Drugs of the Future 2011, 36(10): 751-758

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.10.1622079

MONOGRAPH

SOLITHROMYCIN

Macrolide Antibiotic

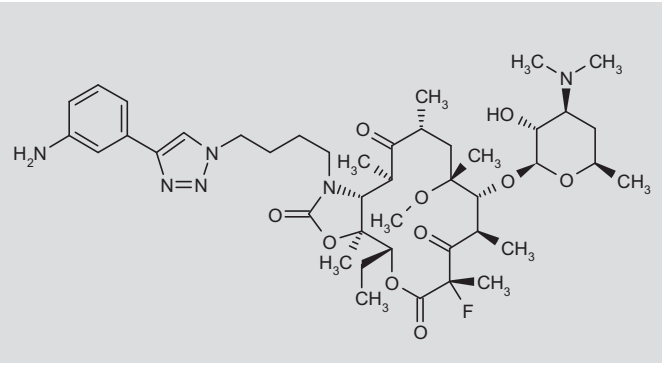
Prop INN; USAN

CEM-101
OP-1068

11-[4-[4-(3-Aminophenyl)-1*H*-1,2,3-triazol-1-yl]butylamino]-11-deoxy-3-des(hexopyranosyloxy) 2-fluoro-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate

(3a*S*,4*R*,7*S*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-1-[4-[4-(3-Aminophenyl)-1*H*-1,2,3-triazol-1-yl]butyl]-4-ethyl-7-fluorooctahydro-11-methoxy-3a,7,9,11,13,15-hexamethyl-10-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-2*H*-oxacyclotetradecino[4,3-*d*]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetrone

InChI: 1S/C43H65FN6O10/c1-12-32-43(8)35(50(40(55)60-43)19-14-13-18-49-23-30(46-47-49)28-16-15-17-29(45)21-28)26(4)33(51)24(2)22-41(6,56-11)37(27(5)36(53)42(7,44)39(54)58-32)59-38-34(52)31(48(9)10)20-25(3)57-38/h15-17,21,23-27,31-32,34-35,37-38,52H,12-14,18-20,22,45H2,1-11H3/t24-,25-,26+,27+,31+,32-,34-,35-,37-,38+,41-,42+,43-/m1/s1



$C_{43}H_{65}FN_6O_{10}$

Mol wt: 845.0088

CAS: 760981-83-7

EN: 378201

SUMMARY

Solithromycin (CEM-101, OP-1068) is the first fluoroketolide in clinical development and belongs to the macrolide antibiotic class. It has broad-spectrum activity against macrolide- and ketolide-resistant bacteria. In addition, it has activity against community-acquired inducibly methicillin-resistant Staphylococcus aureus, enterococci, including vancomycin-resistant enterococci, gonococci, atypical bacteria such as Legionella spp., Mycoplasma spp., Ureaplasma spp. and Chlamydia spp., Mycobacterium avium-intracellulare (MAC) complex, including extensively drug-resistant strains, Plasmodium vivax and Plasmodium falciparum, including azithromycin-resistant strains, and it was curative against Plasmodium berghei in a murine model. Unlike telithromycin, solithromycin does not significantly inhibit nicotinic acetylcholine receptors. Solithromycin has also been shown to be a potent inhibitor of cytokine (TNF-α and IL-8) release and matrix metalloproteinase (MMP) expression, which has been correlated with the antiinflammatory effects of older macrolides. Solithromycin has been well tolerated in phase I studies, with high plasma, tissue and intracellular concentrations. The compound does not have the significant gastrointestinal motility or bitter taste concerns associated with other macrolides. Oral capsule formulations are being tested in phase II clinical trials for community-acquired bacterial pneumonia and an intravenous formulation, which appears to be well tolerated to date, is currently in phase I studies.

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SYNTHESIS

6-*O*-Methylerythromycin A (I) is protected with benzoic anhydride in the presence of triethylamine and DMAP in ethyl acetate to afford 2′,4″-di-*O*-benzoyl-6-*O*-methylerythromycin A (II). Treatment of the protected intermediate (II) with 1,8 diazabicyclo[5.4.0]undec-7-ene (DBU) followed by 1,1-carbonyldiimidazole (CDI) (III) in DMF yields 10,11-anhydro-2′,4″-di-*O*-benzoyl-12-*O*-imidazolylcarbonyl-6-*O*-methylerythromycin A (IV), which is converted to the 2′,4″-di-*O*-benzoyl-11-*N*-(4-azidobutyl)-6-*O*-methylerythromycin A 11,12-cyclic carbamate (V) by treatment with 4-azidobutylamine (XIII) and DBU in DMF. The cladinose sugar is cleaved from carbamate (V) by hydrolysis with 1 N HCl in acetone to provide 11-*N*-(4-azidobutyl)-5-(2′-benzoyldesosaminyl)-3-hydroxy-6-*O*-methylerythronolide A 11,12-cyclic carbamate (VI). 1-*N*-(4-Azidobutyl)-5-(2′-benzoyldesosaminyl)-3-oxo-6-*O*-methylerythronolide A 11,12-cyclic carbamate (VII) is prepared by oxidation of the secondary alcohol of intermediate (VI) with Dess-Martin periodinane (DMP). Fluorination of the keto intermediate (VII) is accomplished with potassium *tert*-butoxide and *N*-fluo-

