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In Vitro Activity of Lefamulin Tested against *Streptococcus pneumoniae* with Defined Serotypes, Including Multidrug-Resistant Isolates Causing Lower Respiratory Tract Infections in the United States

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Lefamulin was evaluated against various *Streptococcus pneumoniae* serotypes that were collected from adults with lower respiratory tract infections. Lefamulin exhibited MIC_{50} and MIC_{90} values of 0.12 and 0.25 μg/ml, respectively, against the entire collection ($n = 822$). Similar results were obtained for lefamulin against each of the most common serotypes as well as against multidrug-resistant isolates and strains that are nonsusceptible to ceftriaxone or erythromycin. These data support the clinical development of lefamulin for the treatment of community-acquired respiratory tract infections.

Community-acquired respiratory tract infections (CARTIs) comprise a series of clinical syndromes, including community-acquired bacterial pneumonia (CABP), bacterial sinusitis, acute otitis media, and acute bacterial exacerbations of chronic bronchitis (1). CARTIs, especially CABP, are among the most frequent infections treated by physicians and represent a major international health problem (2). In addition, CABP represents the leading cause of hospitalizations in the United States and the main cause of morbidity and mortality among children and the elderly, with medical costs estimated at almost $1 billion and $17 billion annually in the United States, respectively (3, 4).

Lefamulin belongs to the pleuromutilin class of antimicrobial agents, which inhibits bacterial protein synthesis by selectively binding to the peptidyl transferase center of the bacterial ribosome and prevents the correct positioning of the 3′-CCA ends of tRNAs for peptide transfer (5–10). Lefamulin is the first pleuromutilin in development for intravenous and oral administration in humans (6), and it is currently in late-stage clinical development for the treatment of CABP and acute bacterial skin and skin structure infections (11–13). Lefamulin exhibits potent antibacterial activity against the most important respiratory and skin pathogens, including *Streptococcus* spp. and *Staphylococcus* spp., fastidious Gram-negative organisms, such as *Haemophilus influenzae*, and atypical respiratory pathogens, including *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila* (14–16). In addition, in healthy human subjects, lefamulin (unbound protein) demonstrated extensive penetration and accumulation in pulmonary epithelial lining fluid, reaching a median total area under the concentration-time curve from 0 to 12 h (AUC_{0-12}) of 5.78 μg · h/ml and a median maximum concentration of drug in serum (C_{max}) of ~0.7 μg/ml after a single 150-mg intravenous infusion over 1 h (17). This study evaluated the *in vitro* activity of lefamulin against specific serotypes of clinical isolates of *Streptococcus pneumoniae*.

A total of 822 *S. pneumoniae* isolates from 58 hospitals located in the nine United States Census regions as part of the SENTRY Antimicrobial Surveillance Program for 2010 were included. Isolates were recovered from lower respiratory tract specimens of adult patients aged ≥18 years and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmation of bacterial identification, which was performed by biochemical algorithms and/or PCR assays as previously described (18). Serotypes were determined according to the sequence of *cpsB* in combination with multiplex PCR assays and the capsular swelling method (18). Isolates were tested for susceptibility by broth microdilution (19). Testing was performed using dry-form panels manufactured by Thermo Fisher Scientific (Cleveland, OH, USA) under appropriate quality assurance (20). Susceptibility interpretive criteria for comparator agents were those established by the Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (20, 21). An isolate was categorized as multidrug resistant (MDR) if it had elevated MIC results for three or more of the following drug classes (drug class probe): penicillins (penicillin, ≥4 μg/ml), cephalosporins (ceftriaxone, ≥2 μg/ml), macrolides (erythromycin, ≥0.5 μg/ml), tetracyclines (tetracycline HCl, ≥2 μg/ml), fluoroquinolones (levofloxacin, ≥4 μg/ml), lincosamides (clindamycin, ≥0.5 μg/ml), or folate pathway inhibitors (trimethoprim-sulfamethoxazole [TMP-SMX], ≥1/19 μg/ml).

