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Lefamulin Activity against Bacterial Pathogens Typically Causing Community-Acquired Pneumonia Collected from European Medical Centres in 2023 and 2024

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Background

- Lefamulin is a novel pleuromutilin protein synthesis inhibitor with a unique mode-of-action, low potential for resistance development and has demonstrated potent clinical efficacy with a good safety and tolerability profile in the treatment of patients with moderate to severe pneumonia.
- Lefamulin was approved for the treatment of adults with community-acquired bacterial pneumonia (CABP) by the European Medicines Agency in 2020 and by the United States Food and Drug Administration (US-FDA) in 2019.
- We evaluated the *in vitro* activity of lefamulin and comparator agents against contemporary bacterial isolates from species responsible for CABP collected in Europe and the Mediterranean region in 2023 and 2024.

Methods

- A total of 2,965 organisms were collected through the SENTRY surveillance program from 39 medical centres in 19 countries:

Belgium	Hungary	Portugal	Sweden
Czechia	Ireland	Romania	Switzerland
France	Israel	Slovakia	Turkey
Germany	Italy	Slovenia	United Kingdom
Greece	Poland	Spain	

- Isolates were from infections of the respiratory tract (70.1%), bloodstream (18.5%), and other sites (11.4%).
- Organisms were susceptibility tested by broth microdilution according to CLSI standards and EUCAST breakpoints were applied when available.
- Multidrug-resistant (MDR) *S. pneumoniae* was defined as nonsusceptibility to 3 or more of the following agents: parenteral penicillin (MIC, ≥4 mg/L), ceftriaxone (MIC, ≥2 mg/L), erythromycin (MIC, ≥0.5 mg/L), clindamycin (MIC, ≥0.5 mg/L), levofloxacin (MIC, ≥4 mg/L), tetracycline (MIC, ≥2 mg/L), and trimethoprim-sulfamethoxazole (MIC, ≥1/19 mg/L).

Results

- All *S. pneumoniae* (n=1,300) were susceptible to lefamulin at ≤0.5 mg/L (EUCAST susceptible breakpoint) and lefamulin activity was not adversely affected by resistance to other antimicrobials (Table 1 and Figure 1).
- *S. pneumoniae* susceptibility rates for other antibacterials that are commonly used to treat CABP were lower: azithromycin (80.4% susceptible), doxycycline (84.1%), and amoxicillin/clavulanic acid (86.7%; Table 1).
- Ceftriaxone was active against 90.6% of *S. pneumoniae* ($MIC_{50/90}$, 0.25/1 mg/L) and showed reduced activity against isolates resistant to azithromycin (68.1% susceptible) or doxycycline (71.0%), and against MDR isolates (62.8%; Table 1).
- Lefamulin was also highly active against *S. aureus* ($MIC_{50/90}$ of 0.06/0.12 mg/L; 99.7% susceptible) and retained potent activity against methicillin-resistant isolates (MRSA; $MIC_{50/90}$ of 0.06/0.12 mg/L; 98.1% susceptible; Table 1 and Figure 2).
- Azithromycin (29.5% susceptible) and levofloxacin (42.9%) showed limited activity against MRSA (Table 1).
- Lefamulin was active against *H. influenzae* (99.5% susceptible per US-FDA and CLSI susceptible breakpoint of ≤2 mg/L), including β-lactamase-positive strains (100.0% susceptible; Table 1 and Figure 3).
- Lefamulin was also active against *S. agalactiae* (n=101; $MIC_{50/90}$, 0.03/0.03 mg/L; highest MIC, 0.06 mg/L), *S. pyogenes* (n=102; $MIC_{50/90}$, 0.03/0.03 mg/L; highest MIC, 0.06 mg/L), and viridans group streptococci (*S. anginosus, S. mitis,* and *S. salivarius* groups; n=79; $MIC_{50/90}$, 0.12/0.5 mg/L; 97.5% inhibited at ≤0.5 mg/L).

