Clinical Utility of Lefamulin: If Not Now, When?

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Abstract

Purpose of Review The looming threat of antimicrobial resistance requires robust stewardship and new developments in infectious diseases pharmacotherapy. This review discusses the pertinent spectrum and clinical data of lefamulin (Xenleta®), with a focus on potential real-world use.

Recent Findings Lefamulin is a novel pleuromutilin antibiotic that obtained Food and Drug Administration labeling for community-acquired bacterial pneumonia (CABP) in 2019. Lefamulin is available in both intravenous and oral formulations, and it inhibits bacterial protein synthesis inhibition through interactive binding to unique sites of the peptidyl transferase center of the 50s bacterial ribosome subunit. Resistance, including cross-resistance with other antibiotics, is infrequent. Lefamulin demonstrates activity against most Gram-positive pathogens and other organisms commonly associated with CABP, i.e., Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Legionella pneumophila, and Chlamydophila pneumoniae. Lefamulin may also be an option for serious public health threats like methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus faecium, and multi-drug-resistant organisms associated with sexually transmitted infections, e.g., Neisseria gonorrhoeae, Mycoplasma genitalium. Lefamulin lacks activity against Pseudomonas aeruginosa, Acinetobacter baumannii, Enterobacterales, most anaerobes, and E. faecalis. In Phase III trials, lefamulin monotherapy was non-inferior to moxifloxacin with or without linezolid for CABP.

Summary Lefamulin is a well-tolerated agent with a unique mechanism, availability in both IV and PO formulations, and it has been rigorously studied for safety and efficacy for CABP.

Keywords Pleuromutilin · Lefamulin · Treatment · Gram-positive · Methicillin-resistant Staphylococcus aureus · Antimicrobial stewardship

Introduction

Antimicrobial resistance is a significant public health threat, and multi-drug-resistant (MDR) pathogens are estimated to infect close to 3 million and kill more than 40,000 people in the USA per year [1, 2]. Strategies to curtail antimicrobial resistance threats are needed, and methods include improving appropriate antimicrobial utilization through stewardship and developing novel antimicrobial agents with activity against these concerning pathogens. While stewardship guidance and activities are growing [3, 4], investment in infectious diseases drug research and development (R&D) has proved challenging due to regulatory barriers, historically poor development incentives, and limited uptake revenue [2]. Lefamulin (Xenleta®) is a recently Food and Drug Administration (FDA)-approved, novel pleuromutilin antibiotic that demonstrates activity against common aerobic Gram-positive organisms, fastidious Gram-negatives, atypicals, and some Gram-positive anaerobes [5, 6], as well as resistant bacteria such as methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus faecium, and MDR Neisseria gonorrhoea [7, 8].

A concerning number of pharmaceutical companies have either sold off infectious diseases R&D programs or filed for...
bankruptcy after a product launch [9]. These breakdowns are attributed to a misaligned health care reimbursement system and investment in the R&D of “me too” agents, or drugs that offer little additional clinical benefit while having similar mechanisms and spectra of activity compared to existing antimicrobials [9, 10]. In this aspect, lefamulin is distinct in that it displays a novel mechanism of action as well as activity against the more common types of bacteria that cause infections in the United States (USA), in addition to concerning Gram-positive organisms like methicillin-resistant Staphylococcus aureus (MRSA) that infect and kill more people than MDR Gram-negative organisms [11].

The pleuromutilin class was first developed in the 1950s, but no systemic agents have been available for human use until recently [12]. Lefamulin obtained an FDA indication for community-acquired bacterial pneumonia (CABP) in 2019, is available in intravenous (IV) and oral (PO) formulations, and has a unique mechanism of action among systemic antimicrobial agents. In this review, we provide an overview of the structural activity relationship, spectrum of activity, and relevant clinical trial and safety data for lefamulin, with a focus on other clinical applications.

Methods

A systematic approach to literature search was performed on PubMed using the terms “lefamulin,” “pleuromutilin,” and “BC-3781,” the investigational drug name for lefamulin. Results were limited to articles available in English and those describing systemic pleuromutilins used in human adults. Other clinical trials focusing on lefamulin were identified from clinicaltrials.gov, and additional data were obtained from pertinent conference proceedings and published abstracts related to lefamulin available through the manufacturer’s webpage [13].

Chemical Structure and Mechanism of Action

Lefamulin is a semisynthetic derivative of the naturally occurring tricyclic diterpenoid pleuromutilin class of antibiotics. Pleuromutilins were first isolated from the fungus Pleurotus mutilus and eventually developed into systemic therapy for veterinary use and as a topical product for human use [5]. The tricyclic mutilin core of lefamulin contains a 14-carbon ring that is essential for antimicrobial activity, as this core interacts with the central portion of bacterial 23S rRNA through hydrophobic interactions, van der Waal forces, and hydrogen bonds. The modified C14 side chain, including a C21 keto group and additional R1 moieties, contributes to the physicochemical drug characteristics of lefamulin that distinguish it from other pleuromutilins (Fig. 1) [5]. This side chain consists of a thioether bond that allows for heightened solubility, potent antimicrobial activity, and metabolic stability that enables lefamulin to be administered in both IV and PO forms [5, 11]. The C14 side chain also helps lefamulin overcome bacterial ribosomal mutations and resistance development by maximizing the number of hydrogen bonds to the target site [11, 12].

Lefamulin inhibits bacterial protein synthesis through a unique mechanism of tight-fit binding to the A and P sites of the 50S ribosomal subunit, creating an interference with peptidyl transferase to subsequently inhibit peptide bond formation and chain elongation [11, 14]. Once elongation has started, lefamulin is ineffective [5, 11].

