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In vitro activity of lefamulin against bacterial pathogens commonly causing community-acquired bacterial pneumonia (CAP): 2015 SENTRY data from Europe

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Background: Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. It is currently in Phase 3 trials for the treatment of CAP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) at two sites. It interacts via four H-bonds and other interactions resulting in an "induced fit" whereby nucleotides in the PTC shift and further tighten the binding pocket around lefamulin.

CAP is the number one reason for death by infectious diseases worldwide, and emerging resistance complicates its treatment. This study investigated the activity of lefamulin and comparators against a contemporary set of bacterial respiratory pathogens collected in Europe.

Material/methods: Unique patients' isolates (*n*=1040) were collected in Europe (19 countries, 36 sites) from patients with respiratory tract infection (87.5%), blood stream infections (8.4%), and other infections (4.1%). Lefamulin and comparators were tested by CLSI broth microdilution methods, and susceptibility was determined using the EUCAST (2016) breakpoints.

Results: Lefamulin displayed potent antibacterial activity against this collection of respiratory pathogens (all isolates inhibited at concentrations ≤2 mg/L). Lefamulin was the most active compound against *S. pneumoniae* ($MIC_{50/90}$ of 0.06/0.12 mg/L), and its activity was not affected by

resistance to other antibiotic classes. *S. pneumoniae* isolates were susceptible to levofloxacin (98.6%) and ceftriaxone (86.8%), whereas 27.6% and 24.6% of isolates were resistant to macrolides and tetracycline, respectively. Against the fastidious respiratory pathogens, lefamulin showed potent activity (*H. influenzae*, $MIC_{50/90}$ of 0.5/1 mg/L, including 12.9% of ß-lactamase producing strains, and *M. catarrhalis* (0.06/0.12 mg/L).

Conclusions: Lefamulin demonstrated potent *in vitro* activity against a contemporary collection of respiratory pathogens from Europe. Lefamulin was active regardless of resistance phenotype to the other antibiotic classes including macrolides, ß-lactams, tetracyclines, or fluoroquinolones. These data support the continued clinical development of lefamulin for the treatment of respiratory tract infections, including CAP.

Table: *In vitro* activity of lefamulin and comparators.

		$MIC_{50/90}$ [mg/L]					
Organism	**N**	**Lefamulin**	**Amoxi/Clav**	**Ceftriaxone**	**Azithromycin**	**Levofloxacin**	**Tetracycline**
S. pneumoniae	710	0.06 / 0.12	≤0.03 / 2	0.03 / 1	0.06 / >4	1 / 1	0.25 / >4
Penicillin non-susceptible	223	0.06 / 0.12	1 / >4	0.5 / 2	>4 / >4	1 / 1	>4 / >4
Macrolide resistant	196	0.06 / 0.12	0.25 / 4	0.5 / 2	>4 / >4	1 / 1	>4 / >4
H. influenzae	170	0.5 / 1	0.5 / 2	≤0.015 / ≤0.015	0.5 / 1	≤0.015 / ≤0.015	0.5 / 0.5
M. catarrhalis	160	0.06 / 0.12	0.12 / 0.25	0.25 / 0.5	0.015 / 0.03	0.03 / 0.06	0.12 / 0.25