

Solithromycin: A Novel Fluoroketolide for the Treatment of Community-Acquired Bacterial Pneumonia

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Abstract Solithromycin is a novel fluoroketolide developed in both oral and intravenous formulations to address increasing macrolide resistance in pathogens causing community-acquired bacterial pneumonia (CABP). When compared with its macrolide and ketolide predecessors, solithromycin has several structural modifications which increase its ribosomal binding and reduce its propensity to known macrolide resistance mechanisms. Solithromycin, like telithromycin, affects 50S ribosomal subunit formation and function, as well as causing frame-shift errors during translation. However, unlike telithromycin, which binds to two sites on the ribosome, solithromycin has three distinct ribosomal binding sites. Its desosamine

sugar interacts at the A2058/A2059 cleft in domain V (as all macrolides do), an extended alkyl-aryl side chain interacts with base pair A752-U2609 in domain II (similar to telithromycin), and a fluorine at C-2 of solithromycin provides additional binding to the ribosome. Studies describing solithromycin activity against *Streptococcus pneumoniae* have reported that it does not induce *erm*-mediated resistance because it lacks a cladinose moiety, and that it is less susceptible than other macrolides to *mef*-mediated efflux due to its increased ribosomal binding and greater intrinsic activity. Solithromycin has demonstrated potent in vitro activity against the most common CABP pathogens, including macrolide-, penicillin-, and fluoroquinolone-resistant isolates of *S. pneumoniae*, as well as *Haemophilus influenzae* and atypical bacterial pathogens. Solithromycin displays multi-compartment pharmacokinetics, a large volume of distribution (>500 L), approximately 67% bioavailability when given orally, and serum protein binding of 81%. Its major metabolic pathway appears to follow cytochrome P450 (CYP) 3A4, with metabolites of solithromycin undergoing biliary excretion. Its serum half-life is approximately 6–9 h, which is sufficient for once-daily administration. Pharmacodynamic activity is best described as $fAUC_{0-24}/MIC$ (the ratio of the area under the free drug concentration–time curve from 0 to 24 h to the minimum inhibitory concentration of the isolate). Solithromycin has completed one phase II and two phase III clinical trials in patients with CABP. In the phase II trial, oral solithromycin was compared with oral levofloxacin and demonstrated similar clinical success rates in the intention-to-treat (ITT) population (84.6 vs 86.6%). Clinical success in the clinically evaluable patients group was 83.6% of patients receiving solithromycin compared with 93.1% for patients receiving levofloxacin. In SOLITAIRE-ORAL, a phase III trial

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which assessed patients receiving oral solithromycin or oral moxifloxacin for CABP, an equivalent (non-inferior) early clinical response in the ITT population was demonstrated for patients receiving either solithromycin (78.2%) or moxifloxacin (77.9%). In a separate phase III trial, SOLITAIRE-IV, patients receiving intravenous-to-oral solithromycin (79.3%) demonstrated non-inferiority as the primary outcome of early clinical response in the ITT population compared with patients receiving intravenous-to-oral moxifloxacin (79.7%). Overall, solithromycin has been well tolerated in clinical trials, with gastrointestinal adverse events being most common, occurring in approximately 10% of patients. Transaminase elevation occurred in 5–10% of patients and generally resolved following cessation of therapy. None of the rare serious adverse events that occurred with telithromycin (i.e., hepatotoxicity) have been noted with solithromycin, possibly due to the fact that solithromycin (unlike telithromycin) does not possess a pyridine moiety in its chemical structure, which has been implicated in inhibiting nicotinic acetylcholine receptors. Because solithromycin is a possible substrate and inhibitor of both CYP3A4 and P-glycoprotein (P-gp), it may display drug interactions similar to macrolides such as clarithromycin. Overall, the in vitro activity, clinical efficacy, tolerability, and safety profile of solithromycin demonstrated to date suggest that it continues to be a promising treatment for CABP.

Key Points

The potent in vitro activity of solithromycin against the most common causes of community-acquired bacterial pneumonia (CABP) (including macrolide-, penicillin-, and fluoroquinolone-resistant isolates of *Streptococcus pneumoniae*), its intravenous and oral dosing, along with clinical efficacy, tolerability, and a favorable safety profile make this new fluoroketolide a promising agent for the treatment of CABP in both the hospital and community settings.

While solithromycin possesses many of the properties required of an ideal antimicrobial agent for treating CABP, more clinical efficacy and safety data are required to fully determine its role in the treatment of CABP.

Pharmacoeconomic considerations will also help to further elucidate the place of solithromycin in the clinician's arsenal of antimicrobial agents available to treat patients with CABP.

1 Introduction

Lower respiratory tract infections (LRTI), including community-acquired bacterial pneumonia (CABP), remain one of the most common reasons for physician visits, and continue to contribute significantly to morbidity and mortality, ranking among the top infectious causes of death worldwide [1, 2]. The availability of effective antimicrobial agents to treat these infections is imperative. While guidelines may vary between countries, macrolides are consistently recommended, as first- or second-line agents, either alone or in combination with a β -lactam [3, 4].

Macrolides exhibit activity against Gram-positive cocci, such as *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus* spp., as well as atypical pathogens (*Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae*), and *Moraxella catarrhalis*. In addition, second-generation macrolides (clarithromycin), the azalide azithromycin, and the ketolide telithromycin, have activity against *Haemophilus influenzae* [5]. The ability of single-agent therapy to cover the most common causes of CABP, namely *S. pneumoniae*, *H. influenzae*, and the atypical bacterial pathogens, is an attractive characteristic [4, 6]. Azithromycin and clarithromycin exhibit added benefits over the first clinically used macrolide, erythromycin A, because of their improved bioavailability, longer half-lives, lower incidence of gastrointestinal adverse effects, and fewer clinically significant drug–drug interactions [7]. The ketolides are semisynthetic derivatives of erythromycin A that were developed to overcome macrolide-resistant *Streptococcus* spp. and demonstrated overall activity that was similar to the second-generation macrolides [5].

The ketolide telithromycin (third-generation macrolide) received US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval in 2004 and 2001, respectively. However, due to hepatotoxicity, its use has been limited, with the FDA restricting approved indications to only CABP in addition to a black box warning, and the EMA recommending restricting its use along with strengthened warnings about serious adverse events [8–10]. With macrolide resistance rates remaining high, (e.g., *S. pneumoniae* resistance to macrolides reported as high as 48.4% in the US), there remains a need for further development of effective, well tolerated agents with stability against macrolide-resistant isolates [11].

A new fourth-generation macrolide, solithromycin (formerly known as CEM-101), is the first fluoroketolide that has recently completed phase III clinical trials and demonstrates potent activity against the pathogens associated with CABP, including macrolide- and penicillin-resistant isolates of *S. pneumoniae* [3, 11]. Unlike

telithromycin and its metabolites, solithromycin lacks the pyridine moiety in its side chain that has been shown to be associated with nicotinic acetylcholine receptor inhibition, which is potentially the cause of the blurry vision, exacerbation of myasthenia gravis, loss of consciousness, and idiosyncratic hepatic failure that had been reported [12, 13]. It has also been suggested that the lack of an imidazole moiety may lower the risk of hepatotoxicity, although further studies are required to confirm this association [13].

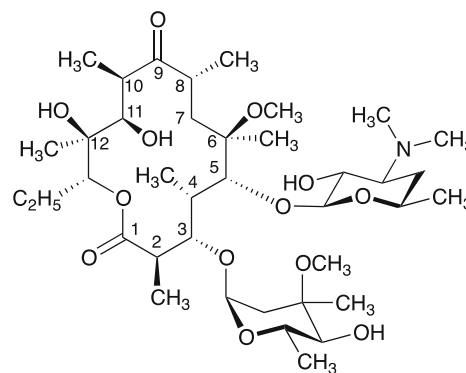
This article reviews the relevant published data on solithromycin and its potential role in CABP, including chemistry, mechanism of action, mechanism of resistance, microbiology, pharmacokinetics, pharmacodynamics, safety and efficacy results from clinical trials, as well as known and potential drug interactions. A comprehensive literature search was completed via PubMed for all articles containing the term 'solithromycin', with results supplemented by posters and abstracts.

As the focus of this paper is the role of solithromycin in CABP, it is not the purpose of this paper to discuss other potential roles for solithromycin such as for the treatment of sexually transmitted infections (e.g., gonorrhea), treatment of maternal–fetal infections, treatment of non-alcoholic steatohepatitis, and use as an anti-inflammatory in chronic obstructive pulmonary disease (COPD).

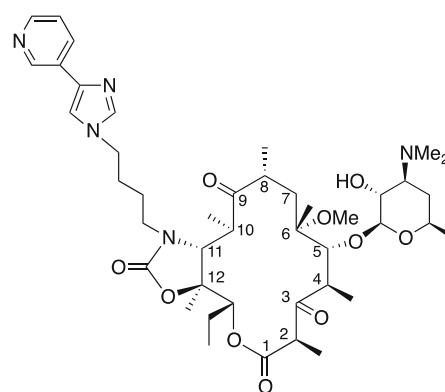
2 Chemistry

Solithromycin shares many structural similarities with telithromycin, which account for its activity against macrolide-resistant isolates of *Streptococcus* spp. First, in comparison with the older macrolides (see Fig. 1, clarithromycin), solithromycin lacks the L-cladinose on C-3 of the erythronolide ring, which results in the hydroxyl group being oxidized to a keto group. This modification increases acid stability as well as antimicrobial potency versus macrolide-resistant isolates, as the keto group does not induce macrolide-lincosamide-streptogramin B (MLS_B) resistance via *erm* determinants, and the removal of the cladinose moiety reduces the effect of methylation at A2058 (*Escherichia coli* numbering used here and elsewhere in the manuscript) in the domain V binding site, which causes a steric clash with cladinose containing macrolides [5, 14]. The lack of the cladinose provides increased freedom of movement of the desosamine sugar, allowing repositioning away from the methylated site [14, 15]. In cases where there is no methylation, the desosamine sugar orients towards the peptidyl transferase center, interacting with the A2058/A2059 cleft [16]. Secondly, the presence of an 11,12-carbamate, in addition to the C-6 methoxy group, improves upon the structure of

