



Lefamulin: A Novel Oral and Intravenous Pleuromutilin for the Treatment of Community-Acquired Bacterial Pneumonia

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Abstract

Lefamulin is a novel oral and intravenous (IV) pleuromutilin developed as a twice-daily treatment for community-acquired bacterial pneumonia (CABP). It is a semi-synthetic pleuromutilin with a chemical structure that contains a tricyclic core of five-, six-, and eight-membered rings and a 2-(4-amino-2-hydroxycyclohexyl)sulfanylacetate side chain extending from C14 of the tricyclic core. Lefamulin inhibits bacterial protein synthesis by binding to the 50S bacterial ribosomal subunit in the peptidyl transferase center (PTC). The pleuromutilin tricyclic core binds to a pocket close to the A site, while the C14 side chain extends to the P site causing a tightening of the rotational movement in the binding pocket referred to as an induced-fit mechanism. Lefamulin displays broad-spectrum antibacterial activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria as well as against atypical bacteria that commonly cause CABP. Pleuromutilin antibiotics exhibit low rates of resistance development and lack cross-resistance to other antimicrobial classes due to their unique mechanism of action. However, pleuromutilin activity is affected by mutations in 23S rRNA, 50S ribosomal subunit proteins *rpIC* and *rpID*, ATP-binding cassette (ABC)-F transporter proteins such as *vga(A)*, and the methyltransferase *cfr*. The pharmacokinetic properties of lefamulin include: volume of distribution (V_d) ranging from 82.9 to 202.8 L, total clearance (CL_T) of 19.5 to 21.4 L/h, and terminal elimination half-life ($t_{1/2}$) of 6.9–13.2 h; protein binding of lefamulin is high and non-linear. The oral bioavailability of lefamulin has been estimated as 24% in fasted subjects and 19% in fed subjects. A single oral dose of lefamulin 600 mg administered in fasted patients achieved a maximum plasma concentration (C_{max}) of 1.2–1.5 mg/L with a time of maximum concentration (T_{max}) ranging from 0.8 to 1.8 h, and an area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) of 8.5–8.8 mg h/L. The pharmacodynamic parameter predictive of lefamulin efficacy is the free plasma area under the concentration-time curve divided by the minimum inhibitory concentration ($fAUC_{24h}/MIC$). Lefamulin efficacy has been demonstrated using various animal models including neutropenic murine thigh infection, pneumonia, lung infection, and bacteremia. Lefamulin clinical safety and efficacy was investigated through a Phase II clinical trial of acute bacterial skin and skin structure infection (ABSSSI), as well as two Phase III clinical trials of CABP. The Phase III trials, LEAP 1 and LEAP 2 established non-inferiority of lefamulin to moxifloxacin in both oral and IV formulations in the treatment of CABP. The United States Food and Drug Administration (FDA), European Medicines Agency (EMA), and Health Canada have each approved lefamulin for the treatment of CABP. A Phase II clinical trial has been completed for the treatment of ABSSSI, while the pediatric program is in Phase I. The most common adverse effects of lefamulin include mild-to-moderate gastrointestinal-related events such as nausea and diarrhea. Lefamulin represents a safe and effective option for treating CABP in cases of antimicrobial resistance to first-line therapies, clinical failure, or intolerance/adverse effects to currently used agents. Clinical experience and ongoing clinical investigation will allow clinicians and antimicrobial stewardship programs to optimally use lefamulin in the treatment of CABP.

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Key Points for Decision Makers

Lefamulin is the first systemic (oral and intravenous) pleuromutilin approved by the United States Food and Drug Administration (FDA) in 2019 and by the European Medicines Agency (EMA) and Health Canada in 2020 for the treatment of community-acquired bacterial pneumonia (CABP).

Lefamulin exhibits broad-spectrum antibacterial activity against Gram-positive, Gram-negative, and atypical bacterial pathogens that commonly cause CABP. Due to its novel mechanism of action, lefamulin demonstrates activity versus pathogens resistant to other chemically unrelated antimicrobial classes used to treat CABP.

Lefamulin represents a safe and effective option for treating CABP in cases of antimicrobial resistance, clinical failure, or intolerance/adverse effects to first-line agents.

1 Introduction

Community-acquired bacterial pneumonia (CABP) remains a significant cause of morbidity and mortality worldwide. Annually in the USA, pneumonia is estimated to cause more than 1.5 million hospitalizations and 100,000 deaths [1]. Mortality rates are expected to increase over time as the average age of our population increases. Standard empiric antimicrobial treatments for CABP include macrolides, fluoroquinolones, tetracyclines, and β -lactams (alone or in combination); however, bacterial resistance rates to these agents are increasing [2]. In some regions of the USA, rates of *Streptococcus pneumoniae* resistance to macrolides exceed 40% [3]. Other concerns related to the treatment of patients with CABP include adverse effects as well as collateral damage to the microbiome with associated risk of *Clostridium difficile* infection [1]. Limitations of existing antimicrobial treatments for CABP encourage new agent development.

Pleuromutilin was isolated in the 1950s from an edible mushroom, *Pleurotus mutilus*, that is now known as *Clitopilus scyphoides* [4] and was observed to inhibit the growth of *S. aureus* [5]. By testing various C14 side chains and altering other structures of the pleuromutilin molecule, tiamulin was identified and became the first pleuromutilin to be approved for clinical (veterinary) use in 1979. Tiamulin was followed by valnemulin in 1999, which was used in veterinary medicine for pulmonary and intestinal infections of pigs, poultry and rabbits [4]. Retapamulin was approved

in 2007 for human topical use in impetigo, infected small lacerations, abrasions, and sutured wounds [5].

In 2006, Nabriva Therapeutics began testing the novel semisynthetic pleuromutilin lefamulin (Xenleta®), formerly known as BC-3781, for systemic use in humans [5]. Lefamulin, an oral and intravenous (IV) pleuromutilin, demonstrated clinical efficacy and a favorable safety profile in the treatment of CABP in two large Phase III clinical trials: LEAP 1 and 2 (Lefamulin Evaluation Against Pneumonia) [6]. In August 2019, the United States Food and Drug Administration (FDA) approved lefamulin for treatment of CABP [7]. The European Medicines Agency (EMA; 28 states of the European Union, as well as Norway, Liechtenstein, and Iceland) approved lefamulin in June 2020 followed by Health Canada in July 2020.

Lefamulin displays a broad spectrum of in vitro activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria, and atypical bacteria, including resistant strains such as methicillin resistant *S. aureus* (MRSA), multidrug-resistant (MDR) *S. pneumoniae* and macrolide-resistant *Mycoplasma pneumoniae* [8]. Low rates of resistance development in pathogens associated with CABP following repeated lefamulin exposures support it as a therapeutic agent for CABP [4]. Lefamulin has demonstrated clinical efficacy in acute bacterial skin and skin structure infections (ABSSSI) in a Phase II clinical trial [5] and Nabriva Therapeutics has an ongoing Phase I trial for oral and IV lefamulin use in pediatric patients [9]. Lefamulin has also demonstrated in vitro activity against *Chlamydomonas trachomatis*, *Neisseria gonorrhoeae*, *M. genitalium*, and *Haemophilus ducreyi* [4].

This paper reviews the existing published data on lefamulin, including relevant chemistry, mechanisms of action, mechanisms of resistance, microbiology, pharmacokinetics, pharmacodynamics, animal models, clinical trials, adverse effects, drug interactions, and its place in therapy. We conducted a comprehensive search of PubMed using the search term “lefamulin” (up to July 2020) to identify references for this paper. Recent publications (manuscripts and scientific posters) related to lefamulin were also obtained directly from Nabriva Therapeutics.

2 Chemistry

The basic pleuromutilin structure with various R groups for lefamulin, tiamulin, valnemulin, and retapamulin is depicted in Fig. 1. The structure contains a tricyclic core consisting of five-, six-, and eight-membered rings with a sulfanyl glycolic ester moiety extending from C14 [4]. The tricyclic mutilin core is stabilized through hydrophobic and Van der Waals interactions in the peptidyl transferase center (PTC)

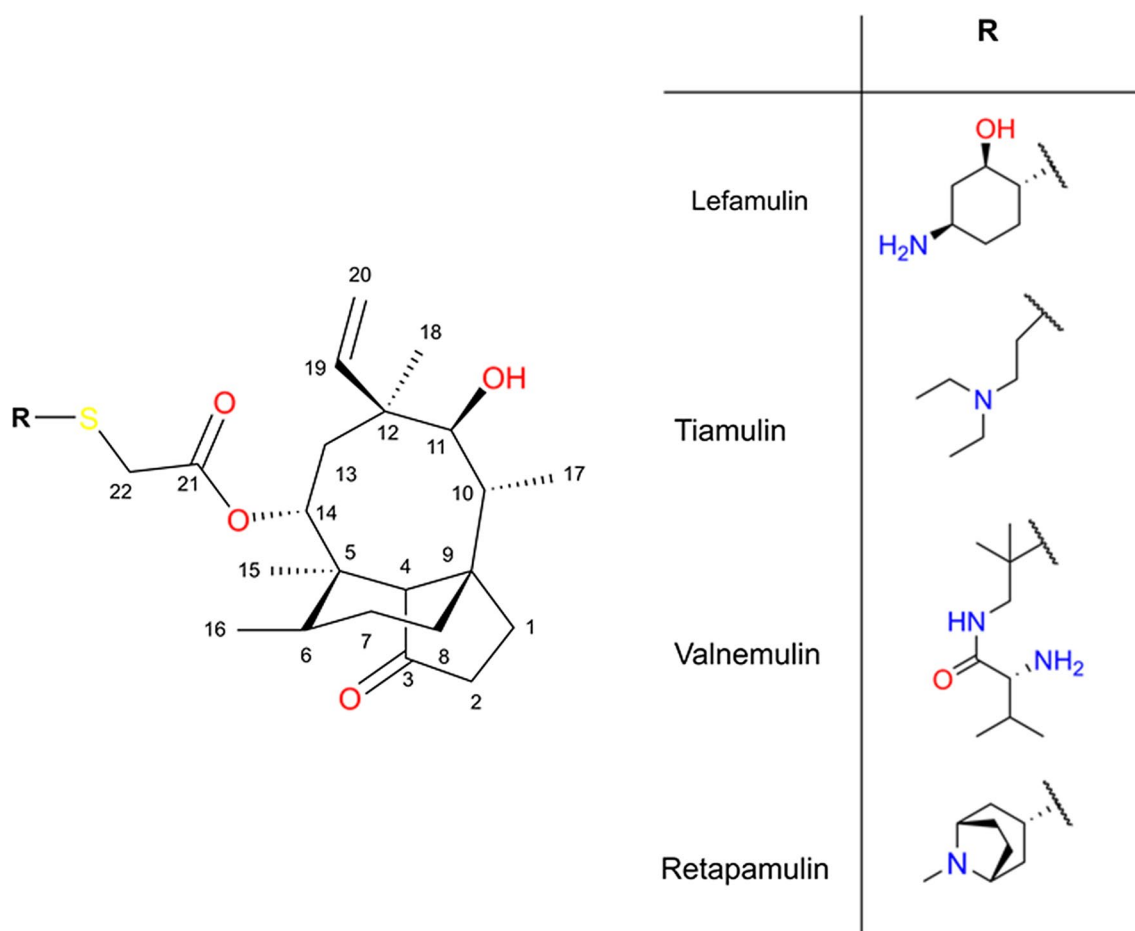


Fig. 1 Chemical structures of pleuromutilins

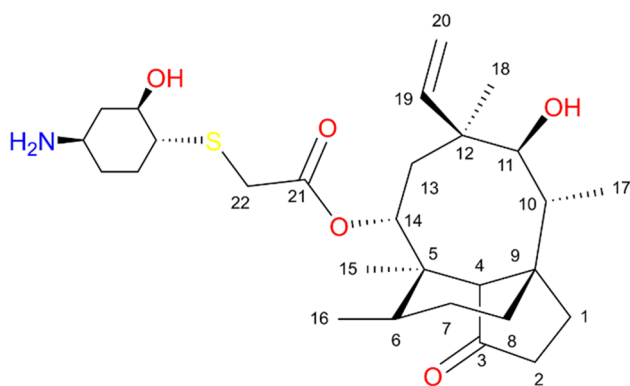


Fig. 2 Chemical structure of lefamulin

of the bacterial ribosome [10]. The C21 carbonyl group is essential for antimicrobial activity and hydrogen bonding to the PTC [5, 11]. The majority of modifications are on the C14 side chain where two types of semisynthetic pleuromutilin analogs are created: the flexible sulfanylacetyl type and the rigid acylcarbamate linker type [4]. So far, only the

sulfanylacetyl type derivatives (lefamulin, retapamulin, tiamulin, valnemulin) have progressed beyond Phase I clinical studies [4, 11]. Pleuromutilin derivatives with substituents on the C14 side chain are active versus macrolide-resistant *M. pneumoniae* and MDR Gram-positive bacteria, including MRSA, penicillin-resistant *S. pneumoniae* (PRSP), and methicillin resistant *S. epidermidis* (MRSE) [12].

