1266842

In Vitro Activity of Lefamulin Against Bacterial Pathogens Collected From Pneumonia Patients in United States and Latin America Medical Centers in 2020-2021

Nabriva Therapeutics
Dublin, Ireland
www.nabriva.com

Susanne Paukner, PhD[1]; S.J. Ryan Arends, PhD[2]; Rodrigo E. Mendes, PhD[2]; Steven P. Gelone, PharmD[3]; Helio S. Sader, MD, PhD[2]

[1] Nabriva Therapeutics, GmbH, Vienna, Austria; [2] JMI Laboratories, North Liberty, Iowa, USA; [3] Nabriva Therapeutics US Inc., Fort Washington, PA, USA

ABSTRACT

Background: Lefamulin (Xenleta®) is a novel pleuromutilin protein synthesis inhibitor approved in the US, Canada, and Europe for the oral and intravenous treatment of community-acquired bacterial pneumonia (CABP) in adults due to typical and atypical pathogens.
This study evaluated the *in vitro* activity of lefamulin and comparators against bacterial isolates from patients with community-acquired respiratory tract infections and hospitalized patients with pneumonia in the US and Latin America in 2020-2021.

Methods: 1,907 unique isolates were collected within the SENTRY surveillance program from 29 medical centers in the US and 8 medical centers in Latin America (Argentina, Brazil, Chile, Colombia, Mexico, Panama). Isolates were susceptibility tested by CLSI reference broth microdilution methods. CLSI breakpoints (M100, 2022) were applied.

Results: Lefamulin inhibited 100% of *S. pneumoniae* isolates at or below its susceptible (S) breakpoint of ≤0.5 mg/L, regardless of resistance to other antibiotics used to treat CABP (MIC_{90} values of 0.12 or 0.25 mg/L, Table 1). The penicillin-resistant (R; 12.7%), azithromycin-R (43.7%), and tetracycline-R *S. pneumoniae* (20.4%) displayed reduced susceptibility to the other CABP drugs tested, except moxifloxacin (>98.2% S) and lefamulin (100% S). Lefamulin was highly potent against *S. aureus*, including MRSA, azithromycin-R, and moxifloxacin-R isolates, with 100% of isolates inhibited at or below the lefamulin S breakpoint of ≤0.25 mg/L. Susceptibility to azithromycin and moxifloxacin was particularly low for MRSA (13.9% and 25.0%, respectively). The fastidious Gram-negative *H. influenzae* and *M. catarrhalis*, of which 24.0% and 98.8%, respectively, were S to lefamulin (>93%) and the other tested CABP drugs (>89%).

Conclusions: Lefamulin displayed potent *in vitro* activity against contemporary CABP pathogens from the US and Latin America. Its activity was unaffected by resistance to other antibiotic classes, including fluoroquinolones, macrolides, β-lactams, and tetracyclines. Lefamulin represents a valuable empiric treatment option for ambulatory and hospitalized patients with CABP, particularly when the causative pathogen is not identified or in settings with high prevalence of resistance.

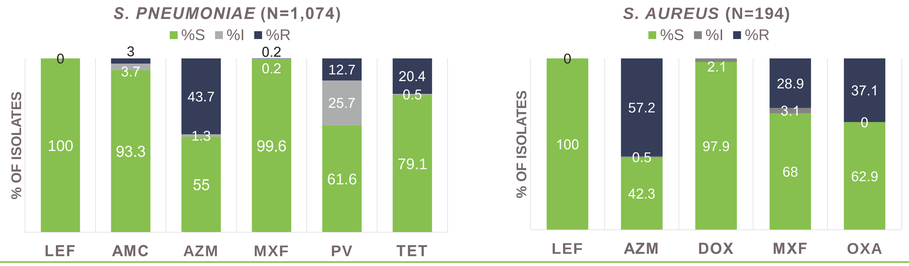
INTRODUCTION

- Community-acquired bacterial pneumonia (CABP) 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]
- *Streptococcus pneumoniae* is the most frequently isolated bacterial pathogen from patients with CABP, with prevalence that varies by geographic region. Other bacterial causes of CABP include *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, as well as atypical pathogens[1,2]
- Increasing resistance rates and safety concerns around available antibiotics have created the need for new CABP treatment options[2,3]
- 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 in global phase 3 clinical trials in CABP patients with moderate to severe pneumonia with a good safety and tolerability profile.[4-7]

