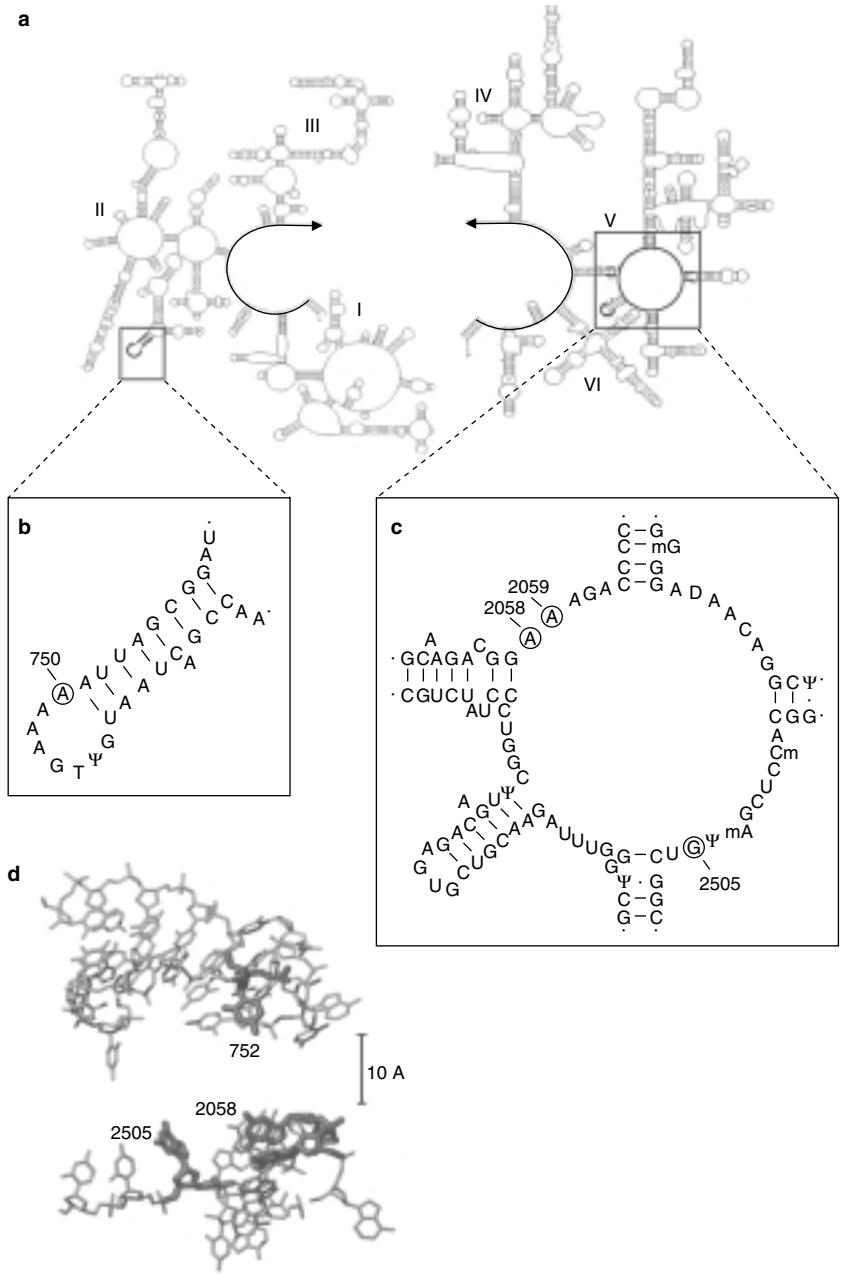


Fig. 3. Schematic representation (**a**) of the bacterial 23S rRNA secondary structure. Boxed are (**b**) hairpin 35 of domain II and (**c**) the central loop of domain V of the rRNA. The encircled nucleotides A752, A2058, A2059 and G2505 (*E. coli* numbering) constitute the binding site for macrolides and ketolides.[16,22] In the tertiary structure (**d**) of the rRNA revealed by crystallographic data on the 50S ribosomal subunit [23,24] these nucleotides fold into close proximity to line the peptide exit channel. The scale bar is in the plane of the page; nucleotide 752 is out of the plane of the page and is slightly more than 15 Å from nucleotide 2058. Erythromycin interacts with A2058 through its 5-desosamine sugar, but is not large enough to make direct contact with A752.[24] Biochemical data [16,22] indicates that ketolides such as telithromycin interact at A2058 in a manner identical to erythromycin, but the C11, 12 carbamate extension of telithromycin additionally spans the distance across the channel to contact A752.

imparts some activity against methylated ribosomes in some species.[10,19,22]

ABT-773 has an unsubstituted 11, 12-carbamate linkage, but contains a 3-quinolyl-propylene chain linked to the position 6 oxygen (figure 1).[25] It was long thought that the 6-position could only accommodate a small substituent, (telithromycin has an O-methyl at the 6-position). However, ABT-773 has excellent *in vitro* activity and it was found that the allyl linkage orients the aromatic group in such a way that it can interact in the same manner as the carbamate side chain in telithromycin. In solution it is believed that the aromatic group interacts with the hydrophobic face of the lactone ring; removal of the L-cladinose and addition of an aromatic ring system increase the hydrophobicity of the ketolides, thus improving the pharmacokinetics of these agents.[18,25,26]

Other modifications have been attempted with the ketolide structure, and may show promise for the design of future chemical entities (figure 2). Position 2 of the lactone ring has been found to require a tetrahedral bond structure to retain activity. This section of the molecule is found within a β-keto ester functional moiety (positions 1 through 3), and it has been postulated that the 2-position may be subject to alkylation reactions. Thus, fluoroketolides have been synthesised to protect this position. Larger substituents, such as chlorine, bromine or methyl, decrease the activity of the compounds, whereas compounds with fluorine at this position retain their antibacterial activity.[7,27] This in turn has allowed the synthesis of a number of 6-O-propargyl derivatives but the *in vitro* activity of these compounds has not been determined.[28] 2-Fluoro-ketolides have been found to have excellent activity and the structure is likely to be incorporated into future antimicrobial compounds.[6,10,29,30]

Position 9 has also been used as a modification point, but most oxime and N-linked tricyclic structures were found to be less active than the corresponding 9-keto compounds and many were inactive against resistant strains.[9] However, recent syntheses of 2-fluoro-6-oxime compounds have shown improved *in vitro* activities against both macrolide-susceptible and -resistant respiratory pathogens.[29] Position 10 has been shown to require a methyl substituent for activity but position 13 can tolerate some structural variation.[31] Azaketolide derivatives have also been synthesised but none have shown activity.[20] These developments show the ketolides have promising *in vitro* activity and are important advances in the rational design of macrolides to overcome bacterial resistance mechanisms (figure 2).

2. Mechanisms of Action and Resistance

2.1 Mechanism of Action

Ketolides have a mechanism of action very similar to erythromycin A from which they have been derived. They inhibit bacterial protein synthesis by interacting close to the peptidyl transferase site of the 50S ribosomal subunit.[10,19] It has been shown that the main sites of macrolide and ketolide interaction are within domains II and V of the 23S rRNA (figure 3).[16,22] Both macrolides and ketolides bind to the ribosome in a 1:1 ratio[16] indicating that domains II and V fold to lie in close proximity in the tertiary structure of the rRNA and thereby form a single drug binding pocket. This structure has recently been conclusively confirmed by the crystallographic models of the 50S subunit.[23,24,32]

The main site of macrolide and ketolide interaction has been defined by chemical footprinting experiments[16,22] and is located at nucleotides A2058 and A2059 in domain V (figure 3). Although both macrolides and ketolides protect these bases from chemical modification, the ketolides display a higher affinity than macrolides for forming interactions with the ribosomes.[18,33] This increased affinity has been shown to be due to the additional interaction at A752 in domain II. This tighter interaction is mediated by the 11, 12-carbamate side chain.[16,21,34]

Telithromycin protects position A752 in domain II from chemical modification, whereas

erythromycin A enhances the reactivity of this position. This implies that ketolides with the 11, 12 carbamate side chain interact directly with the base of A752, whereas drugs without this carbamate side chain probably interact in the vicinity of nucleotide A752, but without directly contacting its base.[16,22] Base substitutions at position A752 reduce the binding of ketolides, but not macrolides, reinforcing the idea that the adenine base at A752 is an important secondary contact site for the carbamate ketolides.[35] This additional contact presumably enables the ketolides to retain activity against bacteria that have base modifications in domain V.[12,33-37]

In addition to inhibiting protein synthesis, the ketolides also demonstrate a significant inhibitory effect on the formation of 50S ribosomal subunits.[10,19] When tested against *S. aureus* cells, the IC_{50} (concentration inhibiting 50%) of formation of the 50S subunit was found to be approximately equivalent to that of the IC_{50} of the inhibition of translation.[10] At higher concentrations, the ketolides with the 11, 12-carbamate side chain inhibit protein synthesis to such an extent that the formation of the 30S ribosomal subunit was also impaired.[19] These results show ketolides to be very potent inhibitors of protein synthesis *in vivo*.

Mechanistically ketolides have other potential advantages over macrolides in treating respiratory tract infections. They have been shown to accumulate at a greater rate than macrolides in bacterial cells.[33] They also accumulate rapidly in human cells giving them potential activity against intracellular pathogens.[38,39] It should be mentioned that high intracellular antibacterial concentrations are of relevance only if the antibacterial is active at that site and if the infection is intracellular. Ketolides become highly concentrated in human polymorphonuclear (PMN) neutrophils, where they mainly reside in the granular fraction.[40-44] Results suggest macrolides and ketolides are actively transported into PMNs.[41] Evidence for carrier-mediated uptake includes Michaelis-Menton saturation kinetics for the macrolides and ketolides, and that uptake can be impeded by agents that block the activity of the Ca^{2+}/Na^{+} ion channel. This latter evidence suggests that the activation of membrane transport requires the presence of extracellular Ca^{2+}, and possibly a second messenger system involving phosphorylation reactions.[40-42] Macrolides also inhibit uptake of the ketolides, suggesting a common transport mechanism for both classes; however, uptake is not affected by the presence of fluoroquinolones.[40,41] It is believed that the ketolides may undergo uptake into phagocytic cells and use these cells as a means of transportation to sites of infection.[39,45] Whether these properties will lead to a clinical advantage is presently unclear.