In general, lefamulin exhibited a log-normal MIC distribution against the population of *S. pneumoniae*, with modal MIC, MIC_{50}, and MIC_{90} results of 0.12, 0.12, and 0.25 μg/ml, respectively. In addition, all isolates were inhibited by lefamulin at

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TABLE 1 Lefamulin *in vitro* activity and cumulative MIC distributions against the overall population of *S. pneumoniae* selected serotypes and resistance subsets

Serotype[a] (no. tested/%)	MIC (μg/ml)		No. of isolates (cumulative %)[b] inhibited at a lefamulin MIC (μg/ml) of:						
	50%	90%	≤0.015	0.03	0.06	0.12	0.25	0.5	1
All (822)	0.12	0.25	7 (0.9)	24 (3.8)	149 (21.9)	**363 (66.1)**	237 (94.9)	39 (99.6)	3 (99.9)
19A (123/15.0)	0.12	0.25	2 (1.6)	3 (4.1)	28 (26.8)	**60 (75.6)**	24 (95.1)	5 (99.2)	1 (100.0)
3 (70/8.5)	0.06	0.12	0 (0.0)	2 (2.9)	**40 (60.0)**	26 (97.1)	2 (100.0)		
35B (54/6.6)	0.12	0.25	0 (0.0)	0 (0.0)	4 (7.4)	**28 (59.3)**	21 (98.1)	1 (100.0)	
6C/6D (53/6.4)	0.12	0.25	0 (0.0)	4 (7.5)	9 (24.5)	**25 (71.7)**	13 (96.2)	2 (100.0)	
22A/22F (48/5.8)	0.12	0.25	0 (0.0)	0 (0.0)	2 (4.2)	**24 (54.2)**	22 (100.0)		
11A/11D (47/5.7)	0.25	0.5	0 (0.0)	0 (0.0)	2 (4.3)	13 (31.9)	**24 (83.0)**	8 (100.0)	
15A/15F (45/5.5)	0.12	0.25	1 (2.2)	0 (2.2)	4 (11.1)	**21 (57.8)**	18 (97.8)	1 (100.0)	
7F (45/5.5)	0.12	0.25	0 (0.0)	0 (0.0)	2 (4.4)	**31 (73.3)**	12 (100.0)		
15B/15C (39/4.7)	0.12	0.25	0 (0.0)	2 (5.1)	6 (20.5)	**17 (64.1)**	13 (97.4)	1 (100.0)	
19F (24/2.9)	0.12	0.25	2 (8.3)	1 (12.5)	2 (20.8)	**13 (75.0)**	5 (95.8)	1 (100.0)	
Other[c] (274/33.3)	0.12	0.25	2 (0.7)	12 (5.1)	50 (23.4)	**105 (61.7)**	83 (92.0)	20 (99.3)	2 (100.0)
Resistance phenotype[d]									
ERY-nonsusceptible (305/37.1)	0.12	0.25	4 (1.3)	7 (3.6)	50 (20.0)	**143 (66.9)**	89 (96.1)	9 (99.0)	3 (100.0)
ERY-susceptible (517/62.9)	0.12	0.25	3 (0.6)	17 (3.9)	99 (23.0)	**220 (65.6)**	148 (94.2)	30 (100.0)	
CRO-nonsusceptible (61/7.4)	0.12	0.25	1 (1.6)	2 (4.9)	12 (24.6)	**33 (78.7)**	13 (100.0)		
CRO-susceptible (761/92.6)	0.12	0.25	6 (0.8)	22 (3.7)	137 (21.7)	**330 (65.0)**	224 (94.5)	39 (99.6)	3 (100.0)
MDR (180/21.9)	0.12	0.25	4 (2.2)	6 (5.6)	34 (24.4)	**83 (70.6)**	48 (97.2)	3 (98.9)	2 (100.0)
Non-MDR (642/78.1)	0.12	0.25	3 (0.5)	18 (3.3)	115 (21.2)	**280 (64.8)**	189 (94.2)	36 (99.8)	2 (100.0)

[a] The 13-valent conjugate vaccine contains coverage against serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.
[b] Modal MIC values are in bold.
[c] This category comprises 28 serotypes including those that are nontypeable.
[d] Erythromycin (ERY)-nonsusceptible and -susceptible groups include isolates with MIC values of ≥0.5 and ≤0.25 μg/ml, respectively (CLSI criteria). Ceftriaxone (CRO)-nonsusceptible and -susceptible groups include isolates with MIC values of ≥2 and ≤1 μg/ml, respectively (CLSI criteria). MDR, multidrug resistant (i.e., isolates displaying resistance phenotype to at least three drug classes); the MDR subset includes the following serotypes/serogroups (no.): 19A (81), 15A/F (42), 15B/15C (10), 19F (11), nontypeable (7), 6C/6D (5), 23A (5), 3 (3), 9N/9L (3), 23F (3), 14 (3), 35B (2), 21 (1), 22F/22A (1), 6A (1), 7F (1), and 34 (1).