(a) Clarithromycin



(b) Telithromycin



(c) Solithromycin

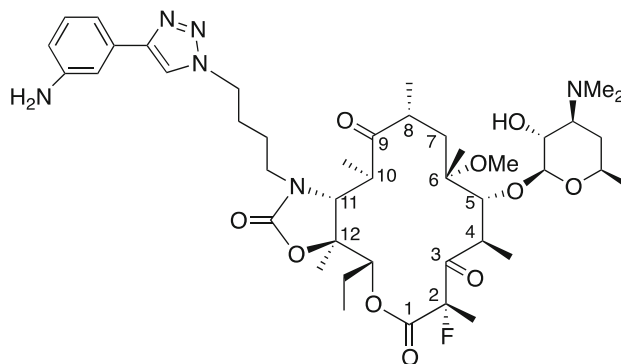


Fig. 1 Chemical structures of clarithromycin (a), telithromycin (b), and solithromycin (c)

older macrolides such as erythromycin because it prevents the formation of 6–9 or 9–12 cyclization within the compound that leads to a hemiketal formation [5]. Clarithromycin, although lacking the 11,12-carbamate, also has a methoxy group at C-6 of the erythronolide ring, which prevents the degradation of this agent to the hemiketal and spiroketal metabolites that have been implicated in being responsible for the gastrointestinal adverse effects of

erythromycin [7]. Third, the addition of an extended alkyl-aryl side chain (in solithromycin, the 11,12-carbamate-butyl-[1,2,3]-triazolyl-aminophenyl) helps compensate for the lack of the L-cladinose, which is important for ribosomal binding in the older macrolides, increasing activity against both macrolide-susceptible and -resistant strains [5]. Specifically, the aromatic nature of the side chain imparts improved activity due to interacting with base pair A752-U2609, serving as an additional binding site in domain II of the 23S rRNA [14]. It is important to note that the interaction of the 11,12-carbamate side chain varies between solithromycin and telithromycin. Based on the atomic displacement parameter from the crystallographic structure of solithromycin bound to an *E. coli* ribosome, solithromycin appears to have better anchoring at this ribosomal binding site, likely due to the exocyclic amino group of the aminophenyl allowing additional hydrogen bonding to occur (acting as a donor to O-4 of A752 and O-6 of G748; H bond acceptor from N-1 of G748) versus that possible with telithromycin's imidazole-pyridine moiety [14]. Further, the lack of the pyridine moiety, as previously mentioned, is important in reducing the off-target inhibition at nicotinic acetylcholine receptors [12, 13].

Solithromycin also varies from telithromycin due to the presence of a fluorine at C-2. When bound to the ribosome, this fluorine is found in close proximity (2.7 Å) to the

glycosidic bond (N-1) of C2611 of 23S rRNA, potentially contributing to drug binding and enhancing its activity [14]. Thus, solithromycin demonstrates binding to three distinct sites on the ribosome whereas telithromycin binds to two ribosomal sites. Solithromycin demonstrated improved growth inhibition of streptococci carrying the *erm* methyltransferase gene compared with analogs lacking the C-2 fluorine, indicating that its presence is one of the factors that may contribute to solithromycin's activity against macrolide-resistant isolates [14]. Finally, this fluorine substituent prevents enolization of the keto group to ensure that the tetrahedral bond structure, which has been shown to be essential for maintaining ketolide activity, is maintained at C-2 [3, 17]. A summary of the structure-activity relationships of solithromycin is presented in Fig. 2.

3 Mechanisms of Action

Solithromycin has been shown to bind to the 50S ribosomal subunit, binding to the peptide exit tunnel close to the peptidyl transferase centre in a similar manner to other macrolides [14, 18]. However, solithromycin also demonstrates increased ribosomal binding in comparison with the other macrolides, as well as with telithromycin, due to the specific chemical characteristics of its structure. When

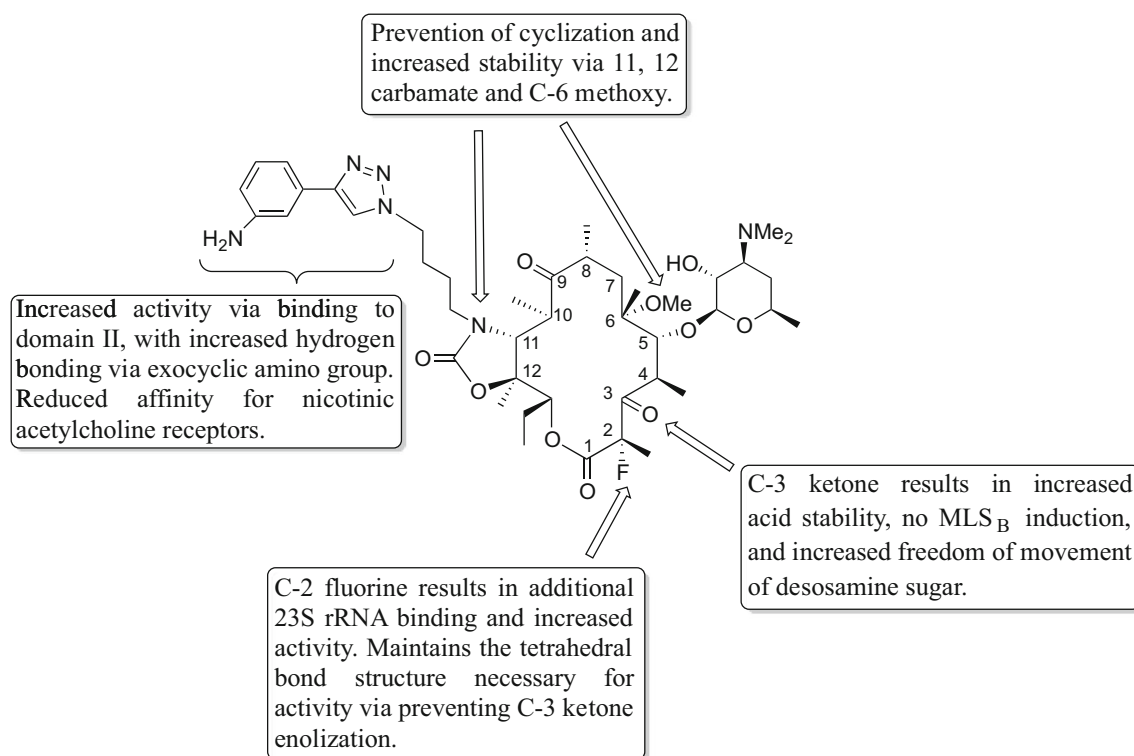


Fig. 2 Structure activity relationships of solithromycin. *MLS_B* macrolide-lincosamide-streptogramin B

bound to the ribosome, its lactone ring forms hydrophobic interactions with the walls of the peptide exit tunnel, the desosamine projects towards the peptidyl transferase centre interacting with the A2058/A2059 cleft, the alkyl-aryl arm orients down the tunnel making contact with A752-U2609, and the fluorine contributes to tighter binding and improved activity [14].

Binding of a macrolide to the peptide exit tunnel can affect protein synthesis via direct interruption of elongation of the nascent peptide chain [18]. Recently, it has also been shown that the binding of solithromycin to the tunnel may have an allosteric influence on the structure of the catalytic site, therefore altering the function of the peptide transferase center in which the growing chain is assembled [19].

Solithromycin, like telithromycin (but unlike other macrolides), also displays a significant inhibitory effect on the formation of the 50S ribosomal subunit, thus affecting both ribosomal formation and function. In comparison with telithromycin, solithromycin demonstrated similar inhibition versus *S. pneumoniae*, methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA), with substantially greater inhibition of the 50S ribosomal subunit in *H. influenzae* [20]. Solithromycin has shown a variable effect on the 30S subunit, suggesting that this is organism-specific: disruption of 30S subunit formation has been demonstrated in MSSA and to a minimal degree in *S. pneumoniae*, but is unaffected in *H. influenzae* [20].

Reduced translation fidelity via frame-shift errors has also been shown to contribute to the effect of solithromycin on protein synthesis, potentially contributing by promoting peptidyl-tRNA drop-off [21]. The occurrence of frame-shifts even when the length of the peptide has not reached solithromycin in the exit tunnel is thought to occur allosterically, with the presence of solithromycin leading to a change in ribosomal properties involved in reading frame maintenance [21].

Solithromycin has also demonstrated the ability to achieve greater intracellular accumulation than its predecessors, both macrolides and ketolides, due to its structural modifications, with accumulation occurring from the same proton trapping mechanism as seen in the other macrolides [22]. The ability to achieve high concentrations within alveolar macrophages (as well as the extracellular epithelial lining fluid) may contribute to its ability to effectively treat both extra and intracellular pathogens associated with lower respiratory tract infections [23]. Aside from its antimicrobial effect, solithromycin demonstrates other characteristics that may be of clinical benefit such as anti-inflammatory effects [24, 25].

4 Mechanisms of Resistance

Resistance to macrolides has been well documented, and first appeared only a few years after the initial clinical use of erythromycin [7]. Common mechanisms of resistance in Gram-positive cocci include *mef* (macrolide efflux) and *erm* (erythromycin ribosomal methylation), with other mechanisms of resistance being less common, including mutations in ribosomal proteins or rRNA [5]. Solithromycin has demonstrated activity and efficacy against macrolide- and multidrug-resistant (MDR) isolates of *S. pneumoniae*, including those with multiple macrolide resistance mechanisms [11, 26–29]. Overall, respiratory tract pathogen resistance to solithromycin to date has been rare, with further resistance development expected to be limited due to its interaction with three ribosomal binding sites in comparison with older macrolides.

When *erm* encoded resistance is expressed, it leads to methylation at site A2058, resulting in steric hindrance and reduced ribosomal binding of older cladinose-containing macrolides [14]. Because solithromycin allows for additional ribosomal binding sites, it has demonstrated binding to ribosomes both mono and dimethylated at A2058 [14]. In isolates with inducible *erm* determinants, the cladinose moiety of macrolides plays a key role in triggering methylation, whereas solithromycin does not activate this resistance mechanism to any appreciable extent [5]. While it has been demonstrated that ketolides can induce *erm* determinants as a result of a frame-shift mutation leading to expression of the downstream gene, the induction occurs to a much lesser extent than experienced with macrolides and is not believed to be sufficient to render pathogens resistant [21]. In telithromycin-non-susceptible *Staphylococcus* spp. displaying a constitutive MLS_B phenotype, solithromycin also demonstrates reduced activity [30].

Macrolide resistance in *H. influenzae* tends to be more complex, and usually involves the expression of efflux pumps that reduce intracellular drug accumulation, resulting in reduced activity in comparison with isolates lacking this mechanism, along with mechanisms such as ribosomal methylase or alterations in ribosomal proteins and rRNA [31]. Although rare, solithromycin-resistant isolates have demonstrated a variety of ribosomal mutations, including rRNA mutations of A2059G and/or mutations in either ribosomal proteins L4 or L22 [16].