Development of resistance to this mechanism has been observed in vitro and in other pleuromutilins used in veterinary medicine, and it is often a result of various ribosomal protein point mutations within the domain V of the 23S rRNA that can affect the peptidyl transferase center (PTC) structure [15]. The most common resistance mechanisms via 23S rRNA mutations include the rplC and rplD genes, which encode for ribosomal proteins L3 and L4. Mutations and substitutions in the rplC and rplD genes can cause conformational changes in the PTC and hinder correct positioning of the pleuromutilins in the tight-fit binding pocket within the A and P sites [5, 15]. Other protein mutations, such as vga(A, B, E), isla(E), and salt(A), can confer pleuromutilin resistance via ribosomal protection [15]. Interestingly, intrinsic pleuromutilin resistance in Enterobacteriaceae is caused by the efflux of pleuromutilins mediated by the AcrAB-TolC efflux pump [5]. Real-world data describing lefamulin resistance via 23S rRNA target site mutations or cross-resistance to other ribosome inhibiting-antibiotics like lincomamides or oxazolidinones has been rarely observed [5, 12].

Spectrum of Activity

Lefamulin possesses a broad spectrum of activity against aerobic Gram-positive organisms. It has limited activity against Gram-negative pathogens, although it is active against fastidious Gram-negative organisms and atypical pathogens associated with CABP. Only three FDA breakpoints are in place for lefamulin susceptibility criteria: methicillin-susceptible S. aureus (≤0.25 µg/mL), S. pneumoniae (≤0.5 µg/mL), and H. influenzae (≤2 µg/mL) [16]. Table 1 compares MIC distributions of lefamulin against other commonly used oral antimicrobials in the USA [18–32]. Global surveillance reports highlight lefamulin’s in vitro activity against S. aureus; E. faecium; susceptible and drug-resistant S. pneumoniae, H. influenzae, M. catarrhalis, L. pneumophila, M. pneumoniae, and C. pneumoniae; and various beta- and alpha-hemolytic streptococci [18]. The genes associated with vancomycin-resistance in E. faecium and S. aureus do not impact susceptibility to lefamulin [15, 18]. Pleuromutilins also demonstrate activity against many common anaerobes like C. acnes, C. perfringens,
Fusobacterium sp., Peptostreptococcus sp., Prevotella sp., and sexually transmitted microbes, although no current FDA breakpoints exist for these organisms [16, 18]. The potential role against multi-drug-resistant enterococci and N. gonorrhoeae is enticing, although clinical data are lacking [7, 8, 18]. Notable gaps in antimicrobial coverage include most Enterobacterales, non-lactose-fermenting Gram-negative pathogens, E. faecalis, Clostridioides difficile, and Bacteroides sp. [18].

Pharmacokinetics

General Pharmacokinetics of Lefamulin

The FDA standard IV and PO lefamulin dosage is 150 mg IV administered over 1 h every 12 h and 600 mg PO every 12 h, respectively [6]. Multiple Phase I trials were performed to assess lefamulin drug tolerability and pharmacokinetic profile in healthy volunteers. Intravenous lefamulin was found to be tolerable in up to 400 mg in a dose-escalation study in healthy volunteers [31]. A pharmacokinetic study in healthy patients who received multiple doses of IV lefamulin 150 mg every 12 h over a 1-h infusion for 5 days found the mean (SD) total plasma maximum concentrations \( C_{\text{max}} \) was 2.06 mg/L (0.737), with a mean (SD) half-life of 13.2 h (5.79) and displayed multiphasic decline [17]. The lefamulin package insert states the half-life of lefamulin is 8 h [6]. The mean (SD) total plasma area under the concentration-time curve over 24 h (AUC\(_{0-24}\)) for the same IV dosing regimen was found to be 16.5 mg h/L (6.21) [17]. A number of pharmacokinetic studies for the PO formulation found the dosage of 600 mg every 12-h dosage achieved similar concentrations compared to 150 mg IV every 12 h [6, 33].

Absorption

In a two-part, open-label, crossover, randomized trial, 12 healthy adults received a single dose of PO immediate-release lefamulin 600 mg in either a fasted-state or after a high-fat meal [17]. Oral lefamulin was well tolerated, and the pharmacokinetics were similar to IV lefamulin 150 mg, but patients in the fed state had reductions in AUC\(_{0-\text{inf}}\) (10%) and \( C_{\text{max}} \) (28%) [17]. Lefamulin is subsequently recommended to be given 1 h before a meal or 2 h after a meal with water [6]. A multi-dose study included 8 healthy adults who received PO lefamulin 600 mg every 12 h for 6 days and a single dose on day 7, which was also well tolerated and displayed predictable pharmacokinetics (Table 1) [17]. The absolute oral bioavailability of lefamulin is 25.8% and 21.0% in fasted and fed states, respectively [17].

Table 1 Summary of steady-state pharmacokinetic data for PO and IV lefamulin [17]

| Administration    | Dosage               | \( T_{\text{max}} \) (hours) | Total \( C_{\text{max}} \) (mg/L) | AUC\(_{0-24}\) (mg h/L) |
|-------------------|----------------------|-----------------------------|---------------------------------|-------------------------|
| Oral, fasted      | 600 mg every 12 h\(^a\) | 2.00 (0.5–3)                | 1.85 (0.61)                     | 21.6 (8.40)             |
| Intravenous       | 150 mg after 5 days\(^b\) | –                           | 2.06 (0.737)                    | 16.5 (6.21)             |

All values are mean (SD), except median (range) is reported for \( T_{\text{max}} \)

