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In Vitro Activity of Lefamulin Against Isolates Commonly Causing Community-Acquired Bacterial Pneumonia Collected During the SENTRY Surveillance Programme 2017 in Europe

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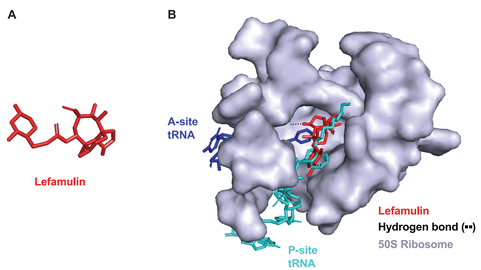
INTRODUCTION & PURPOSE

- Community-acquired pneumonia (CAP) is the most common infection-related cause of death in Europe, with an incidence of 1.7 to 11.6 cases per 1000 person-years[1]
  - Although pneumonia cases vary by country, *Streptococcus pneumoniae* is the most commonly isolated bacterial pathogen
  - Other common causes include *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*[2]
- Increasing rates of bacterial resistance and safety concerns around available antibiotics have created the need for new CAP treatment options[3,4]
- Lefamulin (LEF) is the first antimicrobial in the novel pleuromutilin class under development for intravenous (IV) and oral administration. LEF selectively inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit at the A- and P-sites in the peptidyl transferase centre[5] **(Figure 1)**
- In patients with CAP, LEF was noninferior to moxifloxacin in an IV-to-oral switch phase 3 study[6] and in an oral-only phase 3 study[7]
- The objective of this study was to analyse the *in vitro* activity of LEF and comparators against a contemporary set of typical Gram-positive and fastidious Gram-negative pathogens commonly associated with CAP collected in Europe in 2017

Figure 1. (A) Structure of Lefamulin and (B) Lefamulin in the Peptidyl Transferase Centre



METHODS

- 1766 isolates (1 per patient) were collected in Europe (18 countries, 38 sites) primarily from patients with community-acquired respiratory tract infections (62.5%), patients hospitalised with pneumonia (10.5%), as well as patients with other infections (bloodstream infections, 16.4%; skin/soft tissue infections, 10.0%; other infections, 0.6%) as part of the 2017 SENTRY Surveillance Programme
- LEF and comparators were tested by Clinical and Laboratory Standards Institute broth microdilution,[8] and susceptibility was determined using the European Committee on Antimicrobial Susceptibility Testing (2019) breakpoints[9]

RESULTS

- LEF demonstrated potent antibacterial activity against all tested CAP pathogens and this activity was unaffected by resistance to other antibiotic classes

S. pneumoniae

- *S. pneumoniae* isolates showed considerable resistance to macrolides (23.3%), penicillin (28.1%), trimethoprim-sulfamethoxazole (18.8%), and tetracycline (22.2%), whereas they were largely susceptible (>80%) to the tested cephalosporins and fluoroquinolones **(Table 1)**
- LEF inhibited *S. pneumoniae,* with all isolates inhibited at ≤0.5 mg/L and all resistant subsets showing minimum concentration at which 50% or 90% of the isolates were inhibited ($MIC_{50/90}$) of 0.06/0.12 mg/L for multidrug-resistant and penicillin-resistant isolates, 0.06/0.25 mg/L for macrolide-resistant isolates **(Table 2)**, and 0.06/0.12 mg/L for moxifloxacin-resistant isolates (*n*=18; data not shown in table)

S. aureus

- *S. aureus* isolates overall, and particularly methicillin-resistant *S. aureus* (MRSA) strains, were commonly resistant to macrolides (55.7% resistant to erythromycin) and fluoroquinolones (69.3% resistant to moxifloxacin; **Table 3**)
- LEF demonstrated potent activity against *S. aureus* and MRSA in particular ($MIC_{50/90}$ of 0.06/0.12 mg/L for both; **Table 3**) and also covered resistant subsets, with LEF $MIC_{50/90}$ of 0.06/0.12 mg/L recorded for macrolide-resistant *S. aureus* (43.8% MRSA) and fluoroquinolone-resistant *S. aureus* (*n*=81; 75.3% MRSA; data not shown in table)