robenzenesulfonamide (NFSI) in THF/CH_2Cl_2 at –20 °C to –15 °C to afford the fluoro-azide intermediate (VIII). The triazole intermediate (X) is prepared by a copper-catalyzed azide-alkyne cycloaddition reaction between the fluoro-azide intermediate (VIII) and 3-ethynylaniline (IX) in the presence of copper(I) iodide and DIEA in acetonitrile. Deprotection of the triazole intermediate (X) is accomplished by refluxing in methanol to yield solithromycin (1). Scheme 1.

4-Azidobutylamine (XIII) is prepared by substitution of 1,4-dibromobutane (XI) with sodium azide in DMF/H_2O at 80 °C to produce 1,4-diazidobutane (XII), which, without isolation, is subjected to partial reduction with triphenylphosphine in MTBE to afford 4-azidobutylamine (XIII) (1).

BACKGROUND

Macrolides as a class have been useful antibacterials for treating community-acquired bacterial pneumonia (CABP), urethritis and other infections. Their spectrum of activity covers atypical bacteria, such as *Legionella* spp., allowing them to be used in patients with CABP. Macrolides have proven safe in all age groups, unlike the fluoroquinolones, and have been well tolerated. In recent years, macrolide resistance among pneumococci has risen to 30% (2), and other organisms, such as *Treponema pallidum* and gonococci, have also demonstrated a high level of resistance (3-5). Telithromycin, the first ketolide (a subclass of macrolide), was broadly approved for a number of respiratory tract infections, but, although effective against most macrolide-resistant strains, it suffered from serious side effects (6, 7) and has had limited clinical use. Thus, there is a need for a safe and effective macrolide.

Solithromycin (CEM-101, OP-1068) is a first-in-class fluoroketolide antibiotic developed by Cempra Pharmaceuticals that has progressed to clinical development. It has proven activity against bacteria with known types of macrolide resistance because it binds to three sites on the bacterial ribosome (8), while older macrolides bind to only one site, and telithromycin, the first ketolide, binds to two sites. The number of binding sites correlates with bacterial inhibitory activity but may not necessarily correlate with the inhibition of peptide synthesis. Due to the multiple ribosomal binding sites, it is difficult to select for resistant organisms. The spectrum of activity includes bacteria involved in respiratory tract infections (9-12), gonorrhea, chlamydia and nongonococcal urethritis (13), as well as bacteria that are not generally considered in the macrolide spectrum, such as community-acquired inducibly methicillin-resistant *Staphylococcus aureus* (14, 15), enterococci, including vancomycin-resistant *Enterococcus* (VRE) strains, and *Mycobacterium avium,* including those bacteria resistant to older macrolides. Solithromycin has been shown to be active against *Plasmodium* spp. (18, 19) in vitro, including strains resistant to azithromycin, and demonstrated curative activity in a mouse model of malaria, while azithromycin was not curative in this model.

The safety of a new macrolide is pivotal to its future marketing approval and clinical utility. Solithromycin has shown a good safety profile in preclinical toxicological testing and has been well tolerated in several phase I studies in 159 human subjects. In addition, Bertrand et al. have demonstrated that the pyridine moiety in the side chain of telithromycin is associated with inhibition of nicotinic acetylcholine receptors, which is a potential cause of the severe adverse events, mainly visual disturbances, exacerbation of myasthenia gravis and hepatotoxicity, that were seen with telithromycin use. Solithromycin, like older macrolides, does not show significant inhibition of these receptors (20). Unlike telithromycin, no visual disturbances have been observed in phase I trials with solithromycin.

Macrolides have been commonly used in pediatric populations and a solithromycin suspension is being developed for pediatric use. In order to be able to treat severe bacterial pneumonia, an i.v. formulation has been developed that is in phase I trials.

Targeted indications for solithromycin based on its in vitro activity include CABP, other respiratory tract infections and bacterial urethritis. As with older macrolides, further indications, expected to be tested later, are *Campylobacter* diarrhea, *Helicobacter pylori* gastritis, *Mycobacterium avium* infections, malaria, as well as to decrease steroid use in the treatment of chronic obstructive pulmonary disease and exacerbations of cystic fibrosis.

