Treatment of Community-Acquired Pneumonia: A Focus on Lefamulin

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ABSTRACT

Objective: The goal of this article is to review the clinical pharmacology, pharmacokinetics, efficacy, and safety of lemafulin.

Data Sources: We performed a systematic literature review using the search terms of lefamulin and BC-3781 in the PubMed and EMBASE databases. We also cross-referenced the pertinent articles and searched ClinicalTrials.gov to identify ongoing and nonpublished studies.

Study Selection and Data Extraction: Published data from 2005 to 2019 evaluating the clinical pharmacology, efficacy, and safety studies of lefamulin were analyzed.

Data Synthesis: In phase 3 clinical trials, two multicenter, randomized double-blinded studies—Lefamulin Evaluation Against Pneumonia 1 and 2 (LEAP 1 and 2)—compared the efficacy and safety of lemafulin with moxifloxacin in patients diagnosed with community-acquired bacterial pneumonia (CABP). Lemafulin given in doses of 600 mg orally or 150 mg intravenously were reported to have comparable efficacy to those of moxifloxacin with or without linezolid in patients with CABP. After the trial, the lefamulin group had an early clinical response (ECR) of 87.3% and the moxifloxacin group had an ECR of 90.2%. The difference of -2.9% in the ECR was non-significant (CI -8.5, 2.8).

Relevance to patients and clinical practice: Lemafulin exhibits a unique binding property; therefore, it possess a potentially lower predisposition for the development of bacterial resistance and cross-resistance to other antimicrobial classes. Lefamulin is active against gram-positive including methicillin-resistant strains and atypical organisms which are often implicated in CABP.Lefamulin may be a safe alternative for adult patients with CABP who may not be candidates for respiratory fluoroquinolones.Lefamulin demonstrates both bactericidal and bacteriostatic activity against gram-positive, fastidious gram-negatives, atypical pathogens, and some gram-negative anaerobes. It is bactericidal in vitro against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Mycoplasma pneumoniae* (including macrolide-resistant strains) at concentrations of 0.06, 0.5, and 0.008 μg/ml respectively, and bacteriostatic against *Staphylococcus aureus* and *Streptococcus pyogenes*. The agent also demonstrates both time- and concentration-dependent killing against the pathogens *S. pneumoniae* and

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*S. aureus.*In vitro susceptibility testing demonstrated an $MIC_{50/90}$ of 0.06/0.12 µg/ml against *S. pneumoniae* and *S. aureus*. The SENTRY Antimicrobial Surveillance Program found that at a concentration ≤ 1 µg/ml, lefamulin inhibited 100% *S. pneumoniae* isolates, 99.8% of *S. aureus* isolates, and 99.6% of methicillin-resistant *S. aureus* isolates. It was not affected by resistance to various antibiotic classes such as beta-lactams, fluoroquinolones, or macrolides.

PLAIN LANGUAGE SUMMARY

Lefamulin is the first pleuromutilin antibiotic approved for the treatment of bacterial infections in humans. Pleuromutilin antibiotics exert their unique mechanism of action which makes them less susceptible to the development of bacterial resistance and low probability of cross-resistance to the other antimicrobial classes.

The authors present a critical review of the pharmacology, pharmacokinetics (PK), pharmacodynamics (PD), and data from two pivotal clinical trials of lefamulin in patients with community-acquired bacterial pneumonia (CABP).

Lefamulin exhibits both bactericidal and bacteriostatic activity against gram-positive, fastidious gram-negatives, atypical pathogens, and some gram-negative anaerobes. It has shown activity against organisms known to cause sexually transmitted infections, including *Mycoplasma genitalium* and drug-resistant *Neisseria gonorrhoeae*. Lefamulin demonstrated no activity against Enterobacteriaceae or *Pseudomonas aeruginosa*.

Pharmacokinetic studies involving lefamulin in acutely ill patients at least 18 years of age with three or more CABP symptoms failed to reveal any clinically significant differences in the PK parameters on the basis of age, sex, race, weight, or renal impairment. Lefamulin 600 mg tablets had a mean oral bioavailability of 25%. Consumption of high-fat meals may slightly reduce the blood level of the drug.

In two phase 3 clinical trials, The Lefamulin Evaluation Against Pneumonia 1 and 2 (LEAP 1 and 2) compared the efficacy and safety of lemafulin with moxifloxacin in patients diagnosed with CABP. Lemafulin administered in doses of 600 mg orally or 150 mg intravenously were reported to have comparable efficacy to those of moxifloxacin with or without linezolid in patients with CABP.