Lefamulin, a 14-*O*-{[1R,2R,4R]-4-amino-2-hydroxycyclohexylsulfanyl}-acetyl}-mutilin (Fig. 2), was discovered in 2006 [5]. The C14 side chain of lefamulin plays an important role in its antibacterial activity. Findings have shown a relationship between the C14 side chain and characteristics such as permeability, oral bioavailability, plasma protein binding, metabolism, CYP450 interactions, hERG inhibition, and target organ toxicity [5]. A hydrophilic C14 side chain allows for good drug solubility [10]. The C14 side chain of lefamulin includes a hydroxyl (OH) group and a primary amine (NH₂) group which increases its aqueous solubility. Microbiological activity has been shown for derivatives with a thioether group in place of the hydroxyl group of the glycolic ester in pleuromutilins like lefamulin

[5]. Biological activity and water-solubility are enhanced when there is a thioether in the C14 side-chain [12]. Lefamulin interacts with the ribosomal PTC through four hydrogen bonds, causing an induced-fit in the binding site; less hydrogen bonding may not create the same induced-fit [13]. The induced-fit of lefamulin may account for its greater potency against MRSA [11].

Further, pleuromutilin derivatives with thiazole groups on the side chain have demonstrated promising antibacterial activity against Gram-positive bacteria (Fig. 3) [14]. Piperidinyl groups on the C14 side chain have demonstrated potent activity (MIC = 0.0625–2 mg/L) against MRSE, MSSE, and MSSA [14]. Findings have shown that C14 side chains with a bulky substituent group such as *n*-butyl may decrease the activity of the compound [14]. Compounds with a secondary amino substituent group instead of a tertiary or primary amino group also demonstrated lower activity. Compounds with a para-substituted benzene ring in the C14 side chain demonstrated a key structure activity relationship with substituents with a weak electron donating group resulting in lower antibacterial activity [12]. Electron withdrawing substituents like trifluoromethyl, nitro, cyano, or acyl groups increased antibacterial activity [12]. Para-methoxy, amide, or methyl groups decreased antibacterial activity. In general, pleuromutilin antibacterial activity is enhanced when the para-position substituent on the benzene ring is either a strong electron donating group or an electron withdrawing group [12]. In lefamulin, the NH₂ group in the para-position of the cyclohexane ring acts as a strong electron donating group. Antimicrobial activity also increases with pyrimidine groups on the C14 side chain [10].

3 Mechanisms of Action

Pleuromutilin activity stems from its ability to inhibit prokaryotic protein synthesis through binding to the 50S ribosomal subunit in the PTC [5]. This interaction prevents tRNA from positioning correctly in the A and P (acceptor and donor, respectively) sites which inhibits peptide bond formation [4, 5]. The pleuromutilin tricyclic core binds to a pocket close to the A site and the C14 side chain extends to the P site [5]. The core is considered an anchor for drug binding [15]. The core binds to nucleotides of domain V of 23S rRNA (A2503, U2504, G2505, U2506) with hydrogen bonding between C11 and nucleotides G2505 or A2503 [4]. The pleuromutilin tricyclic core interacts hydrophobically with nucleotides U2504 and C2452 [15]. Other hydrogen bonds within the PTC include the C21 carbonyl and the sulfur of the C14 side chain. The C14 side chain interacts with nucleotides resulting in rotational movements to close the binding pocket around the pleuromutilin substrate in what is known as the induced-fit mechanism [4].

Lefamulin has additional hydrogen bonding from the amino group of the C14 extension [4]. The hydrogen bond between the C14 side chain amino group and U2506 in *S. aureus* may be responsible for tighter binding and stabilization in the pocket. The induced-fit mechanism of lefamulin also creates a U:U interaction between U2506 and U2585 in the *S. aureus* 50S-lefamulin complex which acts as a physical barrier to maintain the tight binding pocket conformation, potentially resulting in greater potency in *S. aureus* [15]. Other interactions between the rRNA nucleotides and

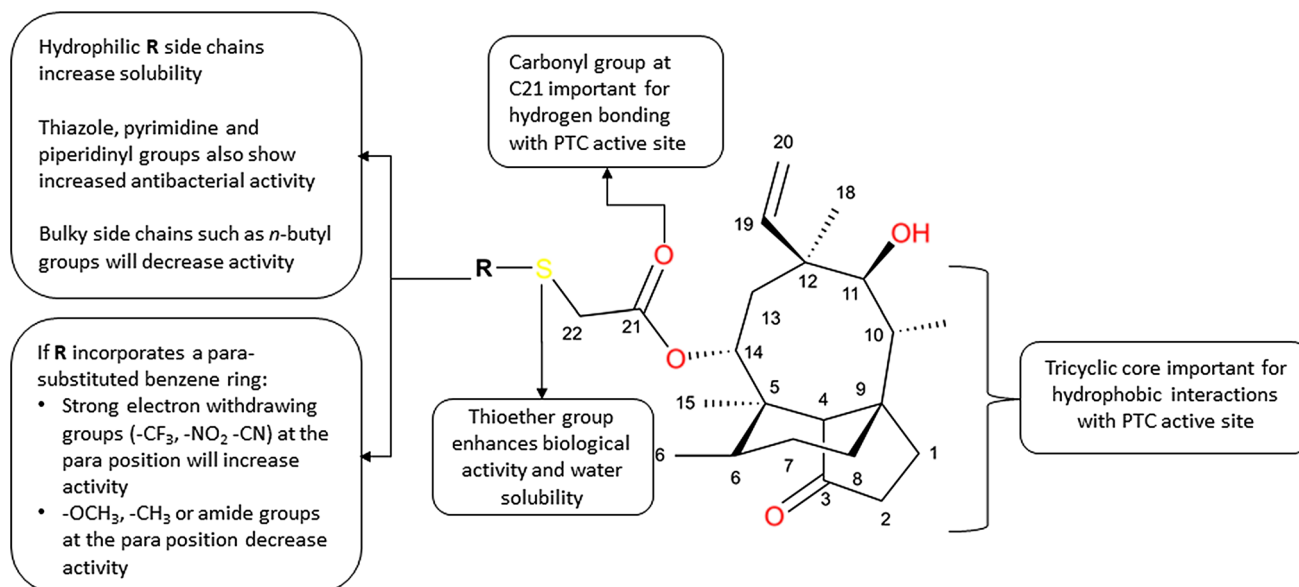


Fig. 3 General structure-activity relationships for pleuromutilins adapted from [4, 10–12, 14]

lefamulin are largely hydrophobic or based on Van der Waals forces [15]. Lefamulin is bactericidal ($\geq 3\log_{10}$ reduction over 24 h) in vitro against *S. pneumoniae*, *H. influenzae*, and *M. pneumoniae*, including macrolide-resistant strains, and bacteriostatic ($< 3\log_{10}$ reduction over 24 h) in vitro against *S. pyogenes* and *S. aureus*, including MSSA and MRSA [16].

Pleuromutilins may also affect translation initiation but not elongation as evidenced by: (1) radioactive tiamulin did not inhibit protein synthesis once chain elongation was initiated, (2) protection of the rRNA bases U2584 and U2585, both involved in the binding of P site tRNA, (3) fMet-tRNA binding is destabilized during translation initiation, and (4) addition of tiamulin to intact cells caused disappearance of polysomes and defective initiation complexes [4, 5]. Pleuromutilins do not have any activity versus eukaryotes due to their ribosome core binding pocket being more rigid and chemically stabilized. Also, the walls of the eukaryotic ribosome binding pocket are open and the pleuromutilin tricyclic core cannot be anchored for activity [15]. The selectivity mechanism of pleuromutilins for bacterial ribosomes is also due to additional base-pairing in the second shell of the PTC (U2500 and A2543) which keeps the binding pocket in a “closed” form to interact with the tricyclic core [15]. This mechanism confers extra stability to the binding pocket.

In general, the pleuromutilin mechanism of action is highly specific due to its structure. The tricyclic core anchors in the 50S ribosomal PTC near the A site and the C14 side chain further stabilizes the mutilin substrate in the P site. The induced-fit mechanism differs from other antibiotic mechanisms and distinguishes the pleuromutilins from other antimicrobial classes that inhibit protein synthesis including the macrolides, tetracyclines and oxazolidinones.

4 Mechanisms of Resistance

Pleuromutilins have a low probability of developing resistance and cross resistance to other antimicrobial classes (e.g. β -lactams, macrolides, fluoroquinolones, tetracyclines, or glycopeptides) because of their unique mechanism of action (i.e. specific mechanism of ribosomal binding) [3, 4]. Pleuromutilin spontaneous mutation frequencies are low ($\leq 10^{-9}$) and progress in a slow and step-wise manner [4]. High-level resistance is only achieved after multiple mutations [3, 4]. Resistance mechanisms affecting the pleuromutilins include: (1) mutations in 23S rRNA, (2) mutations in *rplC* and *rplD* genes, (3) mutations in ATP-binding cassette (ABC)-F transporter genes such as *vga(A)*, and (4) mutations in the methyltransferase *cfr* gene (Table 1) [4].

Mutations in 23S rRNA confer pleuromutilin resistance in *Mycoplasma* spp. and *Brachyspira* spp. since they possess only one copy of 23S rRNA, whereas *Staphylococcus*

Table 1 Pleuromutilin resistance mechanisms and associated resistance genes. Adapted from references [4, 17]

Pleuromutilin resistance mechanism	Resistance gene
23S rRNA mutations	<i>Brachyspira</i> spp.: 2032, 2055, 2447, 2499, 2504, 2572 <i>Mycobacterium smegmatis</i> : 2055, 2447, 2504, 2572 <i>Streptococcus epidermidis</i> : G241T, T669C, T1236C <i>Staphylococcus aureus</i> : A21G, A1557T, and/or A2234G
L3, L4 mutations	<i>rplC</i> , <i>rplD</i>
ATP-binding cassette (ABC)-F transporters	<i>vga(A)</i> , <i>vga(A)v</i> , <i>vga(A)LC</i> , <i>vga(B)</i> , <i>vga(C)</i> , <i>vga(D)</i> , <i>vga(E)</i> , <i>lsa(E)</i>
Methyltransferase Cfr	<i>cfr</i>

spp. and *Streptococcus* spp. have two copies. Mutations in the 23S rRNA have been described to confer resistance to tiamulin in *Brachyspira* spp. and valnemulin in *M. smegmatis* [17]. The SENTRY program reported that a well-known oxazolidinone resistance mechanism (G2576T) in the 23S rRNA affected tiamulin and valnemulin binding to bacterial ribosomes. The G2576T resistance mechanism appears to have less effect on lefamulin than oxazolidinones, likely the result of greater hydrogen bonding of lefamulin to the 50S ribosomal subunit.

Mutations and deletions in *rplC* and *rplD* genes, which encode the L3 and L4 proteins, result in conformational changes in the PTC which affect the pleuromutilin positioning in the binding pocket [4]. *rplC* and *rplD* gene mutations have been reported in *Staphylococcus* spp. and *rplC* mutation has been associated with a loss of fitness [4]. Single and double mutations in *rplC* result in moderate decreases in pleuromutilin binding, that when accompanied by a third mutation in *rplC* results in a significant increase in pleuromutilin MIC [5].

Staphylococcus spp. and *Enterococcus faecium* have demonstrated resistance to pleuromutilins that are attributable to ABC-F transporter *vga(A)* encoded genes and its variant *vga(A)v* [4]. ABC-F transporters likely interfere with translation in the PTC resulting in ribosomal protection [4]; *vga* genes are located on plasmids and can be transferred between bacteria [18]. The most frequent resistance mechanisms detected by the SENTRY global surveillance program were *vga* and *lsa(E)* in staphylococci and streptococci [19].