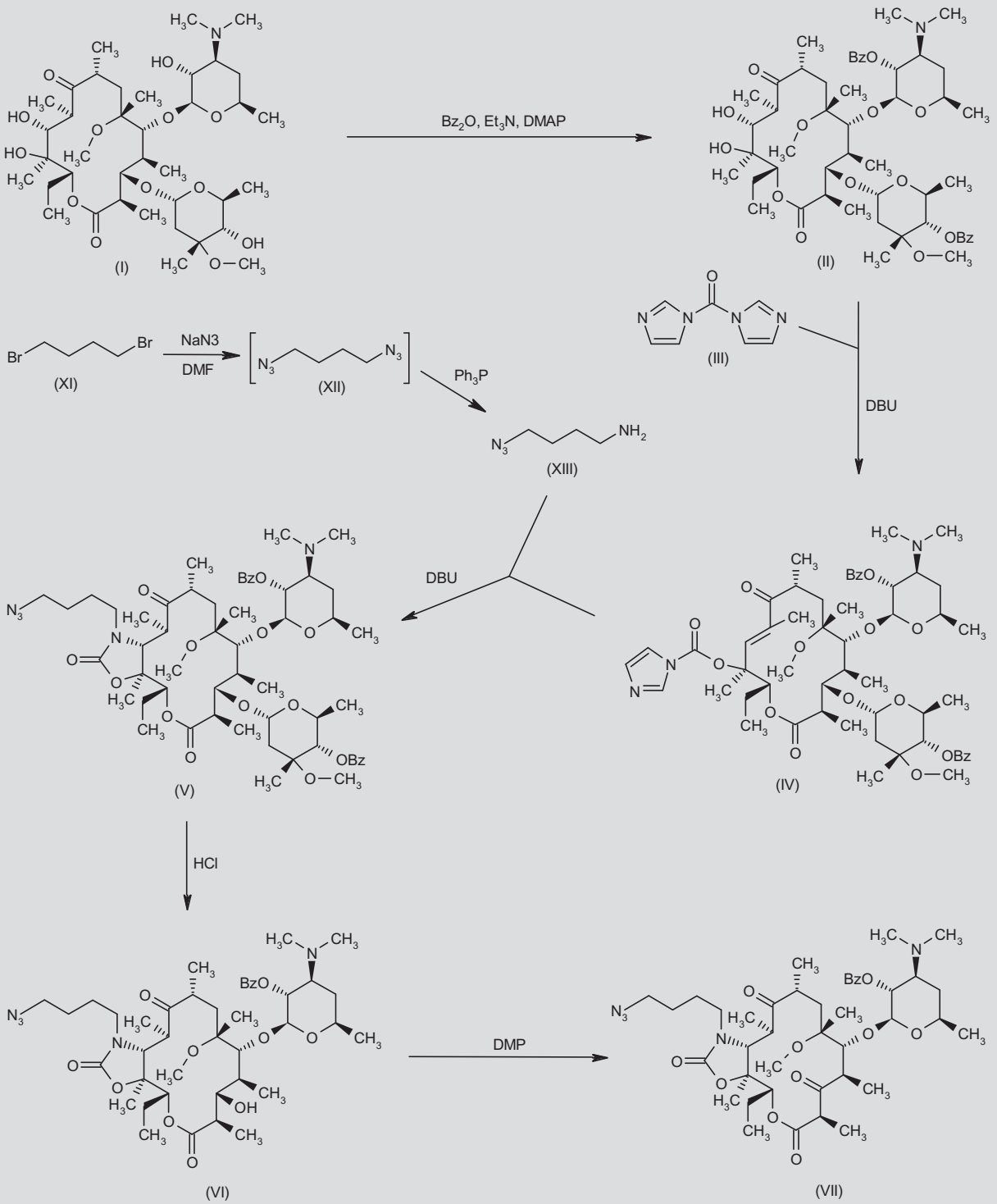
PRECLINCAL PHARMACOLOGY

Solithromycin is highly active against common typical and atypical community-acquired respiratory tract pathogens. Using tentative susceptibility criteria (susceptible ≤ 0.25 μg/mL; intermediate susceptible = 2-4 μg/mL; resistant ≥ 8 μg/mL), 2,901 worldwide CABP isolates of *Streptococcus pneumoniae* (N = 1,738), *Haemophilus influenzae* (N = 976) and *S. aureus* (N = 187) were susceptibility tested by CLSI broth microdilution methods with categorical interpretations (M07-A8, M100-S19) against solithromycin and > 25 comparators. The geographic samples included 1,362 strains from the U.S., 1,273 from Europe and 266 from Latin America. Solithromycin was very potent against *S. pneumoniae* (MIC_{50} = 0.015 μg/mL) and *S. aureus* (MIC_{50} = 0.06 μg/mL). Although strains resistant to telithromycin are rare, at the USA FDA breakpoints for telithromycin solithromycin showed activity against strains of *S. pneumoniae* (100.0% vs. 99.8%), *H. influenzae* (99.1% vs. 98.7%) and *S. aureus* (70.1% vs. 69.5%) that were resistant to telithromycin. These sensitivity rates were greater than levofloxacin, ceftriaxone and all marketed macrolide–lincosamide–streptogramin B (MLS_B) agents (21).