≤1 μg/ml (Table 1). Overall, MIC_{50} and MIC_{90} results for lefamulin remained at 0.12 and 0.25 μg/ml, respectively, when tested against (i) the most common serotypes, (ii) isolates displaying a nonsusceptible phenotype to ceftriaxone or erythromycin, and (iii) the MDR subset (Table 1). Slightly different MIC_{50} and MIC_{90} values were observed for lefamulin when it was tested against serotypes 3 and 11A/11D, showing lefamulin MIC_{50} and MIC_{90} results of 0.06 and 0.12 μg/ml and 0.25 and 0.5 μg/ml, respectively.

The MIC values observed for lefamulin (MIC_{50} and MIC_{90}, 0.12 and 0.25 μg/ml, respectively) against all isolates were similar to those obtained for imipenem (MIC_{50} and MIC_{90}, ≤0.12 and 0.25 μg/ml; 100.0% susceptible) and were 2- to 4-fold lower than those for vancomycin (MIC_{50} and MIC_{90}, 0.25 and 0.5 μg/ml, respectively; 100.0% susceptible), linezolid (MIC_{50} and MIC_{90}, 1 and 1 μg/ml, respectively; 99.9% susceptible; data not shown), and levofloxacin (MIC_{50} and MIC_{90}, 1 and 1 μg/ml, respectively; 98.9% susceptible) (Tables 2 and 3). Other comparators showed decreased antimicrobial activity against all *S. pneumoniae* isolates, including ceftriaxone (MIC_{50} and MIC_{90}, ≤0.06 and 1 μg/ml, respectively; 92.6% susceptible), penicillin (MIC_{50} and MIC_{90}, ≤0.03 and 4 μg/ml, respectively; 89.2% susceptible), clindamycin (MIC_{50} and MIC_{90}, ≤0.25 and >1 μg/ml, respectively; 81.6% susceptible), erythromycin (MIC_{50} and MIC_{90}, ≤0.06 and >8 μg/ml, respectively; 62.9% susceptible), tetracycline (MIC_{50} and MIC_{90}, 0.5 and >8 μg/ml, respectively; 79.7% susceptible), and TMP-SMX (MIC_{50} and MIC_{90}, ≤0.5 and 4 μg/ml, respectively; 71.3% susceptible) (Tables 2 and 3).

Isolates were highly susceptible to penicillin and ceftriaxone except for serotypes 19A and 19F, for which susceptibility ranged from 38.2% to 75.0% (Table 2). When EUCAST breakpoints were applied, the proportions of intermediate and resistant isolates increased for the two compounds, especially for serotypes 19A, 35B, 6C/6D, 15A, and 19F (see Table S1 in the supplemental material). Clindamycin was also active against most serotypes, excluding 19A, 19F, and 15A/15F. In contrast, erythromycin had limited activity, with only serotypes 3 and 7F demonstrating high susceptibility rates (92.9% to 95.6% susceptible). Susceptibility rates obtained for tetracycline and TMP-SMX against most common serotypes varied, with the highest resistance rates among the serotypes 19F and 15A/15F for tetracycline and 19A, 6C/6D, and 19F for TMP-SMX; the proportion of intermediate isolates increased using EUCAST breakpoints.

A total of 21.9% of tested isolates displayed a MDR phenotype, and the majority (51.1%) of these *S. pneumoniae* isolates were serotype 19A or 19F, while 42.8% or 35.6% of MDR isolates are not covered by the 13-valent pneumococcal conjugate vaccine (PCV13) or the 23-valent pneumococcal polysaccharide vaccine (PPSV23), respectively (Table 1). Only lefamulin (MIC_{50} and MIC_{90}, 0.12 and 0.25 μg/ml, respectively) (Tables 1 and 3), vancomycin (MIC_{50} and MIC_{90}, 0.25 and 0.5 μg/ml, respectively), linezolid (MIC_{50} and MIC_{90}, 1 and 1 μg/ml, respectively), and levofloxacin (MIC_{50} and MIC_{90}, 1 and 1 μg/ml, respectively) demonstrated *in vitro* activity against MDR isolates (data not shown).

