

# Antimicrobial Potency of Lefamulin (BC-3781) Tested Against *Streptococcus pneumoniae* with Defined Serotypes, Including Multidrug-resistant Isolates Causing Lower Respiratory Tract Infections in the United States

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## ABSTRACT

**Objectives:** To evaluate the *in vitro* activity of the investigational systemic pleuromutilin, lefamulin (BC-3781), tested against specific serotypes of *S. pneumoniae* clinical isolates responsible for lower respiratory tract infections in the USA. Lefamulin is currently under late-stage development for intravenous and oral administration for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections.

**Methods:** A total of 822 *S. pneumoniae* collected from 58 hospitals located in the nine USA Census regions during 2010 were included (SENTRY Antimicrobial Surveillance Program). Isolates were recovered from lower respiratory tract specimens of adult patients aged  $\geq 18$  years old. Identification was performed by biochemical algorithms and/or PCR assays. Susceptibility testing was performed by CLSI broth microdilution methods, and MIC interpretation applied EUCAST criteria. Isolates displaying resistance phenotype to at least three drug classes were considered as multidrug-resistant (MDR). Serotyping was performed by *cpsB* sequencing, and multiplex PCR assays. Serotypes 6A/6B and 7A/7F were differentiated by Quellung reaction.

**Results:** Lefamulin exhibited a log-normal MIC distribution against all *S. pneumoniae*, with modal MIC, MIC<sub>50</sub> and MIC<sub>90</sub> results of 0.12, 0.12 and 0.25 mg/L, respectively (Table 1). These MIC values were similar to those observed for imipenem (MIC<sub>50/90</sub>  $\leq$  0.12/0.25 mg/L; 100.0% susceptible), and 2- to 4-fold lower than vancomycin (MIC<sub>50/90</sub>, 0.25/0.5 mg/L; 100.0% susceptible), linezolid (MIC<sub>50/90</sub>, 1/1 mg/L; 99.9% susceptible) and levofloxacin (MIC<sub>50/90</sub>, 1/1 mg/L; 98.9% susceptible). Other comparators showed lower antimicrobial coverage (61.9 – 82.6% susceptible), including penicillin (MIC<sub>50/90</sub>,  $\leq$  0.03/4 mg/L; 62.2% susceptible), erythromycin (MIC<sub>50/90</sub>,  $\leq$  0.06/>8 mg/L; 62.9% susceptible) and ceftriaxone (MIC<sub>50/90</sub>,  $\leq$  0.06/1 mg/L; 82.6% susceptible) against all *S. pneumoniae*. Overall, MIC<sub>50</sub> and MIC<sub>90</sub> results for lefamulin remained 0.12 and 0.25 mg/L, respectively, when tested against most common serotypes. Non-susceptibility rates for penicillin (0.0 – 97.8%; MIC,  $\geq$  0.12 mg/L), ceftriaxone (0.0 – 65.9%; MIC,  $\geq$  1 mg/L) and erythromycin (2.0 – 95.6%) varied against common serotypes. However, highest non-susceptibility rates for penicillin were noted for serotypes 19A (84.6%), 35B (92.6%), 6C/6D (50.9%), 15A/15F (97.8%) and 15B/15C (35.9%), while non-susceptibility rates for ceftriaxone were highest against serotypes 19A (65.9%) and 35B (64.8%), and erythromycin non-susceptibility rates among 19A (79.7%), 35B (63.0%), 6C/6D (47.2%), 15A/15F (95.6%) and 15B/15C (43.6%). 13.4% (110/822) of isolates displayed a MDR phenotype and lefamulin demonstrated MIC<sub>50</sub> and MIC<sub>90</sub> results of 0.12 and 0.25 mg/L, respectively, against this subset.

**Conclusions:** Lefamulin demonstrated potent *in vitro* activity against a collection of *S. pneumoniae* responsible for lower respiratory tract infections in the USA. This activity was consistent (MIC<sub>50</sub> results +/- 1 double dilution) across different serotypes, including prevalent serotypes (19A and 35B) with decreased susceptibility to clinically relevant comparator agents and MDR isolates. These data support the continued clinical development of lefamulin for the treatment of CABP.