Ketolides may also have the ability to suppress the inflammatory response that causes significant morbidity and mortality during lower respiratory infections of *S. pneumoniae*. Ketolides have been shown to decrease levels of immune mediators and neutrophil recruitment in response to live or heat killed *S. pneumoniae* in animal models and *in vitro*.[46-48] PMN-induced phospholipid mediators, such as platelet activating factor (PAF), have been shown to induce ciliary slowing and epithelial damage in the airways. Work by Feldman et al.[49] has shown that both HMR-3004 and telithromycin can antagonise the activity of bioactive phospholipids. The exact mechanism of these reactions remains to be elucidated, and additional work *in vivo* is needed to determine if this pharmacodynamic response *in vitro* can be translated into clinical efficacy during infection with *S. pneumoniae* and during other inflammatory conditions such as asthma.

2.2 Mechanism of Resistance

Macrolide resistance in several key pathogens is well documented globally, and it can occur via a number of mechanisms.[2,8] The most common resistance mechanisms in Gram-positive cocci are mediated by *mef*-encoded efflux or *erm*-encoded methylation of 23S rRNA. According to the nomenclature proposed by Roberts et al.[50] efflux resistance in *S. pneumoniae* and *S. pyogenes* is encoded by *mef*A, whereas ribosomal methylation is en-

coded by *erm*B in *S. pneumoniae*, and *erm*B and *erm*A in *S. pyogenes*. In addition to the more common mechanisms, macrolide resistance has also included mutations in the ribosomal proteins or RNA.[8,51,52] Extremely rare mechanisms that are as yet undetected in streptococci, include direct inactivation of erythromycin by esterases, phosphorylases or glycosidases.[8,53]

One of the driving forces behind the development of the ketolides was the search for agents to overcome these various resistance mechanisms. It has been shown that ketolides remain active against bacterial strains expressing efflux resistance.[33,36,37,54,55] While MIC values increase for strains with efflux-mediated resistance, this resistance is less effective against ketolides either because of their high intrinsic activity and/or tight ribosomal binding or because they are poor substrates for efflux pumps.[56] Point mutations in domain V affect ketolide binding but macrolides are affected to a much greater extent.[21,34,51] In clinical strains of *S. pneumoniae*, mutations of A2058/9 → G, and A2062 → C, confer resistance to 14-, 15- and 16-membered MLS_B, but do not affect telithromycin activity.[57,58] Mutations in the L4 ribosomal protein have been shown to affect ketolide binding. An insertion of 6 amino acid residues in L4 confers ketolide resistance, whereas single amino acid substitutions and smaller deletions or insertions in the same region of L4 confer macrolide resistance without giving cross-resistance to ketolides.[51,57]

Expression of an *erm* resistance determinant in bacteria leads to the production of a methyltransferase enzyme which modifies the key nucleotide, A2058, in the MLS_B binding site and thereby confers resistance to these drugs. Expression of *erm* may be constitutive or inducible. Ketolides offer a significant advantage over macrolides in strains that have inducible *erm* genes. It has been found that the L-cladinose moiety contributes to the strong induction effect of the macrolides, leading to expression of the MLS_B phenotype,[11] whereas ABT-773 and telithromycin both lack the capability to induce *erm* expression, giving them clinical activity against strains inducibly resistant to macrolides.[14,19,59] Interestingly, ketolides remain potent agents against most *S. pneumoniae* strains regardless of their erythromycin susceptibility; even retaining activity against isolates constitutively expressing the *erm*B gene.[12,60-62] However, this is not necessarily the case with other streptococci such as *S. pyogenes*.[63] It has been shown that ketolides still have some affinity for the methylated ribosome; however, it is lower than in wild type unmethylated cells.[33] It seems that the activity of ketolides against MLS_B-resistant strains depends on the proportion of ribosomes that *erm*-gene product has managed to methylate.

In vitro and *in vivo* experiments have shown that exposure of streptococci to ketolides is less likely to result in resistance than upon exposure to macrolides.[64-67] These selection experiments typically resulted in only slight increases in MIC values, and they occurred at mutational frequencies lower than those obtained for macrolides under the same conditions.[65] Telithromycin affected the susceptibility of the normal flora of the oropharynx and the bowel less than did clarithromycin, although its *in vivo* use did select for some resistant *Bacteroides* isolates.[67] Therefore, it appears that it may be more difficult to select for ketolide resistance in the clinical setting.

A potential for the development of clinical resistance could occur via mutations in domain II of the 23S rRNA in strains that already express a modified domain V.[35] In areas with documented macrolide resistance, the use of ketolides may put pressure on bacterial species to select for strains with constitutive *erm* expression. This could create ketolide resistance in species like *S. aureus* or *S. pyogenes*.[36,37,54] However, it appears that ketolides will retain activity against the majority of *S. pneumoniae* strains, making them very useful in the treatment of respiratory tract infections.[60-62]

3. *In Vitro* Activity

The *in vitro* activities of the ketolides are presented in tables I to IV. The macrolides clarithromycin and azithromycin are included in these

tables for comparative purposes.[3-6,36,60-64,68-154] The tables present the minimum concentration (μg/ml) of antibacterial required to inhibit growth in 50% of the tested isolates (MIC_{50}) and 90% of the tested isolates (MIC_{90}). The tables also show the range of MIC values for each organism reported in the literature and represent data on thousands of isolates. Data included in the tables were not restricted as to growth conditions or as to methodology of the MIC study.

The ketolides display good activity against the majority of Gram-positive aerobic bacteria (table I).[3-6,36,60-64,68-132] Against the strains of *S. pneumoniae* reported in the references, the macrolide MIC_{90} values were ≥64 μg/ml, whereas the ketolides displayed excellent activity with MIC_{90} values ≤0.12 μg/ml. Against erythromycin susceptible strains, the ketolides showed activity greater than the two macrolides. The ketolides also retained activity against pneumococci with known erythromycin resistance mechanisms, although the MIC values tended to be a few dilutions higher than macrolide susceptible strains. In these cases, the MIC_{90} values were ≤0.12 μg/ml for all ketolides regardless of resistance mechanism. In the literature examined, there was only one clinical isolate with a highly resistant MIC value (≥64 μg/ml) to both telithromycin and ABT-773, which expressed the *erm*B mechanism of resistance.[115]

The ketolides displayed good activity against other *Streptococcus* spp., as well, being in general equally active to or more active than clarithromycin and more active than azithromycin. Against *S. pyogenes*, they had activity against some erythromycin-resistant strains with good activity against isolates with the *erm*A genotype. They showed a slight decrease in activity against strains with *mef*A efflux resistance, but with MIC_{90} values below proposed susceptible breakpoints. However, while they had higher activity than their macrolide comparators, ketolides exhibited markedly decreased activity against strains displaying the *erm*B resistance genotype.[54,60,71] On the basis of the MIC_{90} values, the order of activity of the ketolides against *Streptococcus* spp. is ABT-773 = HMR-3787 > HMR-3004 = HMR-3582 > telithromycin > clarithromycin > azithromycin (table I).

The ketolides were approximately equal in activity against susceptible strains of *S. aureus*, and were more active than the macrolides. However, none of the agents had activity against erythromycin resistant *S. aureus* or coagulase-negative *Staphylococcus* spp.[64,71,78,82] The macrolides displayed poor activity against *Enterococcus* spp. with limited activity against *Enterococcus faecalis* for clarithromycin and no activity against *Enterococcus faecium*. The ketolides were more active against *E. faecalis*, but telithromycin and HMR-3004 exhibited poor activity against *E. faecium*. The activities of HMR-3562 and HMR-3787 against *E. faecium* warrant further investigation against additional isolates to validate the low MIC_{90} values reported in the single study (table I).[6] There was a wide interspecies variability in the susceptibility of *Corynebacterium* spp. to the macrolides and ketolides, but in general, the MIC_{90} values were ≤0.008 μg/ml for all agents except azithromycin. *Corynebacterium diphtheriae* remained highly susceptible to all agents. *Listeria monocytogenes* also showed susceptibility to all agents with MIC_{90} values ≤1 μg/ml (table I).

The activity of ketolides against clinically important Gram-negative aerobic bacteria is presented in table II.[3-6,64,68-72,86,117-130,132-139] The majority of Gram-negative aerobes, including the Enterobacteriaciae and *Pseudomonas aeruginosa*, have proven to be intrinsically resistant to the macrolide class.[1] This is also true of the ketolides.[6,64,71] However, ketolides and macrolides were active against a number of clinically important Gram-negative species. Ketolides display similar (or greater) activity against *H. influenzae* as azithromycin (table II). For the agents listed on table II, this activity is on par with or better than azithromycin. According to the MIC_{90} values, the order of activity of these new agents against *H. influenzae* is HMR-3787 > telithromycin = HMR-3004 = HMR-3565 > ABT-773 = azithromycin > clarithromycin (table II). In addition, the ketolides displayed good activity against *M. catarrhalis*,

Table I. *In vitro* activity of ketolides and comparator macrolides against aerobic Gram-positive bacteria[a]