Ketolide resistance or potentiation of rRNA resistance mutations have been reported to result from mutations in L22, and when assessing the location of solithromycin when bound to the ribosome, the ϵ -amino group of Lys 90 of L22 is located fairly close to solithromycin's aminophenyl group [14]. While close, the distance (>4 Å) suggests that mutations to L22 would act allosterically, unless

insertions or deletions of several amino acids occurred in the Lys 90-containing β -hairpin of L22, which would bring the drug into prohibitively close contact, potentially resulting in reduced ribosomal affinity [14].

Efflux may lead to increased macrolide minimum inhibitory concentrations (MICs); however, this resistance mechanism is less effective versus the ketolides, and solithromycin has been shown to be even more active against *mef*(E)-positive *S. pneumoniae* (with or without *erm*(B)) compared with telithromycin [26]. The decreased effectiveness of this mechanism against solithromycin may be due to the increased ribosomal binding, greater intrinsic activity, and the overall structure of solithromycin, which renders it a poor substrate for the efflux pump [5, 26].

In terms of resistance selection, solithromycin has demonstrated a low tendency to select for resistant mutants, with little or no yields being detected in single-step studies, and the rates of resistance selection being less than or equivalent to those for telithromycin in multistep mutational studies [27, 32].

5 Microbiology

The in vitro activity of solithromycin and comparators (telithromycin, azithromycin, and clarithromycin) against aerobic Gram-positive, aerobic Gram-negative, anaerobic, and other clinically important bacteria are presented in Tables 1, 2, 3 and 4 [5, 7, 11, 26–30, 33–52]. The MIC values, reported in mg/L, are representative of pooled data from studies conducted with solithromycin, with MIC₅₀ and MIC₉₀ representing the most common MIC₅₀ and MIC₉₀ reported for that organism, unless only limited studies (one or two) were found, in which case the lowest MIC₅₀ and MIC₉₀ reported were utilized. Comparator data was pooled from the same studies that utilized solithromycin, when available. The range is composed of the lowest and highest MIC values reported from the cited studies which all utilized standard MIC determination methods (e.g., Clinical and Laboratory Standards Institute [CLSI]). It should be remembered that macrolide MICs may be affected by experimental conditions (e.g., pH, % CO₂, length of incubation, etc.), thus the exact numerical MICs in the following tables should be interpreted with caution.

Although CLSI MIC susceptibility breakpoints have not yet been set for solithromycin (although ≤ 1 mg/L has been proposed by Cempira), it has been reported to display potent activity, relative to macrolides and telithromycin, against the majority of aerobic Gram-positive bacteria (Table 1). With *S. pneumoniae*, solithromycin demonstrates excellent activity, including against macrolide-, penicillin-, and fluoroquinolone-resistant strains, with all MIC₉₀ values

≤ 0.5 mg/L (Table 1). In cases where both *erm*- and *mef*-resistant mechanisms were present, solithromycin showed a 2- to 4-fold lower MIC compared with telithromycin. Similarly for other streptococci, solithromycin displayed activity that was superior to its comparators, including telithromycin. Against macrolide-resistant strains of *Streptococcus pyogenes* (Group A streptococci), solithromycin demonstrated better activity than telithromycin, especially against those isolates that harbored the *erm*(B) determinant, with MIC₅₀ and MIC₉₀ values both being 16-fold lower than telithromycin (MIC₅₀ of 0.5 mg/L vs 8 mg/L; MIC₉₀ of 1 mg/L vs 16 mg/L) (Table 1). Against telithromycin-resistant β -hemolytic streptococci (defined as a telithromycin MIC ≥ 2 mg/L), solithromycin demonstrated excellent activity with MIC₅₀ and MIC₉₀ of 0.12 mg/L and 0.5 mg/L, respectively [29]. For *Streptococcus* spp. that were both macrolide- and clindamycin-non-susceptible, solithromycin had a 4-fold lower MIC₉₀ versus telithromycin (0.25 mg/L vs 1 mg/L) (Table 1). Against *S. aureus*, solithromycin was potent against MSSA and genotypically determined community-associated MRSA (CA-MRSA), with MIC₉₀ values of 0.06 mg/L and 0.12 mg/L, respectively. However, solithromycin demonstrated limited activity versus healthcare-associated MRSA (HA-MRSA), vancomycin-intermediate *S. aureus* (VISA)/heterogeneous vancomycin-intermediate *S. aureus* (hVISA), and vancomycin-resistant *S. aureus* (VRSA), likely due to the presence of the *msrA* gene in these strains (Table 1).

Against Gram-negative bacteria, solithromycin demonstrated activity that was similar to that of telithromycin and azithromycin, although limited studies were available (Table 2). Against *H. influenzae*, β -lactamase status did not influence solithromycin's MIC, with MIC₅₀ and MIC₉₀ remaining consistent at 1 mg/L and 2 mg/L, respectively [29, 35]. Against *H. influenzae* resistant to azithromycin, solithromycin's MIC has been reported to be 8-fold greater than against non-resistant isolates [35].

For anaerobic bacteria, like other macrolides, solithromycin demonstrates poor activity versus *Bacteroides* spp., but greater activity than both telithromycin and azithromycin versus *C. difficile* [37, 45].

Other clinically relevant bacteria demonstrated excellent susceptibility to solithromycin, although studies were limited with most representing data from a single source (Table 4). Against *C. pneumoniae*, solithromycin was slightly less active versus comparators, with the MIC_{50/90} of 0.25 mg/L being 2-fold greater than azithromycin and fourfold that of telithromycin. For *L. pneumophila*, solithromycin demonstrated better activity than azithromycin, with an MIC₉₀ of ≤ 0.015 mg/L versus 1 mg/L. Finally, against *M. pneumoniae*, solithromycin showed high potency, with an MIC₉₀ of ≤ 0.000032 mg/L [48].

Table 1 In vitro activity (MIC, mg/L) of solithromycin and comparators against aerobic Gram-positive bacteria adapted from references [5, 7, 11, 26–28, 30, 33–41, 50, 51]

Organism	Ketolide					Macrolide			
	Solithromycin			Telithromycin		Azithromycin		Clarithromycin	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Bacillus</i> spp.	0.015	0.03	≤0.008–0.03	0.03	0.06	2	4	0.12	0.25
CoNS	0.06	>4	≤0.03 to >16	0.12	>2	1	16	0.25	≥64
<i>Corynebacterium</i> spp.	0.015	0.5	≤0.008–16	0.06	8	>16	>16	8	>16
<i>Enterococcus faecalis</i>	0.06	2	0.015 to >4	0.12	>2	4	>64	2	>32
Vancomycin (S)	0.03	2	0.015–2	0.06	4	NA	NA	NA	NA
Vancomycin (R)	0.25	2	0.015–2	0.5	4	NA	NA	NA	NA
<i>Enterococcus faecium</i>	1	2	≤0.03 to >4	2	>2	16	16	>32	>32
Vancomycin (S)	0.25	2	0.03–2	0.5	4	NA	NA	NA	NA
Vancomycin (R)	2	2	0.25–2	4	4	NA	NA	NA	NA
<i>Enterococcus</i> spp.	0.03	2	≤0.03 to >4	0.06	>2	16	≥64	2	≥64
<i>Listeria monocytogenes</i>	0.03	0.03	0.03	0.06	0.06	0.5	1	0.12	0.12
<i>Micrococcus</i> spp.	0.015	0.03	≤0.008–0.06	0.03	0.06	0.12	0.5	0.06	0.5
<i>Staphylococcus aureus</i>	0.06	0.12	0.008 to >32	0.06	>2	1	8	0.25	≥64
MSSA	0.06	0.06	≤0.03 to >32	0.06	0.25	1	>32	0.25	1
MRSA	0.06	>32	0.008 to >32	0.25	>2	>4	>4	>16	>16
CA-MRSA	0.12	0.12	0.06–0.12	0.25	0.25	NA	NA	32	>32
VISA/hVISA	>16	>16	0.06 to >16	>16	>16	NA	NA	NA	NA
VRSA	>16	NA	0.12 to >16	>16	NA	NA	NA	NA	NA
<i>Streptococcus pyogenes</i> (Group A <i>Streptococcus</i>)	0.06	0.5	0.008–1	0.125	8	8	>64	4	>64
Macrolide (S)	0.015	0.03	0.008–0.03	0.06	0.06	0.125	0.25	0.03	0.06
erm(B)	0.5	1	0.03–1	8	16	>64	>64	>64	>64
mef(A)	0.125	0.25	0.06–0.25	0.5	1	8	8	4	8
erm(A)	0.03	0.125	0.016–0.5	0.06	0.125	16	>64	2	>64
L4 mutation	NA	NA	0.06	NA	NA	NA	NA	NA	NA
Telithromycin (S)	0.015	0.03	≤0.008–0.12	0.003	0.12	0.12	>16	0.03	>16
Telithromycin (R)	0.12	0.5	≤0.015–1	4	>4	NA	NA	NA	NA
<i>Streptococcus agalactiae</i> (Group B <i>Streptococcus</i>)									
Macrolide (S)	≤0.008	0.015	≤0.008–0.03	NA	NA	≤0.125	≤0.125	0.05	0.05
Macrolide (R)	0.03	0.125	≤0.008–1	NA	NA	>256	>256	>256	>256
erm(B)	0.03	0.06	NA	NA	NA	>256	>256	>256	>256
mef(A/E)	0.03	0.125	NA	NA	NA	12	>256	6	>256
Viridans group streptococci	≤0.008	0.06	≤0.008–0.12	0.015	≤0.25	0.12	4	0.03	2
<i>Streptococcus pneumoniae</i>	0.008	0.25	0.002–1	0.015	0.5	0.12	>16	0.03	>16
Macrolide (S)	0.002	0.015	0.002–0.015	0.03	0.03	0.03	0.5	0.03	0.06
Macrolide (R)	0.03	0.5	0.002–0.5	0.5	1	>16	>16	>32	>32
erm(A)	NA	NA	0.008–0.015	NA	NA	NA	NA	NA	NA
erm(B)	0.03	0.25	0.004–1	0.03	0.25	>64	>64	>64	>64
erm(B) + mef(E)	0.25	0.5	NA	0.5	1	NA	NA	NA	NA
erm(B) + mef(A)	0.125	0.25	0.015–1	0.5	1	>64	>64	>64	>64
mef(E)	0.06	0.25	NA	0.25	0.5	NA	NA	NA	NA
mef(A)	0.03	0.125	0.008–0.25	0.125	0.25	4	8	2	4
L4 mutation	0.06	0.125	0.03–0.125	0.125	0.25	>64	>64	16	32
23sRNA mutation	NA	NA	0.002–0.03	NA	NA	NA	NA	NA	NA
Penicillin (S)	0.03	0.125	0.002–0.25	0.06	0.25	4	>64	1	>64
Penicillin (I)	0.03	0.25	0.002–0.25	0.06	0.5	>64	>64	16	>64