## INTRODUCTION

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

Lefamulin (BC-3781) belongs to the pleuromutilin class of antimicrobials agents, which inhibit bacterial protein synthesis by selectively binding to the peptidyl transferase center of the bacterial ribosome and preventing the correct positioning of the CCA ends of tRNAs for peptide transfer<sup>3</sup>. Lefamulin is the first systemic pleuromutilin derivative in development for intravenous and oral administration. This agent is currently under late-stage clinical development for intravenous and oral administration for the treatment of CABP and acute bacterial skin and skin structure infections<sup>4,5,6</sup>. This study evaluated the *in vitro* activity of the investigational systemic pleuromutilin, lefamulin, tested against specific serotypes of *Streptococcus pneumoniae* clinical isolates responsible for lower respiratory tract infections among adult patients in the USA.

## MATERIALS AND METHODS

**Bacterial isolates.** A total of 822 *S. pneumoniae* collected from 58 hospitals located in the nine USA Census regions as part of the SENTRY Antimicrobial Surveillance Program for 2010 were included<sup>6</sup>. Isolates were recovered from lower respiratory tract specimens of adult patients aged  $\geq 18$  years old, determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA)<sup>7</sup>. Bacterial identification was performed by biochemical algorithms and/or PCR assays.

**Antimicrobial susceptibility testing.** Isolates were tested for susceptibility by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07–A10 document<sup>8</sup>. Testing was performed using dry-form panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). Quality assurance was performed by concurrent testing of CLSI-recommended quality control reference strain (*S. pneumoniae* ATCC 49619; M100-S25, 2015)<sup>9</sup>.

Breakpoint criteria for comparator agents were those from European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2015)<sup>10</sup>. Data analysis was performed against all isolates in aggregate, common serotypes, according to the ceftriaxone/erythromycin susceptibility and multidrug-resistant (MDR) phenotype. Isolates displaying resistance phenotype to at least three drug classes were considered as MDR.

**Pneumococcal serotyping.** Isolates were subjected to PCR assays for amplification of the *cpsB* gene<sup>6</sup>. Amplicons were sequenced on both strands and the nucleotide sequences were analyzed using the Lasergene software package (DNASTAR, Madison, Wisconsin, USA).

## RESULTS

Lefamulin exhibited a log-normal MIC distribution against all *S. pneumoniae*, with modal MIC, MIC<sub>50</sub> and MIC<sub>90</sub> results of 0.12, 0.12 and 0.25 mg/L, respectively, and all isolates were inhibited by lefamulin at  $\leq 1$  mg/L (Table 1).

These MIC values were similar to those observed for imipenem (MIC<sub>50/90</sub>,  $\leq$  0.12/0.25 mg/L; 100.0% susceptible), and 2- to 4-fold lower than vancomycin (MIC<sub>50/90</sub>, 0.25/0.5 mg/L; 100.0% susceptible), linezolid (MIC<sub>50/90</sub>, 1/1 mg/L; 99.9% susceptible; data not shown) and levofloxacin (MIC<sub>50/90</sub>, 1/1 mg/L; 98.9% susceptible; Tables 2 and 3).

Other comparators showed lower antimicrobial coverage (61.9 – 82.6% susceptible), including penicillin (MIC<sub>50/90</sub>,  $\leq$  0.03/4 mg/L; 62.2% susceptible), erythromycin (MIC<sub>50/90</sub>,  $\leq$  0.06/>8 mg/L; 62.9% susceptible), ceftriaxone (MIC<sub>50/90</sub>,  $\leq$  0.06/1 mg/L; 82.6% susceptible) and trimethoprim-sulfamethoxazole (TMP-SXT; MIC<sub>50/90</sub>,  $\leq$  0.5/4 mg/L; 75.9% susceptible) against all *S. pneumoniae* (Tables 2 and 3).

Overall, MIC<sub>50</sub> and MIC<sub>90</sub> results for lefamulin remained 0.12 and 0.25 mg/L, respectively, when tested against most common serotypes, isolates displaying a non-susceptible phenotype to ceftriaxone or erythromycin, and against the MDR subset (Table 1). Exceptions were observed against serotype 3 and 11A/11D, which showed lefamulin MIC<sub>50/90</sub> of 0.06/0.12 and 0.25/0.5 mg/L, respectively.