Organism[b]	Ketolide															Macrolide					
	Telithromycin			ABT-773			HMR-3004			HMR-3562			HMR-3787			Azithromycin			Clarithromycin		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Streptococcus pneumoniae	0.015	0.06	≤0.001-≥64	0.004	0.03	≤0.001-≥64	0.06	0.12	0.001-1							0.12	≥64	0.008-≥64	0.03	≥64	0.001-≥64
Erythromycin susceptible	0.008	0.016	≤0.001-0.12	0.004	0.004	≤0.001-0.06	0.015	0.015	0.001-0.008	0.015	0.015	0.008-0.06	0.008	0.008	0.002-0.03	0.06	0.25	0.008-64	0.03	0.06	0.001-1
*erm*B Resistance	0.06	0.12	≤0.001-≥64	0.004	0.06	0.002-≥64	0.12	0.12	0.002-0.008	ND	ND	ND	ND	ND	ND	≥64	≥64	1-≥64	≥64	≥64	0.25-≥64
*mef*A Resistance	0.06	0.5	0.002-2	0.004	0.12	≤0.002-1	0.008	0.12	0.002-1	ND	ND	ND	ND	ND	ND	4	16	0.5-64	1	4	0.06-≥64
Streptococcus pyogenes	0.015	0.015	0.002-≥64	0.008	0.008	≤0.002-32	0.008	0.06	≤0.001-≥8	0.03	0.25	0.015-0.25	0.008	0.25	0.008-0.25	0.12	0.25	0.001-≥64	0.03	0.06	0.001-≥64
Erythromycin susceptible	0.015	0.015	0.002-0.25	0.008	0.008	≤0.002-0.008	0.008	0.06	≤0.002-0.008	ND	ND	ND	ND	ND	ND	0.12	0.25	0.001-0.5	0.015	0.015	0.001-0.06
*erm*A Resistance	0.06	0.12	0.008-0.25	0.03	0.06	≤0.015-≥1	0.008	0.06	ND	ND	ND	ND	ND	ND	ND	32	≥64	0.5-≥64	8	8	0.25-≥64
*erm*B Resistance	2	16	0.12-≥64	0.12	2	≤0.002-32	1	4	≤0.008-≥8	ND	ND	ND	ND	ND	ND	≥64	≥64	0.5-≥64	≥64	≥64	0.25-≥64
*mef*A Resistance	0.5	0.5	0.004-2	0.12	0.12	≤0.002-0.5	0.06	0.12	0.06-1	ND	ND	ND	ND	ND	ND	8	16	1-32	2	8	0.06-8
Streptococcus agalactiae	0.015	0.06	0.004-2	0.008	0.03	0.008-0.12	0.03	0.03	0.015-0.03	ND	ND	ND	ND	ND	ND	0.06	0.12	0.008-≥32	0.03	0.06	0.008-≥32
Viridans group Streptococci	0.06	0.12	0.002-2	0.008	0.06	≤0.008-1	0.015	0.06	0.001-2	0.03	0.06	0.008-0.12	0.015	0.03	0.004-0.25	2	8	0.008-≥64	0.5	8	0.001-≥64
Staphylococcus aureus	0.06	0.12	0.008-≥64	0.03	0.03	≤0.008-≥64	0.06	0.06	0.001-≥64							2	≥64	0.25-≥64	0.25	≥64	0.06-≥64
Erythromycin susceptible	0.06	0.06	0.008-0.5	0.03	0.03	0.008-0.25	0.06	0.06	0.008-8	0.06	0.06	0.06	0.03	0.06	0.03-0.06	2	2	0.25-≥16	0.25	0.25	0.06-0.5
Erythromycin resistant	2	≥64	0.03-≥64	≥64	≥64	≤0.008-≥64	≥64	≥64	0.06-≥64	0.06	≥64	0.06-≥64	0.06	≥64	0.03-≥64	32	≥64	0.5-≥64	≥64	≥64	1-≥64
CNS	0.06	32	0.03-≥64	0.03	8	≤0.015-≥64	0.06	≥32	0.001-≥64	0.06	≥64	0.03-≥64	0.03	≥64	0.03-≥64	1	16	0.06-≥64	0.25	≥64	0.03-≥64

Table I continued

Neisseria spp. and *Bordetella pertussis* (MIC_{90} values ≤0.25 μg/ml). Limited data shows that ketolides have activity against macrolide-susceptible *Helicobacter pylori*. However, it does not appear that macrolide resistant strains will be susceptible to the ketolides (table II).

Ketolide activity against anaerobic bacteria is presented in table III.[3,4,6,71,72,131,132,140-147] In general, ketolides had poor activity against *Bacteroides* species. However, they displayed good activity against *Clostridium perfringens* and limited activity against *Clostridium difficile*. Other *Clostridium* species were variably inhibited, depending upon the organism and the drug. More research is needed to see if the fluoroketolides HMR-3562 and HMR-3787 continue to display low MIC_{90} values against further *C. difficile* isolates. Like macrolides, the ketolides exhibited poor activity against the *Fusobacterium* species. However, they showed good activity against *Peptostreptococcus* species (table III).

Table IV presents *in vitro* activity of the ketolides against the clinically important intracellular and atypical pathogens *C. pneumoniae*, *L. pneumophila*, *M. pneumoniae* and *Ureaplasma urealyticum*.[6,148-154,156] The ketolides were very effective against these organisms with MIC_{90} values ≤0.25 μg/ml for *C. pneumoniae*, ≤0.25 μg/ml for *L. pneumophila*, ≤0.001 μg/ml for *M. pneumoniae* and ≤0.03 μg/ml for *U. urealyticum*. The macrolides tested were also effective against these organisms with MIC_{90} values ≤2 μg/ml (table IV).

4. Pharmacokinetics

The pharmacokinetic properties of the ketolides play an important role in determining activity *in vivo*. Table V shows the pharmacokinetic parameters of telithromycin and ABT-773 after oral administration.[67,157-166]

4.1 Absorption

The bioavailability of telithromycin is approximately 60%, and absorption appears to be rapid, reaching maximum serum concentration (C_{max}) in approximately 1 hour.[157,167,168] ABT-773 appears

Enterococcus species	0.06	4	0.004-≥64	0.03	8	0.004-≥64	2	16	0.001-≥64	ND	ND	ND	ND	ND	ND	16	≥64	0.06-≥64	2	≥64	0.03-≥64
Enterococcus faecalis	0.06	4	0.004-≥16	0.03	8	0.004-≥64	2	8	0.008-≥64	0.03	1	0.015-1	0.015	4	0.015-4	16	≥64	0.03-≥64	2	≥64	0.03-≥64
Enterococcus faecium	8	8	0.015-≥16	1	8	0.008-≥64	4	16	0.008-16	ND	0.5	0.12-1	ND	4	1-4	16	16	2-≥64	≥64	≥64	0.06-≥64
Corynebacterium species	0.004	0.008	0.002-≥64	0.008	0.008	0.002-0.5	0.004	0.004	0.002-≥64	0.002	0.008	0.002-0.008	0.002	0.002	0.002-0.004	≥64	≥64	≤0.015-≥64	0.008	0.008	0.004-≥64
Listeria monocytogenes	0.06	0.06	0.03-0.06	0.03	0.03	0.03-0.06	0.03	0.06	0.015-0.06	0.03	0.03	0.03	0.015	0.03	0.015-0.03	1	1	0.5-2	0.12	0.12	0.06-0.25

a Adapted from references: ABT-773;[4,61,62,69-71,88,110-116,127-130,132,155] Azithromycin;[1,5,36,61,62,64,68,69,71,72,74-80,84-86,88-95,100-102,104,105,109,114,115,119-125,127,129-132] Clarithromycin;[1,3-5,36,61,62,64,71,72,74-79,82,84-86,88-95,101,102,105,105,109,114,115,119-125,127,129-132] HMR-3004;[5,60,64,72,104-110] HMR-3562;[6,126] HMR-3787;[6,126] Telithromycin.[3,4,36,60,63,68,70,72-106,112,114-125,131]

b Macrolide resistance genotypes named according to the proposal set forth by Roberts et al.[50]

CNS = Coagulase negative *Staphylococci;* **MIC**$_{50}$ = minimum inhibitory concentration of 50% of isolates; **MIC**$_{90}$ = minimum inhibitory concentration of 90% of isolates; **ND** = data not available.

Table II to go here

to have a dose-dependent absorption with time to C_{max} (t_{max}) increasing from 0.9 hours to 5.1 hours with increasing dosage (table V). The C_{max} values of telithromycin and ABT-773 are also variable, differ slightly and form linearity with increasing dose.[157,162] However, the plasma C_{max} value for telithromycin after a single 800mg dose was found to range from 1.90 to 2.27 mg/L.[157] Results for ABT-773 have only been reported for healthy volunteers, but plasma C_{max} values range from 0.14 to 1.19 mg/L from a single oral dose within the range of 100 to 1200mg once daily (table V). The values achieved for both telithromycin and ABT-773 in the plasma are above the MIC values reported for the most common respiratory tract pathogens with the potential exception of *H. influenzae* (tables I to IV). Additionally, food does not appear to have a significant effect on either the C_{max} or t_{max} values for both telithromycin and ABT-773.[159,163]

4.2 Distribution

The ketolides have an improved lipophilic character over their macrolide precursors as a result of the removal of the L-cladinose sugar.[18] Macrolides have been shown to exhibit extensive penetration into tissues and fluids outside the blood plasma resulting in an increased volume of distribution and possibly increased activity against organisms localised to these extra-plasma sites.[1] Ketolides have also demonstrated excellent penetration into sites other than the plasma. A number of experiments have been performed *in vitro* showing that ketolides have excellent uptake into macrophages and PMN cells.[39-41,43,44] The kinetics of accumulation depend upon the agent tested, with HMR-3004 showing a rapid uptake initially followed by a slower accumulation over a further 3 hours, which is very similar to monobasic macrolides such as erythromycin A.[40] Telithromycin on the other hand has a slower accumulation that is more similar to azithromycin.[41] In both cases efflux from the PMNs was slow, suggesting that the drugs may be ionically trapped within granules as a result of differences in pH.[40,41]

Table II. *In vitro* activity of ketolides and comparator macrolides against aerobic Gram-negative bacteria[a]

Organism	Telithromycin			ABT-773			HMR-3004			HMR-3562			HMR-3787			Azithromycin			Clarithromycin		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Haemophilus influenzae	1	2	0.002-16	2	4	0.001-16	2	2	0.001-8	1	2	0.5-2	1	1	0.5-2	2	4	0.001-≥64	8	16	0.008-≥64
Moraxella catarrhalis	0.06	0.12	0.001-4	0.06	0.06	≤0.002-0.5	0.06	0.12	≤0.015-1	0.06	0.06	0.008-0.12	0.03	0.06	0.008-0.12	0.06	0.12	0.008-≥64	0.12	0.12	0.008-≥64
Neisseria species	0.12	0.12	0.001-4	0.015	0.25	0.001-0.5	0.06	0.12	≤0.004-4	ND	ND	ND	ND	ND	ND	0.12	0.25	≤0.015-8	0.25	1	0.001-8
Neisseria gonorrhoeae	0.06	0.12	0.002-1	0.015	0.25	0.001-0.5	0.06	0.12	≤0.004-0.5	0.03	0.06	0.008-4	0.03	0.03	0.008-4	0.12	0.25	0.015-0.5	0.25	1	0.001-2
Neisseria meningitidis	0.015	0.12	0.002-0.5	0.015	0.12	0.004-0.12	0.06	0.12	0.008-0.5	0.015	0.06	0.008-0.25	0.015	0.03	0.008-0.12	0.5	1	0.25-2	0.12	0.5	0.004-1
Bordetella pertussis	0.015	0.03	0.004-0.06	ND	ND	ND	0.008	0.03	0.008-0.03	ND	0.06	0.03-0.06	ND	0.06	0.03-0.06	0.03	0.06	0.008-0.06	0.06	0.06	0.015-0.12
Helicobacter pylori(Ery^s)	ND	0.5	ND	0.12	0.25	0.008-0.25	ND	ND	ND	ND	0.25	0.015-0.25	ND	0.12	0.008-0.12	0.25	0.5	0.06-0.5	0.015	0.03	≤0.004-0.03
Helicobacter pylori(Ery^r)	ND	≥64	ND	32	≥64	4-64	ND	ND	ND	ND	ND	ND	ND	ND	ND	≥64	≥64	≥64	ND	ND	ND

a Adapted from references: ABT-773;[4,69,72,127-130,132,138,139,155] Azithromycin;[1,64,69,71,72,118-120,124,125,127,129,130,132-138] Clarithromycin;[1,3,4,64,71,72,118-120,124,125,127,129,130,132-139] HMR-3004;[5,64,72,134-137] HMR-3562;[6,126] HMR-3787;[6,126] Telithromycin.[3,4,68,86,117-125,133-137]

Ery^r = erythromycin resistant; **Ery^s** = erythromycin susceptible; **MIC_{50}** = minimum inhibitory concentration of 50% of isolates, **MIC_{90}** = minimum inhibitory concentration of 90% of isolates, **ND** = data not available.