Table 1 continued

Organism	Ketolide					Macrolide			
	Solithromycin			Telithromycin		Azithromycin		Clarithromycin	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Penicillin (R)	0.06	0.25	0.004–1	0.125	0.5	>64	>64	16	>64
Quinolone (S)	0.03	0.25	0.002–1	0.125	0.5	>64	>64	16	>64
Quinolone (R)	0.008	0.06	0.004–0.25	0.03	0.125	0.125	>64	0.03	>64
<i>Streptococci</i> spp.									
Macrolide (S)	≤0.008	0.015	≤0.008–0.03	0.03	0.03	0.06	0.12	0.03	0.03
Macrolide (NS) CLI + TEL (S)	0.03	0.12	≤0.008–0.25	0.12	0.5	NA	NA	NA	NA
Macrolide, CLI (NS) + TEL (S)	0.06	0.25	≤0.008–0.5	0.12	1	NA	NA	NA	NA

CA-MRSA community-acquired MRSA, CLI clindamycin, CoNS Coagulase negative *Staphylococci*, hVISA heterogeneous vancomycin-intermediate *S. aureus*, (I) intermediate resistance, MIC₅₀ minimum inhibitory concentration of 50% of isolates, MIC₉₀ minimum inhibitory concentration of 90% of isolates, MRSA methicillin-resistant *S. aureus*, MSSA methicillin-susceptible *Staphylococcus aureus*, NA data not available, (NS) non-susceptible (includes intermediate and resistant strains), (R) resistant, (S) susceptible, TEL telithromycin, VISA vancomycin-intermediate *S. aureus*, VRSA vancomycin-resistant *S. aureus*

Table 2 In vitro activity (MIC, mg/L) of solithromycin and comparators against aerobic Gram-negative bacteria adapted from references [5, 11, 29, 35, 37, 39, 42–44, 51, 52]

Organism	Ketolide					Macrolide			
	Solithromycin			Telithromycin		Azithromycin		Clarithromycin	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Campylobacter jejuni</i>	1	4	1–8	NA	NA	NA	NA	2	4
<i>Haemophilus influenzae</i>	1	2	≤0.06 to >8	1	2	0.5	1	4	8
Typeable	1	4	0.5–4	1	2	0.5	1	NA	NA
Non-typeable	1	2	0.12–8	1	2	0.5	1	NA	NA
β-Lactamase (–)	1	2	0.12 to >16	2	4	1	2	8	8
β-Lactamase (+)	1	2	0.12 to >16	2	4	1	2	8	8
<i>Haemophilus parainfluenzae</i>	2	2	1–2	4	4	1	2	8	16
<i>Helicobacter pylori</i>	0.06	0.25	0.03–4	NA	NA	NA	NA	0.03	0.12
<i>Moraxella catarrhalis</i>	0.06	0.12	0.002–0.5	0.12	0.25	0.03	0.06	0.12	0.12
<i>Neisseria gonorrhoeae</i>	0.125	0.25	0.001–32	0.25	1	0.25	8	0.25	4
<i>Neisseria meningitidis</i>	≤0.015	≤0.015	≤0.015–0.06	≤0.015	0.03	0.06	0.12	0.03	0.12
<i>Salmonella</i> spp.	4	>16	1 to >16	8	>16	4	8	0.015	>16
<i>Shigella</i> spp.	8	16	1 to >16	16	16	4	8	>16	>16

MIC₅₀ minimum inhibitory concentration of 50% of isolates, MIC₉₀ minimum inhibitory concentration of 90% of isolates, NA data not available

6 Pharmacokinetics

The results of initial pharmacokinetic studies of oral solithromycin are summarized in Tables 5 [23, 53–57] and 6 [58, 59]. Comparisons of pharmacokinetic parameters with the structurally related macrolides, azithromycin and clarithromycin, are shown in Table 7 [23, 53–65].

Pharmacokinetic data are only available for oral solithromycin (Table 5). In a population pharmacokinetics study by Okusanya et al., the pharmacokinetics of solithromycin were best described by a three-compartment model with auto-inhibition of drug clearance [66].

Absorption was modeled by a Weibull process and capacity-limited first-pass effect where the fraction of drug absorbed increased with dose to a maximum of 82% [66]. The potential for dose-dependent bioavailability may involve solithromycin serving as a substrate and inhibitor of P-glycoprotein (P-gp) [67]. Although bioavailability studies based on intravenous data have not been published, a bioavailability of approximately 67% has been cited following oral solithromycin [3, 53]. In a study by Still et al., food did not influence the bioavailability of solithromycin, with similar maximum plasma concentrations ($C_{\max}$), time to maximum plasma concentration ($T_{\max}$), and

Table 3 In vitro activity (MIC, mg/L) of solithromycin and comparators against anaerobic bacteria adapted from references [5, 7, 37, 45, 46]

Organism	Ketolide					Macrolide			
	Solithromycin			Telithromycin		Azithromycin		Clarithromycin	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Bacteroides fragilis</i>	4	64	1 to >64	32	64	>64	>64	2	8
<i>Bacteroides fragilis</i> group	2	>64	0.5 to >64	8	>64	>64	>64	NA	NA
<i>Bacteroides</i> spp.	0.5	4	0.032–256	NA	NA	32	256	0.25	4
<i>Bifidobacteria</i> spp.	0.008	0.008	0.008–0.5	NA	NA	0.016	0.25	NA	NA
<i>Clostridium difficile</i>	0.032	0.064	0.032 to >64	0.5	>64	0.008	0.5	0.5	>64
<i>Clostridium</i> spp., other ^a	0.06	8	0.008–128	0.12	0.25	128	256	NA	NA
<i>Gardnerella vaginalis</i>	0.015	0.12	≤0.002–0.12	NA	NA	0.06	8	≤0.015	0.25
<i>Lactobacillus</i> spp.	0.008	0.16	0.008–0.5	NA	NA	0.25	256	NA	NA
<i>Peptostreptococcus</i> spp.	0.06	0.25	≤0.03–0.25	0.12	2	8	>64	0.06	≥64
<i>Porphyromonas</i> spp.	≤0.03	0.06	≤0.03–0.06	0.06	0.12	1	2	NA	NA
<i>Prevotella</i> spp.	0.12	2	0.016 to >64	0.25	16	1	>64	NA	NA
<i>Veillonella</i> spp.	0.016	0.032	0.016–1	NA	NA	0.5	4.0	NA	NA

MIC₅₀ minimum inhibitory concentration of 50% of isolates, MIC₉₀ minimum inhibitory concentration of 90% of isolates, NA data not available

^a Includes *C. butyricum*, *C. cadaveris*, *C. clostridioforme*, *C. innocuum*, and *C. perfringens*

Table 4 In vitro activity of solithromycin and comparators against atypical bacteria Adapted from references [5, 7, 29, 39, 47–49, 51]

Organism	Ketolide					Macrolide			
	Solithromycin			Telithromycin		Azithromycin		Clarithromycin	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Chlamydia pneumoniae</i>	0.25	0.25	0.25–1	0.06	0.06	0.12	0.12	0.06	0.06
<i>Chlamydia trachomatis</i>	0.25	0.25	0.12–0.5	0.06	0.06	0.12	0.12	0.06	0.06
<i>Legionella pneumophila</i>	≤0.015	≤0.015	≤0.015–0.06	NA	NA	0.12	1	0.5	0.5
<i>Legionella</i> spp.	NA	NA	≤0.00024–0.016	NA	NA	NA	NA	NA	NA
<i>Mycoplasma pneumoniae</i>	≤0.000032	≤0.000032	≤0.00000063–0.5	0.00025	0.001	0.00025	0.0005	0.002	0.002
<i>Mycoplasma genitalium</i>	NA	NA	0.000032	NA	NA	NA	NA	NA	NA
<i>Mycoplasma fermentans</i>	≤0.008	≤0.008	≤0.008	≤0.008					
<i>Mycoplasma hominis</i>	0.004	0.008				2	4		
<i>Ureaplasma parvum</i>	0.008	0.016				2	4		
<i>Ureaplasma urealyticum</i>	0.008	0.03				2	4	0.03	0.03

MIC₅₀ minimum inhibitory concentration of 50% of isolates, MIC₉₀ minimum inhibitory concentration of 90% of isolates, NA data not available

area under the concentration–time curve (AUC) following a single 400-mg dose in fasted (for at least 10 h) and fed (following a high-fat meal) individuals [53].

The volume of distribution (V_d/F) of solithromycin was 610.5 ± 187 and 676.0 ± 356.9 L in the fed and fasted groups, respectively [54]. For comparison, Jamieson et al. reported a mean V_d/F of 542 L with a multiple-dose regimen of 800 mg followed by 400 mg daily for 4 days in healthy adults [58]. Protein binding of solithromycin is estimated at 81% [23].

Preliminary investigations of the metabolism and excretion of solithromycin have been conducted. In a study of urinary clearance by Jamieson et al., 5 and 10% of the

dose was excreted unchanged in the urine on days 1 and 5, respectively [58]. The major metabolic pathway appears to involve cytochrome P450 (CYP) 3A4, with most of the metabolite undergoing biliary excretion [58]. Although two active metabolites including *N*-acetyl-CEM-101 (via *N*-acetyltransferase) and CEM-214 have been identified, neither are present in significant amounts in human plasma [58, 68].