Highest non-susceptibility rates for penicillin were noted for serotypes 15A/15F (97.8%), 35B (92.6%), 19A (84.6%), 6C/6D (50.9%), 19F (50.0%) and 15B/15C (35.9%). Non-susceptibility rates for ceftriaxone were highest against serotypes 19A (65.9%), 35B (64.8%) and 19F (45.8%), while erythromycin non-susceptibility rates were highest among 15A/15F (95.6%), 19A (79.7%), 35B (63.0%), 19F (50.0%), 6C/6D (47.2%) and 15B/15C (43.6%) (Table 2).

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

Serotype (Total no. tested / %)	Lefamulin MIC (mg/L)		Number of isolates (cumulative %) <sup>a</sup> inhibited at lefamulin MIC (mg/L) of:						
	50%	90%	$\leq 0.015$	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)	<b>363 (66.1)</b>	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)	<b>60 (75.6)</b>	24 (95.1)	5 (99.2)	1 (100.0)
3 (70 / 8.5)	0.06	0.12	0 (0.0)	2 (2.9)	<b>40 (60.0)</b>	26 (97.1)	2 (100.0)		
35B (54 / 6.6)	0.12	0.25	0 (0.0)	0 (0.0)	4 (7.4)	<b>28 (59.3)</b>	21 (98.1)	1 (100.0)	
6C/6D (53 / 6.4)	0.12	0.25	0 (0.0)	4 (7.5)	9 (24.5)	<b>25 (71.7)</b>	13 (96.2)	2 (100.0)	
22A/22F (48 / 5.8)	0.12	0.25	0 (0.0)	0 (0.0)	2 (4.2)	<b>24 (54.2)</b>	22 (100.0)		
11A/11D (47 / 5.7)	0.25	0.5	0 (0.0)	0 (0.0)	2 (4.3)	13 (31.9)	<b>24 (83.0)</b>	8 (100.0)	
15A/15F (45 / 5.5)	0.12	0.25	1 (2.2)	0 (2.2)	4 (11.1)	<b>21 (57.8)</b>	18 (97.8)	1 (100.0)	
7F (45 / 5.5)	0.12	0.25	0 (0.0)	0 (0.0)	2 (4.4)	<b>31 (73.3)</b>	12 (100.0)		
15B/15C (39 / 4.7)	0.12	0.25	0 (0.0)	2 (5.1)	6 (20.5)	<b>17 (64.1)</b>	13 (97.4)	1 (100.0)	
19F (24 / 2.9)	0.12	0.25	2 (8.3)	1 (12.5)	2 (20.8)	<b>13 (75.0)</b>	5 (95.8)	1 (100.0)	
Other <sup>b</sup> (298 / 26.3)	0.12	0.25	4 (1.3)	13 (5.7)	52 (23.2)	<b>118 (62.8)</b>	88 (92.3)	21 (99.3)	2 (100.0)
Resistance phenotype <sup>c</sup>									
ERY-NS (305 / 37.1)	0.12	0.25	4 (1.3)	7 (3.6)	50 (20.0)	<b>143 (66.9)</b>	89 (96.1)	9 (99.0)	3 (100.0)
ERY-S (517 / 62.9)	0.12	0.25	3 (0.6)	17 (3.9)	99 (23.0)	<b>220 (65.6)</b>	148 (94.2)	30 (100.0)	
CRO-NS (143 / 17.4)	0.12	0.25	1 (0.7)	4 (3.5)	28 (23.1)	<b>67 (69.9)</b>	41 (98.6)	1 (99.3)	1 (100.0)
CRO-S (679 / 82.6)	0.12	0.25	5 (0.9)	20 (3.8)	121 (21.6)	<b>296 (65.2)</b>	196 (94.1)	38 (99.7)	2 (100.0)
MDR (110 / 13.4)	0.12	0.25	2 (1.8)	3 (4.5)	23 (25.5)	<b>56 (76.4)</b>	24 (98.2)	1 (99.1)	1 (100.0)
Non-MDR (712 / 86.6)	0.12	0.25	5 (0.7)	21 (3.6)	126 (21.3)	<b>307 (64.5)</b>	213 (94.4)	38 (99.7)	2 (100.0)