Key Summary Points

Lemafulin development emerged following the need to combat the limitations of the currently available drugs to treat community-acquired bacterial pneumonia (CABP).

Lemafulin's unique binding property makes it less likely to develop bacterial resistance and cross-resistance to other antimicrobial classes.

Pleuromutilin antibiotics exert their action by binding to the peptidyl transferase center of the 50S ribosome via several interactions, thereby preventing the binding of transfer ribonucleic acid (tRNA) for peptide transfer and inhibiting protein synthesis.

Lefamulin is active against gram-positive including methicillin-resistant strains and atypical organisms which are often implicated in CABP.

In two-phase 3 clinical trials, lemafulin given in doses of 600 mg orally or 150 mg intravenously produced comparable efficacy to those of moxifloxacin with or without linezolid in patients with CABP.

Lemafulin may be a reasonable option for patients with CABP who are intolerant to beta-lactams, fluoroquinolones, and macrolides.

DIGITAL FEATURES

This article is published with digital features, including a summary slide and plain language summary, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13286402.

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the leading causes of morbidity and mortality worldwide. In 2018, pneumonia was the second leading cause of hospitalization [1]. In the USA, CAP accounts for over 1.5 million hospitalizations and results in more than 14.2 million ambulatory care visits annually [1–3]. It is also the most common infectious cause of death in the USA, accounting for over 50,000 deaths annually [2, 4]. The direct annual cost of CAP in the USA has been estimated to be at least US$17 billion, with a mean cost per hospitalization of US$13,000 [5, 6]. The average length of stay for the treatment of pneumonia is 5.2 days [4]. This contributes to days of work missed and loss of productivity for both patients and caregivers.

CAP is an acute infection of the lung parenchyma characterized by dyspnea, cough, sputum production, chest pain, symptoms of infection such as fever or malaise, and the presence of patchy opacities upon radiographic visualization [7]. Risk factors for pneumonia include age, lifestyle factors, and certain comorbidities. Persons 2 years of age or younger and those over 65 years of age are at the highest risk for succumbing to the disease [8]. Lifestyle factors such as smoking, excessive alcohol intake, and having regular contact with children also increase the risk of developing CAP. Comorbid conditions such as chronic obstructive pulmonary disease and immunocompromising conditions such as the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) can increase the risk of developing pneumonia [9].

Community-acquired bacterial pneumonia (CABP) is one of the most common forms of pneumonia. Infection can be caused by gram-positive, gram-negative, or atypical organisms.

Hospital-acquired pneumonia (HAP), also referred to as nosocomial pneumonia, is pneumonia acquired during or after hospitalization for another illness or procedure with the onset of at least 48 h after hospital admission. The causative pathogens, treatment, and the prognosis are different from those of CAP. Ventilator-associated pneumonia (VAP) is a subclass of HAP. VAP is pneumonia which occurs at least 48–72 h after intubation and mechanical ventilation [10]. The exact incidence of HAP varies widely depending on the case definition of pneumonia and the population being studied. HAP accounts for up to 25% of all intensive care unit (ICU) infections and VAP occurs in 9–27% of all intubated patients [10].

Typical causative bacterial organisms of CAP include *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, and *Legionella pneumophila*; *S. pneumoniae* is the most common causative bacteria pathogen [11, 12].

Pharmacological treatment of pneumonia is dependent on the patient's comorbidities, risk factors, the severity of illness, and the local resistance patterns. As per the 2019 American Thoracic Society, standard pharmacological treatment of non severe inpatient pneumonia includes a β-lactam in combination with macrolide or monotherapy with a respiratory fluoroquinolone [13].

Although there are various agents available for the treatment of CAP, there are limitations to many of them. Current treatment limitations include allergies, antibiotic resistance, inadequate penetration in lung tissues, and undesirable adverse effects, such as *Clostridioides difficile* (*C. diff*) diarrhea [14]. β-Lactam allergies are some of the most common self-reported allergies with a reported incidence of 17% in hospitalized patients. Macrolide and fluoroquinolone allergies are less common; however, they do occur [15–17].