\(^a\) Parameters estimated after a 7-day course

\(^b\) Parameters estimated after a 5-day course
Distribution

The volume of distribution of lefamulin is 86 L, with plasma protein binding 95–97% [6]. Lefamulin concentrations have been evaluated in pulmonary and skeletal/adipose tissues [34]. Pulmonary penetration was assessed in a pharmacokinetic study in 12 healthy men who received a single dose of lefamulin 150 mg IV. Median (range) lefamulin AUC$_{0-24}$ exposures in epithelial lining fluid (8978 [no range provided] ng h/mL) were comparable to total plasma levels (11,554 ng h/mL [1095–2343]) and considerably exceeded free plasma levels (1500.8 ng h/mL [10965–2343]). It is hypothesized that high pulmonary concentrations are due to the active transport of lefamulin into the alveolar-capillary membrane by P-glycoprotein [34]. Additionally, the results of a murine macrophage model determined that lefamulin is unaffected by lung surfactant [35]. These characteristics suggest lefamulin would have utility in treating bacterial pneumonia, as the site of infection is within the alveolar spaces and alveolar lining fluid within the interstitium of the lung [36]. Antibiotic penetration into pulmonary tissue and bronchial secretions is also dependent on several drug-related characteristics, such as molecular weight, low protein binding, and other structural characteristics [36]. A separate pharmacokinetic study performed in healthy volunteers determined that median (range) lefamulin AUC$_{0-24}$ concentrations in skeletal muscle (1264.2 ng h/mL [770–2094]) and adipose tissue (1456.6 ng h/mL [810–1758]) were similar to free lefamulin concentrations in plasma, after a single dose of lefamulin 150 mg IV administered over 1 h [34].

Metabolism

Lefamulin is hepatically metabolized by the hepatic microsomal P450 system, and predominantly the CYP 3A4 pathway. In vitro studies involving with human recombinant CYP450 enzymes established that lefamulin is metabolized by CYP3A as both a substrate and inhibitor [37]. Other studies did not reveal any significant induction of CYP1A2 [37]. Additionally, in vitro evaluation demonstrated that lefamulin is a P-glycoprotein substrate and a weak inhibitor of P-glycoprotein-mediated efflux transport [38].

In one study, PO rifampin 600 mg, a potent CYP3A4 inducer, reduced the mean lefamulin AUC$_{0-inf}$ and $C_{max}$ by 28% and 8%, respectively, when administered concomitantly with a single dose of IV lefamulin 150 mg. A subsequent study found that PO rifampin 600 mg reduced the mean lefamulin AUC$_{0-inf}$ and $C_{max}$ by 72% and 57%, respectively, when concomitantly administered with a single dose of PO lefamulin 600 mg [38]. PO ketoconazole 200 mg twice daily, a strong CYP3A4 inhibitor, increased mean lefamulin AUC$_{0-inf}$ and $C_{max}$ by 31% and 6%, respectively, when administered concomitantly with a single dose of IV lefamulin 150 mg. A separate study found the same dosage of ketoconazole increased the lefamulin AUC$_{0-inf}$ and $C_{max}$ by 165% and 58% when administered with a single dose of PO lefamulin 400 mg [38]. Because of potential efficacy loss due to low exposure of LEF, co-administration of LEF with moderate and strong CYP3A4 or P-glycoprotein inducers should be avoided [6].

No clinically significant differences in the pharmacokinetics of PO digoxin 0.5 mg, a P-glycoprotein substrate, were observed when administered concomitantly with a single dose of lefamulin 600 mg [38]. Lefamulin increased the arithmetic mean $C_{max}$ and AUC$_{0-inf}$ of PO midazolam, a CYP3A4 substrate by approximately 100% and 200%, respectively, when it was administered at 0, 2, or 4 h after administration of a single dose of PO lefamulin 600 mg [38]. Based on animal, clinical trial, and other adverse drug events (ADEs) identified from Phase I–III trials related to QTc prolongation, the concomitant administration of lefamulin with other CYP3A4 substrates that prolong the QTc interval is contraindicated [6, 38]. Lefamulin prolongs the QT interval in a nonlinear, concentration-dependent manner via human-ether-a-go-go-mediated potassium channel current interactions, and data from two Phase III trials found that the mean placebo-corrected changes in QTc from baseline were 13.6 ms and 9.3 ms following administration of lefamulin 150 mg IV every 12 h and lefamulin 600 mg PO every 12 h, respectively [6, 38]. Analysis of all post-baseline QTc values showed the proportions of subjects exposed to lefamulin or moxifloxacin had similar degrees of QT prolongation at day 3 or 4 of the studies; 17.9% of lefamulin subjects and 22.3% of moxifloxacin subjects had a mean change in QTc from baseline of more than 30 ms [38].

Excretion

In a non-pigmented rat model, lefamulin was excreted as 80% unchanged drug in feces and 13% in urine [39]. Additionally, no clinically significant differences in the pharmacokinetics of IV lefamulin 150 mg over 1 h for one dose were observed in 7 human subjects with normal renal function compared to 8 subjects with severe chronic renal impairment and 8 subjects who were receiving hemodialysis [40]. Specifically, the median (range) $C_{max}$ and AUC$_{0-inf}$ of subject with normal function was 3182 ng/mL (697) and 9004 h ng/mL (2591), respectively, compared to 3138 ng/mL (990) and 12,262 h ng/mL (7798) in patients with severe renal disease, and 3341 ng/mL (916) and 8955 h ng/mL (3103) in patients on hemodialysis [40]. No dose reduction recommendations are available for patients with renal dysfunction [6]. Lefamulin pharmacokinetics were also studied in un-infected volunteers with normal hepatic function, moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment, as a single dose of IV lefamulin 150 mg given over 1 h [6]. The half-life of lefamulin was found to be prolonged in patients with Child-Pugh Class C hepatic
impairment compared to normal hepatic function, with a mean (SD) $t_{1/2}$ of 17.6 h (3.4) compared to 11.5 h (1.8). Unbound lefamulin plasma AUC$_{0\text{-inf}}$ was increased 3-fold in subjects with severe hepatic impairment compared to that in subjects with normal hepatic function, due to the high protein binding observed in lefamulin. Based on these data, a dose reduction to lefamulin 150 mg IV every 24 h is recommended in patients with Child-Pugh Class C hepatic impairment. No hepatic impairment data are available for lefamulin PO, and this formulation is not recommended for patients with Child-Pugh Class B or C hepatic impairment [6].