RESULTS

- Macrolide resistance rates in *S. pneumoniae* and *S. aureus* isolates and fluoroquinolone resistance in *S. aureus* collected from CABP patients were high in both regions, US and LA (Figure 1, Table 1)
- Though the number of Penicillin-R and Tetracycline-R *S. pneumoniae* were not very high, these isolates were almost completely non-susceptible to macrolides (Table 1)
- 37% of *S. aureus* were MRSA, which displayed low susceptibility to azithromycin (13.9%) and moxifloxacin (25.0%)
- High cross resistance was also observed for azithromycin and moxifloxacin in *S. aureus* (Table 1)
- Lefamulin displayed potent *in vitro* activity against all tested CABP pathogens (Table 1, Figure 2)

Figure 1. Susceptibility of *S. pneumoniae* and *S. aureus* when applying CLSI breakpoints [9]



AMC, Amoxicillin-clavulanic acid; AZM, Azithromycin; DOX, Doxycycline; LEF, Lefamulin; MXF, Moxifloxacin; OXA, Oxacillin; PV, oral Penicillin V; TET, Tetracycline;

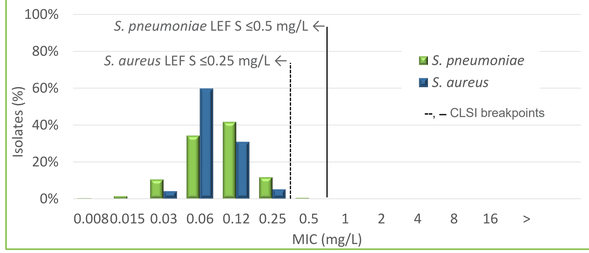
Table 1. Susceptibility of pneumonia pathogens from US and Latin America to lefamulin and other CABP drugs

Organism By Region		$MIC_{50/90}$ (mg/L) (% Susceptible per CLSI)				
By Resistance (R)	**N [a]**	**Lefamulin**	**Amoxi-Clav**	**Azithromycin**	**Moxifloxacin**	**Doxy/Tetra [c]**
S. pneumoniae	1,074	0.12/0.25 (100)	≤0.03/2 (93.3)	0.12/>4 (55.0)	0.12/0.12 (99.6)	0.25/>4 (79.1)
US	991	0.12/0.25 (100)	≤0.03/2 (94.4)	0.12/>4 (55.9)	0.12/0.12 (99.8)	0.25/>4 (80.1)
Latin America	83	0.06/0.25 (100)	0.5/4 (79.3)	2/>4 (44.6)	0.12/0.25 (97.6)	0.25/>4 (67.5)
Penicillin-R [b]	136	0.12/0.25 (100)	4/>4 (47.1)	>4/>4 (5.1)	0.12/0.12 (98.5)	>4/>4 (47.1)
Azithromycin-R	469	0.12/0.25 (100)	0.5/4 (85.2)	>4/>4 (0.0)	0.12/0.12 (99.1)	0.5/>4 (55.8)
Tetracycline-R	219	0.06/0.12 (100)	0.5/>4 (73.4)	>4/>4 (6.4)	0.12/0.12 (98.2)	>4/>4 (0.0)
S. aureus	194	0.06/0.12 (100)	ND	>8/>8 (42.3)	≤0.06/>4 (68.0)	≤0.06/0.5 (97.9)
US	150	0.06/0.12 (100)	ND	>8/>8 (44.0)	≤0.06/>4 (68.0)	≤0.06/0.5 (97.3)
Latin America	44	0.06/0.12 (100)	ND	>8/>8 (36.4)	≤0.06/4 (68.2)	≤0.06/1 (100)
MRSA	72	0.06/0.25 (100)	ND	>8/>8 (13.9)	2/>4 (25.0)	≤0.06/1 (97.2)
Azithromycin-R	111	0.06/0.12 (100)	ND	>8/>8 (0.0)	0.25/>4 (51.4)	≤0.06/1 (96.4)
Moxifloxacin-R	56	0.12/0.25 (100)	ND	>8/>8 (10.7)	4/>4 (0.0)	≤0.06/1 (96.4)
H. influenzae	384	1/2 (97.7)	0.5/2 (92.2)	1/2 (96.4)	0.03/0.06 (99.5)	0.5/0.5 (99.0)
US	322	1/2 (98.4)	0.5/2 (91.3)	1/2 (96.9)	0.03/0.06 (99.7)	0.5/0.5 (98.8)
Latin America	62	0.5/2 (93.5)	0.5/2 (96.8)	1/2 (93.5)	0.03/0.03 (98.4)	0.5/0.5 (100)
ß-lactamase positive	92	1/2 (94.6)	1/4 (89.1)	1/4 (92.4)	0.03/0.06 (98.9)	0.5/0.5 (96.7)
M. catarrhalis	255	0.12/0.12 (100)[d]	0.25/0.25 (100)	0.03/0.03 (100)	0.06/0.06 (-)	0.25/0.5 (98.8)
US	236	0.12/0.12 (100)[d]	0.25/0.25 (100)	0.03/0.03 (100)	0.06/0.06 (-)	0.25/0.5 (98.7)
Latin America	19	0.12/0.12 (100)[d]	0.25/0.25 (100)	0.03/0.03 (100)	0.06/0.06 (-)	0.25/0.5 (100)