Recent reports have indicated a decrease in the prevalence of

TABLE 2 Antimicrobial susceptibility of the overall population of *S. pneumoniae* selected serotypes and resistance subsets based on CLSI breakpoints

Serotype[a] (total no. tested/%)	Percentage susceptible/intermediate/resistant[b]						
	Penicillin	Ceftriaxone	Erythromycin	Clindamycin	Levofloxacin	Tetracycline	TMP-SMX
All (822)	89.2/10.3/0.5	92.6/5.8/1.6	62.9/0.9/36.3	81.6/0.2/18.1	98.9/0.0/1.1	79.7/0.0/20.3	71.3/7.7/21.0
19A (123/15.0)	38.2/59.4/2.4	58.5/35.0/6.5	20.3/1.7/78.0	43.1/0.0/56.9	98.4/0.0/1.6	40.7/0.0/59.3	18.7/2.4/78.9
3 (70/8.5)	100.0/0.0/0.0	100.0/0.0/0.0	92.9/2.8/4.3	95.7/0.0/4.3	98.6/0.0/1.4	87.1/0.0/12.9	100.0/0.0/0.0
35B (54/6.6)	98.1/1.9/0.0	100.0/0.0/0.0	37.0/0.0/63.0	96.3/0.0/3.7	100.0/0.0/0.0	96.3/0.0/3.7	85.2/1.8/13.0
6C/6D (53/6.4)	100.0/0.0/0.0	98.1/1.9/0.0	52.8/1.9/45.3	98.1/0.0/1.9	96.2/0.0/3.8	98.1/0.0/1.9	50.9/0.0/49.1
22A/22F (48/5.8)	100.0/0.0/0.0	100.0/0.0/0.0	85.4/0.0/14.6	95.8/0.0/4.2	97.9/0.0/2.1	100.0/0.0/0.0	93.8/2.0/4.2
11A/11D (47/5.7)	100.0/0.0/0.0	100.0/0.0/0.0	83.0/0.0/17.0	100.0/0.0/0.0	97.9/0.0/2.1	100.0/0.0/0.0	91.5/0.0/8.5
15A/15F (45/5.5)	100.0/0.0/0.0	100.0/0.0/0.0	4.4/0.0/95.6	6.7/0.0/93.3	97.8/0.0/2.2	8.9/0.0/91.1	57.8/31.1/11.1
7F (45/5.5)	100.0/0.0/0.0	97.8/0.0/2.2	95.6/2.2/2.2	100.0/0.0/0.0	100.0/0.0/0.0	100.0/0.0/0.0	97.8/0.0/2.2
15B/15C (39/4.7)	100.0/0.0/0.0	100.0/0.0/0.0	56.4/0.0/43.6	94.9/0.0/5.1	100.0/0.0/0.0	74.4/0.0/25.6	66.7/23.0/10.3
19F (24/2.9)	66.7/29.1/4.2	75.0/12.5/12.5	50.0/0.0/50.0	62.5/0.0/37.5	100.0/0.0/0.0	54.2/0.0/45.8	50.0/4.2/45.8
Other[c] (274/33.3)	98.5/1.5/0.0	99.2/0.4/0.4	80.3/0.4/19.3	92.7/0.7/6.6	99.6/0.0/0.4	92.7/0.0/7.3	81.8/12.4/5.8
MDR[d] (180/21.9)	51.1/46.7/2.2	66.1/26.7/7.2	0.0/0.6/99.4	18.3/0.6/81.1	97/.2/0.0/2.8	12.8/0.0/87.2	22.2/15.0/62.8
Non-MDR (642/78.1)	99.8/0.2/0.0	100.0/0.0/0.0	80.5/0.1/18.5	99.4/0.2/0.4	99.4/0.0/0.6	98.4/0.0/1.6	85.0/5.6/9.3

[a] The 13-valent conjugate vaccine contains coverage against serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.
[b] This is breakpoint criteria according to 2016 CLSI standards. Breakpoints for penicillin (parenteral) nonmeningitis were applied (i.e., susceptible at ≤2 μg/ml, intermediate at 4 μg/ml, and resistant at ≥8 μg/ml). Erythromycin predicts susceptibility rates for azithromycin and clarithromycin.
[c] This category comprises 28 serotypes including those that are nontypeable.
[d] MDR, multidrug-resistant (i.e., isolates displaying a resistance phenotype to at least three drug classes). This includes the following serotypes/serogroups (no.): 19A (81), 15A/F (42), 15B/15C (10), 19F (11), nontypeable (7), 6C/6D (5), 23A (5), 3 (3), 9N/9L (3), 23F (3), 14 (3), 35B (2), 21 (1), 22F/22A (1), 6A (1), 7F (1), and 34 (1).

serotypes associated with PCV13 in children and adults (18, 22, 23), while other studies have documented an increase in non-PCV13 serotypes, including those with decreased antimicrobial susceptibility (24–27). Under these scenarios, additional alternatives for the treatment of CABP are needed. Potent and consistent lefamulin activity was observed regardless of serotype, including those not covered by PCV13 and those with a nonsusceptible phenotype to ceftriaxone or erythromycin or a MDR phenotype. The reasons for the small variation of lefamulin activity within serotypes (i.e., 3 and 11A/11D) need further investigation and may have been due to sample size.