The pleuromutilin antibiotics have a unique structure and mechanism of action, which results in no cross-sensitivity between other classes; this makes them viable options for

patients who are allergic to the other agents. A macrolide resistance rate of more than 30% was found amongst *S. pneumoniae* isolates [18]. Macrolide resistance occurs via two main mechanisms, the first being a mutation that codes for antibiotic efflux pumps that remove the antibiotic from the target sites. The second resistance mechanism results from alterations of the bacterial ribosome, resulting in a phenotype with reduced susceptibility to macrolides, lincosamides, and streptogramin B. The prevalence of each resistance mechanism varies on the basis of geographic region. Lefamulin has activity against macrolide-resistant strains [19]. Another shortcoming of the current medications is the lack of adequate lung penetration. For instance, agents such as vancomycin, daptomycin and aminoglycosides exhibit poor penetration into the epithelial lining fluid, thus resulting in treatment failure [20, 21]. Lefamulin is unaffected by pulmonary surfactants and was found to reach adequate levels in epithelial lining fluid [22]. Undesirable side effects common with standard pneumonia therapies include cardiac arrhythmias, which are associated with macrolides [13] and fluoroquinolones. Other side effects such as hypoglycemia, QTc prolongation, aortic dissection, and psychiatric side effects have all been reported with fluoroquinolones [23–25].

To combat the limitations of the available pharmacotherapeutic agents, novel therapies for the treatment of CABP are warranted. In August 2019, the US Food and Drug Administration (FDA) approved lefamulin for oral and intravenous administration for the treatment of adults with CABP caused by susceptible bacterial organisms [26].

Data Sources

We performed a systematic literature review using the following search terms: lefamulin, BC-378, pharmacology, pharmacokinetics, and clinical studies in the PubMed and EMBASE databases. Also, we cross-referenced the pertinent articles and searched ClinicalTrials.gov to identify ongoing studies.

Study Selection and Data Extraction

Published articles in the English language from 2005 to 2019 evaluating the clinical pharmacology, pharmacokinetics efficacy, and safety studies of lefamulin were assessed and evaluated.

CLINICAL PHARMACOLOGY

Pleuromutilin antibiotics are derived from basidiomycete fungi. Lefamulin is the first pleuromutilin to be approved for systemic use in humans. The first pleuromutilin marked in 1979 was tiamulin, but was intended for veterinary use only [27]. Pleuromutilin antimicrobial agents such as tiamulin and valnemulin are used mostly in swine and to a lesser extent in poultry and rabbits. These agents are indicated for swine dysentery, spirochete-associated diarrhea, porcine proliferative enteropathy, enzootic pneumonia, and other infections where *Mycoplasma* organisms are involved [28].

In 2007, retapamulin was made available for topical use in humans [29].

Lefamulin is a semisynthetic antibiotic indicated for the treatment of adults with CABP caused by *S. pneumoniae*, methicillin-susceptible isolates of *S. aureus*, *H. influenzae*, *L. pneumophila*, *M. pneumoniae*, and *Chlamydophila pneumoniae* [11].

Mechanism of Action

Lefamulin is the first pleuromutilin antibiotic approved for the systemic treatment of bacterial infections in humans. Pleuromutilin antibiotics exert their action by binding to the peptidyl transferase center of the 50S ribosome via several interactions, including four hydrogen bonds. A binding pocket is formed and the bacterial ribosome closes around the mutulin core, preventing the binding of transfer ribonucleic acid (tRNA) for peptide transfer and therefore inhibiting protein synthesis [13, 30]. Owing to its unique binding sites, there is a lower predisposition for the development of bacterial resistance. This unique mechanism of

action also allows for a low probability of cross-resistance to the other antimicrobial classes.

Lefamulin exhibits both bactericidal and bacteriostatic activity against gram-positive, fastidious gram-negatives, atypical pathogens, and some gram-negative anaerobes. It has shown activity against organisms known to cause sexually transmitted infections, including *Mycoplasma genitalium* and drug-resistant *Neisseria gonorrhoeae*. Lefamulin demonstrated no activity against Enterobacteriaceae or *Pseudomonas aeruginosa* [31].

Pharmacokinetics

Pharmacokinetic studies involving lefamulin in acutely ill patients at least 18 years of age with three or more CABP symptoms revealed no clinically significant differences in the pharmacokinetic parameters on the basis of age, sex, race, weight, or renal impairment [19, 32].

Absorption

Lefamulin 600 mg tablets had a mean oral bioavailability of 25%. Peak plasma concentration following oral administration was reached between 0.88 and 2 h in healthy subjects. Consumption of high-fat meals consisting of at least 50% fat or high-calorie meals (800–1000 kcal) resulted in slightly reduced bioavailability [19, 33]. The absolute oral bioavailability is 25.8% in the fasted state and 21.0% in the fed state[34]. The reported free plasma area under the concentration–time curve over 24 h ($fAUC_{0-24}$) and the free plasma maximum concentration (C_{max}) were 1500.8 mg h/L and 330.1 mg/L. respectively.