H. influenzae

- *H. influenzae* isolates were largely susceptible to all comparators except for ampicillin (26.2% resistant) and trimethoprim-sulfamethoxazole (33.3% resistant; **Table 4**)
- β-lactamase–positive and trimethoprim-sulfamethoxazole–resistant *H. influenzae* displayed $MIC_{50/90}$ of 0.5/1 mg/L and 0.5/2 mg/L for LEF, respectively

M. catarrhalis

- A large proportion of *M. catarrhalis* isolates (95.3%) were β-lactamase producers and were largely susceptible to all comparators, including amoxicillin-clavulanic acid **(Table 4)**
- LEF inhibited all isolates at LEF concentrations of ≤0.12 mg/L ($MIC_{50/90}$ of 0.06/0.06 mg/L), including the few tetracycline- (*n*=1) and trimethoprim-sulfamethoxazole–resistant (*n*=2) isolates (MIC of 0.06 mg/L for both antimicrobials)

Table 1. Activity of Lefamulin and Comparators Against *S. pneumoniae*

Antimicrobial Agent	mg/L			EUCAST*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***S. pneumoniae* (*n*=950)**						
Lefamulin†	**0.06**	**0.25**	**≤0.008–0.5**	**[100.0]**		
Amoxicillin-clavulanic acid	≤0.03	2	≤0.03–>4	83.8‡	3.5	12.7
Azithromycin	0.06	>4	≤0.03–>4	76.1	0.1	23.8
Ceftaroline	≤0.008	0.12	≤0.008–>1	99.8	–	0.2
Ceftriaxone	0.03	1	≤0.015–>2	86.5	12.8	0.7
Clindamycin	≤0.25	>2	≤0.25–>2	82.4	–	17.6
Erythromycin	0.03	>16	≤0.015–>16	76.3	0.4	23.3
Levofloxacin	1	2	0.5–>4	97.5	–	2.5
Moxifloxacin	0.12	0.25	≤0.03–>4	98.1	–	1.9
Penicillin	0.015	2	≤0.008–>4	71.9§ 71.9¶	– 22.6	28.1 5.5
Tetracycline	0.5	>4	0.12–>4	77.4	0.4	22.2
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12–>4	78.7	2.5	18.8

EUCAST=European Committee on Antimicrobial Susceptibility Testing; I=intermediate; MIC_{50}=minimum concentrations at which 50% of the isolates were inhibited; MIC_{90}=minimum concentrations at which 90% of the isolates were inhibited; R=resistant; S=susceptible.
*2019 EUCAST criteria.
†Percentages inhibited at proposed lefamulin breakpoint of ≤1 mg/L for *S. pneumoniae* are shown in brackets for comparison purpose only.
‡Using oral breakpoints.
§Using meningitis breakpoints.
¶Using nonmeningitis breakpoints.

Table 2. Activity of Lefamulin and Comparators Against Drug-Resistant *S. pneumoniae*