Resistance to PhLOPS antimicrobial agents (phenicols, lincosamides, oxalidinones, pleuromutilins, and streptogramins) is mediated through methyltransferase Cfr [4]. Methylation of the A2503 nucleotide of 23S rRNA results in steric hindrance, producing the PhLOPS_A resistant phenotype [4, 18]. The *cfr* gene has been identified on the chromosome and on the pSCFS1 plasmid suggesting it has the

ability to spread [4, 8]. Conjugation and transduction of the *cfr*-carrying plasmids from *S. epidermidis* to MRSA indicates that *S. epidermidis* may be a potential reservoir for spread of the *cfr* gene [4].

The SENTRY surveillance program monitored resistance in lefamulin in 2010 and reported low rates of resistance. The total incidence of resistance in pleuromutilins was 0.18% in *S. aureus* and 3.4 in CoNS [4]. In the *S. aureus* isolates, 0.018% had the *cfr* gene, 0.11% had the *vga(A)* gene, and 0.05% had *rpIC* mutation. In the CoNS isolates, 0.11% had the *cfr* gene, 2.5 had *vga(A)*, and 0.34% had *rpID* alterations [4].

5 Microbiology

Published data reporting in vitro activity of lefamulin against Gram-positive and Gram-negative aerobic and anaerobic bacteria, atypical bacteria, and bacteria associated with sexually transmitted infections are summarized in Tables 2, 3, 4, 5 and 6. The MIC values of lefamulin and comparator drugs azithromycin, ceftriaxone, and moxifloxacin were gathered from comparative studies evaluating lefamulin as well as studies that did not evaluate lefamulin.

Table 2 displays the in vitro activities of lefamulin and comparator agents against Gram-positive aerobic bacteria including isolates with common resistance phenotypes [17, 20–52]. Lefamulin possesses activity against *Staphylococcus* spp. and *Streptococcus* spp. Lefamulin is active against *S. aureus* and *S. pneumoniae* regardless of resistance phenotype or genotype. The lefamulin MIC against *Enterococcus* spp. including *E. faecium* is lower than azithromycin.

Table 3 presents the in vitro activity of lefamulin and comparators against Gram-negative aerobic bacteria, including isolates with resistant phenotypes [21–23, 26–29, 31, 35, 37–39, 41–45, 48, 49, 51–53]. Lefamulin is poorly active versus Enterobacterales such as *Escherichia coli* and *Klebsiella pneumoniae*. Lefamulin is active versus *Haemophilus* spp. and *Moraxella catarrhalis*.

Table 4 summarizes the in vitro activities of lefamulin and comparator agents against Gram-negative anaerobes [38, 41, 47, 54]. In general, lefamulin has weak activity against anaerobic bacteria with higher MIC values than azithromycin, ceftriaxone, and moxifloxacin. Lefamulin has potent activity against *Porphyromonas* spp. with a MIC₅₀ of 0.03 mg/L and a MIC₉₀ of 0.03 mg/L.

Table 5 summarizes the in vitro activities of lefamulin and comparator agents against atypical bacteria [26, 35, 51, 53, 55]. Lefamulin displays potent in vitro activity against atypical bacteria regardless of resistant phenotypes. In general, lefamulin has greater activity against atypical bacteria than azithromycin and moxifloxacin. Lefamulin also possesses in vitro activity against bacteria that cause

sexually transmitted infections, including resistant phenotypes (Table 6) [45, 56–59]. Overall, lefamulin demonstrates potent in vitro activity against bacteria that cause sexually transmitted infections, including resistant phenotypes. These data suggest potential future indications for lefamulin in the treatment of some sexually transmitted infections.

6 Pharmacokinetics

The pharmacokinetic (PK) parameters for oral and IV lefamulin are summarized in Tables 7 and 8. Most PK data to date is in healthy volunteers, with limited study in patients with community-acquired pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSI). Lefamulin is orally absorbed with a reported bioavailability of approximately 25% [60, 61]. In a study by Wicha et al [60], the area under the concentration-time curve (AUC_{0–∞}) measurements with 600 mg of lefamulin administered orally in a fasted state were similar to those achieved with 150 mg infused IV. The mean oral to IV ratios of AUC_{0–∞} for capsule and tablet formulations were 97% and 103%, respectively (Table 7) [60]. The same authors characterized the effect of food on oral absorption [60], where the bioavailability of lefamulin was reduced by 25% when administered 1 h after a high-fat, high-calorie meal (i.e., fed to fasted AUC_{0–∞} ratio of 75%) (Table 7) [60]. There was less effect when the meal was consumed 1 h after the oral dose of lefamulin (i.e. fed to fasted AUC_{0–∞} ratio of 91%) [60]. These data are consistent with population-PK modeling by Zhang et al that estimated an oral bioavailability of 24% and 19% in fasted and fed subjects, respectively [61]. To minimize the effects of food on absorption, it is recommended that lefamulin be taken at least 1 h before or at least 2 h after a meal [62].

PK studies of lefamulin report volumes of distribution (V_d) ranging from 82.9 to 202.8 L (Table 8) [60, 63, 64], with a total drug clearance (CL_T) of 19.5–21.4 L/h, and elimination half-life (t_{1/2}) of 6.9 to 13.2 h (Table 8) [60, 63, 64]. Lefamulin is primarily metabolized by CYP3A4 enzymes in the liver [62, 65]. In vitro lefamulin acted as a substrate and potential inhibitor of CYP3A4 but did not induce CYP3A4 or CYP1A2 [65]. A relatively small amount of lefamulin is excreted unchanged. Following a single 150 mg IV dose, 4.2–9.1% and 9.6–14.1% was excreted unchanged in the feces and urine, respectively. After an oral dose of 600 mg, 7.8–24.8% was recovered unchanged in the feces [62].

Lefamulin is highly bound to plasma proteins [62, 66–68]. An in vitro study using equilibrium dialysis also showed non-linear protein binding where the percentage of unbound lefamulin was 12.1% ± 0.3% at 1 mg/L, 17.1% ± 1.7% at 3 mg/L, and 27.3% ± 6.1% at 10 mg/L [66]. In a study of clinical doses in 11 healthy volunteers, the percentage of unbound lefamulin was 2.9% ± 0.6% at 0.25 mg/L and 5.2%

Table 2 In vitro activities (MIC, mg/L) of lefamulin and comparator agents against Gram-positive aerobic bacteria. Adapted from Refs. [17, 20–52]

Bacteria (phenotype)	Lefamulin			Azithromycin		Ceftriaxone		Moxifloxacin	
	MIC ₅₀ ^a	MIC ₉₀ ^b	MIC range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Staphylococcus aureus</i> (all)	0.06	0.12	≤ 0.008–> 32	0.5	> 32	0.5	4	≤ 0.06	4
<i>S. aureus</i> (MSSA)	0.06	0.12	≤ 0.008–> 8	0.5	> 32	4	4	≤ 0.06	≤ 0.06
<i>S. aureus</i> (MRSA)	0.06	0.12	≤ 0.008–> 32	> 32	> 32	> 32	> 32	2	> 4
<i>S. aureus</i> (CA-MRSA)	0.06	0.06	0.06–0.12	0.5	> 4	2	8	0.5	2
<i>S. aureus</i> (HA-MRSA)	0.06	0.12	0.06–0.12	0.5	> 4	> 32	> 32	> 4	> 4
<i>S. aureus</i> (MAC-R)	0.06	0.12	< 0.03 to 0.25	> 32	> 32	> 32	> 32	2	> 4
<i>S. aureus</i> (ERY-R)	0.06	0.12	0.015–> 16	> 32	> 32	2	16	0.12	> 4
<i>S. aureus</i> (FLQ-R)	0.06	0.12	0.03–0.25	> 32	> 32	2	16	> 4	> 4
<i>S. aureus</i> (LEV-R)	< 0.03	0.12	< 0.03 to 0.12	> 4	> 4	2	16	> 4	> 4
<i>S. aureus</i> (MDR)	0.06	0.12	0.03 to 0.25	> 32	> 32	> 32	> 32	4	> 4
<i>S. aureus</i> (XDR)	0.06	0.12	0.03 to 0.25	> 32	> 32	> 32	> 32	4	> 4
Coagulase-negative <i>Staphylococcus</i> (all)	0.06	0.12	≤ 0.008 to > 16	32	> 32	8	32	0.12	4
CoNS (MET-S)	0.06	0.12	≤ 0.008–8	0.5	> 16	1	2	0.06	1
CoNS (MET-R)	0.06	0.12	≤ 0.008–> 16	> 16	> 16	32	> 32	1	2
CoNS (XDR)	0.06	0.25	0.03 to 16	> 32	> 32	> 32	> 32	2	> 4
β-Hemolytic <i>Streptococcus</i> (all)	0.03	0.03	≤ 0.008 to > 32	0.12	8	0.03	0.06	0.12	0.25
<i>Streptococcus agalactiae</i>	0.015	0.03	≤ 0.008–> 32	0.12	> 16	0.06	0.06	0.12	0.25
<i>Streptococcus pyogenes</i>	0.03	0.03	≤ 0.008 to 0.12	0.12	0.25	0.03	0.03	0.12	0.25
<i>Streptococcus dysgalactiae</i>	0.03	0.06	0.015–0.12	0.12	0.25	0.03	0.06	0.12	0.25
<i>S. dysgalactiae</i> (MAC-R)	0.03	0.03	≤ 0.008–16	4	8	0.06	0.06	0.12	0.25
Viridans Group <i>Streptococcus</i> (all)	0.12	0.25	≤ 0.008–> 8	0.12	8	0.25	0.5	0.12	0.25
<i>Streptococcus mitis</i>	0.12	0.5	0.015–0.5	ND	ND	0.12	2	0.12	0.25
<i>Streptococcus anginosus</i>	0.06	0.25	≤ 0.008 to 0.5	ND	ND	0.25	0.25	0.12	0.25
<i>Streptococcus salivarius</i>	0.06	0.12	≤ 0.008 to 0.25	ND	ND	0.12	0.5	0.12	0.25
<i>Streptococcus vestibularis</i>	0.06	0.12	≤ 0.008 to 0.25	ND	ND	ND	ND	ND	ND
<i>Streptococcus gallolyticus</i>	1	2	0.06 to > 32	ND	ND	ND	ND	ND	ND
<i>Streptococcus lutetiensis</i>	0.015	ND	≤ 0.008 to > 32	ND	ND	ND	ND	ND	ND
<i>Streptococcus bovis</i>	1	2	≤ 0.008 to > 16	ND	ND	0.12	0.12	0.25	4
<i>Enterococcus</i> spp. (All)	4	> 16	≤ 0.008 to > 16	4	> 16	> 32	> 32	2	8
<i>Enterococcus faecium</i>	0.12	16	0.015–> 16	> 16	> 16	> 32	> 32	2	8
<i>E. faecium</i> (VAN-S)	0.12	> 16	0.03 to > 16	> 16	> 16	> 32	> 32	1	4
<i>E. faecium</i> (VAN-R)	0.12	8	0.03–> 16	> 16	> 16	> 32	> 32	4	8
<i>Enterococcus faecalis</i>	> 16	> 16	4 to > 16	> 16	> 16	> 32	> 32	0.25	4
<i>Streptococcus pneumoniae</i> (all)	0.06	0.12	≤ 0.008–> 2	0.06	> 4	0.03	1	0.12	0.25
<i>S. pneumoniae</i> (PEN-S)	0.06	0.12	0.015–0.25	2	16	0.015	0.06	0.12	0.25
<i>S. pneumoniae</i> (PEN-I)	0.06	0.12	0.015–0.25	4	> 16	0.25	1	0.12	0.25
<i>S. pneumoniae</i> (PEN-R)	0.06	0.12	≤ 0.015–0.5	> 4	> 4	1	2	0.12	0.25
<i>S. pneumoniae</i> (MAC-R)	0.06	0.12	0.015–2	> 4	> 4	0.25	1	0.12	0.25
<i>S. pneumoniae</i> (CRO-S)									
<i>S. pneumoniae</i> (CRO-I)	0.06	0.12	0.015–0.25	0.06	> 4	1	2	0.12	0.25
<i>S. pneumoniae</i> (CRO-R)	0.06	0.12	0.015–0.25	1	> 4	2	8	0.12	0.25
<i>S. pneumoniae</i> (ERY-S)	0.06	0.12	≤ 0.015–0.5	0.03	0.06	0.03	0.06	0.12	0.25
<i>S. pneumoniae</i> (ERY-I)	0.06	0.12	≤ 0.008–1	1	2	0.06	0.12	0.12	0.25
<i>S. pneumoniae</i> (ERY-R)	0.06	0.12	≤ 0.008–1	> 32	> 32	0.5	2	0.12	0.25
<i>S. pneumoniae</i> (LEV-I)	0.06	0.12	0.015–1	ND	ND	0.06	0.12	1	2
<i>S. pneumoniae</i> (LEV-R)	0.06	0.25	0.015–1	1	2	0.06	0.12	2	8
<i>S. pneumoniae</i> (TET-R)	0.12	0.25	0.015–0.5	> 4	> 4	0.25	2	0.12	0.25