Table III to go here

In addition, telithromycin is extensively concentrated in other tissues and fluids as shown in table VI.[39,43,44,67,169-174] The tissue/plasma or fluid/serum ratios reported for telithromycin are >1 (table VI), suggesting that activity may not correlate with serum drug concentrations. Telithromycin may remain active at sites of infection when the concentration in serum is below the MIC of the infecting organism. The distribution of ABT-773 has not been reported in humans.

4.3 Metabolism and Excretion

Approximately 70% of a telithromycin dose is metabolised (33% presystemic and 37% systemic).[167] Evidence suggests the ketolides are primarily metabolised by the cytochrome 450 (CYP) enzyme system in the liver. The main pathway of metabolism involves hydrolysis of the aryl group from the side chain leaving a hydroxyl group that may be further oxidised to a carboxylic acid. The predominant metabolite excreted is the hydroxyl-containing compound. Four metabolites of telithromycin have been identified in humans: an alcohol, an acid, an N-desmethyl-desosamine and an N-oxide pyridine derivative.[157,175] Studies of ABT-773 metabolism *in vivo* in humans have not been reported, however, preliminary animal data and *in vitro* human hepatocyte experiments show well-characterised metabolism. It appears that the most common metabolic pathway of ABT-773 involves demethylation of the D-desosamine sugar moiety (either singly or doubly) with or without hydroxylation of the C10 methyl group.[176] Neither telithromycin nor HMR-3004 appear to significantly affect the activity of the CYP enzymes *in vitro*, and thus the ketolides may have less potential for drug interactions of this nature.[177,178]

Telithromycin has a biphasic half-life with an overall terminal half-life of approximately 9.5 hours.[157] From a single dose of 800mg, this terminal half-life is 7.2 hours in a healthy male population (table V). This allows for once daily dose administration for telithromycin at the established dose of 800mg, with only slight accumulation of the drug at steady state.[157] The half-life of ABT-

Table III. *In vitro* activity of ketolides and comparator macrolides against anaerobic bacteria[a]

Organism	Ketolide															Macrolide					
	Telithromycin			ABT-773			HMR-3004			HMR-3562			HMR-3787			Azithromycin			Clarithromycin		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Bacteroides species	8	≥64	0.015-≥64	4	4	0.001-≥64	4	8	≤0.015-≥64	2	8	0.25-≥64	2	8	≥64	8	≥64	0.06-≥64	4	≥64	0.06-≥64
Bacteroides fragilis	16	16	0.06-≥64	2	4	0.06-≥64	8	8	1-≥64	ND	ND	ND	ND	ND	ND	8	≥64	0.25-≥64	2	≥64	0.06-≥64
Clostridium species	0.12	≥64	0.004-≥64	0.03	≥64	0.004-≥64	0.12	≥64	≤0.008-≥64	ND	ND	ND	ND	ND	ND	2	≥64	0.12-≥64	0.5	≥64	0.06-≥64
Clostridium perfringens	0.12	0.25	0.004-0.25	0.03	0.03	0.03-≥64	0.03	0.12	≤0.008-0.06	0.03	0.06	0.008-0.06	0.015	0.03	0.008-0.03	0.5	1	0.25-4	0.5	1	0.12-1
Clostridium difficile	0.25	≥64	0.03-≥64	0.25	≥64	0.03-≥64	0.12	≥64	0.06-≥64	0.03	1	0.03-≥64	0.03	1	0.008-≥64	8	≥64	0.5-≥64	0.5	≥64	0.12-≥64
Fusobacterium species	≥64	≥64	0.008-≥64	0.5	≥64	0.008-≥64	32	≥64	≤0.015-≥64	1	32	0.004-≥64	0.5	32	0.004-≥64	8	≥64	≤0.015-≥64	≥64	≥64	≤0.015-≥64
Peptostreptococcus species	0.06	0.06	0.002-≥64	0.03	0.03	0.004-≥32	0.004	0.06	≤0.008-4	0.015	0.03	0.004-0.5	0.008	0.03	0.004-2	4	≥64	0.015-≥64	0.06	≥64	≤0.008-≥64

a Adapted from references: ABT-773;[4,71,132,145-147,155] Azithromycin;[1,71,72,131,132,142,144,145,147] Clarithromycin;[1,3,4,71,72,131,132,142,144,145,147] HMR-3004;[72,143,144] HMR-3562;[6] HMR-3787;[6] Telithromycin.[3,4,72,131,140-143,145]

MIC_{50} = minimum inhibitory concentration of 50% of isolates, **MIC_{90}** = minimum inhibitory concentration of 90% of isolates, **ND** = data not available.

773 ranges from 3.6 to 6.7 hours (table V) after a single oral dose in healthy adult males. Data following multiple doses are not presently available for ABT-773.

Table IV to go here

Absorbed telithromycin is eliminated via various pathways with 7% excreted unchanged in faeces, 13% excreted unchanged in urine and 37% metabolised by the liver.[167,175] No dosage adjustment is required in patients with mild to moderate renal impairment. In the presence of severe renal impairment with or without co-existing hepatic impairment, the dose should be reduced by 50%.[167] No dosage adjustment is necessary in patients with mild, moderate or severe hepatic impairment, unless renal function is severely impaired.[167] No change in the dose is required based on other factors such as age, gender, smoking status or infection severity. Although it was found that these patient groups could affect telithromycin elimination pharmacokinetics in a minor way, none were clinically significant.[161] Data for ABT-773 elimination in humans is not yet available. The effect of telithromycin on normal oropharyngeal and intestinal microflora has been studied.[67] The quantitative effects on the normal microflora were moderate and comparable to clarithromycin. No overgrowth in intestinal flora with yeast or *C. difficile* occurred.

5. Pharmacodynamics

5.1 *In Vitro* Experiments

Macrolides are generally considered bacteriostatic agents against most bacterial species, but have reported bactericidal activity against varying species (the nature of activity depends upon the agent and a number of other factors).[1] In general, ketolides follow this pattern, displaying bacteriostatic activity against many species, but showing bactericidal activity at higher concentrations against some important pathogens. Telithromycin, HMR-3004, ABT-773, HMR-3562 and HMR-3787 show excellent bactericidal activity against *S. pneumoniae*. Importantly, these drugs are bactericidal against *S. pneumoniae* resistant to erythromy-

Table IV. *In vitro* activity of ketolides and comparator macrolides against other clinically important bacteria[a]

Organism	Ketolide															Macrolide					
	Telithromycin			ABT-773			HMR-3004			HMR-3562			HMR-3787			Azithromycin			Clarithromycin		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Chlamydophila pneumoniae	0.06	0.25	0.015-2	0.015	0.015	0.008-0.015	0.004	ND	0.004-0.015	ND	ND	0.06	ND	ND	0.06	0.03	0.25	0.015-0.5	0.03	0.06	0.015-0.12
Legionella pneumophila	0.06	0.12	0.015-0.5	0.03	0.06	0.015-0.06	0.008	0.03	0.008-0.06	0.015	0.06	0.015-0.06	0.004	0.004	0.002-0.008	0.5	2	0.03-2	0.03	0.06	0.015-0.06
Mycoplasma pneumoniae	≤0.001	≤0.001	≤0.001-0.03	≤0.001	≤0.001	≤0.001	ND	ND	≤0.008	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001-0.03	0.002	0.002	≤0.001-0.25
Ureaplama urealyticum	0.03	0.03	0.008-0.06	ND	ND	ND	ND	ND	0.008-0.03	0.015	0.03	0.004-0.06	0.015	0.015	0.004-0.03	0.25	0.25	0.06-2	0.03	0.03	0.008-0.06

a Adapted from references: ABT-773;[153,154] Azithromycin;[1,148-150,152-154] Clarithromycin;[1,148,149,152-154,156] HMR-3004;[151,152,156] HMR-3562;[6] HMR-3787;[6] Telithromycin.[148-151,153,154,156]

MIC_{50} = minimum inhibitory concentration of 50% of isolates, **MIC_{90}** = minimum inhibitory concentration of 90% of isolates, **ND** = data not available.

Table V to go here

cin A.[62,64,78,79,179-183] Telithromycin, HMR-3004 and ABT-773 also demonstrate limited bactericidal activity against *S. pyogenes*, *H. influenzae* and *M. catarrhalis* by 24 hours depending upon the concentration of antibacterial (typically ≥4x the MIC value is required) and the size of the inoculum.[62,64,71,78,133,137,138,179-182,184,185] However, at concentrations in the range of 2x to 10x the MIC, telithromycin, HMR-3004 and ABT-773 are mainly bacteriostatic against *S. aureus*, *Enterococcus* spp., and Gram-positive bacilli.[66,71,74,78,106,181,184,185]

At 24 hours, telithromycin was bactericidal against *H. pylori* at 2x the MIC, while HMR-3004 was bactericidal at 10x the MIC.[186] Telithromycin and HMR-3004 showed bactericidal activity against *Bacteroides fragilis* at 10x the MIC value.[184,185] Against other anaerobes telithromycin also showed some bactericidal activity after 24 hours at higher concentrations (≥4x the MIC), but was mainly bacteriostatic.[187] Telithromycin, HMR-3004 and ABT-773 were slowly bactericidal against *C. pneumoniae* and mainly bacteriostatic against *L. pneumophila*.[151,188-190]

In vitro experiments that simulate human pharmacokinetic elimination have been performed. By simulating human unbound plasma concentrations of telithromycin, it has been shown that this agent is mainly bacteriostatic at the concentrations likely to be achieved *in vivo*.[165,179] In addition, ketolides have been found to display concentration-dependent killing.[186,188] This means activity correlates better with area under the serum concentration time curve (AUC)ketolide/MICpathogen or C_{max}/MICpathogen rather than time above the MIC.[191] Using this knowledge, the dose administration of ketolides can be optimised to achieve bactericidal activity against a number of pathogens and also prevent the development of resistance by achieving an adequate C_{max} or AUC value for the drug.