Antimicrobial Agent	mg/L			EUCAST*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
Penicillin-resistant† *S. pneumoniae* (*n*=52)						
Lefamulin‡	**0.06**	**0.12**	**0.03–0.5**	**[100.0]**		
Amoxicillin-clavulanic acid	>4	>4	2–>4	0.0§	0.0	100.0
Azithromycin	>4	>4	0.06–>4	30.8	0.0	69.2
Ceftaroline	0.12	0.25	0.06–>1	96.2	–	3.8
Ceftriaxone	2	2	1–>2	0.0	90.4	9.6
Clindamycin	>2	>2	≤0.25–>2	42.3	–	57.7
Erythromycin	>16	>16	0.03–>16	30.8	1.9	67.3
Levofloxacin	1	2	1–>4	96.2	–	3.8
Moxifloxacin	0.12	0.5	0.06–>4	96.2	–	3.8
Penicillin	4	4	4–>4	0.0§ 0.0¶	– 0.0	100.0 100.0
Tetracycline	>4	>4	0.25–>4	40.4	0.0	59.6
Trimethoprim-sulfamethoxazole	>4	>4	0.25–>4	5.8	3.8	90.4
Macrolide-resistant† *S. pneumoniae* (*n*=221)						
Lefamulin‡	**0.06**	**0.25**	**0.015–0.5**	**[100.0]**		
Amoxicillin-clavulanic acid	0.5	>4	≤0.03–>4	53.4‖	10.0	36.7
Azithromycin	>4	>4	≤0.03–>4	0.9	0.0	99.1
Ceftaroline	0.06	0.12	≤0.008–>1	99.1	–	0.9
Ceftriaxone	0.5	2	≤0.015–>2	60.6	36.7	2.7
Clindamycin	>2	>2	≤0.25–>2	24.4	–	75.6
Erythromycin	>16	>16	1–>16	0.0	0.0	100.0
Levofloxacin	1	2	0.5–>4	97.3	–	2.7
Moxifloxacin	0.12	0.25	0.06–>4	97.7	–	2.3
Penicillin	0.5	4	≤0.008–>4	29.0§ 29.0¶	– 55.2	71.0 15.8
Tetracycline	>4	>4	0.25–>4	19.9	0.5	79.6
Trimethoprim-sulfamethoxazole	0.5	>4	≤0.12–>4	56.8	5.5	37.7
Multidrug-resistant# *S. pneumoniae* (*n*=63)						
Lefamulin‡	**0.06**	**0.12**	**0.015–0.5**	**[100.0]**		
Amoxicillin-clavulanic acid	2	>4	≤0.03–>4	30.2§	9.5	60.3
Azithromycin	>4	>4	2–>4	0.0	0.0	100.0
Ceftaroline	0.12	0.25	≤0.008–0.5	98.4	–	1.6
Ceftriaxone	1	2	≤0.015–>2	36.5	57.1	6.3
Clindamycin	>2	>2	≤0.25–>2	19.0	–	81.0
Erythromycin	>16	>16	1–>16	0.0	0.0	100.0
Levofloxacin	1	2	0.5–>4	95.2	–	4.8
Moxifloxacin	0.12	0.5	0.06–4	95.2	–	4.8
Penicillin	2	4	0.015–>4	19.0§ 19.0¶	– 39.7	81.0 41.3
Tetracycline	>4	>4	4–>4	0.0	0.0	100.0
Trimethoprim-sulfamethoxazole	>4	>4	4–>4	0.0	0.0	100.0

EUCAST=European Committee on Antimicrobial Susceptibility Testing; I=intermediate; MIC=minimum inhibitory concentration; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited; R=resistant; S=susceptible.
*2019 EUCAST criteria.
†Penicillin MIC ≥2 mg/L for nonmeningitis breakpoint.
‡Percentages inhibited at proposed lefamulin breakpoint of ≤1 mg/L for *S. pneumoniae* are shown in brackets for comparison purpose only.
§Using oral breakpoint.
¶Using meningitis breakpoint.
‖Using nonmeningitis breakpoint.
#Using erythromycin breakpoint.
**Resistant to tetracycline, erythromycin, and trimethoprim-sulfamethoxazole.

Table 3. Activity of Lefamulin and Comparators Against *S. aureus*

Antimicrobial Agent	mg/L			EUCAST*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***S. aureus* (*n*=506)**						
Lefamulin†	**0.06**	**0.12**	**0.015–>16**	**[99.4]**		
Azithromycin	0.5	>32	0.12–>32	75.9	0.6	23.5
Ceftaroline	0.25	0.5	≤0.06–2	97.2‡	2.8	0.0
Clindamycin	0.06	0.06	≤0.03–>2	96.0	0.2	3.8
Doxycycline	0.12	0.25	≤0.06–>8	94.7	3.4	2.0
Erythromycin	0.12	>8	≤0.06–>8	77.1	0.8	22.1
Gentamicin	≤1	≤1	≤1–>8	95.1	–	4.9
Levofloxacin	0.25	>4	0.06–>4	83.8	–	16.2
Linezolid	1	2	0.5–4	100.0	–	0.0
Moxifloxacin	≤0.06	2	≤0.06–>4	84.0	–	16.0
Oxacillin	0.5	>2	0.25–>2	82.6	–	17.4
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>16	99.4	0.0	0.6
Vancomycin	1	1	0.25–2	100.0	–	0.0
MRSA (*n*=88)						
Lefamulin†	**0.06**	**0.12**	**0.03–>16**	**[96.6]**		
Azithromycin	32	>32	0.12–>32	43.2	0.0	56.8
Ceftaroline	1	2	0.25–2	84.1‡	15.9	0.0
Clindamycin	0.06	>2	≤0.03–>2	79.5	0.0	20.5
Doxycycline	0.12	2	≤0.06–>8	89.8	6.8	3.4
Erythromycin	8	>8	≤0.06–>8	43.2	1.1	55.7
Gentamicin	≤1	>8	≤1–>8	85.2	–	14.8
Levofloxacin	>4	>4	0.12–>4	30.7	–	69.3
Linezolid	1	2	0.5–2	100.0	–	0.0
Moxifloxacin	2	>4	≤0.06–>4	30.7	–	69.3
Oxacillin	>2	>2	>2–>2	0.0	–	100.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–16	98.9	0.0	1.1
Vancomycin	1	1	0.5–2	100.0	–	0.0