Table 2 (continued)

Bacteria (phenotype)	Lefamulin			Azithromycin		Ceftriaxone		Moxifloxacin	
	MIC ₅₀ ^a	MIC ₉₀ ^b	MIC range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>S. pneumoniae</i> (FUR-R)	ND	0.12	0.12	1	4	0.12	0.25	0.12	0.25
<i>S. pneumoniae</i> (CLR-R)	ND	0.25	0.25	1	4	0.12	0.25	0.12	0.25
<i>S. pneumoniae</i> (DOX-R)	ND	0.25	0.25	> 4	> 4	0.12	0.25	0.12	0.25
<i>S. pneumoniae</i> (SXT-R)	ND	0.12	0.12	2	4	0.12	0.25	0.12	0.25
<i>S. pneumoniae</i> (MDR)	0.06	0.12	≤ 0.015–1	> 4	> 4	0.5	2	0.12	0.25
<i>S. pneumoniae</i> (XDR)	0.06	0.12	0.015–0.25	> 4	> 4	1	2	0.12	0.25

CA-MRSA community-associated methicillin-resistant *S. aureus*, HA-MRSA hospital-associated methicillin-resistant *S. aureus*, CLR-R clarithromycin-resistant, CRO-I ceftriaxone-intermediate (MIC 1 mg/L), CRO-R ceftriaxone-resistant (MIC ≥ 2 µg/mL), CRO-S ceftriaxone-susceptible (≤ 0.5 mg/L), DOX-R doxycycline-resistant, ERY-R erythromycin-resistant, FLQ-R fluoroquinolone-resistant, FUR-R cefuroxime-resistant, LEV-R levofloxacin-resistant, MAC-R macrolide-resistant, MDR multidrug-resistant, MET-R methicillin-resistant, MET-S methicillin-susceptible, MRSA methicillin-resistant *S. aureus*, MSSA methicillin-susceptible *S. aureus*, ND no data, PEN-I penicillin-intermediate (MIC 0.12–1 mg/L), PEN-R penicillin-resistant (MIC ≥ 2 mg/L), PEN-S penicillin-susceptible (MIC ≤ 0.06 mg/L), SXT-R trimethoprim-sulfamethoxazole-resistant, TET-R tetracycline-resistant, VAN-S vancomycin-susceptible, VAN-R vancomycin-resistant, XDR extensively drug resistant

^aMIC₅₀, minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates

^bMIC₉₀, minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates

Table 3 In vitro activities (MIC, mg/L) of lefamulin and comparator agents against Gram-negative aerobic bacteria. Adapted from Refs. [21–23, 26–29, 31, 35, 37–39, 41–45, 48, 49, 51–53]

Bacteria (phenotype) ^a	Lefamulin			Azithromycin		Ceftriaxone		Moxifloxacin	
	MIC ₅₀ ^a	MIC ₉₀ ^b	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Escherichia coli</i>	32	32	32	> 32	> 32	0.06	> 16	0.06	0.5
<i>Klebsiella pneumoniae</i>	> 32	> 32	> 32	> 32	> 32	0.06	> 16	0.12	0.5
<i>Haemophilus influenzae</i>	0.5	1	0.01–58	1	1	≤ 0.06	≤ 0.06	0.03	0.03
<i>H. influenzae</i> (BLN)	0.5	1	0.015–8	1	2	≤ 0.06	≤ 0.06	0.03	0.03
<i>H. influenzae</i> (BLP)	0.5	1	0.12–8	1	2	≤ 0.06	≤ 0.06	0.03	0.03
<i>Haemophilus parainfluenzae</i>	1	4	0.12–8	1	2	≤ 0.06	≤ 0.06	0.03	0.03
<i>Moraxella catarrhalis</i>	0.06	0.12	≤ 0.008 to 0.25	0.06	0.12	0.25	0.5	0.06	0.06

BLN β-lactamase-negative, BLP β-lactamase-positive

^aMIC₅₀, minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates

^bMIC₉₀, minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates

± 1.3% at 2.35 mg/L, equivalent to 97.1% and 94.8% protein binding, respectively [62, 68].

The plasma concentration profiles of lefamulin have been characterized for the IV and oral doses (Tables 7 and 8). The maximum plasma concentration ($C_{\max}$) after a single 150 mg IV dose infused over 1-h ranged from 1.9 to 2.7 mg/L [60, 63, 64]. In comparison, the $C_{\max}$ with an oral dose of 600 mg in fasted patients was 1.2 to 1.5 mg/L at 0.9 to 1.8 h [60]. The time to reach $C_{\max}$ (i.e. $T_{\max}$) was significantly delayed to 4.5–5 h when lefamulin was administered with food [60]. The AUC_{0–∞} achieved with a single 150 mg IV dose was 7.5–8.2 mg h/L [60, 63, 64], compared to 8.5–8.8 mg h/L with a 600 mg oral dose in a fasted state [60]. A multiple-dose regimen of 150 mg IV every 12 h resulted in an AUC_{0–24 h} of 14.1 ± 5.8 mg h/L on Day 1 versus 16.5 ± 6.2 mg h/L on day 5 [60].

Zeitlinger et al. [63] studied the distribution of lefamulin into epithelial lining fluid (ELF) in 12 healthy males. Following a single 150 mg IV dose, bronchoalveolar lavage was performed in each subject to obtain three ELF samples at 1, 2, 4, and 8 h. Plasma concentrations were measured at various time points, and unbound concentrations were estimated assuming 87% protein binding. The lefamulin AUC_{0–12 h} in ELF was 4.5 mg h/L compared to 5.8 mg h/L (i.e. $fAUC_{0–12 h}$ of 0.8 mg h/L) in plasma.

The PK of lefamulin have been investigated in patients with hepatic and renal impairment [68, 69]. In a study by Wicha et al. a single 150 mg IV dose achieved AUC_{0–∞} values of 7.6 ± 1.6 mg h/L, 8.2 ± 2.3 mg h/L, and 8.9 ± 1.6 mg h/L in subjects with no ($n = 11$), moderate (Child-Pugh Class B, $n = 8$), and severe hepatic impairment (Child-Pugh Class C, $n = 8$), respectively [68]. Given

Table 4 In vitro activities (MIC, mg/L) of lefamulin and comparator agents against anaerobic bacteria. Adapted from Refs. [38, 41, 47, 54]

Bacteria	Lefamulin			Azithromycin		Ceftriaxone		Moxifloxacin	
	MIC ₅₀ ^a	MIC ₉₀ ^b	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Clostridioides</i> spp.	1	> 16	0.06 to > 16	0.5	1	8	32	1	2
<i>Clostridioides difficile</i>	4	8	0.25 to > 32	2	16	32	64	1	2
<i>Clostridioides perfringens</i>	ND	ND	0.06–4	0.25	0.25	2	8	0.5	0.5
<i>Peptostreptococcus</i> spp.	0.06	1	0.03–2	0.25	0.25	0.12	0.25	0.25	0.5
<i>Bacterioides</i> spp.	> 16	> 16	> 16	0.5	4	8	> 128	0.5	1
<i>Bacterioides fragilis</i>	16	> 16	2 to > 16	2	8	8	64	2	8
<i>Fusobacterium</i> spp.	ND	ND	0.03–32	16	≥ 64	0.12	4	0.12	0.5
<i>Porphyromonas</i> spp.	0.03	0.03	0.03	ND	ND	ND	ND	ND	ND
<i>Prevotella</i> spp.	0.5	4	0.015 to > 16	ND	ND	0.5	32	ND	ND

ND no data

^aMIC₅₀, minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates

^bMIC₉₀, minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates

Table 5 In vitro activities (MIC, mg/L) of lefamulin and comparators against atypical bacteria. Adapted from Refs. [26, 35, 51, 53, 55]

Bacteria (phenotype)	Lefamulin			Azithromycin		Ceftriaxone		Moxifloxacin	
	MIC ₅₀ ^a	MIC ₉₀ ^b	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Legionella pneumophila</i>	0.06	0.5	0.06–1	0.015	0.015	ND	ND	0.015	0.015
<i>Chlamydophila pneumoniae</i>	0.02	0.04	0.02–0.08	0.03	0.25	ND	ND	0.5	1
<i>Mycoplasma pneumoniae</i>	≤ 0.001	0.002	≤ 0.001–0.024	16	> 32	ND	ND	0.125	0.25
<i>M. pneumoniae</i> (M-S)	≤ 0.001	≤ 0.001	≤ 0.001	≤ 0.001	≤ 0.001	ND	ND	0.125	0.25
<i>M. pneumoniae</i> (M-R)	0.002	0.002	0.003	32		ND	ND	0.125	0.25

M-R macrolide-resistant, M-S macrolide-susceptible, ND no data

^aMIC₅₀, minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates

^bMIC₉₀, minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates

Table 6 In vitro activities (MIC, mg/L) of lefamulin and comparator agents against bacteria causing sexually transmitted infections. Adapted from Refs. [45, 56–59]

Bacteria (phenotype) ^a	Lefamulin			Azithromycin		Ceftriaxone		Moxifloxacin	
	MIC ₅₀ ^a	MIC ₉₀ ^b	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Mycoplasma genitalium</i>	≤ 0.008	0.06	0.0005–0.06	0.06	> 16	ND	ND	0.125	8
<i>M. genitalium</i> (M-S)	0.004	≤ 0.008	0.005–≤ 0.008	ND	ND	ND	ND	ND	ND
<i>M. genitalium</i> (M-R)	0.016	0.06	0.002–0.06	ND	ND	ND	ND	ND	ND
<i>M. genitalium</i> (MDR)	0.063	ND	0.002–0.063	> 16	ND	ND	ND	8	ND
<i>Neisseria gonorrhoeae</i>	0.12	0.5	0.004–2	0.03	0.5	≤ 0.008	0.03	0.06	2
<i>N. gonorrhoeae</i> (AZI-S)	0.25	0.5	0.004–1	0.25	0.5	0.03	0.03	0.06	2
<i>N. gonorrhoeae</i> (AZI-R)	0.5	1	0.016–2	2	32	0.06	0.12	0.12	4
<i>Chlamydophila trachomatis</i>	0.02	0.04	0.01–0.04	0.1	0.2	ND	ND	0.05	0.05

AZI-R azithromycin-resistant, AZI-S azithromycin-susceptible, MDR multidrug-resistant, M-R macrolide-resistant, M-S macrolide-susceptible, ND no data

^aMIC₅₀, minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates

^bMIC₉₀, minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates

Table 7 Pharmacokinetic parameters for oral lefamulin. Adapted from Ref. [60]

Study	Subjects (healthy adults)	<i>n</i> (M/F)	Oral dose	<i>T</i> _{max} (h)	<i>C</i> _{max} (mg/L)	AUC (mg h/L)	AUC _{0-∞} geometric mean ratio	
							Comparator	Ratio of oral dose to comparator (% CI _{90%})
Wicha et al [60]	33.8 ± 11.8 years, 75.7 ± 12.5 kg	12/8	600 mg tab × 1 (fasted)	1.8 [0.5–5.0] 0.9 [0.5–4.0]	1.2 ± 0.3 1.3 ± 0.3	8.6 ± 2.8 ^a 8.8 ± 2.8 ^a	150 mg IV × 1 150 mg IV × 1	103 (95–123) 97 (91–105)
			600 mg (3 × 200 mg cap) × 1 (fasted)	5.0 [1.1–8.0]	0.9 ± 0.2	7.0 ± 2.3 ^a	150 mg IV × 1	84 (77–92)
			600 mg tab × 1 (fed 1 h before)					
			600 mg tab × 1 (fasted)	1.0 [0.3–4.0] 0.8 [0.33–3.0]	1.4 ± 0.4 1.3 ± 0.5	8.5 ± 1.9 ^a 7.6 ± 2.2 ^a	ND 600 mg tab × 1 (fasted)	ND 91 (82–100) 75 (68–82)
	40.6 (22–54) years, 77.3 (55–92.5) kg	13/0	600 mg tab × 1 (fasted, then fed 1 h after)	4.5 [2.0–6.0]	0.9 ± 0.3	6.5 ± 2.1 ^a	600 mg tab × 1 tab × 1 (fasted)	
			600 mg tab × 1 (fed)					
	40 ± 10.6 years, 75.8 ± 8.5 kg	12/0	600 mg tab q12 h × 7 days (fasted)	0.9 [0.5–5] 2.0 [0.5–3]	1.5 ± 0.4 1.9 ± 0.6	6.4 ± 1.7 ^b 10.8 ± 4.2 ^b	ND ND	ND ND
			Day 1 Day 7					