Overall, when viewed in the context of the high pulmonary penetration observed in human subjects, these *in vitro* data support the continued clinical development of lefamulin for the treatment of patients with CABP, including those clinical cases caused by less-susceptible isolates.

TABLE 3 *In vitro* activity of lefamulin and comparator agents against the overall population of *S. pneumoniae* selected serotypes and resistance subsets

Serotype[a] (total no. tested/%)	MIC result (μg/ml)[b]															
	Lefamulin		PEN		CRO		ERY		CLI		LEV		TET		TMP-SMX	
	50%	90%	50%	90%	50%	90%	50%	90%	50%	90%	50%	90%	50%	90%	50%	90%
All (822)	0.12	0.25	≤0.03	4	≤0.06	1	≤0.06	>8	≤0.25	>1	1	1	0.5	>8	≤0.5	4
19A (123/15.0)	0.12	0.25	4	4	1	2	>8	>8	>1	>1	1	1	>8	>8	4	>4
3 (70/8.5)	0.06	0.12	≤0.03	≤0.03	≤0.06	≤0.06	≤0.06	0.12	≤0.25	≤0.25	1	1	0.5	>8	≤0.5	≤0.5
35B (54/6.6)	0.12	0.25	2	2	1	1	8	>8	≤0.25	≤0.25	1	1	0.5	0.5	≤0.5	>4
6C/6D (53/6.4)	0.12	0.25	0.12	1	0.25	0.5	≤0.06	8	≤0.25	≤0.25	1	1	0.5	0.5	≤0.5	>4
22A/22F (48/5.8)	0.12	0.25	≤0.03	≤0.03	≤0.06	≤0.06	≤0.06	8	≤0.25	≤0.25	1	1	0.5	0.5	≤0.5	≤0.5
11A/11D (47/5.7)	0.25	0.5	≤0.03	≤0.03	≤0.06	≤0.06	≤0.06	8	≤0.25	≤0.25	1	1	0.5	0.5	≤0.5	≤0.5
15A/15F (45/5.5)	0.12	0.25	0.25	0.25	0.12	0.5	>8	>8	>1	>1	1	1	>8	>8	≤0.5	4
7F (45/5.5)	0.12	0.25	≤0.03	≤0.03	≤0.06	≤0.06	≤0.06	≤0.06	≤0.25	≤0.25	1	1	0.5	0.5	≤0.5	≤0.5
15B/15C (39/4.7)	0.12	0.25	≤0.03	0.5	≤0.06	0.12	≤0.06	>8	≤0.25	≤0.25	1	1	0.5	>8	≤0.5	4
19F (24/2.9)	0.12	0.25	≤0.03	4	0.25	4	≤0.06	>8	≤0.25	>1	1	1	0.5	>8	≤0.5	>4
Other[c] (274/33.3)	0.12	0.25	≤0.03	0.25	≤0.06	0.12	≤0.06	8	≤0.25	≤0.25	1	1	0.5	0.5	≤0.5	2
MDR[d] (180/21.9)	0.12	0.25	2	4	1	2	>8	>8	>1	>1	1	1	>8	>8	4	>4
Non-MDR (642/78.1)	0.12	0.25	≤0.03	1	≤0.06	0.5	≤0.06	8	≤0.25	≤0.25	1	1	0.5	0.5	≤0.5	2

[a] The 13-valent conjugate vaccine contains coverage against serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.
[b] PEN, penicillin; CRO, ceftriaxone; ERY, erythromycin; CLI, clindamycin; LEV, levofloxacin; TET, tetracycline; TMP-SMX, trimethoprim-sulfamethoxazole.
[c] This catagory comprises 28 serotypes including those that are nontypeable.
[d] MDR, multidrug-resistant (i.e., isolates displaying a resistance phenotype to at least three drug classes). This includes the following serotypes/serogroups (no.): 19A (81), 15A/F (42), 15B/15C (10), 19F (11), nontypeable (7), 6C/6D (5), 23A (5), 3 (3), 9N/9L (3), 23F (3), 14 (3), 35B (2), 21 (1), 22F/22A (1), 6A (1), 7F (1), and 34 (1).

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