EUCAST=European Committee on Antimicrobial Susceptibility Testing; I=intermediate; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited; MRSA=methicillin-resistant *S. aureus*; R=resistant; S=susceptible.
*2019 EUCAST criteria.
†Percentages inhibited at proposed lefamulin breakpoints of ≤0.5 mg/L for *S. aureus* are shown in brackets for comparison purpose only.
‡Using other than pneumonia breakpoints.

Table 4. Activity of Lefamulin and Comparators Against *H. influenzae* and *M. catarrhalis*

Antimicrobial Agent	mg/L			EUCAST*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***H. influenzae* (*n*=225)**						
Lefamulin†	**0.5**	**2**	**0.015–2**	**[100.0]**		
Amoxicillin-clavulanic acid	0.5	2	0.12–8	93.3‡	–	6.7
Ampicillin	0.5	>8	≤0.12–>8	73.8	–	26.2
Azithromycin	1	1	≤0.12–4	100.0§	–	–
Cefepime	0.12	0.12	0.03–1	98.2	–	1.8
Ceftriaxone	0.004	0.015	≤0.002–0.12	100.0	–	0.0
Ciprofloxacin	0.015	0.015	0.008–>1	99.1	–	0.9
Clarithromycin	8	16	0.25–>16	100.0¶	–	–
Moxifloxacin	0.03	0.03	≤0.008–>2	99.1	–	0.9
Tetracycline	0.5	1	0.25–>8	98.7	0.4	0.9
Trimethoprim-sulfamethoxazole	≤0.06	>4	≤0.06–>4	65.8	0.9	33.3
***M. catarrhalis* (*n*=85)**						
Lefamulin†	**0.06**	**0.06**	**≤0.008–0.12**	**[100.0]**		
Amoxicillin-clavulanic acid	≤0.25	≤0.25	≤0.25–0.5	100.0	–	0.0
Azithromycin	0.015	0.03	≤0.004–0.06	100.0	0.0	0.0
Ceftriaxone	0.25	1	0.004–1	100.0	0.0	0.0
Clarithromycin	≤0.12	≤0.12	≤0.12–0.25	100.0	0.0	0.0
Moxifloxacin	0.06	0.06	0.015–0.06	100.0	–	0.0
Tetracycline	0.25	0.5	≤0.06–>8	98.8	0.0	1.2
Trimethoprim-sulfamethoxazole	0.25	0.25	≤0.06–2	96.5	1.2	2.4

EUCAST=European Committee on Antimicrobial Susceptibility Testing; I=intermediate; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited; R=resistant; S=susceptible.
*2019 EUCAST criteria.
†Percentages inhibited at proposed lefamulin breakpoints of ≤4 mg/L for *H. influenzae* and ≤0.5 mg/L for *M. catarrhalis* are shown in brackets for comparison purpose only.
‡Percentages are the same when applying oral and intravenous breakpoints, respectively.
§Percentage of wild type based on epidemiologic cutoff value. EUCAST version 8.0 2018.

CONCLUSIONS

- LEF demonstrated potent *in vitro* activity against the typical pathogens that commonly cause CAP collected in Europe in 2017, and our data are consistent with surveillance results from previous years
- The activity of LEF was unaffected by resistance to other antibiotic classes, including macrolides, β-lactams, fluoroquinolones, folate-pathway inhibitors, and tetracyclines
- These data—together with the previously reported activity against atypical CAP pathogens like *M. pneumoniae, C. pneumoniae,* and *L. pneumoniae*—support the ongoing clinical development of LEF as empiric IV and oral monotherapy for the treatment of CAP and other respiratory tract infections

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