Data presented as mean (range), mean ± standard deviation, or median [range]

AUC area under the concentration-time curve; cap oral capsule; *C*_{max} maximum plasma concentration; IV intravenous; M/F male/female; ND no data available; tab immediate-release oral tablet; *T*_{max} time to maximum plasma concentration

^aAUC_{0-∞}

^bAUC_{0-12 h}

the concurrent increase in unbound drug from 2.9 to 5.2% (no hepatic disease) to 9.2–13.5% (severe hepatic disease) [68], an extended dosing interval of 150 mg IV every 24 h is recommended for patients with severe hepatic impairment [62]. Since oral lefamulin has not been studied, it is currently not recommended for patients with either moderate or severe hepatic disease [62]. Wicha et al also studied the PK of lefamulin in renal impairment. Following a single 150 mg IV dose, the AUC_{0-∞} in subjects with normal renal function (*n* = 7) was 9.0 ± 2.6 mg h/L compared to 12.3 ± 7.8 mg h/L in those with renal impairment (eGFR < 30 mL/min/1.73 m², *n* = 8) [69]. The AUC_{0-∞} in patients with end-stage renal disease on hemodialysis ranged from 8.6 ± 2.8 mg h/L to 9.0 ± 3.1 mg h/L. No dosing adjustment is recommended for patients with impaired renal function, including those on hemodialysis [62].

In a population PK modeling study, the PK of lefamulin based on data from 849 subjects were best described by a 3-compartment model with first-order elimination and saturable protein binding [70]. The study incorporated data from previously published population PK models [61, 66], and included four Phase I studies in healthy volunteers, one Phase II study in patients with ABSSSI and two Phase III studies in

patients with CAP. The immediate oral absorption rate constant (*k*_a) was 1.2 h⁻¹ with a delayed absorption rate constant (*k*_{a2}) of 2.1 h⁻¹. The PK parameters were scaled to free (*f*) lefamulin levels [66], reporting a total *f*CL of 79.4 L/h (2.1% standard error of the estimate [SEE]), and *f* *V*_d in the central, first peripheral, and second peripheral compartments of 46.3 L (6.9% SEE), 249.0 L (9.1% SEE), and 259.0 L, respectively [66]. Significant covariate relationships were identified between lefamulin *f*CL and serum albumin, and *f* *V*_d (first peripheral compartment) and total bodyweight [66].

7 Pharmacodynamics

There is limited research on the pharmacodynamics (PD) of lefamulin. In a neutropenic murine thigh infection model study, Wicha et al observed that free AUC divided by the MIC (*f*AUC_{24h}/MIC) best correlated with the antibacterial effects of lefamulin [67]. The study characterized lefamulin activity against *S. aureus*, including MSSA and MRSA strains (*n* = 5, lefamulin MIC = 0.06–0.12 mg/L), and *S. pneumoniae*, including penicillin-susceptible, and penicillin- and macrolide-resistant strains (*n*

Table 8 Pharmacokinetic parameters for IV lefamulin. Adapted from Refs. [60, 63, 64]

Study	Subjects	n (M/F)	IV Dose (1 h Infusion)	C _{max} (mg/L)	AUC (mg h/L)	V _d (L)	CL _T (L/h)	t _{1/2} (h)
Wicha et al [60]	Healthy adults, 33.8 ± 11.8 years, 75.7 ± 12.5 kg Adults with ABSSSI, 42.4 ± 13.4 years, 96.7 ± 24.5 kg	12/8 47/24	150 mg IV × 1	2.4 ± 0.3	8.0 ± 1.3 ^a	ND	ND	ND
			150 mg IV q12 h × 5 days	ND	ND	82.9 ± 36.4	20.9 ± 8.9	13.2 ± 5.8
			Day 1	1.9 ± 0.7	14.1 ± 5.8 ^b	ND	ND	ND
			Day 5	2.1 ± 0.7	16.5 ± 6.2 ^b	ND	ND	ND
Zeitlinger et al [63]	Healthy adults, 26.9 ± 8.1 years, 77.6 ± 12.2 kg	12/0	150 mg IV × 1	2.5 [1.8–3.5]	5.8 [4.2–9.0] ^c	202.8 [134–376]	21.0 [13.7–28.4]	6.9 [5.8–9.5]
Wicha et al [64]	Healthy adults including elderly, ≥ 18 years, 78.0 ± 13.9 kg	18/20	150 mg IV × 1	2.5 ± 0.4	7.5 ± 1.8 ^a	159 ± 37.2	21.4 ± 6.1	9.3 ± 1.5
				2.7 ± 0.8	8.2 ± 2.3 ^a	145 ± 35.3	19.5 ± 5.3	9.6 ± 1.3
			Males					
			Females					

Data presented as mean ± standard deviation, or median [range]

ABSSSI acute bacterial skin and skin structure infection, AUC area under the concentration-time curve, CL_T total drug clearance, C_{max} maximum plasma concentration, IV intravenous, ND no data available, t_{1/2} elimination half-life, V_d volume of distribution

^aAUC_{0–∞}

^bAUC_{0–24 h}

^cAUC_{0–12}

= 5, lefamulin MIC = 0.06–0.12 mg/L [67]. Two hours after inoculation, two lefamulin doses (10–320 mg/kg) were administered subcutaneously 12 h apart. Reductions of one log₁₀ or greater in *S. aureus* and *S. pneumoniae* at 24 h were associated with mean fAUC_{24h}/MIC values of 32.8 (21.8–42.2) and 7.0 (3.5–15.1), respectively. This study also investigated the potential for post-antibiotic effect (PAE) against an MSSA isolate and penicillin-susceptible *S. pneumoniae* isolate. In this case, mice were administered a single lefamulin dose of 10, 20, or 40 mg/kg and sacrificed at various times. Although the rate of kill was similar among doses, the suppression of regrowth was dose dependent. The authors reported observations of in vivo PAEs of 1–1.5 h against *S. aureus* and 3–3.5 h against *S. pneumoniae*.

Wicha et al also studied the PD of lefamulin in a neutropenic murine pneumonia model using clinical strains of *S. aureus*, including MSSA and MRSA (*n* = 6, lefamulin MIC 0.06–0.5 mg/L), and *S. pneumoniae*, including penicillin- and macrolide-resistant and MDR strains (*n* = 8, lefamulin MIC 0.03–0.5 mg/L) [71]. Lefamulin doses (1.25–160 mg/kg) were administered at 2 h and 5 h, using a shorter dosing interval given the more rapid drug clearance in mice compared to humans. The PD analysis showed that one and two log₁₀ reductions in *S. aureus* were associated with a mean fAUC_{24h}/MIC in plasma of 2.1 (0.8–5.9) and 6.2 (1.4–15.3),

respectively. The total AUC_{24h}/MIC values in ELF were 21.7 (7.7–60.7) and 63.9 (14.5–157.0) for one and two log₁₀ kill, respectively. For *S. pneumoniae*, one and two log₁₀ reductions were associated with a mean fAUC_{24h}/MIC in plasma of 1.4 (0.7–6.1) and 2.2 (1.1–10.7), respectively. The total AUC_{24h}/MIC values in ELF were 14.0 (6.8–61.8) and 22.0 (10.8–109.0) for one and two log₁₀ kill, respectively. This study also reported that drug uptake into murine macrophages was rapid, and that in vitro bovine lung surfactant did not significantly alter the lefamulin MIC [71].

Lastly, a study by Bhavnani et al used Monte Carlo simulations to predict the probability of target attainment with lefamulin in the treatment of *S. aureus* or *S. pneumoniae* pneumonia. Lefamulin dosing regimens including 150 mg IV every 12 h and 600 mg orally every 12 h in a fed or fasted state were tested [72]. Lefamulin concentration profiles in plasma and ELF were simulated based on a previously published population PK model that used Phase I study data [61]. The PD targets were based on the mean AUC_{24h}/MIC thresholds for one log₁₀ kill identified in the murine pneumonia study described above [71]. The MIC distributions used in the simulations were based on surveillance data for *S. aureus* and *S. pneumoniae* from the 2015/2016 SENTRY Antimicrobial Surveillance Program [31]. The authors predicted that PD target attainment associated with one log₁₀ kill of *S. aureus* and *S. pneumoniae* in plasma and ELF

would exceed 98% for both the IV and oral dosing regimens of lefamulin.

8 Animal Models

The microbiological efficacy of lefamulin has been evaluated in vivo using animal models and is summarized in Table 9 [67, 71, 73, 74]. In both comparative and non-comparative animal model studies utilizing a variety of different pathogens, lefamulin has demonstrated bacteriological efficacy.

Wicha et al [67] used a neutropenic murine thigh infection model to evaluate the in vivo efficacy and PK/PD characteristics of lefamulin against five *S. pneumoniae* and five *S. aureus* strains. The researchers induced neutropenia by using two intraperitoneal injections of cyclophosphamide: injection one was 150 mg/kg and was given four days before infection and injection two was 100 mg/kg and was given the day before infection. The mice were infected in one or both thighs with either *S. pneumoniae* or *S. aureus*, and then treated with single subcutaneous doses of lefamulin (10, 20, or 40 mg/kg) 2 h post infection. The results concluded that lefamulin displays time-dependent killing and AUC/MIC was the best predictor of efficacy. The efficacy target for bacteriostatic 24-h AUC/MIC is approximately 70 [67].

Wicha et al [71] evaluated the in vivo efficacy and PK/PD of lefamulin against *S. pneumoniae* and *S. aureus* in a neutropenic lung infection model, as well as the effect of bovine lung surfactant on lefamulin antibacterial activity. Mice were given two intraperitoneal cyclophosphamide injections to induce neutropenia and infected with *S. pneumoniae* or *S. aureus* by placing the strain on the tip of the nares. Two hours after inoculation, the mice were treated with lefamulin 1.25–160 mg/kg doses twice daily given subcutaneously. The results showed that the bovine lung surfactant did not significantly increase the lefamulin MICs. Distribution of lefamulin from plasma to epithelial lining fluid (ELF) was rapid. One and two log₁₀ colony forming unit (CFU) reductions were associated with median plasma AUC/MIC ratios of 1.37 and 2.15 for *S. pneumoniae* and 2.13 and 6.24 for *S. aureus* [71].

In a neutropenic murine bacteremia model by Wicha et al. lefamulin was compared to daptomycin, vancomycin, linezolid, and tigecycline (Table 9). Immunocompromised and immunocompetent mice were infected with *S. aureus* and received a single subcutaneous dose of lefamulin or comparator 1-h post-inoculation [73]. The results of the study showed that lefamulin efficacy was comparable to daptomycin and vancomycin, but superior to linezolid and tigecycline, as seen in Table 9.

9 Clinical Trials

Lefamulin has been evaluated in a Phase II ABSSSI trial and two Phase III CABP trials (LEAP 1 and LEAP 2), which are described in Tables 10, 11 and 12 [75–77]. Phase I trials for pediatric indications have been initiated, and lefamulin is also being considered the sponsor for the treatment of urinary tract infections (UTIs).