The half-life ($t_{1/2}$) of solithromycin appears to increase with dose, consistent with the observation of parallel first-order and capacity-limited elimination in animal studies [69]. In a single-dose escalation study by Still et al., the $t_{1/2}$ of solithromycin increased from 3 h with doses of 100 mg

Table 5 Pharmacokinetics of oral solithromycin

Subjects	<i>n</i>	Dose (PO)	<i>C</i> _{max} (mg/L)	<i>T</i> _{max} (h)	AUC ^a (mg × h/L)	<i>t</i> _{1/2} (h)	<i>V</i> _d /F (L)	CL/F (L/h)	References
Single-dose studies									
Healthy adults (30 males, 19 females, mean age 37 year [range 20–55], mean weight 74 kg) ^e	5	200 mg × 1	0.26 ± 0.06	3.0 (2.0, 4.0)	1.86 ± 0.55	4.0 ± 0.9	NA	116.0	[53–55]
	5	400 mg × 1	0.78 ± 0.26	4.0 (3.0, 4.0)	7.13 ± 2.88	5.1 ± 1.2	NA	64.0	
	5	800 mg × 1	1.32 ± 0.92	3.5 (2.5, 6.0)	13.84 ± 9.61	6.7 ± 1.0	NA	101.0	
	5	1200 mg × 1	1.96 ± 0.28	6.0 (3.5, 6.0)	26.96 ± 6.44	6.9 ± 0.7	NA	46.8	
	5	1600 mg × 1	2.15 ^b	6.0 (4.0, 6.0)	34.78 ^b	7.4 ± 0.7	NA	106.0	
Healthy adults (mean age 34 year [range 19–50], mean weight 75 kg)	24	400 mg × 1 (fed)	0.63 ± 0.20	3.5 (2.5, 6.0)	5.27 ± 1.77	5.0 ± 0.7	610.5 ± 187.4	84.4 ± 27.7	
	24	400 mg × 1 (fasted)	0.61 ± 0.24	3.5 (2.5, 6.0)	5.61 ± 2.28	5.4 ± 0.8	676.0 ± 356.9	88.0 ± 48.9	
Multi-dose studies									
Healthy adults (22 males, 13 females, mean age 34 year, mean weight 76 kg) ^e	5	200 mg q24 h × 7	0.25 ± 0.08	3.5 (2.5, 3.5)	2.31 ± 0.77	5.8 ± 1.4	NA	NA	[53]
	10	400 mg q24 h × 7	1.09 ± 0.52	4.0 (2.5, 6.0)	13.27 ± 7.35	7.5 ± 1.6	NA	NA	
	10	600 mg q24 h × 7	1.50 ± 0.40	3.5 (2.5, 6.0)	18.41 ± 5.56	8.7 ± 1.2	NA	NA	
Healthy adults (24 males, 6 females)	30	400 mg q24 h × 5	0.90 ± 0.46	3.57 ± 1.10	7.92 ± 4.39	5.6 ± 1.2	NA	NA	[23]
Adolescents with suspected or confirmed infection ^c (10 males, 3 females, median age 16 year [range 12–17], median weight 64 kg [range 30–84])	13	12 mg/kg (max 800 mg) then 6 mg/kg (max 400 mg) q24 h × 2–4 doses ^d	0.74 ± 0.61	NA	9.28 ± 6.30	5.7 ± 1.3	NA	NA	[56, 57]

Data are presented as mean ± standard deviation (if available) or median (minimum, maximum)

AUC area under the concentration–time curve, CL/F apparent clearance, *C*_{max} maximum plasma concentrations, NA data not available, PO oral, q24 h every 24 h, *T*_{max} time to maximum plasma concentration, *t*_{1/2} half-life, *V*_d/F volume of distribution

^a AUC_{0–∞} is from time zero to infinity in single-dose studies, AUC_T is during the dosing interval following the last dose in multiple-dose studies

^b *C*_{max} was 1.78 ± 1.20 mg/L and AUC_{0–∞} 28.86 ± 22.66 mg × h/L including an outlier with very low concentrations

^c Three subjects had cystic fibrosis, and one received blood transfusions on the day of sampling

^d Treatment durations included 3 days (*n* = 6), 4 days (*n* = 3) or 5 days (*n* = 4)

^e Includes placebo controls

to 7 h with doses of 1600 mg [53]. Generally, there were non-linear increases in $C_{\max}$ and $AUC_{0-\infty}$ and a prolongation of $T_{\max}$ from 1.5 to 6 h over the range of doses. Of note, the potential influence of dose-dependent bioavailability on these parameters is not known. For the 400-mg clinical dose, $C_{\max}$, $T_{\max}$, and $AUC_{0-\infty}$ values were 0.6–0.8 mg/L, 3.5–4 h, and 5–7 mg·h/L, respectively, with the single-dose administration. The data for other doses are detailed in Table 5.

Some studies indicate that the $t_{1/2}$ of solithromycin increases over time where relative drug exposure is greater with multiple-dose regimens (i.e., AUC_{τ}) compared with the single dose (i.e., $AUC_{0-\infty}$). Jamieson et al. reported a $t_{1/2}$ of 8.9 h with 800 mg followed by 400 mg daily for 4 days versus the 5.0–5.4 h with a single 400-mg dose [53, 59]. Still et al. also reported an extended $t_{1/2}$ of 7.5 h with a 7-day regimen of solithromycin, whereas Rodvold et al. reported a $t_{1/2}$ of 5.6 h with a 5-day regimen that was more consistent with single-dose studies [23, 53]. Although it is suggested that solithromycin clearance may undergo auto-inhibition by CYP3A metabolism, the determination of elimination parameters and apparent $t_{1/2}$ for drugs with multiple compartments may also be influenced by pharmacokinetic study design including sampling times and data analysis [58]. Multiple-dose studies of 200 mg, 400 mg or 600 mg daily for 7 days showed larger than dose-proportional increases in $C_{\max}$ and AUC_{τ} , particularly between 200-mg and 400-mg regimens [53]. For the 400-mg dose, mean $C_{\max}$, AUC_{τ} and $t_{1/2}$ values were 1.09 ± 0.52 mg/L, 13.27 ± 7.35 mg·h/L, and 7.5 ± 1.6 h, respectively, with the multiple doses. Data for other doses are detailed in Table 5.

A pharmacokinetic study of oral solithromycin in mild (Child-Pugh class A), moderate (class B), and severe (class C) hepatic disease by Jamieson et al. concluded that decreases in dosage should not be required (Table 6) [58]. Eight subjects in each class and nine healthy participants

received an 800-mg loading dose followed by 400 mg every 24 h for 4 days. Investigators noted significant pharmacokinetic variability, particularly in the ratios of $C_{\max}$ and AUC_{τ} among those with hepatic impairment versus healthy subjects. The mean $t_{1/2}$ of solithromycin was only 16% higher in those with mild–moderate disease, but 76% higher in those with severe hepatic disease compared with healthy controls [59]. Despite this significant increase in $t_{1/2}$, the exposure to solithromycin (i.e., AUC_{τ}) was 41% lower in those with severe hepatic disease. Given the concurrent and notable increase in V_d/F (i.e., 1749 vs 542 L in healthy subjects), further study, particularly related to the bioavailability of solithromycin in those with hepatic impairment, is warranted (see Table 7).

Finally, Rodvold et al. studied the tissue distribution of solithromycin in epithelial lining fluid (ELF) and alveolar macrophages [23]. Thirty healthy subjects received 400 mg once daily for 5 days with drug sampling via bronchoalveolar lavage in six subjects at 3, 6, 9, 12, or 24 h after the last dose. The mean ratio of ELF to plasma concentration was 11.9 (range 2.4–28.6), with an ELF to plasma AUC_{0-24} ratio of approximately 10. Solithromycin showed significant accumulation in alveolar macrophages compared with plasma, with a mean macrophage to plasma concentration ratio of 245 (range 44–515) and macrophage to plasma AUC_{0-24} ratio of approximately 200 [23]. Thus it is clear that the structural changes made to solithromycin confer upon the molecule not only a different mechanism of action and enhanced microbiological activity but also different pharmacokinetics compared with macrolides.

7 Pharmacodynamics

A preliminary pharmacodynamic analysis of solithromycin against *S. pneumoniae* was conducted in a neutropenic mouse thigh infection model. Doses of 1–25 mg/kg

Table 6 Pharmacokinetics of oral solithromycin in subjects with hepatic impairment [58, 59]

Subject demographics	n	Dose (PO)	Conc _{4h} (mg/L)	AUC _τ (mg × h/L)	$t_{1/2}$ (h)	V_d/F (L)
Healthy adults (6 males, 3 females, age 58 y [51–66], weight 77 kg [range 66–90])	9	800 mg × 1, then 400 mg q24 h × 4	0.65	10.49	8.9	542
Child-Pugh class A (mild) (5 males, 3 females, age 57 y [49–67], mean weight 77 kg [68–107])	8		0.79	7.90	10.2	778
Child-Pugh class B (moderate) (8 males, age 57 y [49–68], weight 89 kg [71–115])	8		0.68	7.51	10.4	832
Child-Pugh class C (severe) (5 males, 3 females, age 56 y [42–65], weight 85 kg [65–111])	8		0.50	6.18	15.7	1749

Demographic data are presented as mean (range); pharmacokinetic data are presented as mean only as standard deviations were not provided AUC_{τ} area under the concentration–time curve during the dosing interval following the last dose, $Conc_{4h}$ plasma concentration 4 h post-dose, PO oral, $q24$ h every 24 h, $t_{1/2}$ half-life, V_d/F volume of distribution

Table 7 Pharmacokinetic parameters of oral solithromycin compared with oral macrolides adapted from references [23, 53–59] (solithromycin), [60–62] (azithromycin), and [63–65] (clarithromycin)

	Solithromycin	Azithromycin	Clarithromycin
Oral bioavailability (%)	67%	34–52%	50%
Volume of distribution (V_d/F)	542–676 L	121–144 L/kg	191–306 L
Half-life ($t_{1/2}$)	4–9 h	59–72 h	3–7 h
Protein binding (%)	78–84%	7–51%	42–70%

fractionated in 1, 2, 3, or 4 doses were administered over 24 h [70]. Correlations between pharmacodynamics indices in plasma and antibacterial effect were reported for fC_{max} and MIC ($r^2 = 0.83$), $fAUC_{24}$ and MIC ($r^2 = 0.75$), and %time >MIC and MIC ($r^2 = 0.62$). Andes et al. also studied the pharmacodynamics of solithromycin in neutropenic mice [69]. In their study, five isolates of *S. pneumoniae* (MIC range 0.03–0.12 mg/L) were inoculated via inhalation and after 2 h, solithromycin (0.156–160 mg/kg) was administered as a single dose or 2, 4, or 8 divided doses over 24 h. Plasma and ELF (epithelial lining fluid) samples were collected at 1, 2, 6, 9, 12, and 24 h after the dose. Due to low bacterial burden in the controls, two isolates with MICs of 0.03 and 0.06 mg/L were excluded from the pooled pharmacodynamic analysis, which found the $fAUC_{0-24}/MIC$ (the ratio of the area under the free drug concentration–time curve from 0 to 24 h to the MIC of the isolate) as the best correlate for antibacterial effect ($r^2 = 0.83$). The $fAUC_{0-24}/MIC$ values (mean $\pm$ standard error) associated with bacteriostasis, 1-log₁₀ colony-forming unit (CFU) reduction and 2-log₁₀ CFU reduction from baseline were 1.65 ± 0.63 , 6.31 ± 1.45 , and 12.80 ± 1.79 , respectively. Based on an estimated plasma protein binding of 81%, these would correspond to total mean AUC_{0-24}/MIC values of 8.68, 33.21, and 67.37, respectively. In ELF, an AUC_{0-24}/MIC of 1.26 ± 0.64 was associated with bacteriostasis, whereas 15.10 ± 4.38 and 59.80 ± 9.57 were associated with 1 and 2-log₁₀ CFU reductions, respectively.