Distribution

Lefamulin is highly protein-bound, between 94.8% and 97.1% [19, 35]. The mean volume of distribution was 86.1 L in patients following intravenous (IV) administration. After a single 150 mg IV administration infused over 1 h, the highest lefamulin epithelial lining fluid (ELF) concentrations were observed at the end of the infusion. The mean ELF concentration was 3.87 μg h/ml [19].

Metabolism

In vitro studies revealed that lefamulin is both a substrate and an inhibitor of the CYP3A4 isoenzyme [19, 33]. Therefore, the administration of lefamulin should be avoided or administered with caution in patients taking medications that are metabolized by the CYP3A isoenzyme. A reduction in the IV dosage of lefamulin to 150 mg every 24 h in patients with severe hepatic impairment (Child–Pugh class C) is strongly suggested. Lefamulin tablets have not been studied in patients with moderate to severe hepatic impairment, and therefore are not recommended [19].

Elimination

The mean total body clearance of lefamulin is 11.9 L/h in patients with CABP after IV infusion [19, 33]. The mean elimination half-life is approximately 8 h in patients with CABP [11, 36]. Following IV administration of 150 mg of lefamulin, 77% of the dose was excreted in the feces with approximately 4.2–9.1% unchanged and approximately 14.1–15.5% was excreted unchanged in the urine. Following oral administration of 600 mg, 89% was excreted in the feces and 5% was excreted in the urine [19].

Pharmacodynamics

Lefamulin exhibits primarily area under concentration to minimum inhibitory concentration (AUC/MIC) pharmacodynamic activity. Lefamulin is bactericidal in vitro against *S. pneumoniae*, *H. influenzae*, and *M. pneumoniae* (including macrolide-resistant strains) at concentrations of 0.06, 0.5, and 0.008 μg/ml, respectively, and bacteriostatic against *S. aureus* and *S. pyogenes* [19] (Table 1).

Lefamulin demonstrates both time- and concentration-dependent killing against the pathogens *S. pneumoniae* and *S. aureus* [29]. In vitro susceptibility testing demonstrated an $MIC_{50/90}$ of 0.06/0.12 μg/ml against

S. pneumoniae and S. aureus [37]. The SENTRY Antimicrobial Surveillance Program found that at a concentration 1 µg/ml or lower, lefamulin inhibited 100% S. pneumoniae isolates, 99.8% of S. aureus isolates, and 99.6% of methicillin-resistant S. aureus isolates. It was not affected by resistance to various antibiotic classes such as beta-lactams, fluoroquinolones, or macrolides [38].

The requirement for bactericidal activity against mycoplasmal infections is a minimum bactericidal concentration (MBC) at most two dilutions greater than the minimum inhibitory concentration (MIC) [39]. Lefamulin had an MIC of at most 0.008 µg/ml against 18 macrolide-susceptible and 42 macrolide-resistant strains of M. pneumoniae. The MICs which inhibited 90% (MIC_{90}) of macrolide-susceptible and macrolide-resistant M. pneumoniae were at most 0.001 µg/ml and 0.002 µg/ml, respectively [40]. Lefamulin underwent susceptibility testing against other atypical pathogens such as L. pneumophila and C. pneumoniae [41]. Against L. pneumophila and C. pneumoniae lefamulin had an $MIC_{50/90}$ of 0.06/0.5 µg/ml and 0.02/0.04 µg/ml, respectively.

The SENTRY Antimicrobial Surveillance Program recorded the in vitro activity of lefamulin against organisms such as H. influenzae and M. catarrhalis between 2015 and 2016 [42]. Against H. influenzae, lefamulin has an $MIC_{50/90}$ of 0.5/1 µg/ml which was comparable to Augmentin (0.5/2 µg/ml). Against M. catarrhalis, lefamulin has an $MIC_{50/90}$ of 0.06/0.12 µg/ml which was comparable to moxifloxacin (0.06/0.06 µg/ml) [42]. In general, lefamulin demonstrates susceptibility against commonly encountered bacterial pathogens (Table 2).

CRUCIAL CLINICAL STUDIES

Lefamulin Evaluation Against Pneumonia 1 (LEAP 1) and Lefamulin Evaluation Against Pneumonia 2 (LEAP 2) phase 3 trials were pivotal in the assessment of lefamulin in patients with CABP.