A phase II clinical trial by Prince et al. investigated lefamulin as a treatment for ABSSSI caused by Gram-positive pathogens [75]. The trial was double-blinded with a parallel-group design and randomized 210 patients to IV BC-3781 100 mg (lefamulin), BC-3781 150 mg, or vancomycin 1 g every 12 h (Table 10) [75]. The primary endpoint of the study was the clinical success rate at the test of cure visit in the modified intent-to-treat (mITT: all randomized patients who received ≥ 1 dose of study drug and had a Gram-positive pathogen isolated on culture) and clinically evaluable (CE: patients who had a confirmed ABSSSI, met the inclusion/exclusion criteria, and fully complied with the protocol) populations. Patients were eligible for enrollment if they were aged ≥ 18 years with a clinically diagnosed ABSSSI that was known or suspected to be caused by a Gram-positive pathogen and required IV treatment. Treatment was considered successful when signs and symptoms of the infection were resolved or improved to a point where further antimicrobial therapy was no longer necessary [75]. Patient demographics and baseline characteristics were balanced among the three treatment groups with the most common infection types being cellulitis and abscess with cellulitis. The mean duration of treatment was approximately seven days for all study groups [75].

Clinical success rates in the CE and mITT populations using both doses of lefamulin were high and comparable to vancomycin (Table 10). Clinical success rates by baseline ABSSSI pathogens including MRSA were also comparable between lefamulin and vancomycin. When administered intravenously over 5–14 days, lefamulin was well tolerated at both doses [75]. The most common adverse effects for lefamulin were headache, nausea, diarrhea, and infusion site phlebitis. Diarrhea was reported in 4.3% of patients in the lefamulin 100 mg study arm, 5.6% of patients in the lefamulin 150 mg study arm, and 6.1% of patients in the vancomycin study arm [75]. The researchers concluded that lefamulin at both doses used demonstrated efficacy in the treatment of ABSSSI which was comparable to vancomycin.

LEAP 1 (Lefamulin Evaluation Against Pneumonia) was a global, multicenter, randomized (1:1), double-blinded, double-dummy, active-controlled, noninferiority trial of IV to oral antimicrobial therapy for the treatment of CABP (Table 11) [76]. LEAP 1 investigated the efficacy and safety of lefamulin 150 mg IV every 12 h transitioning to 600 mg

Table 9 Animal model studies involving lefamulin. Adapted from Refs. [67, 71, 73, 74]

Study	Animal model	Number of animals tested	Antimicrobial agent	Dose	Number of doses	Bacterial strain (resistance phenotype)	Results
Wicha et al [67]	Neutropenic murine thigh infection model	Ten female ICR/Swiss mice (4 thighs per dosing regimen)	Lefamulin	10, 40, or 160 mg/kg SC	1	<i>S. aureus</i>	1 log kill: 56 mg/kg q12h
						ATCC 25923 (MSSA)	1 log kill: 44.6 mg/kg q12h
						ATCC Smith (MSSA)	1 log kill: 42.9 mg/kg q12h
						ATCC 33591 (MRSA)	1 log kill: 64.3 mg/kg q12h
						UW 307109 (HA-MRSA)	1 log kill: 52.1 mg/kg q12h
						WIS-1 (HA-MRSA)	1 log kill: 34.7 mg/kg q12h
						<i>S. pneumoniae</i>	1 log kill: 7.98 mg/kg q12h
						ATCC 10813 (PEN-S)	1 log kill: 11.9 mg/kg q12h
						CDC 145 (PEN-R, MAC-R)	1 log kill: 19.8 mg/kg q12h
						CDC 1020 (PEN-R, MAC-R)	1 log kill 9.59 mg/kg q12h
						CDC 1293 (PEN-R, MAC-R)	
						CDC 1329 (PEN-R, MAC-R)	
Wicha et al [71]	Neutropenic murine pneumonia model	60 neutropenic female mice (6 females/group)	Lefamulin	1.24–160 mg/kg SC twice daily	2	<i>S. pneumoniae</i>	2 log kill in ELF: 109 (AUC/MIC)
						B1378 (PEN-I)	2 log kill in ELF: 40.5 (AUC/MIC)
						B1382 (PEN-S)	2 log kill in ELF: 10.8 (AUC/MIC)
						B1383 (PEN-R, MAC-R)	2 log kill in ELF: 10.8 (AUC/MIC)
						B1385 (PEN-S)	2 log kill in ELF: 22.0 (AUC/MIC)
						B1386 (PEN-I, MAC-R)	2 log kill in ELF: 22.0 (AUC/MIC)
						<i>S. aureus</i>	2 log kill in ELF: 17.0 (AUC/MIC)
						B154 (MSSA)	2 log kill in ELF: 17.0 (AUC/MIC)
						B341 (MRSA)	2 log kill in ELF: 34.9 (AUC/MIC)
						B1118 (MRSA)	2 log kill in ELF: 85.7 (AUC/MIC)
						B1325 (MRSA)	2 log kill in ELF: 14.5 (AUC/MIC)
						B1331 (MRSA)	2 log kill in ELF: 64.0 (AUC/MIC)
							2 log kill in ELF: 157 (AUC/MIC)
Wicha et al. [74]	Neutropenic murine lung infection model	Six neutropenic female mice	Lefamulin	1.25–320 mg/kg in two divided doses	2	<i>S. pneumoniae</i>	1 log kill plasma/ELF: 1.37/14.0 (AUC/MIC)
						<i>S. aureus</i>	1 log kill plasma/ELF: 2.13/21.7 (AUC/MIC)

Table 9 (continued)

Study	Animal model	Number of animals tested	Antimicrobial agent	Dose	Number of doses	Bacterial strain (resistance phenotype)	Results
Wicha et al [73]	Neutropenic and immunocompetent murine bacteremia model	Eight mice infected with <i>S. aureus</i>	Lefamulin Daptomycin Vancomycin Linezolid Tigecycline	70 mg/kg 22.5 mg/kg 160 mg/kg 80 mg/kg 6.5 mg/kg	1 1 1 1 1	<i>S. aureus</i>	$\Delta\log_{10}$: – 4.50 CFU/mL in non-neutropenic, – 4.14 CFU/mL in neutropenic $\Delta\log_{10}$: – 4.58 CFU/mL in non-neutropenic, – 4.26 CFU/mL in neutropenic $\Delta\log_{10}$: – 4.58 CFU/mL in non-neutropenic, – 3.79 CFU/mL in neutropenic $\Delta\log_{10}$: – 1.97 CFU/mL in non-neutropenic, – 0.37 CFU/mL in neutropenic $\Delta\log_{10}$: – 3.67 CFU/mL in non-neutropenic, – 2.91 CFU/mL in neutropenic

ELF epithelial lining fluid, *HA-MRSA* hospital-acquired methicillin-resistant *Staphylococcus aureus*, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-susceptible *S. aureus*, *MAC-R* macrolide-resistant, *PEN-I* penicillin-intermediate, *PEN-R* penicillin-resistant *PEN-S* penicillin-susceptible, *SC* subcutaneously

Table 10 Phase II clinical trial of lefamulin. Adapted from Ref. [75]

Trial description	Number of patients randomized	Treatment regimens	Clinical response (%) in patients at TOC	
			CE	mITT
NCT01119105 Randomized, double-blinded, parallel-group, IV treatment for acute bacterial skin and skin structure infection (ABSSSI)	210 (207 received ≥ 1 dose of study medication)	Lefamulin 100 mg IV q12h $\times$ 5–14 days ($n = 70$) Lefamulin 150 mg IV q12h $\times$ 5–14 days ($n = 71$) Vancomycin 1 g IV q12h $\times$ 5–14 days ($n = 66$)	Lef 100 mg: 90.0% (54/60) Lef 150 mg: 88.9% (48/54) Vancomycin 1 g: 92.2% (47/51)	Lef 100 mg: 82.0% (41/50) Lef 150 mg: 82.4% (42/51) Vancomycin 1 g: 82.4% (42/51)

Data presented as rate of clinical response [% (no. successful/total no.)] in patients administered study medication. Clinically evaluable (CE) defined as patients who had a confirmed ABSSSI, met the inclusion/exclusion criteria, and fully complied with the protocol. Modified intent-to-treat (mITT) defined as patients in the intent-to-treat (ITT) population (received ≥ 1 dose of study drug) who had a Gram-positive pathogen isolated from a culture of blood or the ABSSSI site. Clinical success, defined as resolution of all signs and symptoms of infection or improvement such that no further antimicrobial therapy was required, was assessed at 7–14 days after treatment (test of cure, TOC) in the CE and mITT populations.
IV intravenously, q12h every 12 h, Lef/lefamulin

orally every 12 h in comparison with moxifloxacin 400 mg IV every 24 h transitioning to 400 mg orally every 24 h. If MRSA was suspected during screening, patients were administered placebo in the lefamulin arm or linezolid 600 mg IV every 12 h in the moxifloxacin arm. Linezolid was discontinued if a baseline culture did not confirm MRSA. LEAP 1 consisted of adults (aged ≥ 18 years) having fulfilled the FDA entry criteria for CABP trials which included radiographic findings suggesting pneumonia, Pneumonia Outcomes Research Team (PORT) risk classes of III or higher, acute illness (≤ 7 days), and ≥ 3 CABP symptoms (dyspnea, new or increased cough, purulent sputum production, chest pain). Of the 586 patients screened, 551 were enrolled in the trial: 276 were randomized to treatment with lefamulin while 275 were randomized to treatment with moxifloxacin [76]. Patient demographics and baseline characteristics were balanced between the two treatment groups: 52.2% were aged < 65 years in the lefamulin group (60.7% in the moxifloxacin group), 86.6% were white in the lefamulin group (86.9% in the moxifloxacin group), the majority of patients had a CURB-65 score of 1 or 2 in both treatment groups, 2.5% were bacteremic in the lefamulin group

(1.1% in the moxifloxacin group), 1.1% had severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$) in both groups, and 43.8% had normal renal function in lefamulin group (48.7% in the moxifloxacin group). The distribution of patients by PORT risk class was comparable between the lefamulin group and moxifloxacin group. The percentage of patients in PORT risk classes III and IV were 71.0% and 27.5% for the lefamulin group and 73.1% and 25.5% for the moxifloxacin group, respectively.

Patients were evaluated through early clinical assessment ($96 \text{ h} \pm 24 \text{ h}$ after the first dose of study drug), end of treatment (within 2 days after the last dose of study drug), test of cure (TOC; 5–10 days after the last dose of study drug), and late follow-up visits (30 ± 3 days after the first dose of study drug) [76]. The FDA primary endpoint was the early clinical response (ECR; assessed at $96 \text{ h} \pm 24 \text{ h}$ after the first dose of study drug) in the intent-to-treat (ITT) population. The European Medicines Agency (EMA) co-primary endpoints consisted of an investigator assessment of clinical response (IACR) at TOC in the mITT (all randomized patients who received ≥ 1 dose of study drug) and CE (no indeterminate clinical response, completed $\geq 48 \text{ h}$ of study

Table 11 Phase III clinical trials of lefamulin. Adapted from Refs. [76, 77]

Trial description	Number of patients randomized	Treatment regimens	Clinical response rate (%)		
			FDA	EMA	
			ECR ITT	IACR mITT	IACR CE-TOC
Phase III LEAP 1 NCT02559310 Multicenter, randomized, double-blinded, double-dummy, active-controlled, noninferiority trial of IV to oral antimicrobial therapy for the treatment of CABP	551	Lefamulin: 150 mg IV q12h, then on or after 3 days of IV treatment, possible transition to 600 mg orally q12h ($n = 276$)	87.3% (241/276)	81.7% (223/273)	86.9% (205/236)
		Moxifloxacin ^a : 400 mg IV q24h, then on or after 3 days of IV treatment, possible transition to 400 mg orally q24h ($n = 275$)	90.2% (248/275)	84.2% (230/273)	89.4% (219/245)
Phase III LEAP 2 NCT02813694 Multicenter, randomized, double-blinded, double-dummy, non-inferiority trial of oral antimicrobial therapy for the treatment of CABP	738	Lefamulin: 600 mg orally q12h $\times$ 5 days ($n = 370$)	90.8% (336/370)	87.5% (322/368)	89.7% (296/330)
		Moxifloxacin: 400 mg orally q24h $\times$ 7 days ($n = 368$)	90.8% (334/368)	89.1% (328/368)	93.6% (305/326)

Data presented as rate of clinical response [% (no. successful/total no.)] in patients administered study medication. Intent-to-treat (ITT) consists of all randomized patients. Early clinical response (ECR) defined as improvement in two or more CABP signs/symptoms, no worsening of any CABP sign/symptom, and no receipt of a nonstudy antimicrobial for CABP. ECR was assessed at $96 \pm 24 \text{ h}$ after the first dose of the study drug in the ITT population. Modified intent-to-treat (mITT) consists of all randomized patients who received ≥ 1 dose of study drug; analyzed based on randomized treatment group. Clinically evaluable (CE) consists of patients that met the following predefined criteria: no indeterminate clinical response, completed $\geq 48 \text{ h}$ of study drug (unless death occurred), no receipt of a nonstudy, systemic antibacterial with likely or documented activity against CABP pathogens, and no additional factor that might confound the assessment of efficacy. Investigator assessment of clinical response (IACR) success defined as resolution or improvement in CABP signs/symptoms such that no further antimicrobial therapy was required. IACR was determined at 5–10 days after the last dose of the study drug (test of cure, TOC) in the mITT and CE populations.