Conclusions

- Lefamulin displayed potent *in vitro* activity against contemporary CABP pathogens from Europe and its activity was not adversely affected by resistance to other antibiotic classes, including fluoroquinolones, macrolides, β-lactams, and tetracyclines.
- Lefamulin represents a valuable empiric treatment option in its ability to overcome resistance to common respiratory pathogens associated with ambulatory, and hospitalized patients with CABP.

References

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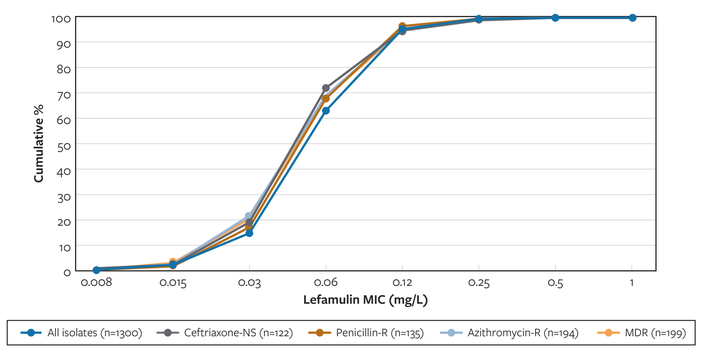
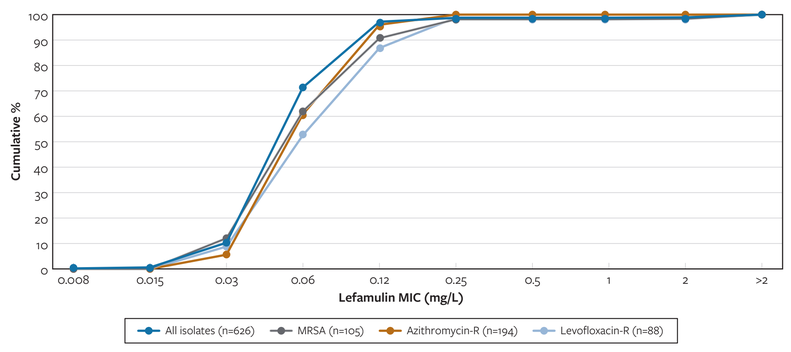
Figure 1. Lefamulin cumulative MIC distribution for *S. pneumoniae* and selected resistant subsets



Abbreviations: NS, nonsusceptible; R, resistant; MDR, multidrug-resistant.

Figure 2. Lefamulin cumulative MIC distribution for *S. aureus* and selected resistant subsets



Abbreviations: MRSA, methicillin-resistant *S. aureus*; R, resistant.

Figure 3. Lefamulin cumulative MIC distribution for β-haemolytic streptococci (BHS), viridans group streptococci (VGS), *H. influenzae*, and *M. catarrhalis*

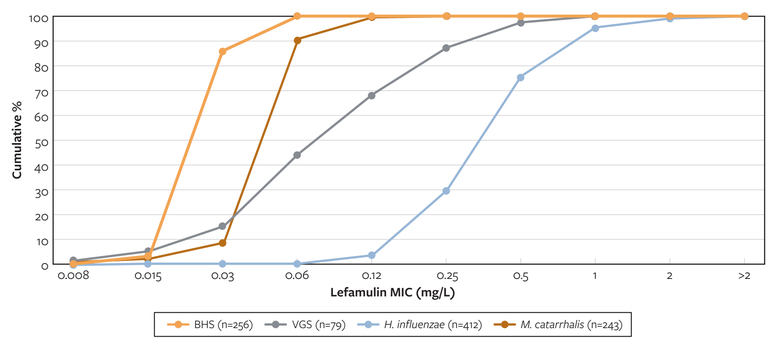


Table 1. Antimicrobial susceptibility of bacterial pathogens typically causing pneumonia collected from European medical centers (2023 and 2024)