Table 1 In vitro activities of lefamulin activity against common pathogens [18]

	Gram-positive bacteria	Gram-negative bacteria	Other bacteria
Activity shown in vitro and in clinical infections	Streptococcus pneumoniae Streptococcus aureus (methicillin-susceptible isolates)	Haemophilus influenzae	Mycoplasma pneumoniae Chlamydophila pneumoniae Legionella pneumophila
Activity in vitro, but safety and efficacy in treating clinical infections has not been established in clinical trials	Streptococcus aureus (methicillin-resistant [MRSA] isolates) Streptococcus agalactiae Streptococcus anginosus Streptococcus mitis Streptococcus pyogenes Streptococcus salivarius	Haemophilus parainfluenzae Moraxella catarrhalis	

Lefamulin Evaluation Against Pneumonia 1 (LEAP 1) [43]

LEAP 1 was conducted as a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study in which 551 participants with CABP were randomly assigned (1:1) to receive either lefamulin or moxifloxacin. Participants received lefamulin 150 mg IV every 12 h, with the option of switching to an oral study drug after six doses if the pre-specified improvement criteria were met ($n = 276$), or moxifloxacin 400 mg IV every 24 h ($n = 275$). Participants receiving moxifloxacin also received linezolid 600 mg IV every 12 h if MRSA was suspected at screening. Linezolid placebo was added to lefamulin in such cases. If MRSA was no longer suspected after a baseline culture, linezolid or the placebo was discontinued. The length of therapy for the participants ranged from 5 to 10 days.

Participants were required to meet the following inclusion criteria: adults greater than the age of 18, radiographic imaging that was indicative of pneumonia, Pneumonia Outcomes Research Team (PORT) risk class III or higher, an illness that initially presented within 7 days of enrollment, and three or more CABP symptoms (dyspnea, new or increased cough, purulent sputum production, chest pain). Study participants were excluded from the trial if they fell into any of the following categories: received a dose of antibiotics for the current illness within 3 days of randomization, have been hospitalized for at least 2 days within 90 days of the onset of symptoms, have confirmed or suspected CABP caused by *P. aeruginosa* or any member of the Enterobacteriaceae family, and a noninfectious cause of pulmonary infiltrates.

At baseline, of the 551 participants, 86.7% were white, 7.9% Asian, and 4.1% black; 43.5% of the participants were at least 65 years old, and 59.8% were male.

The FDA primary endpoint was an early clinical response (ECR) in the intention-to-treat population (ITT) at 96 ± 24 h after the first study drug dose [14]. At the conclusion of the trial, the lefamulin group had an ECR of 87.3% (241/276) and the moxifloxacin group had an ECR of 90.2% (248/275). The difference of $- 2.9\%$ in the ECR was non-significant (CI $- 8.5$, 2.8). The European Medicines Agency (EMA) co-primary endpoint was an investigator assessment of clinical response (IACR) at test of cure (TOC) (5–10 days after last study drug dose) in the modified ITT (mITT) and clinically evaluable (CE) populations. Lefamulin demonstrated noninferiority for the EMA primary endpoint of IACR. The lefamulin treatment group had an IACR (mITT) of 80.8% versus 83.6% in the moxifloxacin treatment group. The difference of $- 2.8\%$ in the IACR (mITT) was non-significant (CI $- 9.6$, 3.9). Additionally, the lefamulin group had an IACR CE-TOC of 86.9% versus 89.4% in the moxifloxacin group. The difference of $- 2.5\%$ in the IACR CE-TOC group was insignificant (CI $- 8.4$, 3.4).

The differences in ECR in the treatment of class III and IV CABP were non-significant. As a result of the small sample size (< 10), the differences in ECR could not be evaluated in class II and V CABP. Lefamulin met the study criteria for noninferiority (Table 3).

Lefamulin Evaluation Against Pneumonia 2 (LEAP 2) [44]

LEAP 2 was a randomized, non-inferiority, double-blind, double-dummy, multicenter, parallel-group study comprising 738 participants. A total of 370 participants with confirmed CABP received 600 mg PO every 12 h for 5 days in the lefamulin group and 368 participants received 400 mg PO every 24 h for 7 days in the moxifloxacin group.

Inclusion criteria were similar to those specified in LEAP 1. Patients were required to meet the following inclusion criteria: adults greater than the age of 18, radiographic imaging that was indicative of pneumonia, PORT risk class III or higher, illness that initially presented within 7 days of enrollment, and three or more CABP symptoms (dyspnea, new or increased cough, purulent sputum production, chest pain). Patients were excluded from the trial if they fall into any of the following categories: received a dose of antibiotics for the current illness within 3 days of randomization, hospitalized for two or more days within 90 days of the onset of

Table 2 Summary of Lefamulin susceptibility against pathogens [38], [41–43]