a. Modal MIC values are in bold.  
b. Includes 27 serotypes and a nontypeable isolate.  
c. ERY=erythromycin, CRO=ceftriaxone, NS=non-susceptible, S=susceptible. ERY-nonsusceptible and -susceptible groups include isolates with MIC values of  $\geq 0.5$  and  $\leq 0.25$  mg/L, respectively (EUCAST criteria). CRO-nonsusceptible and -susceptible groups include isolates with MIC values of  $\geq 1$  and  $\leq 0.5$  mg/L, respectively (EUCAST criteria). MDR = multidrug-resistant (i.e. isolates displaying resistance phenotype to at least three drug classes); includes serotypes/serogroups (n): 14 (2), 15A/F (5), 15B/15C (2), 23F (2), 19A (81), 19F (10), 6C/6D (2), 7F/7A (1), 35B (2), nontypeable (3). The non-MDR subset includes 36 serotypes and 11 nontypeable isolates.

A total of 13.4% (110/822) of isolates displayed a MDR phenotype, mostly represented by serotype 19A (73.6%; 81/110; Tables 1 and 2). Lefamulin (MIC<sub>50/90</sub>, 0.12/0.25 mg/L) demonstrated MIC results 2- to 4-fold lower than vancomycin (MIC<sub>50/90</sub>, 0.25/0.5 mg/L; 100.0% susceptible), linezolid (MIC<sub>50/90</sub>, 1/1 mg/L; 99.9% susceptible; data not shown) and levofloxacin (MIC<sub>50/90</sub>, 1/1 mg/L; 95.5% susceptible; Tables 2 and 3) against this subset.

**Table 2.** Antimicrobial susceptibility of *S. pneumoniae* serotypes included in this study.

Serotype (Total no. tested/%)	% susceptible / intermediate / resistant <sup>a</sup>				
	Penicillin	Ceftriaxone	Erythromycin <sup>b</sup>	Levofloxacin	TMP-SXT <sup>c</sup>
All (822)	62.2 / 27.0 / 10.8	82.6 / 15.8 / 1.6	62.9 / 0.8 / 36.3	98.9 / - / 1.1	75.9 / 3.1 / 21.0
19A (123 / 15.0)	15.4 / 22.8 / 61.8	34.1 / 59.4 / 6.5	20.3 / 1.7 / 78.0	98.4 / - / 1.6	19.5 / 1.6 / 78.9
3 (70 / 8.5)	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0	92.9 / 2.8 / 4.3	98.6 / - / 1.4	100.0 / 0.0 / 0.0
35B (54 / 6.6)	7.4 / 90.7 / 1.9	35.2 / 64.8 / 0.0	37.0 / 0.0 / 63.0	100.0 / - / 0.0	87.0 / 0.0 / 13.0
6C/6D (53 / 6.4)	49.1 / 50.9 / 0.0	98.1 / 1.9 / 0.0	52.8 / 1.9 / 45.3	96.2 / - / 3.8	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	97.9 / - / 2.1	95.8 / 0.0 / 4.2
11A/11D (47 / 5.7)	97.9 / 2.1 / 0.0	100.0 / 0.0 / 0.0	83.0 / 0.0 / 17.0	97.9 / - / 2.1	91.5 / 0.0 / 8.5
15A/15F (45 / 5.5)	2.2 / 97.8 / 0.0	95.6 / 4.4 / 0.0	4.4 / 0.0 / 95.6	97.8 / - / 2.2	73.3 / 15.6 / 11.1
7F (45 / 5.5)	97.8 / 2.2 / 0.0	97.8 / 2.2 / 0.0	95.6 / 2.2 / 2.2	100.0 / - / 0.0	97.8 / 0.0 / 2.2
15B/15C (39 / 4.7)	64.1 / 35.9 / 0.0	97.4 / 2.6 / 0.0	56.4 / 0.0 / 43.6	100.0 / - / 0.0	79.5 / 10.2 / 10.3
19F (24 / 2.9)	50.0 / 16.7 / 33.3	54.2 / 33.3 / 12.5	50.0 / 0.0 / 50.0	100.0 / - / 0.0	54.2 / 0.0 / 45.8
MDR <sup>d</sup> (110 / 13.4)	1.8 / 18.2 / 80.0	12.7 / 75.5 / 11.8	0.0 / 0.0 / 100.0	95.5 / - / 4.5	1.8 / 0.9 / 97.3
Non-MDR <sup>e</sup> (712 / 86.6)	71.5 / 28.4 / 0.1	93.4 / 6.6 / 0.0	72.6 / 9.8 / 26.4	99.4 / - / 0.6	87.4 / 3.4 / 9.3