Organism	$MIC_{50/90}$ [mg/L] (% Susceptible per EUCAST)					
	Lefamulin	**Ceftriaxone**	**Amox-Clav**	**Azithromycin**	**Levofloxacin**	**Doxy/Tetra[a]**
S. pneumoniae (1,300)	**0.06/0.12 (100.0)**	0.015/0.5 (90.6)	≤0.03/2 (86.7)	0.06/>4 (80.4)	1/1 (99.4)	0.12/>1 (84.1)
Penicillin-R (135)	**0.06/0.12 (100.0)**	1/2 (12.7)	2/>4 (0.7)	>4/>4 (34.1)	1/1 (95.6)	1/>1 (50.4)
Ceftriaxone-NS (122)	**0.06/0.12 (100.0)**	1/2 (0.0)	2/>4 (0.0)	>4/>4 (33.6)	1/1 (95.6)	0.5/>1 (50.8)
Azithromycin-R (254)	**0.06/0.12 (100.0)**	0.25/1 (68.1)	0.25/>4 (53.9)	>4/>4 (0.0)	1/1 (96.9)	>1/>1 (29.5)
Doxycycline-R (207)	**0.06/0.12 (100.0)**	0.25/1 (71.0)	0.25/>4 (57.5)	>4/>4 (13.5)	1/1 (97.6)	>1/>1 (0.0)
MDR (199)	**0.06/0.12 (100.0)**	0.25/1 (62.8)	1/>4 (49.7)	>4/>4 (1.0)	1/1 (96.0)	>1/>1 (16.1)
S. aureus (626)	**0.06/0.12 (99.7)**	(83.2)[b]	Not tested	1/>16 (69.0)	0.25/>4 (85.9)	≤0.06/0.12 (97.8)
MRSA (105)	**0.06/0.12 (98.1)**	(0.0)[b]	Not tested	16/>16 (29.5)	4/>4 (42.9)	≤0.12/1 (94.3)
Azithromycin-R (194)	**0.06/0.12 (100.0)**	(61.9)[b]	Not tested	>16/>16 (0.0)	0.25/>4 (75.3)	≤0.06/1 (97.4)
Levofloxacin-R (88)	**0.06/0.25 (98.9)**	(31.8)[b]	Not tested	16/>16 (45.5)	>4/>4 (0.0)	≤0.06/0.12 (96.6)
β-haemolytic strep. (256)	**0.03/0.06 ([c])**	0.03/0.06 (100.0)	Not tested	0.03/>16 (75.0)[f]	0.5/1 (98.4)	0.25/>1 (57.4)
Viridans gr. strep. (79)[d]	**0.12/0.5 (97.5)[e]**	0.25/0.5 (96.2)	Not tested	≤0.015/8 (65.8)[f]	0.5/1 (100.0)[g]	0.12/>1 (100.0)[g]
H. influenzae (412)	**0.5/1 (99.5)[g]**	0.004/0.015 (100.0)	0.5/2 (96.1)[g]	0.5/2 (98.8)[b]	0.015/0.03 (97.8)	0.5/0.5 (99.3)
β-lactamase-pos. (76)	**0.5/1 (100.0)[g]**	0.004/0.015 (100.0)	0.5/2 (96.1)[g]	0.5/1 (98.7)[b]	0.03/0.03 (98.7)	0.5/0.5 (100.0)
M. catarrhalis (243)	**0.06/0.06 ([h])**	0.25/0.5 (99.6)	0.12/0.25 (100.0)[b]	0.03/0.03 (99.6)	0.03/0.06 (99.2)	0.25/0.25 (100.0)

[a] Doxycycline for *S. pneumoniae*, *S. aureus*, β-haemolytic streptococci, and viridans group streptococci and tetracycline for *H. influenzae* and *M. catarrhalis*.
[b] Based on oxacillin susceptibility.
[c] Highest MIC of 0.06 mg/L.
[d] Includes *Streptococcus anginosus, S. mitis,* and *S. salivarius* groups.
[e] % inhibited at ≤0.5 mg/L.
[f] Based on results for erythromycin.
[g] CLSI and/or US-FDA breakpoints were applied.
[h] Highest MIC of 0.25 mg/L.
Abbreviations: Amox-Clav, amoxicillin-clavulanate; R, resistant; NS, nonsusceptible; MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*.