Solithromycin has been shown to be very active against Gram-positive organisms, including streptococci (MIC_{50} ≤ 0.008-0.015 μg/mL) and methicillin-susceptible staphylococci (MIC_{50} = 0.06-0.12 μg/mL), being twofold more potent than telithromycin. It was also shown to have bactericidal activity (MBC/MIC ratios of ≤ 4) when tested against streptococci and some *S. aureus*. Solithromycin showed an exposure- and concentration-dependent postantibiotic effect at four times the MIC, with values of 2.3 hours (*S. aureus* ATCC 29213), 3.0 hours (*S. pneumoniae* ATCC 49619), 6.1 hours (*Streptococcus pyogenes* 1612A), 3.2 hours (*H. influenza*e ATCC 49247) and 6.3 hours (*Moraxella catarrhalis* 10142A) (22); the long postantibiotic effects reflect the additional ribosomal binding sites. In vitro synergy studies using microbroth dilution methods as described by CLSI showed no antagonism with other antibiotics, with additive effects being noted mostly for combinations of solithromycin with ceftriaxone, gentamicin and trimethoprim–sulfamethoxazole (23).

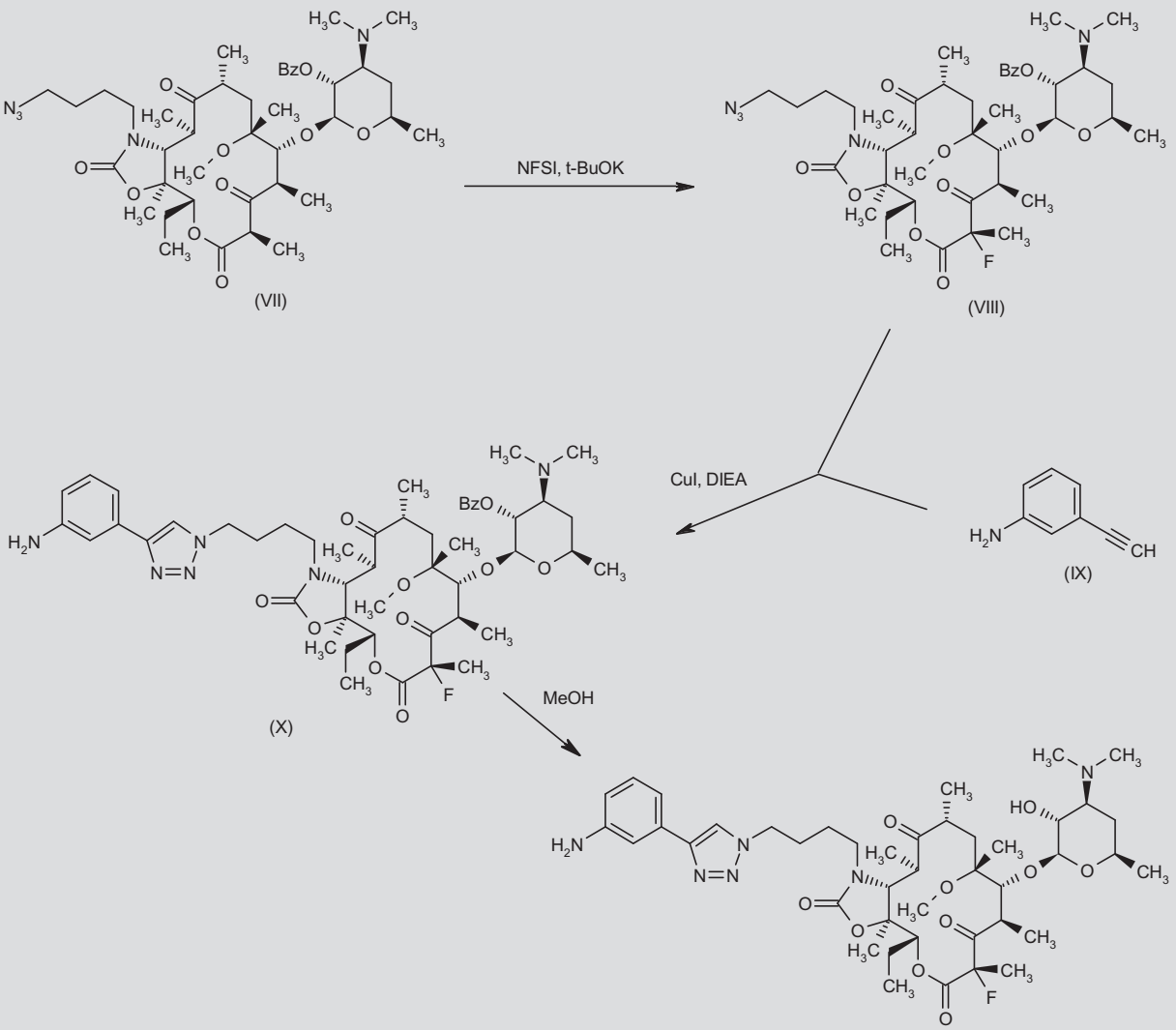
Solithromycin was tested in vitro against *S. pneumoniae* and *S. pyogenes* with defined macrolide resistance mechanisms. Against macrolide-susceptible pneumococci, solithromycin had MIC ranges of 0.002-0.016 μg/mL, and against macrolide-resistant phenotypes of 0.004-1 μg/mL. Only three strains with *ermB* ± *mefA* phenotypes