In a study of *S. pneumoniae* (MIC range 0.002–0.5 mg/L; minimum bactericidal concentration (MBC)₅₀, 0.12 mg/L; MBC₉₀, 1 mg/L), Magnet et al. reported MBC/MIC ratios of ≤ 2 for 45% (15/33) of isolates and ratios of ≤ 4 for 67% (22/33) of isolates [28]. The MBC₅₀ and MBC₉₀ was 0.004 mg/L and 0.06 mg/L, respectively, for macrolide-susceptible strains ($n = 8$) compared with 0.25 mg/L and 1 mg/L for macrolide-resistant strains ($n = 25$). The potential for bactericidal activity was also demonstrated in a study of *H. influenzae* (MIC range 0.12–8 mg/L) where 17 of 20 isolates had MBC/MIC ratios of ≤ 2 [43]. Finally, a study of *C. pneumoniae* ($n = 10$) showed no difference between MIC and MBC values (MIC range 0.25–1.0 mg/L; MIC₉₀ 0.25 mg/L; MBC₉₀ 0.25 mg/L) [47].

Woosley et al. described concentration-dependent antibacterial activity for solithromycin in time-kill studies of single isolates of various Gram-positive organisms [32]. Bactericidal activity, defined as ≥ 3 log₁₀ bacterial kill over 24 h, was reported at two times the MIC against a macrolide-susceptible isolate of *S. pneumoniae* (MIC, 0.008–0.015 mg/L), a macrolide-susceptible isolate of *S. aureus* (MIC, 0.06–0.12 mg/L), and one isolate each of *S. epidermidis* (MIC, 0.12 mg/L), *S. mitis* (MIC, ≤ 0.008 mg/L), and macrolide-resistant *S. pyogenes* (MIC, 0.06 mg/L). Bactericidal activity was observed at eight times the MIC for an isolate of macrolide-susceptible *S. pyogenes* (MIC, 0.015 mg/L), whereas only bacteriostasis was achieved against an isolate of *S. pneumoniae* harboring the *ermB* determinant (MIC, 0.015–0.03 mg/L).

Woosley et al. also conducted checkerboard synergy testing of solithromycin in combination with ceftriaxone, gentamicin, levofloxacin, trimethoprim-sulfamethoxazole, and vancomycin against *S. aureus* ($n = 9$), *S. pyogenes* ($n = 6$), and *S. pneumoniae* ($n = 7$) [32]. In general, the combinations were indifferent with the MIC remaining the same for both agents or increasing by only twofold for only one of the agents. Complete synergy with MICs decreasing by at least fourfold for both agents was only noted with solithromycin plus gentamicin against two isolates of *S. pneumoniae*. No cases of antagonism were observed.

Finally, Lemaire et al. studied the activity of solithromycin against *S. aureus*, *Listeria monocytogenes*, and *Legionella pneumophila* over a range of pH values and in THP-1 macrophages [22]. Over a range of pH from 7.4 down to 5.5, solithromycin MICs increased significantly from 0.06 to 0.5 mg/L for *S. aureus*, from 0.004 to 0.25 mg/L for *L. monocytogenes*, and from 0.005 to 0.01 mg/L for *L. pneumophila*. Compared with clarithromycin, azithromycin, and telithromycin, solithromycin retained the most activity over the pH range tested. Further study of *S. aureus* in THP-1 macrophages was conducted at two concentrations (0.7 mg/L and 4 mg/L) of solithromycin and azithromycin. A significant reduction of approximately 1.5 log₁₀ CFU/mL was observed with both solithromycin concentrations, whereas no consistent antibacterial effect was evident with azithromycin. A concentration–response analysis conducted for *S. aureus* in

broth and macrophages and for *L. monocytogenes* and *L. pneumophila* in the latter showed concentration-dependant activity characterized by the Hill equation.

8 Clinical Trials

Two phase II and two phase III clinical trials have been completed with solithromycin. The phase II trials have evaluated solithromycin safety and efficacy in the treatment of CABP (ClinicalTrials.gov registration no. NCT01168713) and treatment of uncomplicated urogenital gonorrhea (ClinicalTrials.gov registration no. NCT01591447). The two phase III trials have assessed non-inferiority of oral solithromycin versus oral moxifloxacin for the treatment of CABP (ClinicalTrials.gov registration no. NCT01756339) as well as intravenous-to-oral solithromycin versus intravenous-to-oral moxifloxacin for CABP (ClinicalTrials.gov registration no. NCT01968733). Results are summarized in Table 8. Adverse effects are covered in Sect. 9. Phase II and phase III trials are recruiting for the treatment of adolescents and children with CABP (NCT02605122) and a phase III trial is currently underway for the treatment of gonorrhea (NCT02210325). Solithromycin is also being investigated in clinical trials for non-infectious conditions including steatohepatitis without cirrhosis and treatment of inflammation associated with COPD. However, as described earlier, the focus of this paper is to review efficacy and safety of solithromycin for CABP.

8.1 Phase II Trials

The efficacy and safety of oral solithromycin (800 mg on day 1, followed by 400 mg daily on days 2–5) has been assessed in comparison with oral levofloxacin (750 mg daily for 5 days) in patients with moderate to moderately severe CABP in a randomized, double-blind trial (Table 8) [71]. This study was not powered sufficiently to assess statistical differences. Randomization was stratified by age (<50 and ≥50), and Pneumonia Outcome Research Team (PORT) scores. The 800 mg on day 1 followed by a 400-mg daily dose of solithromycin was selected for CABP clinical trials based upon Monte Carlo simulations using a population pharmacokinetic model of solithromycin based on healthy volunteer plasma and ELF data and previously determined murine ELF and free drug plasma AUC/MIC targets (72). This dose resulted in the best target attainment versus *S. pneumoniae*.

Inclusion criteria included males and females, ≥18 years of age, with PORT risk classifications of II (score 51–70), III (score 71–90), IVa (91–98) and IVb (99–105), who had at least three of the following signs and

symptoms: cough with production of purulent sputum or a change in sputum consistent with bacterial infection, dyspnea or tachypnea, chest pain due to pneumonia, fever ≤24 h prior to randomization, rales, or evidence of pulmonary consolidation. Patients could not have received systemic antibiotics for their pneumonia prior to enrollment, with the exception of treatment failures (after ≥48 h of prior therapy) or isolation of a resistant organism while on the previous treatment. Finally, findings consistent with bacterial pneumonia on a chest radiograph or computed tomography of the thorax were required within 48 h before the first dose. Exclusion criteria included patients with PORT risk classifications of I (≤50) or IV (>105), those with ventilator-associated pneumonia (VAP), documented stage IV COPD, history of hospitalization within 90 days or residence in a long-term care facility within 30 days prior to the onset of symptoms, those with corrected QT interval (QTc) >450 ms or concurrent use of drugs that were known to increase QTc, as well as known HIV, hepatitis B, or hepatitis C infection. A total of 132 patients from 26 centers in the US and four centers in Canada were enrolled in this trial, with 65 patients randomized to receive solithromycin (64 received solithromycin) and 67 to receive levofloxacin (68 received levofloxacin; one patient randomized to receive solithromycin received levofloxacin in error). The majority of patients (99%) were enrolled as outpatients. Efforts were made in all patients to identify the causative pathogen via isolation from blood, respiratory sample, urinary antigen, or serology testing, with successful identification of a CABP pathogen occurring in 32 patients (24%). *S. pneumoniae* was the most common organism identified, accounting for 31% of baseline pathogens, followed by *H. influenzae* at 22%.

The primary objective was to determine the clinical success rate at the test-of-cure (TOC) visit 4–11 days after the last dose in both the intent-to-treat (ITT) and clinically evaluable (CE) populations (with ITT defined as all randomized patients; CE refers to the subset of ITT patients who adhered to protocol and received ≥2 doses of study drug in 48 h if a clinical failure, or who had received ≥4 doses of study drug in those deemed a clinical success). Clinical success (defined as complete or nearly complete resolution of disease-specific signs and symptoms present at enrollment, with no new symptoms or complications attributable to CABP, and radiographic resolution, improvement, or stability and having received ≥4 days of study drug) in the ITT population was observed in 55 (84.6%) of the patients that received solithromycin and 58 (86.6%) of the patients that received levofloxacin (Table 8). In the CE population, 46 (83.6%) and 54 (93.1%) of the patients that received solithromycin and levofloxacin, respectively, demonstrated clinical success (no statistical analysis listed). Clinically evaluable patients