Pharmacodynamics

The 24-h free-drug area-under-curve (AUC) to minimal inhibitory concentration (MIC) ratio, or $f$AUC$_{0-24}$/MIC, has been shown to be the pharmacodynamic index associated with the antibacterial activity of lefamulin [41]. Lefamulin displayed a moderate post-antibiotic effect against $S. pneumoniae$ and $S. aureus$ in a neutropenic mouse model [41]. In the same study, lefamulin achieved 3- to 6-fold higher potency in the murine lung model when compared to the thigh model, consistent with pharmacokinetic data suggesting lefamulin achieves high pulmonary concentrations [41]. In a separate neutropenic murine lung and thigh study, the lefamulin $f$AUC$_{0-24}$/MIC required for stasis was 8-fold lower in the lung model when compared to the thigh model [42]. An additional neutropenic murine thigh model determined plasma $f$AUC$_{0-24}$/MIC ratios of 1.37 and 2.15 resulted in a 1- and 2-log$_{10}$ CFU reductions, which corresponded with ELF AUC$_{0-24}$/MIC ratios of 21.7 and 63.9 [43].

Target attainment analyses for IV and PO lefamulin dosage selection in CABP were calculated using population pharmacokinetic models from Phase I/II data and from pharmacokinetic-pharmacodynamic targets associated with efficacy in $S. pneumoniae$ and $S. aureus$ [33]. Monte Carlo simulation was performed for IV lefamulin 150 mg every 12 h and lefamulin 600 mg PO every 12 h [33]. The probability of target attainment (PTA) was calculated for the total-drug ELF AUC/MIC and free-drug plasma AUC/MIC ratio targets associated with a 1- and 2-log$_{10}$ CFU reduction from baseline for both $S. pneumoniae$ and $S. aureus$. The PTA in ELF for a 1-log$_{10}$ CFU reduction from baseline in $S. pneumoniae$ ranged from 99.2 to 100% for IV and all PO regimens at the MIC$_{90}$ (0.12 mg/L). In another $S. pneumoniae$ simulation at the MIC$_{90}$ (0.25 mg/L) and for the same target log$_{10}$ CFU reduction, PTA was 96.7%, 82.1%, and 96.3% for IV and both fed and fasted PO-dosing regimens, respectively. The PTA for the total-drug ELF AUC/MIC ratio target associated with a 2-log$_{10}$ CFU reduction from baseline was also calculated for $S. pneumoniae$ at the MIC$_{90}$, and the PTA for IV and PO dosing regimens under fed and fasted conditions was 99.2%, 92.3%, and 99.2%, respectively. For the free-drug plasma AUC/MIC ratio target associated with either 1- or 2-log$_{10}$ CFU reduction, percentage probabilities were 100% for each dosing regimen at MIC$_{90}$ or MIC$_{99}$ values. Similar PTA analyses were performed for $S. aureus$, and for the total-drug ELF, AUC/MIC ratio target for a 1-log$_{10}$ CFU reduction from baseline was within a range of 92.7 to 99.3% all dosing regimens at the MIC$_{90}$ value (0.12 mg/L). To achieve a 2-log$_{10}$ CFU reduction from baseline for $S. aureus$ at the MIC value of 0.03 mg/L, and the PTA ranged from 98.4 to 100% for all dosing regimens. For the free-drug plasma AUC/MIC ratio target associated with either endpoint and a MIC$_{90}$ or value of 0.25 mg/L, percentage probabilities were $\geq 99.5$% for each dosing regimen [33].

A population pharmacokinetic model was also performed for PO lefamulin 600 mg every 12 h in fasted and fed states [44]. The percentage probabilities of target attainment, associated with a 1-log$_{10}$ CFU reduction for $S. aureus$ and $S. pneumoniae$, were 100% at the MIC$_{90}$ and 95.5% or higher at the MIC$_{99}$ [33]. For $f$AUC$_{0-24}$/MIC targets associated with 2-log$_{10}$ CFU reduction, percentage probabilities were 91.9% or higher at MIC$_{90}$ values. Overall percentage probabilities of attaining $f$AUC$_{0-24}$/MIC targets for 1- and 2-log$_{10}$ CFU reductions of $S. pneumoniae$ and $S. aureus$ were 99.4 and 91.7% or higher, respectively, and the probabilities of target attainment were similar under fasted and fed conditions. A more in-depth pharmacokinetic and pharmacodynamic review of lefamulin is published elsewhere [45].

