Abstract 01381

In Vitro Activity of Lefamulin against *Staphylococcus aureus and Haemophilus influenzae*, Common Pathogens in Cystic Fibrosis (CF), Collected from non-CF Paediatric Patients (SENTRY Surveillance 2015-2019)

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INTRODUCTION & OBJECTIVE

- Lefamulin (Xenleta™) is a novel pleuromutilin antibiotic approved for oral and IV treatment of community-acquired pneumonia (CAP) in adults
  - Approved in Europe, United States, Canada
- Paediatric formulations are in development for treatment of CAP and other bacterial respiratory tract infections including cystic fibrosis (CF)
- There is a particular need for new oral antibiotic treatment options in CF patients with *S. aureus* (MRSA) and *H. influenzae*
  - Treatment options are limited due to resistance, adverse events, contraindicated drug class or concerns of renal toxicity
- This study investigated the *in vitro* activity of lefamulin and comparators against susceptible and resistant *S. aureus* and *H. influenzae* collected from patients aged from 0 to 17 years

MATERIAL & METHODS

- 2,004 organisms (1/patient) were collected worldwide by 120 medical centers in 33 countries in 2015-2019 as part of the SENTRY Surveillance Programme
- from patients aged 0-17 with
  - lower respiratory tract infections (63.4%),
  - skin and soft tissue infections (20.6%),
  - blood stream infections (14.5%), and others
- Resistant subsets were defined using CLSI (2021) breakpoints
- Lefamulin and comparators were tested by CLSI broth microdilution and EUCAST and FDA breakpoints, respectively (2021) were applied (Table 1)

Table 1. Lefamulin Breakpoints Assigned by EUCAST and FDA

Organism	Susceptible Breakpoint EUCAST (2021)	Susceptible Breakpoint FDA (2019)
S. aureus	≤ 0.25 mg/L	≤ 0.25 mg/L (MSSA)
H. influenzae	-	≤ 2 mg/L

RESULTS

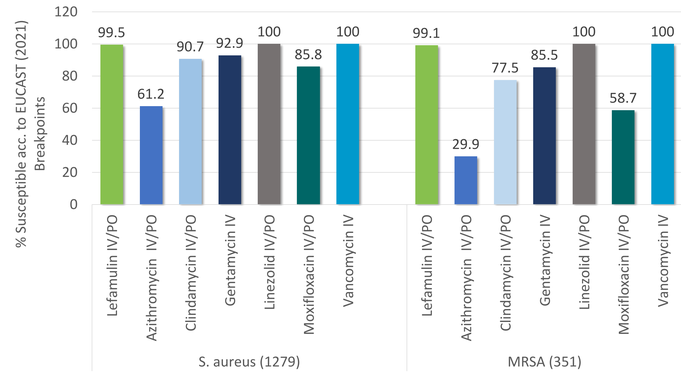
- Lefamulin demonstrated **potent antibacterial *in vitro* activity against *S. aureus* including MRSA** ($MIC_{50/90}$ of 0.06/0.12 mg/L, Table 2 and Figure 1)
  - Susceptibility to lefamulin was high among *S. aureus* (99.5%), whereas only 61.2% and 85.8% were susceptible to azithromycin and moxifloxacin, respectively
  - Susceptibility to azithromycin was low for isolates collected in US (52.6%), while it was 70.7% in Europe (data not shown in Table)
  - Susceptibility was particularly low for MRSA isolates (e.g. 29.9% to azithromycin 58.7% to moxifloxacin)
- The lefamulin activity was **not adversely affected by resistance** to one or a combination of the following antibiotic classes: ß-lactams, macrolides, lincosamides, fluoroquinolones or aminoglycosides
- Lefamulin was **active against *H. influenzae*** ($MIC_{50/90}$ of 0.5/2 mg/L) including isolates which were **ß-lactamase positive or resistant to trimethoprim-sulfamethoxazole**

Table 2. Antimicrobial activity of lefamulin and comparators against *S. aureus* and *H. influenzae* collected from paediatric patients (2015-2019)

Organism (No. of Isolates) Resistant (R) Subset [a]	$MIC_{50/90}$ in mg/L (% Susceptible per EUCAST criteria)				
	Lefamulin IV/PO	Azithromycin IV/PO	Moxifloxacin [b] IV/PO	Vancomycin IV	Linezolid IV/PO or Amoxi-Clav IV [c]
***S. aureus* (1,279 [b])**	**0.06/0.12 (99.5)**	**0.5/>4 (61.2)**	**≤0.06/1 (85.8)**	**0.5/1 (100)**	**1/2 (100)**
MRSA (351)	0.06/0.12 (99.1)	>4/>4 (29.9)	≤0.06/2 (58.7)	1/1 (100)	1/2 (100)
Erythromycin-R (419)	0.06/0.12 (99.0)	>4/>4 (0.0)	≤0.06/2 (63.6)	1/1 (100)	1/2 (100)
Clindamycin-R (113)	0.06/0.12 (97.3)	>4/>4 (0.9)	1/>4 (37.0)	1/1 (100)	1/1 (100)
Moxifloxacin-R (86)	0.06/0.12 (100)	>32/>32 (16.3)	2/>4 (0.0)	1/1 (100)	1/1 (100)
MDR (31)	0.06/0.12 (100)	>32/>32 (0.0)	2/>4 (0.0)	1/1 (100)	1/1 (100)
XDR (5)	0.06/ND (100)	>32/ND (0.0)	2/ND (0.0)	1/ND (100)	1/ND (100)
***H. influenzae* (725 [b])**	**0.5/2 (99.3) [d]**	**1/2 (97.7) [d]**	**0.03/0.06 (99.8)**	**ND**	**0.5/2 (91.3)**
ß-lactamase positive (178)	0.5/2 (99.4) [d]	1/2 (97.2) [d]	0.03/0.06 (98.5)	ND	1/4 (87.1)
ß-lac-pos. + Trimethoprim-Sulfa-R (75)	1/2 (98.7) [d]	1/2 (96.0) [d]	0.03/0.12 (96.5)	ND	2/4 (77.3)

MDR, multi-drug resistant; MRSA resistant to erythromycin, clindamycin and moxifloxacin; ND, not determined; R, resistant; XDR, extensively drug resistant: MRSA resistant to erythromycin, clindamycin, moxifloxacin and gentamycin.
[a] Resistant subsets were determined based on CLSI (2021) breakpoints.
[b] N=932 *S. aureus* and N=511 *H. influenzae* isolates tested for susceptibility to moxifloxacin.
[c] Linezolid tested against *S. aureus*; Amoxicillin-clavulanic acid tested for *H. influenzae* and parenteral breakpoints applied.
[d] CLSI breakpoints (2021) applied since no breakpoints established by EUCAST

Figure 1. Susceptibility of *S. aureus* and MRSA from paediatric patients collected from paediatric patients (SENTRY 2015-2019)



SUMMARY / CONCLUSIONS

- Lefamulin demonstrated potent *in vitro* activity against this collection of *S. aureus* and *H. influenzae* and remained fully active against resistant and multi-drug resistant isolates
- Lefamulin's potent *in vitro* activity is of particular importance in CF patients, where treatment options are extremely limited
- Studies are warranted to further explore susceptibility profiles in respiratory isolates from CF patients and the pharmacokinetics and safety of lefamulin in CF patients

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