An additional consideration in optimising the dose administration schedule of antibacterial agents is the post-antibiotic effect or PAE. PAE values represent an agents continued antibacterial activity after removal of the agent from the medium. Macrolides have been found to have extensive PAE

Table V. Pharmacokinetic properties of telithromycin and ABT-773

Drug	Dose (mg)	% F	C_{max} (μg/ml)	t_{max} (h)	AUC (mg•h/L)	$t_{½}$ (h)	Vd/F (L)	Protein binding (%)	Excreted unchanged (%)	Dose adjustment[a]		Effect of food on absorption[b]	References
										Renal	Hepatic		
Telithromycin	800	60	1.90	1.0	9.0	7.2	ND	70%	12.7	No	No	↔	67,157-161, 165-167
ABT-773	100	ND	0.14	0.9	0.63	3.6	940	ND	ND	ND	ND	↔	162,163
	200		0.18	1.5	0.87	5.3	1975						
	400		0.61	2.3	3.84	6.7	1366						
	600		1.19	2.7	6.83	5.6	1674						
	800		0.99	3.9	9.55	6.7	1255						
	1200		1.17	5.1	10.96	6.6	1300						

a Dosage adjustment refers to whether or not the ketolide requires any dosage adjustment in patients with impaired renal or hepatic function.

b Effect of food on absorption refers to whether food increases (↑), decreases (↓) or does not affect (↔) absorption.

AUC = area under the concentration time curve; **C_{max}** = peak concentration reached in the plasma; **F** = bioavailability; **ND** = data not available; **$t_{½}$** = half life; **t_{max}** = time to reach C_{max}; **Vd** = volume of distribution.

Table VI. Tissue distribution of telithromycin presented as tissue/plasma or fluid/serum ratio

Bronchial mucosa[a]	Epithelial lining fluid[a]	Saliva[b]	Sputum[c]	Middle ear fluid[d]	Tonsils[d]	Sinus fluid[d]	WBC[a]	Alveolar macrophages[a]	PMN[e]	References
12.1	16.8	1.6	4.8	2.4	7.8	4.0	≥500	≥500	135 - 613	39,41,43-45,67,167, 169-174

a Data reported as the ratio of tissue or fluid concentration over plasma concentration 24 hours after last dose.

b Results reported as a ratio of $AUC_{saliva}/AUC_{plasma}$.

c Results reported as a ratio of maximum sputum concentration/maximum plasma concentration after telithromycin 600mg once daily for 7 days.

d Results reported as a ratio of tissue or fluid concentration over plasma concentration 6 hours after a single dose.

e Results reported from *in vitro* experiments and show variation depending upon source of the PMN, extracellular antibacterial concentration and time point of sample.

AUC = area under the concentration time curve; **PMN** = polymorphonuclear neutrophil; **WBC** = white blood cell.

values against the majority of important respiratory pathogens, allowing the extension of the dose administration intervals. This allows more convenient dose administration and better patient compliance. Recent work with the newer ketolides has demonstrated PAE values equal to or improved over macrolide comparators.[62,138,179,181,182,184] Munckhof et al.[191] conducted a number of PAE experiments at different concentrations for telithromycin and HMR-3004 and concluded that these ketolides would have a theoretical maximum PAE value against different isolates as exposure concentration of the ketolide increased. The report calculated maximum PAE values of 3.7 hours for *S. aureus*, 8.9 hours for *S. pyogenes* and 9.7 hours for *S. pneumoniae* (macrolide-susceptible) with telithromycin and a range of 3.1 to 4.9 hours with HMR-3004. PAE results for telithromycin against *H. influenzae* were also good, with values ≥6.7 hours at an exposure to 10x the MIC, and ≥1.3 hours against *M. catarrhalis* at 4x the MIC.[179,181] Telithromycin and HMR-3004 at 10x the MIC exhibit extensive PAE (≥5 hours) and PASME (post antibiotic sub-MIC effect; ≥12 hours) values against *H. pylori*.[186]

ABT-773 also displays extensive PAE values against a number of species. For *S. pneumoniae*, ABT-773 gave PAE values at 10x the MIC of ≥1.7 hours (macrolide-susceptible and macrolide-resistant), and values were greater than for comparator macrolides.[62,182] Against *H. influenzae*, ABT-773 gave PAE values ≥4.9 hours, which is comparable to azithromycin, the macrolide with the longest PAE.[138,182] Against *S. aureus*, the PAE values obtained were ≥3.41 hours and against *M. catarrhalis*, the values were ≥3.8 hours.[182] ABT-773 also gave PAE values of ≥2 hours against *L. pneumophila*.[190]

5.2 *In Vivo* Pharmacodynamics

A number of pre-clinical *in vivo* animal trials have shown the efficacy of the ketolides in a variety of models of respiratory tract infections (table VII).[47,134,156,192-201] Simulated respiratory infections have shown the ketolides to be equal in efficacy to macrolides against susceptible *S. pneumoniae* and *H. influenzae*.[134,192-196,202] The ketolides typically demonstrated increased survival rates and lower ED_{50} values than macrolides (see table VII for definitions). Both telithromycin and ABT-773 were able to achieve bactericidal activity against *S. pneumoniae* in animal models.[194,196,199] In addition, the ketolides exhibited higher activity than comparator macrolides against erythromycin-resistant *S. pneumoniae in vivo* (table VII).[192-196,199-201] Telithromycin treatment was shown to decrease the bacterial load in *C. pneumoniae* lung infections in mice by day 5, and demonstrated considerable bacterial cure by day 13 (table VII). In addition, telithromycin reduced the severity of lung tissue inflammation in a dose-dependent fashion compared with the untreated control.[198] Telithromycin also allowed survival of a lethal *L. pneumophila* lung infection model, although neither telithromycin nor the macrolide eradicated bacte-

Table VII. *In vivo* treatment of animal respiratory tract infections with ketolides

Study	Animal model	Drug	Dosage[a]	Duration	No. of animals	Results
Telithromycin (T)						
Piper et al.[134]	*H. influenzae* pneumonia in mice	T	50 mg/kg q6h	4 doses	12	3/12 (25%) sterile
		3004	50 mg/kg q6h	4 doses	14	9/14 (64%) sterile
		A	25 mg/kg q6h	4 doses	15	0/15 (0%) sterile
		AZ	100 mg/kg q6h	4 doses	18	5/18 (28%) sterile
		CI	100 mg/kg q6h	4 doses	13	3/13 (23%) sterile
		C	100 mg/kg q6h	4 doses	12	0/12 (0%) sterile
		E	100 mg/kg q6h IP	4 doses	12	0/12 (0%) sterile
		P	100 mg/kg q6h	4 doses	14	0/14 (0%) sterile
		Cx			35	0/35 (0%) sterile
Piroth et al.[195]	*S. pneumoniae* pneumonia in rabbits[b]	T	800mg bid	3 doses	ND	Ery^r lung log cfu/g 2.57
						Ery^s lung log cfu/g 1.00
						Ery^r lung log cfu/g 4.80
		A	1000mg tid	5 doses	ND	Ery^r lung log cfu/g 1.00
						Ery^s lung log cfu/g 1.50
						Ery^r lung log cfu/g 5.24
		E	500mg qid	6 doses		Ery^r lung log cfu/g 6.13
						Ery^s lung log cfu/g 1.16
						ND
		Cx				Ery^r lung log cfu/g 6.18
						Ery^s lung log cfu/g 4.72
						Ery^r lung log cfu/g 4.76
Chuah et al.[196]	*H. influenzae* pneumonia in mice[c]	T	25 mg/kg bid	3d	9	9/9 (100%) cured
		T	50 mg/kg bid	3d	8	8/8 (100%) cured
		E	50 mg/kg bid	3d	7	5/7 (71%) cured
		C	50 mg/kg bid	3d	9	7/9 (78%) cured
		Cx	Saline			3/7 (43%) cured
Törmäkangas et al.[197]	*C. pneumoniae* pneumonia in mice	T	25 mg/kg	10d	10	9/10 (90%) culture negative at 13d PI
		T	50 mg/kg	10d	10	10/10 (100%) culture negative at 13d PI.
		T	100 mg/kg	10d	10	10/10 (100%) culture negative at 13d PI
		Cx			10	0/10 (100%) culture negative at 13d PI
Edelstein and Edelstein[156]	*L. pneumonphila* pneumonia in guinea pigs	T	10 mg/kg od	5d	16	16/16 (100%) survival
		T	10 mg/kg bid	5d	16	16/16 (100%) survival
		E	30 mg/kg bid	5d	16	14/16 (88%) survival
		Cx			12	0/12 (0%) survival
ABT-773 (773)						
Mitten et al.[194]	Lung infections in rats[d]	773	ND	3d	5/group	*S. pneumoniae* ED_{50} <0.6 - 17 mg/kg/day
						H. influenzae ED_{50} 19.8 - 29 mg/kg/day
		T	ND	3d	5/group	*S. pneumoniae* ED_{50} 2.3 - >80 mg/kg/day
						H. influenzae ED_{50} 53 - 68 mg/kg/day
Meulbroek et al.[193]	*S. pneumoniae* lung infections in rats[e]	773	ND	3d	ND	ED_{50} 2.0 - 15.1 mg/kg/day
		AZ	ND	3d	ND	ED_{50} 6.0 - >100 mg/kg/day
Azoulay-Dupuis et al.[192]	*S. pneumoniae* pneumonia in mice	773	6.25 mg/kg bid	3d	ND	Ery^s - 86% survival; Ery^r - 14%
		773	12.5 mg/kg bid	3d	ND	Ery^s - 100% survival; Ery^r - 38%
		773	25 mg/kg bid	3d	ND	Ery^s - 100% survival; Ery^r - 100%
		E	37.5 mg/kg bid	3d	ND	Ery^s - 0% survival
		E	75 mg/kg bid	3d	ND	Ery^r - 8%
		E	150 mg/kg bid	3d	ND	Ery^r - 0%

