FRIDAY - 85

# *In Vitro* Activity of Lefamulin against Bacterial Pathogens Collected from Patients with Community-Acquired Bacterial Pneumonia (CABP) – SENTRY 2015 US Data

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## ABSTRACT

**Background:** Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans and is currently in Phase 3 trials for the treatment of CABP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the A- and P-site of the peptidyl transferase center (PTC) via an induced fit mechanism whereby nucleotides in the PTC shift and tighten the binding pocket around lefamulin. This study investigated the in vitro activity of lefamulin and comparators against contemporary bacterial respiratory pathogens collected in the US.

**Methods:** Unique patients' isolates (*n*=945) were collected in the US (62 sites) from patients with CABP. Lefamulin and comparators were tested by CLSI broth microdilution methods and susceptibility was determined using CLSI (2016) breakpoints.

**Results:** Lefamulin showed potent *in vitro* activity against this collection of respiratory pathogens, with 100% of *Streptococcus pneumoniae* inhibited at ≤0.5 mg/L. Isolates were highly susceptible to ceftriaxone (98.3%), levofloxacin (99.5%) and tetracycline (81.7%), while only 56.3% and 63.3% were susceptible to azithromycin and penicillin, respectively. Lefamulin was also active against *Haemophilus influenzae* (99.3% inhibited at ≤2 mg/L) and *Moraxella catarrhalis* (100.0% inhibited at ≤0.12 mg/L). All *H. influenzae* were susceptible to amoxicillin/clavulanic acid, azithromycin and levofloxacin, and 98.6% to tetracycline; higher resistance rates were observed for ampicillin (29.4%) and trimethoprim/sulfamethoxazole (30.8%). Lefamulin's activity was not affected by resistance to other antibiotics.

**Conclusion:** Lefamulin was highly active against pathogens collected from CABP patients in the US in 2015, and its activity was not affected by resistance to other antibiotic classes. These data support the ongoing development of lefamulin for the treatment of CABP.

**Table 1. $MIC_{50/90}$ [mg/L] of lefamulin and comparators**

| Organisms (No. of isolates) | Lefamulin | Amoxi/Clav | Azithro-mycin | Levo -floxacin |
|---|---|---|---|---|
| ***S. pneumoniae* (649)** | 0.06 / 0.12 | ≤0.03 / 2 | 0.12 / >4 | 1 / 1 |
| **Penicillin non-susc: (238) [a]** | 0.12 / 0.25 | 1 / 4 | >4 / >4 | 1 / 1 |
| **Macrolide resistant (282)** | 0.12 / 0.12 | 0.25 / 4 | >4 / >4 | 1 / 1 |
| ***H. influenzae* (143)** | 0.5 / 2 | 0.5 / 2 | 1 / 2 | ≤0.015 / ≤0.015 |
| ***M. catarrhalis* (153)** | 0.06 / 0.06 | 0.12 / 0.25 | 0.015 / 0.03 | 0.03 / 0.03 |

[a], Used oral penicillin breakpoints according to CLSI (2017)

## INTRODUCTION

CAP is the number one infectious diseases cause of death worldwide and emerging resistance complicates its treatment.[1]

Lefamulin is the first representative of pleuromutilin class in clinical development for systemic administration. Pleuromutilins inhibit bacterial protein synthesis of Gram-positive and Gram-negative organisms, as well as atypical respiratory pathogens. Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) via four H-bonds and other interactions at the A- and P-site resulting in an "induced fit." [2,3] (Figure 1) Lefamulin's antibacterial profile includes activity against typical and atypical respiratory pathogens.[4,5] Phase 1 and 2 trials have demonstrated that IV and oral administration of lefamulin are well tolerated. Furthermore, lefamulin (100mg or 150 mg IV q12 hours) showed similar efficacy to IV vancomycin in a clinical Phase 2 trial in patients with acute bacterial skin and skin structure infections.[6] Currently, lefamulin is in late stage development for the treatment of community-acquired bacterial pneumonia (CABP).

This study investigated the activity of lefamulin and comparators against a contemporary set of bacterial respiratory pathogens collected in the US.

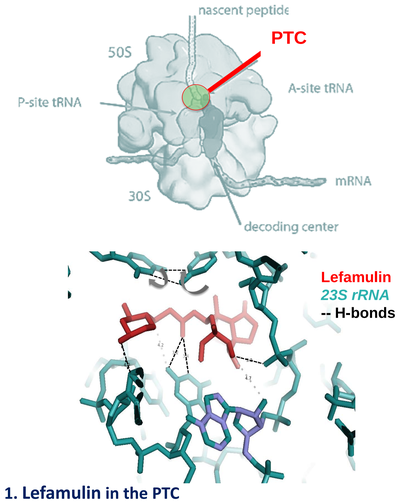


**Figure 1. Lefamulin in the PTC**

## RESULTS

- Lefamulin displayed potent antibacterial activity against this collection of contemporary respiratory pathogens collected from patients with community-acquired respiratory tract infections (Table 2).