Summary of Clinical Trial Data

Community-Acquired Bacterial Pneumonia

With potent activity against CABP pathogens and high pulmonary concentrations, lefamulin demonstrates antimicrobial properties ideal for respiratory tract infections. The Lefamulin Evaluation Against Pneumonia (LEAP)-1 and -2 studies were similarly designed multicenter randomized controlled trials that tested non-inferiority of lefamulin against moxifloxacin in adults with CABP [46, 47]. Study details and comparisons of population characteristics and endpoints are in Tables 2 and 3. Early clinical response (ECR) was the FDA primary endpoint, defined as the response rate in the intent-to-treat (ITT) population at 96 h after the first study drug dose. “Responders” had $>1$ signs of clinical improvement and no worsening CABP symptoms. The FDA endpoint was evaluated using 12.5% and 10% non-inferiority margins in LEAP-1 and LEAP-2 studies, respectively. The European Medicines Agency (EMA) co-primary endpoint, investigator assessment of clinical response (IACR), was resolution of signs and symptoms, without need for additional antimicrobial assessed 5-10 days after the last dose of study drug. In the primary and
Activity of lefamulin and other oral antimicrobials against common skin and respiratory pathogens [18–32]

| Lefamulin | Levofloxacin | Moxifloxacin | Delafloxacin | Erythromycin | Amoxicillin-clavulanate | Doxycycline | Omadacycline | Linezolid | TMP-SMX |
|-----------|--------------|--------------|--------------|--------------|------------------------|-------------|--------------|-----------|---------|
| **MIC (mcg/mL)** | **MIC50** | **MIC90** | **MIC50** | **MIC90** | **MIC50** | **MIC90** | **MIC50** | **MIC90** | **MIC50** | **MIC90** | **MIC50** | **MIC90** | **MIC50** | **MIC90** | **MIC50** | **MIC90** | **MIC50** | **MIC90** | **MIC50** | **MIC90** |
| **S. aureus** | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 |
| **MRSA** | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 |
| **S. pneumoniae** | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 | 0.06 | 0.12 | 0.25 | >4 |
| **PRSP** | 0.12 | 0.25 | 0.5 | >16 | 0.06 | 0.12 | 0.25 | >16 | 0.06 | 0.12 | 0.25 | >16 | 0.06 | 0.12 | 0.25 | >16 | 0.06 | 0.12 | 0.25 | >16 | 0.06 | 0.12 | 0.25 | >16 |
| **S. pyogenes** | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 |
| **S. agalactiae** | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 | 0.03 | 0.06 | 0.12 | >16 |
| **S. viridans** | 0.02 | 0.04 | 0.08 | 0.5 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 |
| **S. anginosus** | 0.06 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 |
| **H. influenzae** | 1 | 2 | <0.015 | 0.03 | 1 | 2 | <0.015 | 0.03 | 1 | 2 | <0.015 | 0.03 | 1 | 2 | <0.015 | 0.03 | 1 | 2 | <0.015 | 0.03 | 1 | 2 |
| **M. catarrhalis** | 0.12 | 0.25 | 0.008 | 0.015 | 0.12 | 0.25 | 0.008 | 0.015 | 0.12 | 0.25 | 0.008 | 0.015 | 0.12 | 0.25 | 0.008 | 0.015 | 0.12 | 0.25 | 0.008 | 0.015 | 0.12 | 0.25 | 0.008 | 0.015 |
| **L. pneumophilia** | 0.02 | 0.04 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 | 0.12 | 0.25 | 0.5 | 1 |
| **M. pneumoniae** | 0.02 | 0.04 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 |
| **C. pneumoniae** | 0.02 | 0.04 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 | 0.12 | 0.015 | 0.03 | 0.06 |

*Less than 10 isolates

co-primary endpoints, lefamulin was found non-inferior to moxifloxacin in both trials. The most common organism identified in each study was *S. pneumoniae*, and while lefamulin maintains potent activity against MRSA, those who were at risk of developing MRSA pneumonia were unfortunately excluded from the LEAP-2 trial, and few patients from both trials combined had MRSA isolated. Most patients had Pneumonia Patient Outcomes Research Team (PORT) risk class ≤3 in both studies, or less severe pneumonia.

The LEAP-1 trial evaluated ECR with IV/PO lefamulin compared to IV/PO moxifloxacin ± linezolid [46]. If MRSA was suspected at the initial screening, patients randomized to moxifloxacin also received adjunctive linezolid 600 mg IV every 12 h, and patients randomized to lefamulin received additional placebo. Patients were eligible to switch to PO therapy after receiving at least six IV doses, were hemodynamically stable and afebrile for 24 h, had improving pneumonia symptoms, and had a functioning gastrointestinal tract. The populations were well balanced, although fewer patients <65 years of age were in the lefamulin arm (52% vs 61%). The median duration of therapy was 7 days for both study drugs, and 38 and 44% of lefamulin and moxifloxacin courses, respectively, were switched from IV to PO. The overall rates of ECR (87% vs 90%) and IACR (82% vs 84%) were similar. In subgroup analysis, moxifloxacin had more favorable ECR in patients with >2 American Thoracic Society (ATS) severity criteria, i.e., confusion, uremia, respiratory rate ≥30 breaths/min, hypotension, PaO2/FiO2 < 250 mmHg, multi-lobar infiltrates, leucopenia, thrombocytopenia, or hypothermia, (76% vs 94%), and <65 years of age (85% vs 93%). The differences in ECR in younger patients was determined to be confounded by the presence of minor ATS criteria, and no specific ATS variables were found to be driving these differences in logistic regression analyses [LEAP-1]. In the microbiologic intent to treat-1 group, the most commonly isolated organisms were *S. pneumoniae* (60%), *H. influenzae* (34%), and atypical pathogens (29%), and no MRSA was isolated. Of 6 lefamulin-treated patients with pneumococcal bacteremia, 1 achieved treatment success, while 5 were treatment failures for IACR at test of cure (TOC). Gastrointestinal disturbances such as diarrhea were more frequent in the moxifloxacin arm (1% vs 8%) while there was more infusion site pain in the lefamulin arm (3% vs 0%).