Table VII. Contd

Study	Animal model	Drug	Dosage[a]	Duration	No. of animals	Results
HMR-3004 (3004)						
Duong et al.[47]	*S. pneumoniae* pneumonia in mice	3004	12.5 mg/kg bid	5d	12	Treatment initiated at 24h 100% survival
		3004	12.5 mg/kg bid	5d	12	Treatment initiated at 48h 100% survival
		3004	12.5 mg/kg bid	5d	12	Treatment initiated at 72h 60% survival
		Cx				0% survival
HMR-3562 (3562) and HMR-3787 (3787)						
Levasseur et al.[202]	*S. pneumoniae* pneumonia in mice	3562	50 mg/kg bid	3d	ND	Ery^s - 100% survival; Ery^r - 89% survival
		3562	100 mg/kg bid	3d	ND	Ery^s - 100% survival; Ery^r - 90% survival
		3787	50 mg/kg bid	3d	ND	Ery^s - 100% survival; Ery^r - 45% survival
		3787	100 mg/kg bid	3d	ND	Ery^s - 80% survival; Ery^r - 60% survival
		E	50 mg/kg bid	3d	ND	Ery^s - ND; Ery^r - 0% survival
		E	100 mg/kg bid	3d	ND	Ery^s - 100% survival; Ery^r - 10% survival
		Cx				Ery^s - 0% survival; Ery^r - 0% survival

a All dosing is PO unless stated otherwise.

b Dosing is a simulation that achieves concentrations in rabbits similar to reported concentrations in humans if they were dosed in a similar manner; lung tissues sampled 48 hours after inoculation with infecting organism.

c Results summarised are for middle-aged mice; data in abstract also included young and old mice cohorts.

d ED_{50} is the concentration of antibiotic that gives a reduction of 2 log cfu/ml in 50% of the population.

e ED_{50} is the concentration of antibiotic that gives a reduction of 3 log cfu/ml in 50% of the population.

A = amoxicillin; **AZ** = azithromycin; **bid** = twice daily; **C** = clarithromycin; **cfu** = colony forming units; **CI** = ciprofloxacin; **Cx** = control; **E** = erythromycin; **ED_{50}** = effective dose in 50% of animals; **Ery^r** = Erythromycin resistant; **Ery^s** = erythromycin susceptible; **IP** = intraperitoneal; **ND** = no data presented; **od** = once daily; **P** = pristinamycin; **PI** = post infection; **PO** = orally; **q6h** = every 6 hours; **qid** = four times daily; **T** = telithromycin; **tid** = three times daily.

ria completely from the lungs.[156,203] On the basis of the evidence from these animal respiratory models, both telithromycin and ABT-773 appear to reach the lung tissue and demonstrate considerable success in treating bacterial infections.

In vivo animal trials have also evaluated the efficacy of the ketolides in a number of non-respiratory infections.[64,204-213] In peritoneal models, ketolides produced similar or improved efficacy to their macrolide comparators.[64,204-206,210] The ketolides show good activity against erythromycin-susceptible enterococci and *Toxoplasma gondii*, and ABT-773 displayed activity equivalent to clarithromycin against *Mycobacterium avium* in a mouse model.

The use of animal models allows the development of pharmacodynamic data that may be useful in predicting clinical success in human infections. Increasing ketolide MIC or minimum bactericidal concentration (MBC) values in the pathogenic isolate corresponds to increased ED_{50} (effective dose in 50% of animals) or PD_{50} values (dose to prevent death in 50% of animals). Piroth et al.[196] determined that the activity of telithromycin correlated better to the MBC than to MIC in treating *S. pneumoniae* infections. Data collected *in vivo* supports *in vitro* kill data that suggested ketolides are concentration dependent, and that AUC/MIC is highly correlated with efficacy.[193,199-201,204,206] For erythromycin-resistant *S. pneumoniae*, the dose required for bacteriostatic inhibition at 24 hours is higher than in susceptible strains, however, the 24-hour AUC/MIC ratio remains roughly equivalent (an 11-fold difference from lowest to highest value).[200] This should allow prediction of treatment success in humans when the MIC of an isolate is determined and compared with human kinetic parameters.

6. Clinical Trials

The ketolides are a new class of antibacterials showing promising activity *in vitro* and *in vivo* against bacteria commonly causing community acquired respiratory tract infections. Currently only telithromycin is approved for clinical use in several European countries, while ABT-773 is presently in phase III development. Available clinical trials with telithromycin are summarised in table VIII.[214-228]

The summarised clinical trials consisted of adult populations in the majority of cases, with adolescents included in the pharyngitis trials.[164,167,213-228,232] The trials included analysis of both the intent-to-treat population (mITT = modified intent-to-treat; any patient enrolled in the study that received at least one dose of antibacterial), as well as the per-protocol population (PP = the number of patients who did not have any major protocol violations as predefined in the protocol). Clinical cure was defined as improvement in signs and symptoms or a return to pre-infection state without the need for additional antimicrobials and assessed 10 to 14 days after the end of treatment. In addition, trials evaluated bacterial eradication when a causative pathogen could be identified.

6.1 Community Acquired Pneumonia

Three randomised, double-blind, comparative trials and three non-blind trials of telithromycin for treatment of community acquired pneumonia (CAP) have been presented in abstract form.[214,218,222,225,229,230] In the first non-blind study, telithromycin 800mg once daily showed efficacy in 79.6% of patients in the mITT population and 92.9% in the PP population after 7 to 10 days.[214] In the second non-blind trial, patients received oral telithromycin 800mg for 7 to 10 days.[167,229] The clinical cure rate was 93.6% (175/187). In the third non-blind study, patients received telithromycin 800mg once daily for 7 days, with a clinical cure rate of 93% (332/357) in the PP population.[230]

The comparative trials had similar results, with telithromycin achieving efficacy in 94.6, 88.3 and 90.0% of the PP populations of each trial, respectively (table VIII). Comparatively, amoxicillin, clarithromycin and trovafloxacin achieved cure rates of 90.1, 88.5 and 94.2%, respectively.[164,167] Telithromycin achieved clinical cure rates of 85.9, 78.9 and 82.0% in the mITT populations versus 78.5, 80.7 and 85.6% for amoxicillin, clarithromycin and trovafloxacin, respectively.[164,167]

High bacterial eradication rates were also achieved for telithromycin in the six trials, with values of 88.9, 89.7, 91.9, 90.0, 89.3 and 92.9% at the test of cure visit. In the comparative trials, amoxicillin achieved 87.5% eradication, clarithromycin 96.4% and trovafloxacin 100%.[167] When causative bacteria were isolated and typed, telithromycin was effective in CAP caused by the major pathogenic species such as *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and atypical pathogens like *C. pneumoniae*, *L. pneumophila* and *M. pneumoniae* (table VIII).[214,222] Bacterial eradication rates against infections caused by erythromycin- and/or penicillin-resistant *S. pneumoniae* were high (success rate of 67/73 or 91.8% compared with 7/10 or 70.0% for the pooled comparators).[225] Telithromycin exhibited a clinical cure rate against *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* of 256/280 patients or 91.4%. The pooled comparators in these trials achieved a clinical success rate of 88.6%.[222]

In each trial, subgroups of the PP population were also analysed for clinical efficacy. Patients over 65 years of age achieved clinical cures with telithromycin of 85.7, 87.5, >80% and 100%. Infection severity was also assessed and clinical cures were achieved in 92.1, 91.2, >80 and 100% of patients with Fine Scores ≥3.[1] These results were higher than in patients treated with amoxicillin, and similar to patients being treated with clarithromycin or trovafloxacin (table VIII). Telithromycin also showed considerable success (clinical cure in 27/30 patients or 90.0%) in treating bacteraemia associated with CAP.[219]

Table VIII. Clinical trials presented for telithromycin (T)

Study	Design	Indication and study population	No. of pts ()[a]	Regimen	Length of treatment	Clinical response (%) [cured and improved]		Bacterial eradication (%)
Community-acquired pneumonia (CAP)								
Carbon et al.[214]	Non-blind, noncomparative	Adults (18-79y) with mild to moderate CAP	240 (197)	T 800mg od	7-10d	mITT	191/240 (79.6)	40/45 (88.9)
						PP	183/197 (92.9)	
VanRensburg et al.[229]	Non-blind, noncomparative	Adults (18-79y) with acute or hospitalised CAP	212 (187)	T 800mg od	7-10d	mITT	182/212 (85.8)	80/85 (90.9)
						PP	175/187 (93.6)	61/68 (89.7)
Fogarty et al.[230]	Non-blind, noncomparative	Adults (13-92y) with acute or hospitalised CAP	418 (357)	T 800mg od	7-10d	mITT	357/418 (85.4)	215/239 (90.0)
						PP	332/357 (93.0)	137/149 (91.9)
Hagberg et al.[167,218]	Randomised, double-blind, double-dummy, parallel-group, multicentre	Adults (≥18y) with CAP	404 (301)	T 800mg od	10d	mITT	171/199 (85.9)	49/56 (87.5)
						PP	141/149 (94.6)	36/40 (90.0)
				A 1000mg tid	10d	mITT	161/205 (78.5)	46/54 (85.2)
						PP	137/152 (90.1)	35/40 (87.5)
Tellier et al.[167,225]	Randomised, double-blind, parallel-group, multicentre	Adults (18-92y) with CAP	416 (318)	T 800mg od	10d	PP	143/162 (88.3)	25/28 (89.3)
				C 500mg bid	10d	PP	138/156 (88.5)	27/28 (96.4)
Pullman et al.[167,222]	Randomised, double-blind, parallel-group, multicentre	Adults (18-99y) with CAP	204 (166)	T 800mg od	7-10d	PP	72/800 (90.0)	13/14 (92.9)
				TR 200mg od	7-10d	PP	81/86 (94.2)	22/22 (100)
Acute exacerbations of chronic bronchitis (AECB)								
Aubier et al.[213]	Randomised, double-blind, parallel-group, multicentre	Adults (18-84y) with COPD experiencing AECB	320 (227)	T 800mg od	5d	mITT	130/160 (81.3)	27/39 (69.2)
						PP	99/115 (86.1)	
				A/C 500/125mg tid	10d	mITT	125/160 (78.1)	21/30 (70.0)
						PP	92/112 (82.1)	
DeAbate et al.[167,217]	Randomised, double-blind, parallel-group, multicentre	Adults (19-97y) with AECB	373 (282)	T 800mg od	5d	PP	121/140 (86.4)	60/67 (89.6)
				CA 500mg bid	10d	PP	118/142 (83.1)	22/28 (78.6)
Streptococcal pharyngitis								
Norrby et al. and Chang et al.[167,216,221]	Randomised, double-blind, double-dummy, parallel-group, multicentre	Adults and adolescents (15-74y)	395 (234)	T 800mg od	5d	mITT	170/198 (85.9)	110/138 (79.7)
						PP	109/115 (94.8)	97/115 (84.3)
				PV 500mg tid	10d	mITT	169/197 (85.8)	119/150 (79.3)
						PP	112/119 (94.1)	106/119 (89.1)
Quinn et al.[167,223]	Randomised, double-blind, parallel-group, multicentre	Adults and adolescents (13-81y)	463 (285)	T 800mg od	5d	PP	139/150 (92.7)	137/150 (91.3)
				C 250mg bid	10d	PP	123/135 (91.1)	119/135 (88.1)
Sinusitis								
Roos et al.[227]	Randomised	Adults (18-65y) with acute sinusitis	335 (256)	T 800mg od	5d	mITT	138/167 (82.6)	65/70 (92.9)
						PP	112/123 (91.1)	
				T 800mg od	10d	mITT	147/168 (87.5)	62/69 (89.9)
						PP	121/133 (91.0%)	
Buchanan et al.[167,231]	Randomised, double-blind, multicentre	Adults (14-84 years of age) with acute sinusitis	356 (278)	T 800mg od	5d	PP	161/189 (85.2)	84/100 (84.0)
				CA 250mg bid	10d	PP	73/89 (82.0)	32/40 (80.0)
Tellier et al.[167,226]	Randomised, double-blind, parallel-group, multicentre	Adults (16-84 years of age) with acute sinusitis	607 (424)	T 800mg od	5d	PP	110/146 (75.3)	6/7 (85.7)
				T 800mg od	10d	PP	102/140 (72.9)	6/7 (85.7)
				A/C 500/125mg tid	10d	PP	102/138 (74.5)	6/8 (75.0)