Table 8 Phase II and III clinical trials of solithromycin

Trial description	Number of randomized patients	Treatment regimens	Primary outcomes	Primary outcome results <i>n/N</i> (%) [95% CI]	Secondary outcomes	Secondary outcome results <i>n/N</i> (%) [95% CI]
Phase II randomized, double-blind study evaluating the safety and efficacy of oral treatment for CABP in adults [71] ClinicalTrials.gov ID: NCT01168713	132	Oral solithromycin 800 mg × 1 then 400 mg q24 h × 4 days (<i>n</i> = 65) Oral levofloxacin 750 mg q24 h × 5 days (<i>n</i> = 67)	Clinical success ^a in the ITT population at TOC visit Clinical success in the CE population at TOC visit	Solithromycin 55/65 (84.6) [73.5–92.4] Levofloxacin 58/67 (86.6) [76.0–93.7] Solithromycin 46/55 (83.6) [71.2–92.2] Levofloxacin 54/58 (93.1) [83.3–98.1]	Clinical success in the mITT population Clinical success in the ME population	Solithromycin 14/18 (77.8) [52.4–93.6] Levofloxacin 10/14 (71.4) [41.9–91.6] Solithromycin 12/15 (80.0) [51.9–95.7] Levofloxacin 10/13 (76.9) [46.2–95.0]
Phase III randomized double-blind, double-dummy, active controlled, non-inferiority trial of oral treatment for CABP in adults [73] ClinicalTrials.gov ID: NCT01756339	860	Oral solithromycin 800 mg × 1 then 400 mg q24 h × 4 days then placebo q24 h × 2 days (<i>n</i> = 426) Oral moxifloxacin 400 mg q24 h × 7 days (<i>n</i> = 434)	Early clinical response ^b in the ITT population	Solithromycin 333/426 (78.2) Moxifloxacin 338/434 (77.9) Margin for non-inferiority >10% Difference 0.29% (–5.5 to 6.1) Solithromycin non-inferior	ECR in the CE population ECR in the mITT population Clinical success at SFU in the ITT population	Solithromycin 326/403 (80.9) Moxifloxacin 330/407 (81.1) Difference –0.19% (–5.8 to 5.5) Solithromycin 176/235 (74.9) Moxifloxacin 178/226 (78.8) Difference –3.87% (–12.0 to 4.3) (mITT non-inferiority margin –15%) Solithromycin 360/426 (84.5) Moxifloxacin 376/434 (86.6) Difference –2.13% (–7.1 to 2.8)
Phase III randomized, double-blind, active-controlled non-inferiority trial of IV to oral treatment for CABP in adults [51] ClinicalTrials.gov ID: NCT01968733	863	400 mg IV solithromycin q24 h switching to 800 mg oral solithromycin × 1 day, then 400 mg q24 h when clinically indicated ^c (total 7-day treatment) (<i>n</i> = 434) 400 mg IV moxifloxacin q24 h switching to oral when clinically indicated ^c (total 7-day treatment) (<i>n</i> = 429)	Early clinical response ^d in the ITT population	Solithromycin 344/434 (79.3) Moxifloxacin 342/429 (79.7) Margin for non-inferiority >10% Difference –0.46% (–6.1 to 5.2) Solithromycin non-inferior	ECR with vital sign normalization in the ITT population ECR in the mITT population Clinical success at SFU in the ITT population	Solithromycin 185/434 (42.6) Moxifloxacin 167/429 (38.9) Difference 3.70% (–3.1 to 10.5) Solithromycin 139/173 (80.3) Moxifloxacin 121/153 (79.1) Difference 1.26% (–8.1 to 10.6) (mITT non-inferiority margin –15%) Solithromycin 367/434 (84.6) Moxifloxacin 380/429 (88.6) Difference –4.02% (–8.8 to 0.8) Solithromycin 338/386 (87.6) Moxifloxacin 359/388 (92.5) Difference –4.96% (–9.4 to –0.5)

CABP community-acquired bacterial pneumonia, CE clinically evaluable, ECR early clinical response, ITT intention to treat, ME CE subset with identified pathogen, mITT ITT subset with identified pathogen, q24 h every 24 h, SFU short-term follow up 5–10 days after end of treatment, TOC test of cure visit 4–11 days following last dose of study drug

^a Defined as complete or nearly complete resolution of disease-specific signs and symptoms present at enrollment, with no new symptoms or complications attributable to CABP, and radiographic resolution, improvement, or stability, and having received ≥4 days of study drug

^b Defined as an improvement at 72 h after the first dose in at least two of four symptoms (cough, chest pain, sputum production, dyspnea) with no worsening in any symptom

^c Criteria for switching: improved signs and symptoms vs baseline, afebrile, respiratory rate ≤24 bpm, systolic blood pressure ≥90 mmHg, O₂ saturation ≥90% on room air

^d Defined by improvement at 72 h after the first dose in at least two of four symptoms (cough, chest pain, sputum production, dyspnea) with no other systemic antibiotics received

^e Results presented as modified-CE (exclusion of 5 solithromycin patients due to discontinuation of study drug because of insufficient supply of IV solithromycin)

represented 85% of the patients that received solithromycin and 87% of the patients that received levofloxacin, with the majority of patients excluded due to X-rays initially classified as being consistent with pneumonia by investigators but not being read as pneumonia after review by a radiologist. A post hoc analysis of early clinical response on day 3 in ITT groups, consistent with the FDA- and Foundation for the National Institutes of Health (FNIH)-proposed primary endpoints, was also completed. To be considered a success, patients had to report no worsening of and an improvement in at least two cardinal signs and symptoms, namely cough, chest pain, shortness of breath, and sputum production. Rates were similar for patients that received solithromycin (72.3%) and levofloxacin (71.6%).

8.2 Phase III Trials

The efficacy and safety of oral solithromycin (800 mg on day 1 followed by 400 mg daily on days 2–5, then placebo daily on days 6–7) versus oral moxifloxacin (400 mg daily for 7 days) for the treatment of CABP has been assessed in a global, double-blind, double-dummy, randomized, active controlled, non-inferiority trial (SOLITAIRE-ORAL) (Table 8) [73]. In this study, patients from 114 centers in North America, Latin America, Europe, and South Africa were block randomized, with randomization stratified based on geographical location, PORT risk class (II versus III or IV), and medical history of asthma or COPD. Inclusion criteria included patients being ≥ 18 years old with clinically and radiographically confirmed pneumonia, with PORT risk classes of II (capped at 50% to ensure enrollment of patients with moderately severe disease), III, or IV, with acute onset or worsening in three of four symptoms: cough, dyspnea, chest pain due to pneumonia, or difficulty with sputum production. Up to 25% of enrolled patients could have received a single dose of a short-acting systemic antimicrobial agent for treatment of the current CABP within the previous week. Exclusion criteria included recent hospital admission or having resided in a nursing home/healthcare facility, being immunosuppressed, QTc of >450 ms at baseline, and use of CYP3A4-inducing drugs or drugs with a narrow therapeutic index metabolized by CYP3A4.

A total of 860 patients were randomly assigned, with 426 receiving solithromycin and 434 receiving moxifloxacin. Blood, sputum, oropharyngeal and nasopharyngeal, and urine samples were used for baseline pathogen identification, with *S. pneumoniae* (23% of total patients), *H. influenzae* (16%) and atypical bacterial pathogens (24%) being most common. Successful baseline pathogen identification occurred in 55% of patients receiving solithromycin and in 52% of patients receiving moxifloxacin.

The primary outcome was early clinical response, as defined by improvement in at least two of four symptoms (cough, chest pain, sputum production, and dyspnea) with no worsening in any symptom at 72 h after the first dose, in the ITT population. With a non-inferiority margin set at $\geq 10\%$, solithromycin was non-inferior to moxifloxacin, having early clinical response in 78.2 versus 77.9% of patients receiving moxifloxacin (95% CI -5.5 to 6.1). As a secondary end point, early clinical response was also evaluated in CE patients (as defined by patients having been adherent to key protocol inclusion/exclusion criteria and procedures). Solithromycin demonstrated non-inferiority to moxifloxacin, with 80.9% of patients receiving solithromycin and 81.1% of patients receiving moxifloxacin showing early clinical response in this group (95% CI -5.8 to 5.5). Treatment failure at short-term follow up, which occurred 5–10 days following the end of treatment, occurred in 12% of patients receiving solithromycin and 9% of patients receiving moxifloxacin. This included a lack of resolution, worsening of baseline or development of new symptoms, and the need for new antibacterial treatment. Death occurring any time following enrollment was included in these values, accounting for six patients per group, with no serious adverse events leading to death being classified as resulting directly from the study drug. Other adverse event information will be covered in Sect. 9.

In a separate phase III trial, SOLITAIRE-IV, the efficacy and safety of intravenous-to-oral solithromycin was assessed against intravenous-to-oral moxifloxacin for the treatment of CABP (Table 8) [51]. In this randomized, global, double-blind, active-controlled, non-inferiority trial, all patients began treatment with 400 mg intravenous solithromycin or moxifloxacin, with a switch to the oral form of the medication (800 mg then 400 mg daily of solithromycin; 400 mg daily for moxifloxacin) when clinically indicated for a total treatment duration of 7 days. It is unclear to us what the necessity of the 800-mg oral loading dose of solithromycin was following the administration of solithromycin 400 mg intravenously. The criteria for switching to oral therapy were improved signs and symptoms versus baseline, with patients being afebrile with a respiratory rate ≤ 24 beats per minute, systolic blood pressure ≥ 90 mmHg, and O_2 saturation $\geq 90\%$ on room air. Patients were enrolled from 147 centers in 22 countries, with randomization stratified by geographic region, PORT score (II versus III or IV), and a history of asthma or COPD. PORT II accounted for $\leq 25\%$ and PORT IV for $\geq 25\%$ of patients enrolled. Inclusion criteria included patient age ≥ 18 years, with clinically and radiographically confirmed pneumonia of PORT class II–IV (pneumonia severity index scores of 51–130). Patients had to have experienced an acute onset or worsening of three of four cardinal symptoms—cough, dyspnea, chest pain, or

purulent sputum production—plus one of the following: fever, hypothermia, rales, and/or pulmonary consolidation. Exclusion criteria included prior systemic antimicrobial agent therapy within 1 week (with the exception of a single dose of a short-acting antimicrobial agent prior to randomization being acceptable in $\leq 25\%$ of patients), hospitalization within 90 days or residence in a nursing home or healthcare facility within 30 days, immunosuppression, QTc >460 ms, and current use of CYP-inducing therapies or specific drugs metabolized via CYP3A4.

A total of 863 patients were enrolled, with 434 randomized to receive solithromycin, and 429 to receive moxifloxacin. Similar to other studies, efforts to identify the baseline pathogen were made, and a pathogen was identified in 37.8% of patients. *S. pneumoniae* was the most common pathogen, accounting for $>45\%$ of baseline pathogens, followed by *M. pneumoniae* ($>19\%$), with *H. influenzae*, *Legionella* spp. and *S. aureus* each accounting for $\geq 10\%$ as well.

The primary endpoint was early clinical response (defined by improvement at 72 h after the first dose in at least two of the four cardinal symptoms, with no other antimicrobial agents received) in the ITT population. With a non-inferiority margin of $\geq 10\%$, solithromycin was shown to be non-inferior to moxifloxacin (79.3% of patients who received solithromycin showed early clinical response versus 79.7% of patients who received moxifloxacin [95% CI -6.1 to 5.2]). In both treatment arms, there was a median 3-day duration of intravenous treatment and 4 days of oral treatment. Patients who received intravenous treatment for the entire 7-day duration accounted for 22% of patients receiving solithromycin and 25.6% of patients receiving moxifloxacin. Death occurred in a total of 12 patients during the study (5 receiving solithromycin and 7 receiving moxifloxacin), with all deaths unrelated to the antimicrobial agent received. These deaths were deemed efficacy failures attributable to underlying disease or catastrophic events. Further information on adverse events will be covered in Sect. 9.