LEAP-2 evaluated similar endpoints of ECR and IACR, except only using fixed durations of oral formulations for lefamulin (5 days) and moxifloxacin (7 days) in both inpatient and outpatient settings and a non-inferiority margin of 10% for both FDA and EMA endpoints [47]. A major difference in study design from LEAP-1 and LEAP-2 was the focus on the use of PO agents only without the addition of linezolid in the moxifloxacin group. Additionally, fewer patients in the LEAP-2 study had severe pneumonia as characterized by the
Table 3  Summary of Lefamulin Evaluation Against Pneumonia (LEAP) trial data [46, 47]

| Treatment assignments | LEAP-1 (n = 551) | LEAP-2 (n = 738) |
|-----------------------|-----------------|-----------------|
| Lefamulin 150 mg IV Q12H with PO transition vs moxifloxacin 400 mg IV Q24H, option to add linezolid for suspected MRSA; both groups able to treat up to 10 days | Lefamulin 600 mg PO BID for 5 days versus 7 days moxifloxacin 400 mg PO daily |
| Patients | Clinical, laboratory, radiographic findings of pneumonia | Clinical, laboratory, radiographic findings of pneumonia |
| Notable exclusions | - Receipt of non-study antibiotics  
- Hospitalized 2 days or more in the last 90 days  
- Confirmed/suspected for MRSA, Pseudomonas, resistant pathogens  
- Attributable etiologies other than CABP (VAP, HAP, aspiration, etc)  
- Resided in long-term care within 30-days of symptom onset  
- Immunosuppression  
- PORT I (least severe) or V (most severe)  
- Severe hepatic, renal, cardiac, or hematologic disease |
| Enrollment location | | |
| - Eastern Europe | 78.9% | 61.5% |
| - Latin America | 2.5% | 9.8% |
| - Asia and Africa | not specified | 20.7% |
| - N. America | 0.5% | 4.4% |
| PORT class | | |
| I | 0% | 0.4% |
| II | 0.2% | 50.4% |
| III | 72.0% | 37.7% |
| IV | 26.5% | 11.1% |
| V | 1.3% | 0.4% |
| CURB-65 | | |
| 0 | 10.3% | 22.6% |
| 1 | 45.6% | 53.3% |
| 2 | 35.4% | 20.5% |
| 3 | 8.0% | 3.4% |
| 4 | 0.7% | 0.3% |
| 5 | – | – |
| Pathogen identified | 318 (57.7) | 391 (53.0) |
| - S. pneumoniae | 197 (35.8) | 249 (33.7) |
| - S. aureus | 14 (2.5) | 19 (2.6) |
| - H. influenzae | 108 (19.6) | 106 (14.1) |
| - M. catarrhalis | 36 (6.5) | 32 (4.3) |
| - M. pneumoniae | 39 (7.1) | 34 (4.6) |
| - L. pneumophila | 32 (5.8) | 33 (4.5) |
| - C. pneumoniae | 30 (5.4) | 28 (4.0) |
| Early clinical response | 87.3% vs 90.2% | 90.8% vs 90.8% |
| Clinical response (modified ITT) | 88.2% vs 93.8% | 87.5% vs 89.1% |
| Test of cure, clinically evaluable | 86.9% vs 89.4% | 89.7% vs 93.6 |
| Treatment-emergent adverse events leading to death | 2.2% vs 1.8% | 1.4% vs 0.8% |
| Adverse drug event | Lefamulin | Moxifloxacin | Lefamulin | Moxifloxacin |
| - Diarrhea | 38.1% | 37.7% | 32.6% | 25.0% |
| - Nausea/vomiting | 0.7% | 7.7% | 12.2% | 1.1% |
| - QTc prolongation | 2.9% (+13.8 ms) | 2.2% (+16.4 ms) | 8.5% (+9.5 ms) | 2.7% (+11.6 ms) |
PORT score and CURB-65 when compared to the LEAP-1 trial. ECR in both groups were 90.8%, and there were no differences in microbiologic outcomes or in other subgroups. Similar to the LEAP-1 trial, the most commonly isolated organisms from LEAP-2 were *S. pneumoniae* (57%), followed by *H. influenzae* (24%). MRSA was isolated in 3 patients overall, but no notable outcome differences were noted by organism. In the lefamulin arm, 6 patients had bacteremia and four had baseline pathogens covered by lefamulin (3 with *S. pneumoniae* and 1 with *S. aureus*). Two of these patients achieved ECR and had an outcome of investigator assessment of clinical response success at TOC. The LEAP-1 and LEAP-2 trials concluded that lefamulin is an effective option for CABP. While the short-term adverse event profile was comparable to that of moxifloxacin, rare adverse drug events and long-term safety outcomes have not been identified.

**Potential Clinical Application of Lefamulin**

**Lefamulin Use in Multi-Drug-Resistant Organisms**

**Methicillin-Resistant *Staphylococcus aureus***

Methicillin-resistant *S. aureus* remains a significant cause of hospital- and community-acquired infections, ranging from minor acute bacterial skin and skin structure infections to more severe diseases including, but not limited to, bacteremia, osteoarticular disease, and infective endocarditis [50]. Despite medical advancements, invasive MRSA infections remain associated with high morbidity and mortality and are more prevalent than the sum of all health care-associated MDR Gram-negative bacilli infections in the USA [1]. In 2017, the CDC estimated 323,700 cases of invasive MRSA infections, resulting in 10,600 deaths [1]. Furthermore, the USA opioid epidemic has significantly contributed to injection drug-use–related staphylococcal infections [51].

