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P1823 Antimicrobial activity of lefamulin against a large longitudinal collection of clinical bacterial isolates collected worldwide: results from the SENTRY antimicrobial surveillance program

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Background: Lefamulin is a semi-synthetic pleuromutilin antibiotic in late-stage clinical development for intravenous and oral treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections. We evaluated the *in vitro* activity of lefamulin and comparators against clinical bacteria collected worldwide over 3 years of surveillance.

Materials/methods: 15,036 isolates, including 6,018 *Streptococcus pneumoniae* (SPN) and 4,463 *Staphylococcus aureus* (SA), among others, were collected from medical centers in Europe (n=5,712 [19 nations]), United States (n=5,731), Asia-Pacific region (n=2,132 [10 nations]), and Latin America (n=1,461 [6 nations]) from 2015-2017 as part of the SENTRY Antimicrobial Surveillance Program, and susceptibility was tested against lefamulin and numerous comparators by reference broth microdilution method. Lefamulin resistance mechanisms were evaluated by whole genome sequencing and *in silico* analysis.

Results: Lefamulin was highly active against SPN ($MIC_{50/90}$, 0.06/0.12 mg/L; highest MIC, 1 mg/L; Table) and retained activity against isolates resistant to erythromycin (n=2,080), clindamycin (n=1,048), tetracycline (n=1,424), and/or trimethoprim-sulfamethoxazole (n=1,091) with $MIC_{50/90}$, 0.06/0.12 mg/L for these subsets. Lefamulin was also active against levofloxacin-nonsusceptible ($MIC_{50/90}$, 0.06/0.25 mg/L) and penicillin-resistant (at >4 mg/L) SPN ($MIC_{50/90}$, 0.12/0.12 mg/L). SPN susceptibility to penicillin (at ≤0.06 mg/L), azithromycin, amoxicillin-clavulanate, and tetracycline was 65.6%, 65.0%, 93.5%, and 75.9%, respectively. Lefamulin was active against SA independent of oxacillin resistance ($MIC_{50/90}$, 0.06/0.12 mg/L); only 9 (0.2%) isolates exhibited lefamulin MIC >1 mg/L, and oxacillin resistance varied from 22.3% (Europe) to 41.4% (United States; 32.1% overall). Lefamulin exhibited similar activity against beta-lactamase-positive (24.2% overall) and -negative *Haemophilus influenzae*, with $MIC_{50/90}$ values of 0.5/1 mg/L for both groups. Lefamulin MIC values were generally low among beta-haemolytic streptococci ($MIC_{50/90}$, 0.03/0.03 mg/L), with only 5 (0.6%, all *S. agalactiae*) isolates showing MIC >0.12 mg/L. Lefamulin was also active against coagulase-negative staphylococci ($MIC_{50/90}$, 0.03/0.12 mg/L), viridans group streptococci ($MIC_{50/90}$, 0.06/2 mg/L), and *H. parainfluenzae* ($MIC_{50/90}$, 1/4 mg/L). Isolates with elevated lefamulin MIC results were rare and mainly caused by *vga* in staphylococci and *lsa*(E) in streptococci.

Conclusions: Lefamulin displayed stable and potent *in vitro* activity against a large, 3-year, contemporary worldwide collection of bacterial isolates regardless of resistance phenotype to other antibiotic classes, including β-lactams, tetracyclines, and macrolides.

Organism/organism group (no. of isolates)	Cumulative % at lefamulin MIC (mg/L) of:										MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	> [a]	(mg/L)	
Streptococcus pneumoniae (6,018)	1.7	11.0	52.8	91.4	99.6	99.9	100.0					0.06	0.12
Penicillin-resistant (>4 mg/L; 29)	3.4	6.9	44.8	100.0								0.12	0.12
Staphylococcus aureus (4,463)		21.5	86.3	98.8	99.5	99.6	99.8				100.0	0.06	0.12
Methicillin-resistant (1,433)		22.8	75.4	97.1	99.1	99.2	99.5				100.0	0.06	0.12
Haemophilus influenzae (1,656)				2.1	19.2	65.0	90.8	99.3	99.9	100.0		0.5	1
Moraxella catarrhalis (897)	3.2	14.3	89.9	99.9	100.0							0.06	0.12
β-haemolytic streptococci (819)	26.4	94.1	98.3	99.4	99.4	99.4	99.4	99.4	99.4	99.6	100.0	0.03	0.03
Coagulase-neg. staphylococci (544)	9.2	55.0	89.0	91.7	92.5	95.0	96.5	97.4	98.3	99.1	100.0	0.03	0.12
Viridans group streptococci (327)	17.1	27.2	52.9	70.0	79.5	86.5	89.6	96.0	99.1	99.4	100.0	0.06	2
Haemophilus parainfluenzae (312)				8.7	17.3	32.7	55.1	84.6	97.8	100.0		1	4

[a] Greater than the highest concentration tested.