Scheme 1. Synthesis of Solithromycin



Continued

Scheme 1. *Cont.* Synthesis of Solithromycin



had MICs of 1 μg/mL, with 98.6% (218/221) having MICs ≤ 0.5 μg/mL. For *S. pyogenes*, MICs ranged from 0.008 to 0.03 μg/mL against macrolide-susceptible strains and from 0.015 to 1 μg/mL against macrolide-resistant strains. Pneumococcal multistep resistance studies showed a low potential for the selection of resistant mutants by solithromycin; 7 of 8 strains of pneumococci that were already resistant to older macrolides due to *ermB*, *mefA* and L4 mutations, when passaged up to 50 times in solithromycin-containing medium remained susceptible to solithromycin (24), and no resistant strains of *S. pyogenes* could be isolated when 8 strains, already carrying *ermA*, *ermB* and *mefA*, were passaged up to 50 times in solithromycin-containing medium.

Another experiment tested solithromycin against macrolide-resistant respiratory tract pathogens. The in vitro activity of solithromycin was compared with that of telithromycin, azithromycin, erythromycin, levofloxacin and doxycycline against a total of 199 resistant *S. pneumoniae* and 191 resistant *H. influenzae* strains using agar dilution procedures (CLSI, M7-A7, M100-S18). The tested strains included erythromycin-resistant (*ermB* genotype: 107 isolates; *mefE* genotype: 54) and ciprofloxacin-resistant *S. pneumoniae* (*gyrA* and *parC* genotype: 38) and also erythromycin-resistant (*ermA*,*B*,*C* genotype: 138) and ciprofloxacin-resistant *H. influenzae* (*gyrA* and *parC* genotype: 53). Against erythromycin-resistant *S. pneumoniae* strains (*ermB* genotype), the activity of solithromycin (MIC_{90} = 1 μg/mL) and levofloxacin (MIC_{90} = 2 μg/mL) was superior to all comparators

tested: telithromycin (MIC_{90} = 4 μg/mL), azithromycin (MIC_{90} ≥ 64 μg/mL), erythromycin (MIC_{90} ≥ 64 μg/mL) and doxycycline (MIC_{90} = 32 μg/mL). Against erythromycin-resistant *S. pneumoniae* (*mefE* genotype) strains, solithromycin (MIC_{90} = 0.25 μg/mL) was the most active agent, followed by levofloxacin (MIC_{90} = 2 μg/mL), telithromycin (MIC_{90} = 8 μg/mL), doxycycline (MIC_{90} = 16 μg/mL), azithromycin (MIC_{90} ≥ 64 μg/mL) and erythromycin (MIC_{90} ≥ 64 μg/mL). Against ciprofloxacin-resistant *S. pneumoniae* strains (*gyr*A and *parC* genotype), solithromycin (MIC_{90} = 0.25 μg/mL) was also the most active agent tested, followed by telithromycin (MIC_{90} = 1 μg/mL), levofloxacin (MIC_{90} = 2 μg/mL), doxycycline (MIC_{90} = 16 μg/mL), azithromycin (MIC_{90} ≥ 64 μg/mL) and erythromycin (MIC_{90} ≥ 64 μg/mL). In general, all macrolides are less active against *H. influenzae* in vitro than against Gram-positive pathogens such as pneumococci and β-hemolytic streptococci. Against erythromycin-resistant *H. influenzae* (*ermA*,*B*,*C* genotype) strains, solithromycin (MIC_{90} = 4 μg/mL) was the most active macrolide tested, followed by telithromycin (MIC_{90} = 16 μg/mL), azithromycin (MIC_{90} = 16 μg/mL) and erythromycin (MIC_{90} ≥ 64 μg/mL). Against ciprofloxacin-resistant *H. influenzae* (*gyrA* and *parC* genotype) strains, solithromycin (MIC_{90} = 2 μg/mL) was slightly more active than telithromycin (MIC_{90} = 4 μg/mL) and levofloxacin (MIC_{90} = 4 μg/mL) (11).