ND, not determined.
a. Number of isolates tested (N) for lefamulin; N may vary slightly (<1%) for the other antibiotics tested.
b. Using oral breakpoints for penicillin.
c. Tetracycline tested *against S. pneumoniae, H. influenzae*, and *M. catarrhalis*; doxycycline tested against *S. aureus.*
d. Lefamulin susceptible breakpoint of ≤0.5 µg/mL applied (CLSI, winter meeting minutes 2021).

- Lefamulin susceptibility rates were 100% for *S. pneumoniae*, *S. aureus* and *M. catarrhalis* (CLSI S breakpoints of ≤0.5, ≤0.25 and ≤0.5 mg/L) and 97.7% for *H. influenzae* (CLSI S breakpoint of ≤2 mg/L)
- Lefamulin remained fully active against macrolide-, fluoroquinolone-, tetracycline, penicillin- or oxacillin-resistant subsets (Table 1, Figure 1)

Figure 2. Lefamulin MIC distributions



CONCLUSIONS

- **Potent *in vitro* activity was demonstrated by Lefamulin against this contemporary CABP pathogens from the US and Latin America**
- **Lefamulin's activity was unaffected by resistance to other antibiotic classes, including fluoroquinolones, macrolides, β-lactams, and tetracyclines.**
- **Lefamulin represents a valuable empiric treatment option for ambulatory and hospitalized patients with CABP, particularly when the causative pathogen is not identified or in settings with high prevalence of resistance.**

REFERENCES

(1) Gibson GJ et al. (2013) Eur Respir J 42:559-63. (2) Welte T et al (2012) *Thorax* 67:71-79. (3) Peyrani P et al. (2019) *Expert Rev Respir Med* 13:139-152. (4) Xenleta (2019). *Full Prescribing Information.* Nabriva Therapeutics US, Inc., www.xenleta.com. accessed 24 March 2022. (5) File T et al (2021) *BMC Pulm Med.* 21(1):154. (6) Paukner S et al (2021) *Antibiotics* 10(12):1489. (7) Paukner S et al. (2022) *J Glob Antimicrob Resist.* 29:434-443. (8) CLSI *M07Ed.11* (2018). (9) CLSI *M100Ed31* (2021)

Acknowledgments
This study was supported by Nabriva Therapeutics. JMI Laboratories received compensation fees for services related to preparing this poster.

Disclosures
Paukner S. and Gelone S. are employees and stockholders of Nabriva Therapeutics plc.

Scan this QR code with your electronic device to receive a PDF file of the poster or visit www.nabriva.com/news

IDWeek 2022, Washington, D.C., October 19–23, 2022