CABP community-acquired bacterial pneumonia, IV intravenously, q12h every 12 h, q24h every 24 h, FDA The US Food and Drug Administration, EMA The European Medicines Agency

^aMoxifloxacin $\pm$ linezolid 600 mg IV q12h if MRSA was suspected at screening

drug, no receipt of a non-study, systemic antibacterial with likely or documented activity against CABP pathogens, and no additional factor that might confound the assessment of efficacy) populations. ECR responders showed improvement in ≥ 2 CABP signs and symptoms, no worsening in any CABP sign/symptom, and had not received a concomitant, non-study antibiotic for CABP. IACR success was defined as CABP signs/symptoms resolved or improved such that no additional anti-bacterial therapy was administered for CABP. The treatment duration in LEAP 1 was 5–10 days. In the lefamulin group, 38.1% of patients transitioned from IV to oral therapy versus 44.3% for the moxifloxacin group [76].

In the LEAP 1 trial, lefamulin demonstrated noninferiority to moxifloxacin for the FDA and EMA primary endpoints (Table 11). Lefamulin had an 87.3 responder rate compared to 90.2% for moxifloxacin $\pm$ linezolid for the FDA primary endpoint ECR in the ITT population. The difference between both treatment groups was -2.9% (95% CI $-8.5, 2.8$) [76]. Lefamulin demonstrated success rates of 81.7% and 86.9% for the two EMA primary endpoints (IACR at the TOC visit in the mITT and CE populations, respectively), whereas moxifloxacin demonstrated success rates of 84.2% and 89.4% [76]. The difference between both groups was -2.6% (95% CI $-8.9, 3.9$) for IACR in the mITT population and -2.5% (95% CI $-8.4, 3.4$) for IACR in the CE population. In a subpopulation analysis, IACR success in the mITT population was higher for moxifloxacin than lefamulin among patients aged < 65 years and those that met modified American Thoracic Society (ATS) severity criteria (baseline presence of ≥ 3 of the following: respiratory rate ≥ 30 breaths/min, oxygen saturation $< 90\%$ or partial pressure of arterial oxygen < 60 mmHg, blood urea nitrogen ≥ 20 mg/dL, white blood cell count < 4000 cells/mm³, confusion, multi-lobe infiltrates, platelets $< 100,000$ cells/mm³, temperature < 36 °C, and systolic blood pressure < 90 mmHg) [76]. The microbiological-ITT (micro-ITT) population consisted of 159 patients in the lefamulin arm and 159 patients in the moxifloxacin arm with a baseline pathogen detected [76]. Overall, lefamulin and moxifloxacin exhibited similar ECR and IACR success rates in the micro-ITT population for baseline CABP pathogens, as depicted in Table 12.

The rates of treatment emergent adverse effects-TEAE were similar between lefamulin and moxifloxacin. Most TEAEs were mild or moderate for both treatment groups [76]. The most common adverse effects in the lefamulin group were hypokalemia, nausea, insomnia, and infusion site pain (2.9% for all) [76]. Diarrhea was more common in the moxifloxacin group (7.7%) compared to lefamulin (0.7%).

LEAP 2 was a Phase III, randomized (1:1), double-blinded, double-dummy, noninferiority trial that compared five days of oral lefamulin with seven days of oral

moxifloxacin for the treatment of CABP (Table 11) [77]. Adults aged ≥ 18 years with a PORT risk class of II, III, or IV, radiographically documented pneumonia, acute illness, ≥ 3 CABP symptoms, and ≥ 2 vital sign abnormalities were eligible for inclusion. Exclusion criteria was defined as: receipt of ≥ 1 dose(s) of a short-acting oral or IV antibacterial for CABP within 72 h before randomization, hospitalization for ≥ 2 days within 90 days, confirmed or suspected MRSA, being at risk for major cardiac events of dysfunction, and having significant hepatic disease. The FDA primary end point was ECR at $96 \text{ h} \pm 24 \text{ h}$ after the first dose of study drug in the ITT population (all randomized patients). Patients were considered ECR responders if they were alive, demonstrated improvement in ≥ 2 of the 4 CABP symptoms, had no worsening of any CABP symptom, and did not receive a non-study antibacterial for the current CABP episode. The EMA co-primary endpoints (FDA secondary endpoints) were IACR at 5–10 days after the last dose (TOC) in the mITT and CE populations [77]. IACR success at test of cure was defined as improved or resolved CABP without the need for additional antibacterial therapy [77].

Three hundred and seventy patients were randomized to receive lefamulin 600 mg orally every 12 h for 5 days and 368 patients were randomized to receive moxifloxacin 400 mg orally every 24 h for 7 days [77]. The demographic and baseline characteristics of the ITT population were balanced between the lefamulin and moxifloxacin treatment groups. The LEAP 2 trial was slightly more diverse, and representative of race compared to the LEAP 1 trial. Patients in the lefamulin arm were white (74.1%), Asian (13.0%), American Indian or Alaskan native (6.5%), black or African American (5.1%), and Hispanic or Latino ethnicity (12.2%); a similar distribution was observed in the moxifloxacin arm.

Five days of oral lefamulin demonstrated noninferiority to seven days of oral moxifloxacin using both the FDA and EMA primary endpoints (Table 11) [77]. Both lefamulin and moxifloxacin demonstrated high clinical response rates for all baseline CABP pathogens in the micro-ITT population (patients in the ITT population with baseline pathogen) as depicted in Table 12. The overall early clinical response for patients in the micro-ITT population was 90.7% for lefamulin and 93.0% for moxifloxacin. The overall IACR success rate for patients in the micro-ITT population was 85.9% for lefamulin and 87.6% for moxifloxacin [77]. In LEAP 2, the researchers concluded that oral lefamulin was well-tolerated and the gastrointestinal-related TEAE were mild to moderate and manageable [77].

Table 12 Phase III clinical trials of lefamulin showing ECR and IACR rates by baseline pathogen. Adapted from Refs. [76, 77]

Baseline CABP Pathogen	LEAP 1 trial				LEAP 2 trial			
	ECR micro-ITT		IACR at TOC micro-ITT		ECR-micro-ITT		IACR at TOC micro-ITT	
	Lefamulin	Moxifloxacin ^a	Lefamulin	Moxifloxacin ^a	Lefamulin	Moxifloxacin	Lefamulin	Moxifloxacin
<i>Streptococcus pneumoniae</i>	88.2% (82/93)	93.8% (91/97)	84.9% (79/93)	87.6% (85/97)	89.4% (110/123)	91.3% (115/126)	85.4% (105/123)	85.7% (108/126)
<i>S. pneumoniae</i> (MDR)	100% (6/6)	83.3% (5/6)	100% (6/6)	66.7% (4/6)	100% (8/8)	83.3% (10/12)	100% (8/8)	91.7% (11/12)
<i>Staphylococcus aureus</i> ^b	100% (10/10)	100% (4/4)	80.0% (8/10)	100% (4/4)	100% (13/13)	100% (6/6)	92.3% (12/13)	83.3% (5/6)
<i>Haemophilus influenzae</i>	92.2% (47/51)	94.7% (54/57)	84.3% (43/51)	84.2% (48/57)	89.3% (50/56)	91.7% (44/48)	92.9% (52/56)	83.3% (40/48)
<i>Moraxella catarrhalis</i>	92.0% (23/25)	100% (11/11)	80.0% (20/25)	100% (11/11)	85.7% (18/21)	100% (11/11)	81.0% (17/21)	100% (11/11)
<i>Mycoplasma pneumoniae</i>	84.2% (16/19)	90.0% (18/20)	84.2% (16/19)	95.0% (19/20)	100% (20/20)	100% (14/14)	95% (19/20)	100% (14/14)
<i>Legionella pneumophila</i>	88.9% (16/18)	85.7% (12/14)	77.8% (14/18)	78.6% (11/14)	81.3% (13/16)	94.1% (16/17)	81.3% (13/16)	88.2% (15/17)
<i>Chlamydomydia pneumoniae</i>	90.9% (10/11)	94.7% (18/19)	72.7% (8/11)	68.4% (13/19)	93.8% (15/16)	100% (12/12)	75.0% (12/16)	83.3% (10/12)

Data presented as rate of clinical response [% (no. successful/total no.)] in patients given study medication. CABP community-acquired bacterial pneumonia, MDR multidrug-resistant *S. pneumoniae*; isolates displaying resistance phenotype to ≥ 2 of the following: oral penicillin, moxifloxacin, ceftriaxone, clindamycin, azithromycin or erythromycin, doxycycline, or trimethoprim/sulfamethoxazole. Intent-to-treat (ITT) consists of all randomized patients. Microbiological-intent-to-treat (micro-ITT) consists of all patients in the ITT analysis set who had ≥ 1 baseline pathogen detected. Early clinical response (ECR) defined as improvement in two or more CABP signs/symptoms, no worsening of any CABP sign/symptom, and no receipt of a nonstudy antimicrobial for CABP. ECR was assessed at 96 ± 24 h after the first dose of the study drug in the micro-ITT population. Investigator assessment of clinical response (IACR) success defined as resolution or improvement in CABP signs/symptoms such that no further antimicrobial therapy was required. IACR was determined at 5–10 days after the last dose of the study drug (test of cure, TOC) in the micro-ITT population.

^aMoxifloxacin $\pm$ linezolid 600 mg IV q12h if MRSA was suspected at screening

^bAll *Staphylococcus aureus* isolates in the LEAP 1 trial were susceptible to methicillin

10 Adverse Effects

The safety and tolerability results for lefamulin as investigated in Phase II and III comparative clinical trials are shown in Table 13 [75–77].

In a Phase II ABSSSI trial, the safety of lefamulin was evaluated against vancomycin [75]. Patients received: lefamulin 100 mg IV q12h ($n = 70$), lefamulin 150 mg IV q12h ($n = 71$), or vancomycin 1 g IV q12h ($n = 66$) for a total treatment duration of 5–14 days. Adverse reactions were reported by 71.5% of all patients [75]. Although the incidence of drug-related adverse events was lower in patients treated with lefamulin (both 100 mg and 150 mg treatment arms) than vancomycin, due to the small number of patients studied, these differences were not statistically significant (Table 13). The most common adverse reactions with lefamulin were headache, nausea, and diarrhea, which were described as mild or moderate in intensity. There were no cases of *C. difficile* infection [75]. In comparison to vancomycin, local injection site reactions including pain and

phlebitis were more common in the lefamulin treatment arms than vancomycin. The most common adverse reactions for vancomycin were headache, nausea, and pruritis. Increased alanine aminotransferase was comparable in both lefamulin 100 mg and 150 mg arms (2.9% and 2.8% respectively), whereas vancomycin was 4.5% [75]. Minor ECG changes in all treatment arms were deemed not to be of clinical significance (all three treatment groups displayed a slight increase in the QTcF interval) [75]. The study concluded that lefamulin is well-tolerated in patients with ABSSSI.