a. Breakpoint criteria according to EUCAST (2015).  
b. Predicts susceptibility rates for azithromycin and clarithromycin.  
c. TMP-SXT = trimethoprim-sulfamethoxazole.  
d. MDR = multidrug-resistant (i.e. isolates displaying resistance phenotype to at least three drug classes). Includes serotypes/serogroups (n): 14 (2), 15A/F (5), 15B/15C (2), 23F (2), 19A (81), 19F (10), 6C/6D (2), 7F/7A (1), 35B (2), nontypeable (3).  
e. Includes 36 serotypes and 11 nontypeable isolates.

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

Serotype (Total no. tested / %)	MIC <sub>50</sub> and MIC <sub>90</sub> results (mg/L)											
	Lefamulin		Penicillin		Ceftriaxone		Erythromycin		Levofloxacin		TMP-SXT <sup>a</sup>	
All (822)	0.12	0.25	$\leq 0.03$	4	$\leq 0.06$	1	$\leq 0.06$	>8	1	1	$\leq 0.5$	4
19A (123 / 15.0)	0.12	0.25	4	4	1	2	>8	>8	1	1	4	>4
3 (70 / 8.5)	0.06	0.12	$\leq 0.03$	$\leq 0.03$	$\leq 0.06$	$\leq 0.06$	0.12	1	1	$\leq 0.5$	$\leq 0.5$	
35B (54 / 6.6)	0.12	0.25	2	2	1	1	8	>8	1	1	$\leq 0.5$	>4
6C/6D (53 / 6.4)	0.12	0.25	0.12	1	0.25	0.5	$\leq 0.06$	8	1	1	$\leq 0.5$	>4
22A/22F (48 / 5.8)	0.12	0.25	$\leq 0.03$	$\leq 0.03$	$\leq 0.06$	$\leq 0.06$	$\leq 0.06$	8	1	1	$\leq 0.5$	$\leq 0.5$
11A/11D (47 / 5.7)	0.25	0.5	$\leq 0.03$	$\leq 0.03$	$\leq 0.06$	$\leq 0.06$	0.12	8	1	1	$\leq 0.5$	$\leq 0.5$
15A/15F (45 / 5.5)	0.12	0.25	0.25	0.25	0.12	0.5	>8	>8	1	1	$\leq 0.5$	4
7F (45 / 5.5)	0.12	0.25	$\leq 0.03$	$\leq 0.03$	$\leq 0.06$	$\leq 0.06$	$\leq 0.06$	$\leq 0.06$	1	1	$\leq 0.5$	$\leq 0.5$
15B/15C (39 / 4.7)	0.12	0.25	$\leq 0.03$	0.5	$\leq 0.06$	0.12	$\leq 0.06$	>8	1	1	$\leq 0.5$	4
19F (24 / 2.9)	0.12	0.25	$\leq 0.03$	4	0.25	4	$\leq 0.06$	>8	1	1	$\leq 0.5$	>4
MDR <sup>b</sup> (110 / 13.4)	0.12	0.25	4	4	2	4	>8	>8	1	1	4	>4
Non-MDR <sup>c</sup> (712 / 86.6)	0.12	0.25	$\leq 0.03$	1	$\leq 0.06$	0.5	$\leq 0.06$	>8	1	1	$\leq 0.5$	2

a. TMP-SXT = trimethoprim-sulfamethoxazole.  
b. MDR = multidrug-resistant (i.e. isolates displaying resistance phenotype to at least three drug classes). Includes serotypes/serogroups (n): 14 (2), 15A/F (5), 15B/15C (2), 23F (2), 19A (81), 19F (10), 6C/6D (2), 7F/7A (1), 35B (2), nontypeable (3).  
c. Includes 36 serotypes and 11 nontypeable isolates.

## CONCLUSIONS

Lefamulin demonstrated potent *in vitro* activity against a collection of *S. pneumoniae* responsible for lower respiratory tract infections among adult patients in the USA.

The lefamulin *in vitro* activity was consistent across different serotypes. In addition, consistent lefamulin activity was observed against isolates displaying a non-susceptible phenotype to ceftriaxone or erythromycin, or a MDR phenotype.

These data support the continued clinical development of lefamulin for the treatment of CABP.

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