Solithromycin and comparators were tested against a collection of contemporary respiratory tract infection (RTI) isolates. A worldwide sample of organisms was used, including *S. pneumoniae* (n = 168; 59.3% erythromycin-resistant and 18 multidrug-resistant [MDR] serogroup 19A strains), *M. catarrhalis* (n = 21; 11 β-lactamase-positive), *H. influenzae* (n = 100; 48 β-lactamase-positive), *Haemophilus parainfluenzae* and *Haemophilus haemolyticus* (n = 12), and *Legionella pneumophila* (n = 30). Solithromycin was very potent against *S. pneumoniae* (MIC_{90} = 0.25 μg/mL; highest MIC = 0.5 μg/mL) and was 2- and ≥ 32-fold more active than telithromycin and clindamycin, respectively. Solithromycin also demonstrated potent activity against *S. pneumoniae* MDR-19A strains (MIC_{90} = 0.5 mg/L). Solithromycin was the most potent antimicrobial agent tested against *L. pneumophila*, with MIC values of ≤ 0.015 mg/L (telithromycin MIC_{90} = 0.03 μg/mL). Solithromycin was as potent as azithromycin against *Haemophilus* spp. RTI pathogens (MIC_{90} = 2 μg/mL), with no variations for β-lactamase production. Solithromycin MIC values against *M. catarrhalis* were ≤ 0.5 μg/mL. Interestingly, solithromycin potency was ~6 log_2 dilutions greater than telithromycin MIC results among 44 β-hemolytic streptococci, including group Q, group B, group C, group F and group G strains, with telithromycin MICs ≥ 2 μg/mL. Solithromycin exhibited the greatest potency and widest spectrum of activity against RTI pathogens among the tested MLS_B ketolide agents (azithromycin, clarithromycin, erythromycin, telithromycin, clindamycin and quinupristin/dalfopristin) and was comparable overall to levofloxacin (25).

Solithromycin has an expanded spectrum of activity against pathogens in other important therapeutic areas where new therapies are urgently needed, including *Mycobacterium avium* infections (solithromycin has bactericidal activity against *M. avium*) (17), biodefense threats (*Bacillus anthracis* and *Francisella tularensis*) (26), other mycobacterial infections (16) and malaria (18, 19).

In murine models, orally administered solithromycin was effective in reducing bacterial density in systemic infections caused by *S. pneumoniae*, *S. pyogenes* and *S. aureus,* in abscesses caused by *S. pneumoniae* and *S. pyogenes*, in neutropenic thigh infections caused by *S. pneumoniae* and *S. aureus*, and in pulmonary infections caused by *S. pneumoniae* (27, 28).

Solithromycin efficacy against *S. pneumoniae* was evaluated in murine models using a variety of macrolide-susceptible and -resistant strains, including *mefA*, *mefE+ermB*, and serotype 19A. In contrast to the efficacy of solithromycin in these animal models (murine systemic infection and neutropenic thigh abscess) for *mefA* strains, clarithromycin and azithromycin were not effective. Solithromycin was effective against an *S. pneumoniae* 19A strain from Hungary (MIC = 0.008 μg/mL), while clarithromycin and erythromycin (MIC > 8 μg/mL) were not (29).

Solithromycin was effective in rat pneumonia models against both a macrolide-susceptible strain (MIC = 0.25 μg/mL) and a macrolide-resistant strain of *H. influenzae* (MIC = 1 μg/mL). This is notable, as solithromycin is metabolized rapidly to less active metabolites in rats. Solithromycin demonstrated significant efficacy, achieving 1- and 2-log_{10} reductions in colony-forming units (CFUs) at 32 and 44 mg/kg when assessed at 24 hours post-treatment. This reduction in bioload persisted when the time of lung harvest was extended to 48 hours post-treatment. At 48 hours post-treatment, 1- and 2-log_{10} CFU reductions were achieved with 31 and 42 mg/kg of solithromycin. Clarithomycin was unable to elicit a significant reduction in the lung bioburden levels of *H. influenzae* in this model. Solithromycin demonstrated significant efficacy in this difficult-to-treat infection model of *H. influenzae* by its ability to effect a bactericidal response. Not only did solithromycin demonstrate reductions in bioloads at the classic 24-hour post-treatment harvest assessment, but it also demonstrated significant efficacy when the harvest time was extended to 48 hours post-treatment (30).

In a murine lung infection model, free drug plasma $AUC_{0\text{-}24}$:MIC was found to be the pharmacokinetic–pharmacodynamic measure best associated with efficacy against *S. pneumoniae*. Free drug plasma $AUC_{0\text{-}24}$:MIC ratios associated with net bacterial stasis and 1- and 2-log_{10} CFU reductions from baseline were 1.65, 6.31 and 12.8, respectively, while the ratios for total drug epithelial lining fluid (ELF) were 1.26, 15.1 and 59.8, respectively (31).

Based on its promising in vitro antimalarial activity, solithromycin was tested in a murine *Plasmodium berghei* model, as previously described (32). Solithromycin was first studied at a single dose of 100 mg/kg in either of two different vehicles (DMSO or HPMC). In the second experiment, solithromycin was given as a dose of 100 mg/kg/day for 4 days in both vehicles. Following the single dose, solithromycin showed antiparasitic activity of 80.05% and 81.45%, respectively, and mouse survival was 15.2 and 12.7 days, respectively. Following daily doses of 100 mg/kg for 4 days solithromycin showed antiparasitic activity of 99.79% in both vehicles. A total of 9 of 9 mice survived for 30 days, with no evidence of parasitemia in either experiment, and solithromycin is thus considered to be fully curative in this model; the azithromycin-treated mice that survived to 30 days all had evidence of parasitemia (18).