	Lefamulin		Linezolid		Vancomycin		Daptomycin	
	MIC_{50} µg/ml	MIC_{90} µg/ml	MIC_{50} µg/ml	MIC_{90} µg/ml	MIC_{50} µg/ml	MIC_{90} µg/ml	MIC_{50} µg/ml	MIC_{90} µg/ml
Gram positive bacteria								
Staphylococcus aureus (n = 5327)	0.12	0.12	1	1	1	1	0.25	0.5
MRSA	0.12	0.25	1	1	1	1	0.25	0.5
B-Hemolytic streptococcus (n = 763)	0.03	0.03	1	1	0.25	0.5	≤ 0.06	0.5
Streptococcus Pyogen group A	0.03	0.03	1	1	0.25	0.5	≤ 0.06	≤ 0.06
Streptococcus agalactiae, group B	0.03	0.03	1	1	0.5	0.5	0.12	0.25
Streptococcus Viridans (n = 245)	0.12	0.5	1	1	0.5	0.5	0.25	0.5
Enterococcus faecium (n = 536)	0.12	4	1	1	> 16	> 16	2	2
Streptococcus pneumonia (n = 1473)	0.12	0.25	1	1	0.25	0.5	–	–
Gram negative bacteria								
Haemophilus influenzae (n = 360)	1	2	≤ 0.05	≤ 0.05	1	2	≤ 0.06	≤ 0.06
Moraxella catarrhalis (n = 253)	0.12	0.25	≤ 0.05	≤ 0.05	≤ 0.25	≤ 0.06	≤ 0.25	≤ 0.5
Atypical organisms								
Legionella pneumophila (n = 30)	0.12	0.5	0.06	0.12	0.06	0.12	–	–
Chlamydophila pneumoniae (n = 50)	0.02	0.04	–	–	–	–	–	–
Mycoplasma pneumoniae (n = 50)	0.006	0.006	–	–	–	–	–	–

MRSA methicillin-resistant *Staphylococcus aureus*, *MIC* minimum inhibitory concentrations

symptoms, at risk for major cardiac events or dysfunction, having significant hepatic disease, having confirmed or suspected CABP caused by MRSA, *P. aeruginosa*, or any member of the Enterobacteriaceae family, and a noninfectious cause of pulmonary infiltrates.

At baseline, of the 738 participants, 73.7% were white, 13.5% Asian, 11.2% Hispanic or Latino, and 5.5% black; 37.5% of the participants were at least 65 years old, 52.4% were male, and 50.1% were classified as having kidney impairment. Hypertension (36.2%), asthma

Table 3 Lefamulin Evaluation Against Pneumonia 1 (LEAP 1), $n = 551$ [28]

Intervention			
Lefamulin 150 mg IVq12 h ($n = 276$)		Moxifloxacin 400 mg IV q24 h ($n = 275$)	
Early clinical response			
87.30%		90.20%	
Response by pathogen			
S. pneumoniae	82/93 (88.2%)	S. pneumoniae	91/97 (93.8%)
S. aureus	10/10 (100.0%)	S. aureus	4/4 (100%)
H. influenzae	47/51 (92.2%)	H. influenzae	54/57 (94.7%)
M. catarrhalis	23/25 (92.0%)	M. catarrhalis	11/11 (100%)
M. pneumoniae	16/19 (84.2%)	M. pneumoniae	18/20 (90.0%)
L. pneumophila	16/18 (88.9%)	L. pneumophila	12/14 (85.7%)
C. pneumoniae	10/11 (90.9%)	C. pneumoniae	18/19 (94.7%)
Reported AE			
$n = 104$	38.10%	$n = 103$	37.70%
Most common AE			
Hypokalemia	2.90%	Diarrhea	7.70%
Nausea	2.90%	Hypokalemia	2.20%
Insomnia	2.90%	Nausea	2.20%
Infusion site pain	2.90%	Rise in ALT	2.20%
Infusion site phlebitis	2.20%	Hypertension	2.20%
ALT increase	1.80%	Insomnia	1.80%

or chronic obstructive pulmonary disease (16.7%), and diabetes (13.4%) comprised the most common preexisting conditions reported.

The FDA's primary endpoint was an ECR at 96 h ($\pm$ 24 h) after receipt of the first dose of either study drug in the ITT population. Lefamulin met the criteria for noninferiority to moxifloxacin. Both treatment groups had an ECR of 90.8. The difference of 0.1% in the ECR was non-significant (CI $-$ 4, 4.5). As was the case in LEAP 1 trial, the EMA co-primary end points (FDA secondary end points) were IACR at TOC (5–10 days after last dose) in the mITT population and in the CE population. Rates of IACR success were found to be insignificant at 87.0% with lefamulin and 89.1% with moxifloxacin in the mITT population (difference $-$ 2.1%; CI $-$ 7.0, 2.8) (Table 4).