While not clinically studied in severe MRSA infections, lefamulin has demonstrated activity against MRSA from...
surveillance data, with reported a MIC90 of 0.12 [18]. In a Phase II skin soft tissue infection trial, the most common organism isolated was *S. aureus*, with a high frequency of methicillin resistance and Panton-Valentine leukocidin (PVL) positivity [48]; other trials have not evaluated the presence of toxin production from clinical *S. aureus* isolates. Lefamulin was also found to have superior efficacy compared to vancomycin or linezolid in a murine *S. aureus* peritonitis-induced bacteremia model that included MRSA [52], and lefamulin also displayed a superior reduction in bacterial burden when compared to linezolid and tigecycline against MSSA, with comparable efficacy to daptomycin or vancomycin [53].

Other areas with potential clinical application but lacking data include prosthetic joint infections, osteomyelitis, periorbital cellulitis, or oral chronic suppressive therapy.

The current infectious diseases landscape focuses on PO antibiotics for the management of invasive infections to reduce central line complications and streamline transitions of care. This concept was recently demonstrated in the Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) randomized trial where non-inferiority of PO step-down was established for bone and joint infections [54]. Clinicians and investigators are becoming more comfortable transitioning patients with uncomplicated *S. aureus* bloodstream infections to PO regimens [55–57]. Regardless, lefamulin bone/joint concentration data and clinical evidence for patients with bloodstream infection are not available. While there are multiple available oral antibiotics with activity against MRSA, i.e., trimethoprim-sulfamethoxazole, linezolid, fluoroquinolones, most are associated with notable toxicities and intolerances, which ultimately could define a role for lefamulin.

**Vancomycin-Resistant Enterococcus faecium**

Infections due to vancomycin-resistant *E. faecium* are a continued threat given the limited number of antimicrobial agents with activity against this organism, and the associated morbidity and mortality [58]. Both daptomycin and linezolid non-susceptible strains, which are considered first-line therapies, have been increasing in the USA primarily in immunocompromised and antibiotic-experienced patients [59, 60]. Infections caused by *E. faecium* are typically of intra-abdominal, urinary, skin, or vascular access etiology. Before lefamulin can be employed as targeted therapy for resistant enterococcal infections, additional clinical and pharmacodynamic data would better facilitate the use of lefamulin for severe enterococcal infections. The Phase II ABSSSI study did not report outcomes related to isolation of *E. faecium*, and there are no published prospective or retrospective data on the topic to date [48]. Unfortunately, prospective randomized trials on severe *E. faecium* infections are logistically difficult to complete and it is unlikely to have such studies in the near future. With higher MIC distributions, the likelihood of target attainment based on thresholds using other organisms may be low. Readily accessible susceptibility testing in institutional microbiology labs would also be necessary, as susceptibility to other antimicrobial classes would not predict efficacy with lefamulin.

**Sexually Transmitted Infections: Neisseria gonorrhoeae and Mycoplasma genitalium**

Drug-resistant *N. gonorrhoeae* is considered an urgent threat by the CDC due to its ease of transmission, ability to develop resistance, and the complications associated with untreated infections [1]. Lefamulin exhibited minimal cross-resistance to gonococcus when macrolide-, quinolone-, and tetracycline-non-susceptible isolates were tested, which can certainly be beneficial in the future scope of global and public health. The MIC50/90 against 251 *N. gonorrhoeae* strains were 0.25/1 mg/L and ranged from 0.004–2 mg/L [7]. In another in vitro analysis examining 25 strains, the MIC50/90 were 0.12/0.5 mg/L. The activity of lefamulin was not impacted by inactivation of MacAB/NorM efflux pumps; however, a significant change in MIC (4–6-fold) was observed when MtrCDE efflux pump was inactivated [7]. Further data studying lefamulin’s pharmacokinetics, pharmacodynamics, resistance, and clinical efficacy in the setting of MDR. *N. gonorrhoeae* infections are needed; there are no active clinical trials for lefamulin in the setting of sexually transmitted infection (STI).

Lefamulin is also active against *M. genitalium*, another STI implicated in the most recent issue of the CDC threats report [1, 61]. In the presence of macrolide resistance, *M. genitalium* infections become very difficult to treat. Although the target binding site for both lefamulin and macrolides is the 50S ribosome, lefamulin maintained potency against the five macrolide-resistant strains of *M. genitalium* with MICs ranging from 0.016 to 0.063 mg/L. Another analysis examined 21 macrolide-resistant strains and observed similar potency and MIC range [8]. Lefamulin is also active against *C. trachomatis* and thus may be useful in co-infection [61].

**Specialized Populations**

**High-Risk/Recurrent Clostridiodes difficile Infections**

If over 50% of hospitalized patients receive an antimicrobial during hospitalization [62], and 1 in 5 exposed patients develop an antimicrobial-related ADE, in theory, 10% of all hospitalized adults suffer from an ADE [63]. This is likely underestimated, given that the lack of available data describing incidence/duration of microbiota disruption and its subsequent consequences—an ADE that is not easily measured in large cohorts. *Clostridiodes difficile* can be rare in patients otherwise at low risk, receiving broad-spectrum antibiotics,
hence low incidence in LEAP-1 and LEAP-2. However, an often unmeasured, and more frequent antibiotic-related, ADE is the collateral damage that leads to colonization of *C. difficile* and resistant organisms. Restriction of oral antimicrobials commonly used for respiratory tract infections (i.e., amoxicillin-clavulanate, fluoroquinolones, clindamycin, cephalosporins) significantly reduces incidence of CDI [64]. Lefamulin could be considered to have a reduced amount of “collateral damage” compared to other commonly used oral antimicrobials. Lefamulin’s spectrum of Gram-positive, atypical, and limited Gram-negative organisms is similar to tetracyclines, which as a class are far less implicated in CDI [61]. There were no significant differences in incidence of *C. difficile* or multi-drug-resistant organisms when compared to moxifloxacin, and interestingly, more diarrhea with oral lefamulin (but less with IV) [46, 47]. This could be advantageous if adopted as CABP therapy in comparison to other recommended agents. Thorough microbiome studies have yet to be conducted with lefamulin, and no antimicrobial is free of risk.