Solithromycin has been shown to accumulate intracellularly in THP-1 macrophages, to a concentration 300-350 times the extracellular concentration within 24 hours (versus approximately 20, 30 and 160, respectively, for telithromycin, clarithromycin and azithromycin). This

intracellular accumulation was suppressed by incubation at a pH of 6 and by monensin (a proton ionophore) and was unaffected by verapamil (a P-glycoprotein inhibitor; twofold accumulation increase for azithromycin) or gemfibrozil. This has been shown to increase its activity significantly (15-100 times more potent than azithromycin) against intracellular pathogens, such as phagocytosed *S. aureus*, *L. pneumophila* and *Listeria monocytogenes* (33).

Solithromycin, like azithromycin, causes phospholipidosis when tested at high doses in toxicological studies. It has been found that this phospholipidosis is related to the inhibition of phospholipase A1 and is not associated with apoptosis or reactive oxygen species generation (34). Solithromycin retains activity both in the cytosol, as shown by in vitro activity against *Listeria,* and in phagolysosomes, as demonstrated by in vitro activity against *Legionella*. High intracellular concentrations may help to increase activity against other pathogens, such as *Chlamydia trachomatis* and *Chlamydophila pneumoniae* (12), against which macrolides have proven efficacy.

In addition to its antibacterial activity, solithromycin has been demonstrated to be a potent inhibitor of the release of cytokines, such as TNF-α, IL-8 and MMP-9, from activated cells in vitro and has been shown to restore corticosteroid sensitivity through upregulation of histone deacetylase 2 (HD2) and restoration of histone deacetylase (HDAC) activity (35). These results are suggestive of antiinflammatory activity, as has been noted with older macrolides. The effects of solithromycin on phorbol 12-myristate 13-acetate (PMA)-induced MMP-9 production and lipopolysaccharide-induced IL-8 and TNF-α release in human histiocytic lymphoma U-937 cells have been evaluated and compared with the effects of erythromycin, clarithromycin, azithromycin and telithromycin. Solithromycin concentration-dependently inhibited MMP-9, IL-8 and TNF-α production in U-937 cells with IC_{50} values of 28.9 ± 1.6, 78.2 ± 9.5 and 41.6 ± 1.9 μM, respectively. In contrast, clarithromycin had 10 times less antiinflammatory activity than solithromycin. Erythromycin, azithromycin and telithromycin did not show significant antiinflammatory activity in these assays (36). Corticosteroid sensitivity was determined by the calculation of the IC_{50} value of dexamethasone on TNF-α-induced IL-8 production in U-937 cells. HDAC activity and Akt phosphorylation levels, as a marker of phosphatidylinositol 3-kinase (PI3K) activation, were measured by a fluorescence-based activity assay and Western blotting, respectively. HD2 mRNA expression was also determined in type II alveolar epithelial cells. Cells were exposed to oxidative stress, such as hydrogen peroxide (H_2O_2) or cigarette smoke extract, to induce steroid insensitivity. Oxidative stress decreased corticosteroid sensitivity with concomitant downregulation of total HDAC activity/HD2 expression and increased Akt phosphorylation. Treatment with solithromycin (10 μM) restored corticosteroid sensitivity in H_2O_2-exposed cells. In addition, solithromycin (10-100 μM) restored the HDAC activity and HD2 expression that was reduced under oxidative stress and also inhibited Akt phosphorylation. In these studies, solithromycin was more potent than any currently marketed macrolide (35).

PHARMACOKINETICS AND METABOLISM

In mice, solithromycin displays somewhat non-linear pharmacokinetics after oral administration. A mean C_{max} of 3.5 μg/mL and mean AUC_{0-24} of 30.8 μg.h/mL were reached after a dose of 25 mg/kg. In a separate study, a mean C_{max} of 1.4 μg/mL and mean AUC_{0-24} of 4.7 μg.h/mL were reached after a dose of 10 mg/kg. The half-life ($t_{1/2}$) ranged from 1.39 to 4.36 hours. By 24 hours, plasma concentrations were below the quantifiable limit for all doses (27, 28).

Two primary metabolites of solithromycin, *N*-acetyl-CEM-101 and CEM-214, have been quantified in mouse, rat, rabbit, monkey and human plasma, with significant amounts detectable following oral administration in monkeys (*N*-acetyl-CEM-101 and CEM-214) and rats (mostly *N*-acetyl-CEM-101), intermediate amounts in rabbits and low amounts in mice and humans relative to parent compound. In both rats and monkeys, the C_{max} and AUC of *N*-acetyl-CEM-101 are similar to those of solithromycin. CEM-214 concentrations increased significantly only in the monkey and reached levels similar to corresponding solithromycin plasma concentrations (37).

Interestingly, following i.v. administration of solithromycin, these primary metabolites are insignificant in dogs, monkeys and humans. In a 28-day, repeat-dose study in monkeys, doses of 25 mg/kg/day i.v. were well tolerated, with no limiting vein irritation or pain, achieving C_{max} values of 5.4 and 5.9 μg/mL, respectively, on day 1 and day 28 (38).