9 Adverse Effects

The safety and tolerability of solithromycin have been assessed in phase I, II, and III clinical trials. The most commonly reported treatment-emergent adverse events (TEAEs) have been gastrointestinal in nature, occurring in about 10% of patients. A general representation of the incidence of TEAEs is listed in Table 9 [7–74]. There have been no reported deaths in any trial that have been attributed directly to solithromycin. In a small group of hepatically impaired individuals whose transaminase values were

already above normal at baseline, no clinically important changes were noted [58].

In the phase II CABP study previously described, a total of seven (10.9%) patients randomized to solithromycin reported at least one TEAE that was considered related to the study drug, compared with 13 (19.1%) TEAEs in patients receiving the comparator, levofloxacin [71]. No patient discontinued treatment with solithromycin due to a TEAE, and there were no serious adverse events (SAEs) attributed to solithromycin. In the SOLITAIRE-ORAL trial, 155 (37%) patients receiving solithromycin reported at least one TEAE, with 10% of TEAEs being considered due to the study drug [73]. This was similar to moxifloxacin, where 154 (36%) patients reported at least one TEAE, with 13% attributed to moxifloxacin. There were no SAEs attributed to solithromycin. Discontinuation directly attributed to solithromycin occurred in four (1%) patients (two patients due to nausea, one patient due to vomiting, and one patient due to allergic dermatitis). Grade 3 and 4 (>8 times upper limit of normal [ULN]) alanine transaminase elevations occurred in 19 (4.6%) and 3 (0.7%) solithromycin patients, respectively. Of those with a Grade 3 or 4 increase, peak values $>3\times$ baseline occurred in 14 patients (3.4%). Grade 3 aspartate transaminase increases occurred in seven patients (1.7%), and Grade 4 ($>8\times$ ULN) in three patients (0.7%). Grade 3 or 4 aspartate transaminase increases and a peak $>3\times$ baseline occurred in seven (1.7%) patients. Grade 3 and 4 bilirubin elevations were observed in one patient each [73]. No patients experienced laboratory changes that met the criteria for Hy's Law that weren't attributable to another cause.

In the SOLITAIRE-IV trial, 223 (51.6%) of solithromycin patients compared with 148 (34.7%) of moxifloxacin patients reported TEAEs [51]. Adverse events associated with infusion of solithromycin occurred in almost a third of patients (31.3%), compared with 5.4% of patients receiving moxifloxacin, with pain and phlebitis being most commonly reported (10% each) (Table 9). Discontinuation due to TEAEs occurred in 5.8% of patients receiving solithromycin compared with 4.2% of patients treated with moxifloxacin. Two SAEs were deemed to be due to solithromycin, with one patient experiencing urticaria and another an anaphylactic reaction, both of which occurred during the initial infusion. Increases in transaminases were asymptomatic and generally resolved and were not associated with increased bilirubin. Increases in alanine transferase $>3\times$ ULN were observed in 9.1% of solithromycin patients while a level $>5\times$ ULN was observed in 3.1% of patients, compared with 3.7 and 0.7%, respectively, of moxifloxacin recipients. No increases $>10\times$ ULN were observed in the study.

On November 4, 2016, the Antimicrobial Drugs Advisory Committee of the FDA assessed the new drug

application of solithromycin [74]. Regarding potential solithromycin hepatotoxicity, Cempra concluded that solithromycin exposure is associated with ALT (and AST) elevations that are typically asymptomatic and without bilirubin elevation. In addition, it was stated that to date, none of the rare SAEs that occurred with telithromycin (i.e., hepatotoxicity) have been noted with solithromycin, possibly due to the fact that solithromycin (unlike telithromycin) does not possess a pyridine moiety in its chemical structure, which has been implicated in inhibiting nicotinic acetylcholine receptors. The FDA stated that within the <1000-patient solithromycin safety database, a hepatic injury signal was seen with solithromycin with a dose- and duration-dependent elevation in ALT, multiple toxicity patterns including hepatocellular, cholestatic, and possibly hypersensitivity, but with no Hy's law cases. Based on all the available data, the FDA voted 13 (yes) to 0 (no) votes in favor of efficacy of solithromycin for CABP, 1 (yes) to 12 (no) votes as to whether the risk of hepatotoxicity with solithromycin had been adequately characterized, and 7 (yes) to 6 (no) regarding whether the efficacy results of solithromycin for treating CABP outweigh the risks including hepatotoxicity, and that it should be approved for treating patients with CABP. From these data, it is clear that more safety data are required with solithromycin to fully assess its safety profile.

The effect of oral solithromycin on the oropharyngeal and intestinal microbiota was assessed after an 800-mg loading dose on day 1 and 400 mg once daily for days 2–7 [75]. Solithromycin decreased the numbers of intestinal enterobacteriaceae, enterococci, lactobacilli, bifidobacteria, and *Clostridium* spp., but they all normalized shortly after termination of treatment. No change occurred with *Bacteroides* spp. and no *Clostridium difficile* strains or toxins were detected. In the oropharyngeal microbiota, the numbers of streptococci, lactobacilli, prevotella, and fusobacteria were decreased on solithromycin but normalized after termination of solithromycin exposure.

10 Drug Interactions

There is limited information available regarding specific drug interactions involving solithromycin. As previously mentioned, solithromycin has been cited as being both a CYP3A4 substrate and mechanism-based inhibitor, and it does not induce CYP3A isoenzymes [67]. Based on solithromycin's interaction with CYP3A4, it may show a drug interaction profile similar to that of clarithromycin or telithromycin, both of which are inhibitors of CYP3A4 and demonstrate several clinically significant drug–drug interactions (azithromycin demonstrates fewer clinically relevant interactions due to its minimal inhibition of CYP

Table 9 Adverse events reported for solithromycin adapted from references [23, 51, 53, 56, 58, 71, 73]

Adverse effects	Occurrence
General	
Gastrointestinal (any)	++
Nausea	+
Vomiting	+
Diarrhea	+
Transaminase elevation	++
Headache	+
Dizziness	+
Insomnia	±
Hypokalemia	±
Hyponatremia	±
Anaphylaxis	±
Urticaria	±
Bilirubin elevation	±
Vision blur	–
<i>C. difficile</i> colitis	–
Intravenous-specific	
Any infusion related event	++++
Pain	++
Phlebitis	++
Erythema	+
Paresthesia	+
Thrombosis	+

– Indicates adverse event has not been observed, ± indicates adverse event occurred in <1% of patients, + indicates adverse event occurred in 1–5% of patients, ++ indicates adverse event occurred in 5–10% of patients, +++ indicates adverse event occurred in 10–25% of patients, ++++ indicates adverse event occurred in >25% of patients

enzymes) [5, 7, 76]. Until more information is available, the same caution should be used when co-administering solithromycin with drugs that have demonstrated interaction with the older macrolides, including telithromycin.

In addition to the potential for CYP3A4 interactions, solithromycin has been reported to be both an inhibitor and substrate of P-gp in vitro [67]. The effect of solithromycin on digoxin, a P-gp substrate, has been evaluated in a small group of healthy adults [67]. In this study, oral digoxin was administered for a total of 10 days (0.5 mg every 12 h for a total of two doses, then 0.125 mg daily for days 2–10), with solithromycin administered starting on day 6 as an 800-mg loading dose and then 400 mg daily for a total of five doses. Following the loading dose of solithromycin on day 6, digoxin demonstrated an increase in $AUC_{0-\tau}$ of 26%, and an increased C_{max} of 30% in comparison with the plasma concentrations obtained on day 5. On day 10, the $AUC_{0-\tau}$ of digoxin demonstrated an increase of 38%, and an increase in C_{max} of 46%. Thus, solithromycin appears to

affect digoxin plasma concentrations, which may be a result of its interaction with P-gp. While no study subject attained digoxin plasma concentrations exceeding 2 ng/mL or experienced any SAEs with co-administration, close monitoring of digoxin plasma concentrations has been suggested with the use of solithromycin [67].

11 Place of Solithromycin in Therapy

Solithromycin displays activity against the most common pathogens associated with CABP, including penicillin-, macrolide-, and fluoroquinolone-resistant isolates of *S. pneumoniae*. Based on its microbiological activity and demonstrated clinical efficacy in patients with PORT class II–IV pneumonia, solithromycin may be a potential oral therapy for outpatients, which could help limit the use of respiratory fluoroquinolones (thus minimizing exposure to their potential adverse effects as well as resistance selection). Oral solithromycin has been shown to be clinically effective, well tolerated, and to have the convenience of once daily dosing for a 5-day treatment regimen. Intravenous solithromycin may provide an additional option for those patients with moderately severe pneumonia requiring hospitalization, or for those who cannot tolerate oral therapy, with the ability to step down to oral treatment as clinically indicated. Intravenous solithromycin demonstrates infusion-related events more frequently than fluoroquinolones, however, its clinical efficacy and overall safety profile with similar discontinuation rates due to adverse effects to moxifloxacin still makes it a possible option in this setting. To date, none of the serious adverse events that were associated with telithromycin have been reported with solithromycin. In addition to efficacy and safety, the potential role of solithromycin in the treatment of CABP may be affected in part by economic/cost considerations.

12 Conclusion

CABP remains a relevant concern worldwide. Solithromycin, a novel fluoroketolide, covers the most common pathogens associated with CABP, including macrolide-resistant isolates. Similar to telithromycin, solithromycin inhibits protein synthesis as well as affecting ribosomal formation, and is thought to cause frame-shift mutations. However, solithromycin has key structural differences compared with telithromycin which are not only believed to reduce the risk of encountering the serious adverse events associated with telithromycin, but that also lead to increased ribosomal binding and reduced susceptibility to *mef* and *erm* macrolide resistance mechanisms. Solithromycin demonstrates multi-compartment pharmacokinetics with a large

volume of distribution and $t_{1/2}$ that allows for once-daily administration. The pharmacodynamics of solithromycin are best described by the $fAUC_{0-24}/MIC$ ratio. Its ability to concentrate in ELF and alveolar macrophages may contribute to its efficacy in treating CABP. Drug interactions are relatively unknown, but possibly predictable based on its likely interaction with CYP3A4 and P-gp, similar to other macrolides. In phase II and phase III clinical trials for CABP, solithromycin demonstrated both efficacy and safety compared with levofloxacin and moxifloxacin. Solithromycin represents a promising oral and intravenous agent that could potentially be used in monotherapy for the treatment of CABP.

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Compliance with Ethical Standards

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