a Number of patients in the modified intent to treat population (mITT), with the number of patients that were clinically evaluable at the end of treatment (PP) in brackets.
A = amoxicillin; **A/C** = amoxicillin/clavulanic acid; **bid** = twice daily; **C** = clarithromycin; **CA** = cefuroxime axetil; **COPD** = chronic obstructive pulmonary disease; **od** = once daily; **PV** = phenoxymethyl penicillin (penicillin V); **tid** = three times daily; **TR** = trovafloxacin.

6.2 Acute Exacerbations of Chronic Bronchitis

Two randomised, double-blind clinical trials have been presented for treatment of acute exacerbations of chronic bronchitis (AECB) with telithromycin.[213,217] A trial by Aubier et al.[213] compared telithromycin 800mg once daily for 5 days to amoxicillin/clavulanic acid 500mg/125mg three times daily for 10 days. Telithromycin showed slightly improved success over the β-lactam with clinical cure in 81.3% of the mITT population and in 86.1% of the PP population compared with 78.1 and 82.1%, respectively, in the amoxicillin/clavulanic acid group (table VIII). In patients with causative pathogens isolated, bacteriologic resolution was approximately equal at 69.2% for telithromycin and 70.0% for amoxicillin/clavulanic acid. However, reinfections at the late post-therapy visit were slightly more common for amoxicillin/clavulanic acid than telithromycin (9 versus 2).[213] Patients greater than 65 years of age and patients with a forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio <60% had similar cure rates in both groups, and were approximately equal to the general PP population. However, telithromycin appeared to be more effective in patients with a more severe infection, as defined by the investigators (81.8% for telithromycin versus 62.5% for amoxicillin/clavulanic acid).[213]

In the second trial, DeAbate et al.[167,217] compared telithromycin 800mg once daily for 5 days with cefuroxime axetil 500mg twice daily for 10 days. Both treatments were equivalent in efficacy, with clinical cure in 86.4% of the telithromycin group and 83.1% in the cefuroxime axetil group (table VIII). When causative pathogens were identified, a satisfactory bacteriological outcome was achieved in 89.6% in the telithromycin group versus 78.6% in the cefuroxime axetil group. Both drugs had significant activity against the most common respiratory pathogens.[217] Relapses or reinfection occurred in a small number of patients in both groups at the late post-therapy visit (10 in the telithromycin group and 8 in the cefuroxime axetil group). Treatments were equivalent in patients greater than 65 years of age, smokers, patients with a history of chronic obstructive pulmonary disease and in patients with an FEV_1/FVC <60%.[217]

6.3 Pharyngitis

Telithromycin has been evaluated in the treatment of pharyngitis in two randomised, double-blind clinical trials.[221,223] In the first trial by Norrby et al.[221] telithromycin 800mg once daily for 5 days was compared to phenoxymethylpenicillin (penicillin V) 500mg three times daily for 10 days. Satisfactory outcomes were achieved in both arms of the trial, with 84.3% bacteriological eradication in the PP population of the telithromycin group and 89.1% bacteriological eradication in the penicillin group. In the mITT populations, cure was achieved in 79.7% and 79.3% respectively (table VIII). Eradication of *S. pyogenes* was greater than 85% in both groups. Reinfection rates were low in both groups, but were slightly higher in the penicillin group. Telithromycin also achieved clinical cure in all patients (6/6) with isolated *S. pyogenes* that proved to be resistant to erythromycin (MIC ≥1 μg/ml).

The second trial compared telithromycin 800mg once daily for 5 days to clarithromycin 250mg twice daily for 10 days in treating pharyngitis shown to be caused by *S. pyogenes* in both adolescents and adults.[223] Both treatment arms were highly effective, with satisfactory bacteriological outcomes in the PP population of 91.3% for telithromycin and 88.1% for clarithromycin. Reinfections at the late post-therapy follow up were low in both groups (3 patients in each group). In patients with erythromycin-resistant *S. pyogenes*, clinical cure was achieved in 4/5 patients treated with telithromycin and 2/4 patients treated with clarithromycin.[223] The treatments were equivalent in patients with >1 group A streptococci (GAS) infection in the last year, patients presenting with exudates, and patients with cervical lymphadenopathy. In general, cure rates reflected the results of the general population.[223] Eradica-

tion of *S. pyogenes* was greater than 88% in both groups.[167]

6.4 Acute Sinusitis

Telithromycin has been evaluated for the treatment of acute sinusitis in three randomised trials, two of which were double-blind comparative trials.[226,227] In addition to the general definition of clinical cure provided in section 6 introduction, both studies also evaluated sinus radiograph findings in all patients. In the first trial by Roos et al.[227] telithromycin 800mg once daily was compared in a 5-day course versus a 10-day course. Both courses were found to have satisfactory outcomes and were equivalent in efficacy, with 91.1% cure in the 5-day group PP population versus 91.0% cure in the 10-day PP population. Cure rates in the mITT populations were 82.6% and 87.5% in the 5-day and 10-day groups, respectively (table VIII). Cure rates were also equivalent regardless of infection severity or duration of symptoms prior to treatment. Bacteriological outcomes were also good for both treatments (92.9% for the 5-day course and 89.9% for the 10-day course) and covered all of the most common causative agents effectively.[227] The authors concluded that the 5-day course of treatment would be effective in the treatment of acute sinusitis and may result in better patient compliance.

In the second trial by Tellier et al.,[226] telithromycin 800mg for 5 days was compared with telithromycin 800mg for 10 days and amoxicillin/clavulanic acid 500mg/125mg three times daily for 10 days. Results in the PP population were lower than in the trial by Roos et al., but were equivalent for all three treatment modalities (75.3% for telithromycin 5 day, 72.9% for telithromycin 10 day and 74.5% for amoxicillin/clavulanic acid 10 day).[167,226] Satisfactory bacteriological outcomes were equivalent for the two telithromycin groups (87%) and were slightly higher than the amoxicillin/clavulanic acid group (75.0%). Incidence of reoccurrence of infection at the late post-therapy visit was low and roughly equal in all treatment arms (5 patients in each telithromycin group and 3 patients in the amoxicillin/clavulanic acid group).[167,226] In the third study by Buchanan et al.[231] telithromycin 800mg once daily for 5 days was compared with cefuroxime axetil 250mg twice daily for 10 days. Clinical cure rates in the PP population were equivalent (85.2% versus 82.0%, respectively). Clinical cure rates in the mITT populations were 80.4% for telithromycin versus 72.4% for cefuroxime axetil. Bacteriological outcomes were similar for both treatments (84.0% and 80.0%, respectively).

7. Adverse Effects

As a class, the macrolides are a well-tolerated and safely used group of therapeutic agents.[1] With respect to the newer ketolides, early clinical trials suggests the ketolides telithromycin and ABT-773 have similar safety profiles to the newer macrolides (clarithromycin and azithromycin).[67,157,167,233]

Clinical trials to date have demonstrated that most adverse events in patients receiving telithromycin 800mg once daily for up to 10 days are mild to moderate in intensity and discontinuation because of treatment-related adverse events is uncommon (4%).[167] In eight comparator-controlled studies, the incidence and profile of adverse events was similar for telithromycin and comparators.[167] The most common adverse effects associated with telithromycin (n = 2045) in the eight randomised, double-blind, comparative phase III studies were gastrointestinal (GI) such as diarrhoea (13.3%), nausea (8.1%) and vomiting (2.8%).[228] The majority of cases of diarrhoea were mild (69%) or moderate (25%) in severity and those resulting treatment discontinuation (0.9% of all telithromycin-treated patients) were similar to pooled comparators (0.8%) and lower than amoxicillin/clavulanic acid (2.4%).[167] The incidence of more serious adverse effects of telithromycin was reported to be similar to that of the pooled comparators in trials in patients with CAP, AECB, sinusitis and pharyngitis (table IX).[167]

The tolerability profile of telithromycin versus comparators in clinical trials has been summarised by Sharma et al. (table IX).[233] The total treatment-

related GI effects were higher for the telithromycin arms than for the pooled comparators at 26.1 versus 15.9%, respectively. However, most were of mild to moderate severity and rates of discontinuation were similar between all agents. Total treatment discontinuations secondary to adverse effects were 4.8% for telithromycin versus 4.4% for the comparator agents.[233]