CLINICAL STUDIES

The safety and efficacy of oral solithromycin for the treatment of CABP have been evaluated in a randomized, double-blind, multicenter phase II clinical trial (39, 40). Seven phase I trials have been completed to date, showing that orally administered solithromycin was safe and well tolerated in 159 healthy adult subjects when administered as single doses up to 1600 mg, multiple doses of 200, 400 and 600 mg administered once daily for 7 days, multiple doses of 400 mg administered once daily for 5 days, and a loading dose regimen of 800 mg on day 1 followed by 400 mg administered once daily for 4 days.

For single oral doses, the mean C_{max} and AUC increases were more than dose-proportional from 50 to 400 mg, and were then dose-proportional across the higher range of doses studied. The C_{max} ranged from 0.02 to 1.9 μg/mL and the AUC_{0-inf} ranged from 0.6 to 28.8 μg.h/mL. The mean t_{max} increased from 1.5 to 6.0 hours and the mean $t_{1/2}$ increased from 3.16 to 7.42 hours over the 50- to 1600-mg dose range. These levels indicate that single oral doses of solithromycin for bacterial urethritis could be well tolerated. For multiple oral doses, the increases in C_{max} and AUC_{0-24} were more than dose-proportional, from 200 to 400 mg, and then approximately dose-proportional from 400 to 600 mg. In all dose groups solithromycin demonstrated higher exposure on day 7 than day 1 following 7 days of daily administration, indicating that accumulation occurred over the dosing period. The pharmacokinetic parameters are shown in Table I for the 400-mg dose on day 1 and day 7 of the multiple-dose study.

Another study showed that food had no significant effect on the pharmacokinetics of solithromycin. No QT prolongation, clinically significant adverse events (AEs) or clinically significant laboratory abnormalities have been observed in any phase I study (1).

Another phase I study in healthy subjects showed excellent distribution into the lung and penetration into ELF and alveolar macrophages

Table I. *Pharmacokinetic parameters for 400 mg oral solithromycin in plasma on days 1 and 7 of multiple-dose protocols.*

Pharmacokinetic parameters	400 mg/day (N = 10)
	Mean (CV%)
Day 1	
C_{max} (μg/mL)	0.579 (64.5)
t_{max} (h)[a]	3.50 (3, 4)
$t_{1/2}$ (h)[b]	4.82 (18.7)
$AUC_{(0-24)}$ (μg.h/mL)	4.835 (64.3)
$AUC_{(0-inf)}$ (μg.h/mL)	5.062 (63.3)
Day 7	
C_{max} (μg/mL)	1.09 (47.7)
t_{max} (h)[a]	4.00 (2.5, 6)
$t_{1/2}$ (h)[b]	7.47 (21.4)
$AUC_{(0-24)}$ (μg.h/mL)	13.27 (55.4)
Accumulation index[c]	5.22 (2)

[a]Expressed as median (minimum, maximum); [b]expressed as harmonic mean (CV from pseudo-SD); [c]$AUC_{(0-24)}$ day 7/$AUC_{(0-24)}$ day 1 expressed as mean (median value).

(AMs). Following five daily oral doses of 400 mg of solithromycin and bronchoalveolar lavage, mean AUC_{0-24} values in ELF and AM were 63.2 and 1282 μg.h/mL, and the ratios of these AUC values to plasma AUC values were 8.88 for ELF and 180 for AM (42).

An ongoing phase I study of ascending doses of the i.v. formulation of solithromycin (25-800 mg) showed no serious AEs, clinically significant systemic AEs, QT prolongation or clinically significant laboratory abnormalities. The pharmacokinetics (C_{max} and AUC_{inf}) appear linear up to 200 mg and slightly more than dose-proportional at higher doses. Clearance decreased with dose and the volume of distribution was large and relatively constant over the dose range. Clinically relevant plasma concentrations (approx. 4 μg/mL) were obtained at doses of 800 mg and i.v. exposure was 1.3- to 3-fold higher than that observed with equivalent oral doses (43).

Results from the phase II clinical trial investigating the efficacy, safety and tolerability of oral solithromycin in comparison with levofloxacin for the treatment of CABP were recently reported. A total of 132 patients were randomized to receive either solithromycin 800 mg on day 1 followed by 400 mg on days 2-5, or levofloxacin 750 mg on days 1-5. The primary outcome measure was continued improvement or complete resolution of baseline signs and symptoms in the intent-to-treat and clinically evaluable populations at the test of cure visit, which was completed 5-10 days after the last dose. Solithromycin demonstrated comparable efficacy to levofloxacin and a favorable safety and tolerability profile, with a lower incidence of treatment-emergent AEs compared to levofloxacin (40).

Future phase II and III studies are planned to determine the safety and efficacy of solithromycin in patients with CABP.

SOURCE

Cempra Pharmaceuticals, Inc. (US).

DISCLOSURES

The authors are employees of Cempra Pharmaceuticals.

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