**A Steward’s Perspective in a Looming Antimicrobial Crisis**

It remains unclear where the predominant uptake of systemic pleuromutilins will be. There have been numerous calls to action to bring antimicrobials with novel mechanisms of action to the market [65]. And despite achieving the goal of 10 new antimicrobials approved in the USA by 2020 as outlined in the Infectious Diseases Society of America 10 × ’20 initiative of 2010 [66], antibiotic development continues to be an uphill battle. Given that there are several readily available and less costly agents recommended by societal guidelines, the immediate and frequent use of lefamulin for more common indications such as CABB and ABSSSI in hospitalized adults is unlikely without significant reimbursements. Health systems are paid out on diagnosis-related group (DRG) models which do not specifically include antimicrobial expenditures. Thus, there are pressures that drive cost avoidance with antimicrobial use, which may not always be in the best interest of a patient [67]. Ambulatory patients with qualifying insurance plans may be a larger population of usage, pending the local availability and operationalization of additional steps such as prior authorization. Even with the availability of newer, safer, and more effective antimicrobials for MDR Gram-negative infections, the uptake of novel agents in the USA has been slow while systemic polymyxin use has not drastically decreased [68].

Lefamulin was granted Qualified Infectious Disease Product (QIDP) status by the FDA which allows 5 years of marketing exclusivity and eligibility for Fast Track designation [69, 70]. However, the current pull incentives alone have not been able to keep the highest producers of new antimicrobials in the market. Clinical trials cost millions, and clinicians seek answers in patient populations that are difficult to identify and/or enroll, which requires robust multicenter studies that will ultimately span over years. Over 30 million United States dollars (USD) were provided from the Biomedical Advanced Research and Development Authority (BARDA) to support the development of meropenem/vaborbactam, one of the two available beta-lactam-beta-lactamase-inhibitor combinations available in the USA for carbapenemase-producing Enterobacteriales (CRE) [71]. Achaeeogen received almost US$150 million from BARDA and the US Department of Health and Human Services to develop plazomycin, a unique aminoglycoside antibiotic that was added to the World Health Organization Essential Medicines List. These incentives were still inadequate due to low distribution volumes and price points for small patient populations, leading to both companies filing for bankruptcy [67, 72]. Medications in the oncology space, such as avapritinib (Aykavit®), can be fast tracked and granted orphan drug status following small, open-label single-arm studies in patients with rare conditions; effectiveness against specific mutations can also expand use and indications [73]. Perhaps the market entry process for antimicrobials is overly rigorous, demanding large and costly randomized trials to evaluate endpoints in disease states, e.g., ABSSSI, urinary tract infections, rather than populations where the drug may benefit most, e.g., multi-drug resistance. Recently, the antiviral remdesivir was granted Orphan Drug status by the FDA for the management of SARS-CoV-2; however, the request was rescinded after criticisms of monopolizing the therapy [74].

Can pharmaceutical companies with a new antimicrobial such as lefamulin succeed in an era of intense antimicrobial stewardship and costs-savings initiatives? A bill was put forward in 2018 excluding antimicrobials from the DRG. The act, DISARM (Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act of 2019), would allow add-on payments to hospitals enrolled with Medicare using a qualified agent beginning in 2020 [75]. Others describe the development model as ineffective and suggest a path involving non-profit organizations to promote antibiotic R&D and avoid the pressures of higher profit margins [9]. Some have even pointed towards stewards, physicians, and pharmacies as those among other responsible parties who “killed antibiotic development” [72, 76]. Regardless, as responsible clinicians and prescribers, prompt initiation of optimal medication should be a priority. While an agent with a novel mechanism such as lefamulin should be protected, stewardship involves identification of the populations that would benefit most, such as those with severe intolerances, historical *C. difficile*, or multi-drug-resistant infections.
Conclusion

Lefamulin is a pleuromutilin antibiotic that inhibits protein synthesis inhibition and has a spectrum of activity that includes most Gram-positive and atypical organisms, *H. influenzae*, *M. catarrhalis*, and some pertinent anaerobes. Lefamulin has been shown to be an effective option in treating CABP, and other Phase II studies suggest efficacy in treating ABSSSI. Until more appropriate reimbursement models are developed, we suspect that health systems will continue to utilize existing, generic antibiotics (i.e., beta-lactams ± macrolide/tetracycline, or fluoroquinolones) over newly developed agents for treatment of CABP and ABSSSI due to cost and lack of presence in treatment guidelines. Populations who may benefit from lefamulin over traditional therapies include those in settings with a high prevalence of community-associated MRSA, patients at higher risk of adverse effects from fluoroquinolone use, and in patients with history of *C. difficile* or multiple antimicrobial intolerances. Interesting opportunities for use also exist in multi-drug-resistant Gram-positive and sexually transmitted organisms, although we are unlikely to see clinical trial data in these populations soon and will await real-world experiences. While a hospital’s and patient’s ability to financially cope and comply with therapy must always be considered, cost alone should not dictate treatment. We operate in an era where the development of antimicrobials is undesirable due to the lack of profitability and have witnessed the disappearance of multiple agents and manufacturers. Lefamulin is a well-tolerated agent with a novel mechanism, availability in both IV and PO formulations, and it has been rigorously studied for safety and efficacy for CABP.

Authors’ Contributions NJM and MPV both contributed equally to the design and writing of this manuscript.

Data Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest MPV has received grant funding from Paratek Pharmaceuticals.

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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