More serious treatment related but less common adverse effects (0.4%) observed with telithromycin in clinical trials include allergic reactions, liver injury, pseudomembranous colitis, erythema multiforme, blurred vision, gastroenteritis and severe vomiting.[167,228] These occurrences are comparable to other antibacterial agents currently used in treating respiratory infections.[167] No incidences of ototoxicity were reported. There were no treatment-related deaths attributable to telithromycin in any of the trials.[167]

Laboratory results have also been analysed in telithromycin clinical trials. Elevations in liver function tests (aspartate aminotransferase and alanine aminotransferase) have been reported in patients receiving telithromycin. In patients receiving 800mg once daily, elevations in liver enzymes occurred in <1.0% in patients with normal baseline enzyme levels being treated for respiratory infections other than CAP, and in <2.0% of patients with CAP with normal baseline levels. The incidence of elevated hepatic enzyme levels was higher in patients with abnormal baseline enzyme levels.[167] However, overall the elevations in liver enzymes were similar to comparator agents.[167]

Telithromycin showed no significant effect on the QT interval at therapeutic dosages, with a change in QTc (ΔQTc) interval after 2 hours equivalent to clarithromycin and to placebo.[167] Results showed no significant ΔQTc interval when telithromycin dosage ranged from 800mg to 2400 mg/day. Studies measuring cardiovascular adverse effects also included a small population of high-risk subjects with underlying cardiovascular disease.[167]

At the time of writing, clinical trials with ABT-773 have not been published, however, preliminary human pharmacokinetic data suggests that adverse effects associated with ABT-773 are dose-related, and involve symptoms similar to those described for telithromycin.[162,163] No significant adverse effects or changes in laboratory values were recorded for ABT-773 in these pharmacokinetic studies.[162,163]

Table IX. Adverse effects reported for telithromycin[167,233]

Adverse effects	Telithromycin
Gastrointestinal	
abdominal pain	+
nausea	+ +
vomiting	+
diarrhoea	+ + +
Blurred vision	+
Allergic reactions	+/–
Hepatic function abnormality	+
Ototoxicity	–
Taste perversion	+
Cardiovascular events	+/–
Central nervous system	
headache	+
dizziness	+

– indicates adverse effect has not been observed; **+/–** indicates adverse effect occurs in <1% of patients; **+** indicates that adverse effect occurs in 1-5% of patients; **++** indicates that adverse effect occurs in 5-10% of patients; **+++** indicates adverse effect occurs in >10% of patients.

8. Drug Interactions

As derivatives of the macrolide class of antibacterials, ketolides may interact with concomitant medications in a similar manner. Clinically significant interactions between macrolides and other drugs have been summarised in a previous review.[1] The majority of these interactions involve pronounced inhibition by the macrolides of CYP 3A4 enzymes resulting in the impairment of drug metabolism of the certain co-administered medications. Only preliminary studies have been conducted with telithromycin, and it is probable that the full range of drug interactions remains to be expanded upon introduction into clinical practice. Drug interactions with other ketolides have yet to be determined.

In vitro studies of the interaction of telithromycin with the CYP enzyme system have determined that this agent does not form nitrosoalkane complexes with these enzymes unlike some macrolide agents such as troleandomycin.[178] Telithromycin interacts with these enzymes reversibly and is a competitive inhibitor of some enzyme subgroups.[167] This has also been observed *in vivo*, where telithromycin has shown some indication of clinically significant interactions. As with macrolides, administration of telithromycin with drugs that are metabolised by CYP3A4 results in increased plasma concentrations of the latter, including cisapride, simvastatin and midazolam.[167] Results of studies with telithromycin are summarised in table X.[167,234-237]

Telithromycin has been shown to significantly affect the metabolism of simvastatin, an HMG CoA reductase inhibitor.[167] Simvastatin concentrations are increased in a manner similar to that observed previously for macrolides. Rhabdomyolysis has been observed when macrolides were concomitantly administered, although this has not been observed with telithromycin to date.[1,167] Nevertheless, the concomitant administration of telithromycin with this class of agents should be avoided.

Inhibition of CYP3A4 metabolism of cisapride has been noted with the co-administration of telithromycin resulting in increased serum cisapride concentrations.[167] Because of the increased potential for QT interval irregularities and ventricular arrhythmias, concomitant administration of cisapride with macrolides is contraindicated.[1,167]

Other medications known to be affected by macrolides were also administered concomitantly with telithromycin in drug interaction studies. Telithromycin also caused a moderate increase in digoxin concentrations; however, the mechanism of this interaction was not presented.[167] Because of the low therapeutic index of digoxin, caution is warranted with co-administration. Oral contraceptives, warfarin, theophylline and paroxetine were all shown to be unaffected to any clinically significant degree by the administration of telithromycin.[167,234-236]

Telithromycin concentrations were shown to be minimally affected by the CYP3A4 inhibiting drugs itraconazole and ketoconazole.[167] Finally, absorption of telithromycin was unaffected by agents affecting gastric pH in the stomach, such as antacids or the histamine H_2 receptor blocker ranitidine.[236]

Table X. Drug interactions reported for telithromycin[167,234-236]

Drug	Effect
Triphasic contraceptives	Telithromycin slightly increases the C_{max}, AUC and $t_{1/2}$ at steady state of levonorgesterol, but does not affect ethinyl oestradiol or the reliability of the contraceptive in preventing ovulation. Not clinically significant
Warfarin	No clinically signifcant interaction
Simvastatin	Inhibition of CYP3A4 by telithromycin leads to significant increase in C_{max} (5.3x) and AUC (8.9x). Avoid concomitant administration
Cisapride	Inhibition of CYP3A4 by telithromycin results in a 1.9x increase in C_{max} and a 2.6x increase in AUC. Avoid concomitant administration
Itraconazole, ketoconazole	Inhibition of CYP3A4 by these agents leads to slightly increased C_{max} and AUC of telithromycin. Not clinically significant
Digoxin	Telithromycin results in a moderate increase of 1.2x C_{min} and 1.4x AUC. Monitor, use with caution
Theophylline	Inhibition of metabolism by telithromycin results in a modest increase in theophylline concentrations. Monitor
Paroxetine	None
Agents affecting gastric pH (Mg and Al hydroxides, ranitidine)	None

AUC = area under the concentration time curve; **C_{max}** = maximum serum concentration; **CYP** = cytochrome P450; **$t_{1/2}$** = elimination half-life.

9. Pharmacoeconomic and Formulary Considerations

There is a paucity of pharmacoeconomic evaluations because of the recent development of the ketolides. As derivatives of the macrolide class specifically targeted for respiratory infections, efficacy and cost effectiveness will need to be established for indications involving the upper and lower respiratory tract. A number of considerations will apply when analysing the overall cost effectiveness of these agents and their place in practice. Factors to consider for the ketolides include acquisition cost, adverse effects of the agent, drug interaction potential, activity against the most likely pathogens, frequency of administration and patient compliance, monitoring parameters required, cost of treatment failure, reduction in morbidity, income or productivity lost as a result of the infection, and effect of the treatment on patient quality of life.

Consideration of these factors compared to current treatment options is essential in determining the role of ketolides in treating respiratory tract and other infections. The practice of choosing the correct antibacterial for an indication based on activity, patient considerations and treatment cost will become a necessity when treating infections in healthcare systems faced with rising rates of bacterial resistance to existing agents and under increasing pressure to lower the cost of treatment.

Data to date for telithromycin has been for the oral treatment of community acquired respiratory tract infections. The efficacy of telithromycin in community acquired respiratory infections makes it a suitable empirical treatment for mild to moderate illness in adults. The availability of parenteral and liquid dosage formulations would expand its use to more serious infections and to the paediatric population. Considerations for the addition of telithromycin to a formulary include local epidemiology, the prevalence of bacterial resistance, patterns of prescribing, severity of the illness, the ease of administration and costs relative to current agents. Oral telithromycin has the advantage of convenient dose administration, in early trials the efficacy is comparable with other first line treatments, and it has demonstrated *in vitro* and *in vivo* activity against a wide range of the most likely respiratory tract pathogens.[214-229]

10. Potential Use of Ketolides

The prevalence of resistance to antibacterials among respiratory tract pathogens has been increasing over the past decade with pathogens gaining resistance to penicillins and macrolides.[2,238,239] This has prompted the search for new antibacterials such as the ketolides. The development of ketolides provides tools for clinicians to overcome resistance mechanisms that render macrolides ineffective. Ketolides display a broad spectrum of activity typical of earlier macrolides with the added benefit of activity against species such as *S. pneumoniae* and *S. pyogenes* that are macrolide resistant.

The ability to rationally design antibacterials with the ability to overcome resistance mechanisms is an important step forward in infectious disease treatment. However, equally important is correct application of these agents to prevent further resistance development. Ketolides have shown less frequent development of resistance *in vitro*, but the potential is still there to develop resistance to new agents as their use increases. The development of proper dose administration regimens and prescribing will minimise the emergence of bacterial resistance while maintaining the usefulness this class of antibacterials.[191] Telithromycin displays excellent pharmacokinetic parameters allowing for once daily administration and can be administered in short duration therapy for most respiratory infection indications. Coupled with high plasma drug concentrations achieved after dose administration, and higher tissue concentrations achieved during therapy, telithromycin is able to achieve high C_{max}/MIC and AUC/MIC values against the majority of clinical isolates, which may be a predictor of clinical success.

The final aspect to consider is the tolerability and drug interaction profile of a new agent when it is being evaluated for a place in therapy. Limited

data with telithromycin and ABT-773 demonstrate a similar drug interaction profile to the newer macrolide agents, such as azithromycin and clarithromycin. In addition, early trials with telithromycin indicate that it has a good safety profile with only mild to moderate adverse effects resulting in minimal treatment discontinuation, which are similar in prevalence to comparators. However, careful follow-up is needed upon widespread use to ensure use in the general population supports these early findings.

In summary, early clinical trials support the clinical efficacy of the ketolides in common respiratory tract infections. The promising activity of the ketolides in the presence of macrolide resistance among respiratory tract pathogens is a useful addition to the armamentarium of antimicrobials for the treatment of mild to moderate respiratory tract infections. Considerations such as local epidemiology, patterns of resistance and ketolide adverse effects, drug interactions and cost relative to existing agents will define the role of these agents. The addition of the ketolides in the era of bacterial resistance provides clinicians with more options in the treatment of respiratory infections.

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