SAFETY CONSIDERATIONS

Adverse Events

Adverse reactions such as injection site reactions, including infusion site pain, phlebitis, elevated transaminases, nausea, hypokalemia, and headache were reported by more than 2% of participants receiving lefamulin intravenously. In those receiving lefamulin orally, more than 2% of study participants experienced nausea, vomiting, diarrhea, and elevated

Table 4 Lefamulin Evaluation Against Pneumonia 2 (LEAP 2) [39], *n* = 738

Intervention			
Lefamulin 600 mg PO q12 h for 5 days (*n* = 370)		Moxifloxacin 400 mg PO q24 h for 7 days (*n* = 368)	
Early clinical response			
90.80%		90.80%	
Response by pathogen			
S. pneumoniae	110/123 (89.4%)	*S. pneumoniae*	115/126 (91.3%)
S. aureus	13/13 (100%)	*S. aureus*	6/6 (100%)
H. influenzae	50/56 (89.3%)	*H. influenzae*	44/48 (91.7%)
M. catarrhalis	18/21 (85.7%)	*M. catarrhalis*	11/11 (100%)
M. pneumoniae	20/20 (100%)	*M. pneumoniae*	14/14 (100%)
L. pneumophila	13/16 (81.3%)	*L. pneumophila*	16/17 (94.1%)
C. pneumoniae	15/16 (93.8%)	*C. pneumoniae*	12/12 (100%)
Reported AE			
n = 120	32.60%	*n* = 92	25.00%
Most common AE			
Diarrhea	12.20%	Nausea	1.90%
Nausea	5.20%	UTI	1.60%
Vomiting	3.30%	Headache	1.60%
Hypertension	1.40%	Hypertension	1.40%
Viral respiratory tract infection	1.40%		

transaminases. Less common adverse reactions include atrial fibrillation, anemia, thrombocytopenia, oropharyngeal and vulvovaginal candidiasis, anxiety, and urinary retention [19]. Lefamulin has the potential to prolong the QTc interval in some patients. *C. difficile*-associated diarrhea is a clinically significant adverse reaction that may occur following the oral or intravenous administration of lefamulin, as antibacterial agents alter the colon's normal flora and can cause an overgrowth of *C. difficile* [19]. In the LEAP 1 and LEAP 2 trials treatment discontinuation as a result of adverse events was 2.9% and 3.3% of participants, respectively [43, 44]. The adverse events leading to treatment discontinuation included infusion site phlebitis, QTc prolongation, bradycardia, and severe vomiting.

The overall mean (standard deviation) change from baseline in QT interval corrected according to Fridericia (QTcF) on day 3 post dose was 13.8 (19.8) ms for lefamulin and 16.4 (21.4) ms for moxifloxacin. There were eight patients (*n* = 3 lefamulin; *n* = 5 moxifloxacin) who presented with nonserious treatment emergent adverse events of prolonged QT intervals. However, in four patients (*n* = 1 lefamulin; *n* = 3 moxifloxacin), the event led to study drug discontinuation [42].

Drug–drug Interactions

The concomitant oral or intravenous administration of lefamulin with strong and/or moderate CYP3A or P-glycoprotein inducers can

reduce the efficacy of the drug and should be avoided. Conversely, oral or IV coadministration of lefamulin with drugs that strongly or moderately inhibit CYP3A or P-glycoprotein inhibitors may increase the risk of adverse reactions. Close monitoring of patients on concomitant therapy is warranted [19].

Contraindications

Lefamulin is contraindicated in patients with a known hypersensitivity to pleuromutilin drugs or to any of the agent's excipients. Lefamulin can prolong the QTc interval and should be avoided in patients with prolonged QTc. Lefamulin should be avoided in patients with a history of ventricular arrhythmias including torsades de pointes. Its use is therefore contraindicated with CYP3A4 inhibitors such as amiodarone, macrolides, verapamil, azoles, and protease inhibitors. Additionally, the coadministration of lefamulin with any of the following agents such as the class IA and class III antiarrhythmics, antipsychotics, tricyclic antidepressants, and the fluoroquinolones should be avoided [19].

Use in specific populations

The effects of lefamulin have not been studied in pregnant women. However, teratogenicity was demonstrated in animal studies involving lefamulin [19]. Therefore, pregnancy status should be assessed in women of childbearing age before starting lefamulin. Therapy with lefamulin may reduce the efficacy of oral contraceptives; therefore, women should use an additional forms of contraception during treatment and for at least 2 days after the completion of therapy. There are currently no studies evaluating the presence of lefamulin in human breast milk or its effect on a breastfed infant. To reduce the risk of serious adverse reactions, human milk should be discarded during treatment and for at least 2 days following treatment [19].