**Table 2. Susceptibility of CABP pathogens against lefamulin and comparators [mg/L]**

| Organism (*N*) | $MIC_{50}$ | $MIC_{90}$ | $MIC_{99}$ | Range [mg/L] | % S [a] | % I [a] | % R [a] |
|---|---|---|---|---|---|---|---|
| ***S. pneumoniae* (649)** | | | | | | | |
| **Lefamulin** | **0.06** | **0.12** | **0.25** | **≤0.008 to 0.5** | - | - | - |
| Amoxicillin-clavulanic acid | ≤0.03 | 2 | >4 | ≤0.03 to >4 | 95.5 | 2.3 | 2.2 |
| Azithromycin | 0.12 | >4 | >4 | ≤0.03 to >4 | 56.3 | 0.6 | 43.1 |
| Ceftaroline | ≤0.008 | 0.12 | 0.25 | ≤0.008 to 0.5 | 100.0 | - | b |
| Ceftriaxone | 0.03 | 1 | 2 | ≤0.015 to >2 | 98.3 | 0.9 | 0.8 [b] |
| Clindamycin | ≤0.12 | >1 | >1 | ≤0.12 to >1 | 87.5 | 0.5 | 12.0 |
| Cotrimoxazole | ≤0.5 | 4 | >4 | ≤0.5 to >4 | 74.4 | 11.9 | 13.7 |
| Erythromycin | 0.06 | >2 | >2 | ≤0.015 to >2 | 55.9 | 0.6 | 43.5 |
| Levofloxacin | 1 | 1 | 2 | 0.5 to >4 | 99.5 | 0.0 | 0.5 |
| Penicillin | ≤0.06 | 1 | 4 | ≤0.06 to 4 | 63.3 | 29.3 | 7.4 [b] |
| Tetracycline | 0.25 | >4 | >4 | ≤0.12 to >4 | 81.7 | 0.2 | 18.2 |
| ***H. influenzae* (143)** | | | | | | | |
| **Lefamulin** | **0.5** | **2** | **2** | **0.25 to 4** | - | - | - |
| Amoxicillin-clavulanic acid | 0.5 | 2 | 4 | ≤0.12 to 4 | 100.0 | - | 0.0 |
| Ampicillin | 0.5 | >8 | >8 | 0.12 to >8 | 70.6 | 0.0 | 29.4 [c] |
| Azithromycin | 1 | 2 | 4 | 0.25 to 4 | 100.0 | - | - |
| Ceftriaxone | ≤0.015 | ≤0.015 | 0.06 | ≤0.015 to 0.25 | 100.0 | - | - |
| Clarithromycin | 8 | 8 | >16 | 4 to >16 | 92.3 | 6.3 | 1.4 |
| Levofloxacin | ≤0.015 | ≤0.015 | 0.25 | ≤0.015 to 0.5 | 100.0 | - | - |
| Tetracycline | 0.5 | 0.5 | 8 | 0.25 to 8 | 98.6 | 0.0 | 1.4 |
| Cotrimoxazole | 0.06 | >4 | >4 | ≤0.03 to >4 | 67.8 | 1.4 | 30.8 |
| ***M. catarrhalis* (153)** | | | | | | | |
| **Lefamulin** | **0.06** | **0.06** | **0.12** | **≤0.008 to 0.12** | - | - | - |
| Amoxicillin-clavulanic acid | 0.12 | 0.25 | 0.25 | ≤0.03 to 0.25 | 100.0 | - | 0.0 |
| Azithromycin | 0.015 | 0.03 | 0.03 | 0.008 to 0.06 | 100.0 | - | - |
| Ceftriaxone | 0.25 | 0.5 | 1 | ≤0.015 to 1 | 100.0 | - | - |
| Erythromycin | 0.12 | 0.12 | 0.25 | ≤0.015 to 0.25 | 100.0 | - | - |
| Levofloxacin | 0.03 | 0.03 | 0.06 | ≤0.015 to 1 | 100.0 | - | - |
| Tetracycline | 0.12 | 0.25 | 0.25 | 0.06 to 0.25 | 100.0 | 0.0 | 0.0 |

[a], Criteria as published by CLSI [2017][7]
[b], Non-meningitis breakpoints applied for penicillin
[c], ß-lactamase positive, reported as resistant for penicillins without inhibitors

## RESULTS continued

- Lefamulin was the most active compound against *S. pneumoniae* ($MIC_{50/90}$ of 0.06/0.12 mg/L) with 100% of isolates inhibited at a lefamulin concentration of 0.5 mg/L.
  - *S. pneumoniae* isolates were largely susceptible to ceftaroline (100%), ceftriaxone (98.3%) and levofloxacin (99.5%) , whereas 43.5% and 18.2% of isolates were resistant to macrolides and tetracycline, respectively.
- Lefamulin's activity was not affected by resistance to other antibiotic classes
  - 100% of *S. pneumoniae* resistant to penicillin (*n*=29, oral breakpoint ≥ 2 mg/L) were inhibited by lefamulin concentrations of ≤0.12 mg/L; ($MIC_{50/90}$ of 0.06/0.12 mg/L) whereas 91.7% and 56.2% were resistant to macrolides and tetracyclines, respectively.
  - 99.6% of macrolide-resistant *S. pneumoniae* (*n*=282) were inhibited by ≤0.25 mg/L of lefamulin ($MIC_{50/90}$ 0.12/0.12 mg/L, range 0.008-0.5 mg/L)
- Against *H. influenzae* and *M. catarrhalis* lefamulin also displayed potent activity, including ß-lactamase-producing strains.
  - *H. influenzae*, $MIC_{50/90}$ of 0.5/2 mg/L (29.4% ß-lactamase producing)
  - *M. catarrhalis*, $MIC_{50/90}$ of 0.06/0.06 mg/L

## CONCLUSIONS

- **Lefamulin demonstrated potent *in vitro* activity against this contemporary collection of respiratory pathogens from USA regardless of resistance phenotype to the other antibiotic classes including macrolides, ß-lactams, tetracyclines or fluoroquinolones.**
- **Results are consistent with those obtained from previous studies including a variety of *S. pneumoniae* serotypes.[8]**
- **These data support the continued clinical development of lefamulin for the treatment of respiratory tract infections, including CABP.**

## REFERENCES

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