In the LEAP 1 trial, the safety of IV and oral lefamulin was evaluated against IV and oral moxifloxacin [76]. Patients were randomized and administered lefamulin 150 mg IV q12h ($n = 273$) and then given the option to transition to oral lefamulin 600 mg q12h on or after 3 days of treatment. Alternatively, patients were randomized to moxifloxacin 400 mg IV q24h ($n = 273$) with the option to transition to oral moxifloxacin 400 mg q12h. If MRSA was suspected then patients received blinded linezolid 600 mg IV q12h with moxifloxacin, or linezolid placebo

Table 13 Adverse effects of lefamulin in comparative Phase II and Phase III clinical trials. Adapted from Refs. [75–77]

Study	Treatment dose	Number (%) of patients with adverse event	Adverse effects
Prince et al. [75]	Lefamulin 100 mg IV q12h for 5–14 days	5/70 (7.1%)	Headache
		5/70 (7.1%)	Nausea
		4/70 (5.7%)	Infusion site phlebitis
		3/70 (4.3%)	Diarrhea
		3/70 (4.3%)	Vomiting
		2/70 (2.9%)	Alanine aminotransferase increased
		2/70 (2.9%)	Pruritus generalized
		2/70 (2.9%)	Creatine phospholipase increased
		2/70 (2.9%)	Phlebitis
		2/70 (2.9%)	Vulvovaginal mycotic infection
	Lefamulin 150 mg IV q12h for 5–14 days	9/71 (12.7%)	Headache
		6/71 (8.5%)	Nausea
		4/71 (5.6%)	Diarrhea
		2/71 (2.8%)	Infusion site phlebitis
		2/71 (2.8%)	Vomiting
		2/71 (2.8%)	Alanine aminotransferase increased
		2/71 (2.8%)	Abdominal pain
		2/71 (2.8%)	Pruritus
		2/71 (2.8%)	Infusion site pain
		2/71 (2.8%)	Tinnitus
	Comparator: Vancomycin 1 g IV q12h for 5–14 days	10/66 (15.2%)	Headache
		10/66 (15.2%)	Nausea
		8/66 (12.1%)	Pruritus
		4/66 (6.1%)	Diarrhea
		4/66 (6.1%)	Pruritus generalized
		3/66 (4.5%)	Vomiting
		3/66 (4.5%)	Alanine aminotransferase increased
		3/66 (4.5%)	Constipation
		2/66 (3.0%)	Aspartate aminotransferase increased
		2/66 (3.0%)	Insomnia
File Jr et al. [76]	Lefamulin 150 mg IV q12h, then on or after day 3, option to transition to 600 mg orally q12h for total 5–10 days	8/273 (2.9%)	Hypokalemia
		8/273 (2.9%)	Nausea
		8/273 (2.9%)	Insomnia
		8/273 (2.9%)	Infusion site pain
		6/273 (2.2%)	Infusion site phlebitis
		5/273 (1.8%)	Alanine aminotransferase increased
		2/273 (0.7%)	Hypertension
		2/273 (0.7%)	Diarrhea
	Comparator: Moxifloxacin 400 mg IV q24h, then on or after Day 3, option to transition to 400 mg orally q24h for total 5–10 days ($\pm$ linezolid 600 mg IV q12h)	21/273 (7.7%)	Diarrhea
		6/273 (2.2%)	Hypokalemia
		6/273 (2.2%)	Nausea
		6/273 (2.2%)	Alanine aminotransferase increased
		6/273 (2.2%)	Hypertension
		5/273 (1.8%)	Insomnia
		3/273 (1.1%)	Infusion site phlebitis

Table 13 (continued)

Study	Treatment dose	Number (%) of patients with adverse event	Adverse effects
Alexander et al. [77]	Lefamulin 600 mg orally q12h for 5 days	45/368 (12.2%)	Diarrhea
		19/368 (5.2%)	Nausea
		12/368 (3.3%)	Vomiting
		5/368 (1.4%)	Hypertension
		4/368 (1.1%)	Headache
		4/368 (1.1%)	Gastritis
		3/368 (0.8%)	Alanine aminotransferase increased
		2/368 (0.5%)	Aspartate aminotransferase increased
	Comparator: Moxifloxacin 400 mg orally q24h for 7 days	7/368 (1.9%)	Nausea
		6/368 (1.6%)	Headache
		5/368 (1.4%)	Hypertension
		4/368 (1.1%)	Diarrhea
		4/368 (1.1%)	Alanine aminotransferase increased
		4/368 (1.1%)	Aspartate aminotransferase increased
		4/368 (1.1%)	Anemia
		4/368 (1.1%)	Insomnia
		3/368 (0.8%)	Vomiting

IV intravenous, q12h every 12 h, q24h every 24 h

added to lefamulin. The most common adverse effects for lefamulin were hypokalemia, nausea, insomnia, and infusion site pain (Table 13). In the moxifloxacin treatment group, the most common adverse effects were diarrhea, hypokalemia, and nausea [76]. Diarrhea was lower in lefamulin (0.7%) than moxifloxacin (7.7%) [76]. In the moxifloxacin treatment group, the most common adverse reactions were diarrhea, hypokalemia, and nausea. LEAP 1 reported a higher percentage of patients experiencing hypertension in the moxifloxacin ± linezolid group (2.2%) compared to lefamulin (0.7%) [76]. There was a slight increase in frequency of infusion site phlebitis in lefamulin (2.2%) compared to moxifloxacin (1.1%). Serious treatment-related adverse effects-TEAEs (TEAE defined as an adverse event that starts or worsens with or after the first dose of the study drug) were experienced by 1.1% of the patients receiving lefamulin compared to 0.4% of patients receiving moxifloxacin. TEAE leading to death was similar between both groups: 2.2% for lefamulin and 1.8% for moxifloxacin. TEAE leading to discontinuation of the study drug or withdrawal from study was 2.9% and 1.8%, respectively, for lefamulin; moxifloxacin was 4.4% and 4.0%, respectively [76]. Overall, the LEAP 1 trial determined that lefamulin treatment was generally safe and well-tolerated.

The LEAP 2 trial evaluated the safety of oral lefamulin against oral moxifloxacin [77]. Subjects were given oral lefamulin 600 mg q12h for 5 days ($n = 370$) or moxifloxacin 400 mg q24h for 7 days ($n = 368$). The most frequent adverse effects of oral lefamulin were diarrhea, nausea and vomiting (Table 13). A greater portion of

patients receiving lefamulin experienced gastrointestinal related adverse effects compared to moxifloxacin [77]. Diarrhea and nausea were higher in the lefamulin group compared to the moxifloxacin group: 9.2% and 4.1%, respectively, for lefamulin, and 0.8% and 1.6%, respectively, for moxifloxacin [77]. The most common adverse effects for moxifloxacin were nausea, headache, and hypertension. However, frequency of hypertension was similar between both treatment groups (1.4%). Anemia (1.1%) and insomnia (1.1%) were documented in the moxifloxacin treatment group, but not observed in the lefamulin group [77]. LEAP 2 showed a smaller frequency of increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) for lefamulin, 0.8% and 0.5%, respectively [77]. Compared to moxifloxacin, the percentage of patients experiencing increased ALT and AST were both 1.1%. In the lefamulin group, 4.6% of TEAEs (TEAE defined as an adverse event that starts or worsens with or after the first dose of the study drug) were serious, 1.4% TEAEs led to death, 3.3% TEAEs led to discontinuation of study drug, and 1.4% of TEAEs led to withdrawal from the study (4.9%, 0.8%, 2.4%, 1.4% for moxifloxacin respectively). The researchers concluded that oral lefamulin was well tolerated and the gastrointestinal-related TEAEs were mild to moderate and manageable [77].

Lefamulin has been shown to cause fetal harm in animal studies. Adverse effects of lefamulin during pregnancy and lactation include fetal loss and stillbirths, low fetal body weight, malformations, and deaths during lactation [78].

11 Drug Interactions

Currently, limited data are available regarding drug interactions with lefamulin. As previously discussed, lefamulin is metabolized by CYP450 (primarily CYP3A4) and acts as a substrate and inhibitor of CYP450 [65]. Lefamulin in vitro, does not induce CYP1A2 or 3A4 enzymes.

A recent study investigated the interaction between lefamulin and midazolam, as well as lefamulin and ketoconazole [65]. Lefamulin did not significantly inhibit CYP3A4 metabolism of midazolam in vivo. When lefamulin was administered with ketoconazole, there was no increase in the maximum serum concentration of lefamulin, suggesting that there is a weak interaction between ketoconazole and lefamulin. Lexicomp interactions recommend avoiding the administration of oral lefamulin tablets with ketoconazole [79]. The serum concentration of oral lefamulin may be increased by ketoconazole whereas the IV lefamulin formulation is not likely affected by strong CYP3A4 inhibitors. Overall, concomitant use of strong CYP3A4 inhibitors should be avoided with oral lefamulin.

Administration of lefamulin with P-glycoprotein (P-gp) inducers may decrease serum concentrations of lefamulin, and P-gp inhibitors may increase serum concentrations of lefamulin [79]. According to Lexicomp interactions, the clinical impact of the effect of P-gp inducers and inhibitors may be greater with oral lefamulin than with the IV formulation [80]. Lexicomp interactions recommend avoiding the use of P-gp inducers and inhibitors with lefamulin unless the benefits outweigh the risks.

The combination of oral lefamulin should be avoided with QT-prolonging CYP3A4 substrates [81]. According to Lexicomp interactions, lefamulin may increase the QTc-prolonging effect and thus the lefamulin prescribing information categorizes the combination as contraindicated. In Lexicomp interactions, lefamulin may increase the serum concentrations of apixaban and monitoring for bleeding is recommended [82]. As well, lefamulin may increase the serum concentrations of domperidone, and use of lefamulin with domperidone is not recommended [83]. Lexicomp recommends to lower initial doses of sirolimus when using lefamulin, as lefamulin may increase the serum concentrations of sirolimus [84].

12 Place in Therapy

Lefamulin is the first oral and IV pleuromutilin antimicrobial agent approved for human use. Its unique mechanism of action confers high bacterial susceptibility rates along with limited cross resistance to other chemically unrelated antibacterial classes. In addition, lefamulin is

associated with low rates of resistance development upon repeated exposure. Lefamulin's broad-spectrum activity against Gram-positive, Gram-negative, and atypical bacteria including MRSA, MDR *S. pneumoniae* and macrolide-resistant *M. pneumoniae* make it an ideal candidate for the treatment of CABP. Completed Phase III clinical trials have confirmed the efficacy and safety of oral and IV lefamulin when compared to moxifloxacin for the treatment of CABP leading the FDA, EMA, and Health Canada to approve lefamulin for treatment of CABP in adults. Although clinical data are limited, IV lefamulin may be considered in place of an IV β -lactam/macrolide combination in the setting of resistance, clinical failure, or intolerance/adverse effects to this regimen. IV lefamulin may also be considered in place of an IV fluoroquinolone (e.g. levofloxacin, moxifloxacin) in the setting of resistance, clinical failure, or intolerance/adverse effects to these agents or as a fluoroquinolone sparing regimen to avoid fluoroquinolone-associated musculoskeletal, neurologic, and psychiatric adverse effects. Orally, lefamulin may be considered in lieu of an oral β -lactam/macrolide combination or a fluoroquinolone in the setting of resistance, clinical failure, or intolerance/adverse effects to either regimen or as a fluoroquinolone sparing regimen. Oral lefamulin may also be an option to treat patients with CABP in clinical settings with high rates of macrolide- and doxycycline-resistant *S. pneumoniae*. Clinical experience and ongoing clinical investigation will allow clinicians and antimicrobial stewardship programs to optimally use lefamulin in the treatment of CABP.

Declarations

Conflict of interest Dr. Zhanel has received research grants from Sunovion Pharmaceuticals and Nabriva Therapeutics. No conflicts are declared for Christina Deng, Sheryl Zelenitsky, Courtney K. Lawrence, Heather J. Adam, Alyssa Golden, Rachel Hink, Liam Berry, Frank Schweizer, Michael A. Zhanel, Denice Bay, Philippe Lagacé-Wiens, Andrew Walkty, Lionel Mandell, Joseph P. Lynch III and James A. Karlowsky. Dr. Irfan is part of the Sunovion speaker's bureau.

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entire manuscript and drafting chemistry and microbiology sections), Frank Schweizer (involved in design and concept of entire manuscript and drafting chemistry and microbiology sections), Michael A. Zhanel (involved in design and concept of entire manuscript and drafting introduction, mechanisms of action/resistance, chemistry and microbiology sections), Neal Irfan (involved in design and concept of entire manuscript and drafting adverse effects, drug interactions and place in therapy sections), Denise Bay (involved in design and concept of entire manuscript and drafting introduction, mechanisms of action/resistance sections), Philippe Lagacé-Wiens (involved in design and concept of entire manuscript and drafting animal models section), Andrew Walkty (involved in design and concept of entire manuscript and drafting clinical trials, adverse effects and place in therapy sections), Lionel Mandell (involved in design and concept of entire manuscript and drafting clinical trials section), Joseph P. Lynch III (involved in design and concept of entire manuscript and drafting clinical trials and place in therapy sections), and James A. Karlowsky (involved in design and concept of entire manuscript and drafting all sections).

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