DOSAGE AND ADMINISTRATION

Lefamulin is indicated for the treatment of adults with CABP caused by the following susceptible microorganisms: *S. pneumoniae*, *S. aureus* (methicillin-susceptible isolates), *H. influenzae*, *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*.

For the treatment of CABP, the recommended dose of lefamulin is 150 mg infused intravenously over 60 min every 12 h for 5–7 days. Alternatively, the drug can be administered orally with 600 mg given every 12 h for 5 days. The oral tablets should be administered at least 1 h before or 2 h after meals and should be swallowed whole with 6–8 oz of water. Lefamulin tablets should not be crushed or chewed. In patients with severe hepatic impairment (Child–Pugh class C), the intravenous dose of lefamulin should be decreased to 150 mg infused over 1 h, every 24 h. Lefamulin oral tablets have not been studied in those with moderate or severe hepatic impairment (Child–Pugh class B or C) and are not currently recommended in this population. Currently, there are no dosing adjustments for those with renal impairment or in patients who are on hemodialysis [19].

P&T Committee Considerations

The American Thoracic Society CAP 2019 guidelines recommend amoxicillin, doxycycline, or a macrolide if resistance is below 25% in patients without comorbidities or risk factors for MRSA/*P. aeruginosa*. Also, these patients should not have prior respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization and receipt of parenteral antibiotics in the last 90 days. The Society recommended treating patients with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia with a beta-lactam and a macrolide/doxycycline or monotherapy with a respiratory fluoroquinolone [13]. Lefamulin's place in therapy may be in patients who have contraindications or intolerances to the preferred regimens and where resistance to preferred treatment is high.

Lefamulin is a single drug regimen with a novel mechanism of action. It is efficacious against *S. pneumoniae*, *S. aureus* (methicillin-susceptible isolates), *H. influenzae*, *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae* pathogens.

Renal and hepatic adjustment are not warranted; thus, lefamulin may be an alternative agent for patients with renal and hepatic insufficiency. Lefamulin is not associated with tendon rupture or neuropathy like the fluoroquinolones nor hepatotoxicity, nor dietary/drug–drug interactions with divalent cations like doxycycline and the fluoroquinolones.

Lefamulin should augment the current antimicrobial drugs to treat CABP. The high cost and prevalence of gastrointestinal side effects may make the widespread use of lefamulin in CABP implausible. However, there is a serious need for safe and effective oral options to treat bone, joint, and soft tissue infections particularly in outpatient settings.

CONCLUSION

Lefamulin is a novel pleuromutilin antibiotic with a broad spectrum of activity against grampositive and atypical organisms [14]. It is indicated for the treatment of adults with CABP caused by susceptible microorganisms.

The cost compared to the currently available agents for CABP may serve as a barrier to the use of lefamulin. The average wholesale price of the IV formulation of lefamulin is US$205 per day, and the oral formulation will cost US$275 per day, whereas older antibiotics are available at a fraction of this cost. Although lefamulin has been approved as an alternative therapy in the treatment of CAP, the American Thoracic Society and the Infectious Disease Society of America have recommended additional research in the outpatient setting [13, 26]. Lefamulin is also undergoing several phases 1 trial for various indications, including prosthetic joint infections, sexually transmitted infections, osteomyelitis, and pediatric infections. In a phase 2 study, lefamulin was evaluated in 210 patients with acute bacterial skin and skin structure infection (ABSSSI) caused by a gram-

positive pathogen. Randomized patients received either lefamulin 100 mg or 150 mg, or vancomycin 1 g intravenously every 12 h. Treatment response was assessed daily and at the TOC. Baseline characteristics, including the frequency of MRSA, were comparable between the different treatment groups. Clinical success at TOC in the clinically evaluative population occurred in 54 (90.0%) patients in the lefamulin 100mg group, 48 (88.9%) in the lefamulin 150-mg group, and 47 (92.2%) in the vancomycin group. On day 3, the clinical response rate was similar across the three treatment groups. Lefamulin also demonstrated comparable clinical efficacy in ABSSSIs caused by gram-positive pathogens, including MRSA, to those of vancomycin. The incidence rate for drug-related adverse events was lower for patients receiving lefamulin (34.3% and 39.4% in the 100-mg and 150-mg groups, respectively) than those receiving vancomycin (53.0%) [45]. The outcomes of these trials are forthcoming.

ACKNOWLEDGEMENTS

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