Received: October 14, 2020
REVIEW

Treatment of Community-Acquired Pneumonia: A Focus on Lefamulin

Nathaniel Eraikhuemen • Daniel Julien • Alandra Kelly • Taylor Lindsay • Dovena Lazaridis

N. Eraikhuemen
Division Director and Associate Professor of Clinical Practice (Corresponding Author)
Florida A&M University College of Pharmacy & Pharmaceutical Sciences, Institute of Public Health, Davie, Florida, USA
Email: nathan.Eraikhuemen@famu.edu

D. Julien
Memorial Regional Hospital – South, Hollywood, Florida, USA

A. Kelly • T. Lindsay
Florida A&M University College of Pharmacy & Pharmaceutical Sciences, Institute of Public Health, Davie, Florida, USA

D. Lazaridis
Department of Pharmacy, Memorial Regional Hospital, Hollywood, Florida, USA

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 assessed.

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 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. At the conclusion of the trial, the lefamulin group had an ECR of 87.3% to an ECR of 90.2% in the moxifloxacin group. 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, 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 *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. The agent also demonstrates both time and concentration-dependent killing against the pathogens *S. pneumoniae* and *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.

Keywords: BC-3781; Clinical pharmacology; Community-acquired pneumonia; Lemafulin; Mechanism of action

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), pharmacodynamic (PD), and two pivotal clinical trial data 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 *Mycobacterium genitalium* and drug-resistant *Neisseria gonorrhea*. Lefamulin demonstrated no activity against *Enterobacteriaceae* or *Pseudomonas aeruginosa*.

Pharmacokinetic studies involving lefamulin in acutely ill patients ≥18 years of age with ≥3 CABP symptoms failed to reveal any clinically significant differences in the PK parameters based on 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 CABP.
- Lemafulin unique binding property makes it less likely to the development of 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; preventing the binding of transfer ribonucleic acid (tRNA) for peptide transfer and therefore 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 intollerant to the beta-lactam, fluoroquinolones, and the 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 2nd leading cause of hospitalization.[1] In the United States (US), CAP leads to over 1.5 million hospitalizations and results in more than 14.2 million ambulatory care visits yearly.[1-3] It is also the most common infectious cause of death in the US, causing over 50,000 deaths every year.[2,4] The direct annual cost of CAP in the US has been estimated to be at least 17 billion, with a mean cost per hospitalization of $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 lungs 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 pneumonia.[8] Lifestyle factors such as smoking, excessive alcohol use, and having regular contact with children also increase the risk of developing CAP. Comorbid conditions such as chronic obstructive pulmonary disease, immunocompromising conditions such as 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 hrs after hospital admission. The causative pathogens, treatment, and 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 hours of intubation and mechanical ventilation.[10]

The exact incidence varies widely depending on the case definition of pneumonia and the population being studied. HAP accounts for up to 25% of all 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 Streptococcus pneumoniae* is the most common causative bacteria pathogens.[11,12]

Pharmacological treatment of pneumonia is dependent on the patient's comorbidities, risk factors, the severity of illness, and 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 the agents. Current treatment limitations include allergies, antibiotic resistance, inadequate penetration in lungs 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; thus, making them viable options for patients who are allergic to the other agents. Macrolide resistance rate of >30% was found amongst *S. pneumonia* isolates.[18]

Macrolides resistance occur via two main mechanisms, the first being a mutation that codes for

antibiotic efflux pumps. These pumps 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 the macrolides, lincosamides, and the streptogramin B. The prevalence of each resistance mechanism varies based on geographic region. Lefamulin has activity against macrolide resistant strains.[19] Another short coming of current medications is the lack of adequate lung penetration. Drugs such as vancomycin and aminoglycosides are 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 the macrolides [13] and the fluoroquinolones. Other side effects such as hypoglycemia, QTc prolongation, aortic dissection, psychiatric side effects have all been reported with the fluoroquinolone. [23-27]

To combat the limitations to available pharmacotherapeutic agents, novel therapies for the treatment of CAP are warranted. In August 2019, the U.S Food and Drug Administration (FDA) approved lefamulin for oral and intravenous administration in the treatment of adults with CABP caused by susceptible bacterial organisms[28].

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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. In addition, we cross-referenced the pertinent articles and searched ClinicalTrials.gov to identify ongoing studies.

Study selection and Data Extraction

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

CLINICAL PHARMACOLOGY

Pleuromutilin antibiotics are derived from the basidiomycete fungi. Lefamulin is the first pleuromutilin to be approved for systemic use in humans. The first pleuromutilin marked in 1979 was tiamulin; intended for veterinary use only.[29] Pleuromutilins 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.[30]

In 2007, retapamulin was made available for topical use in humans.[31]
Lefamulin is a semi-synthetic antibiotic indicated for the treatment of adults with CABP caused by *Streptococcus pneumoniae*, methicillin-susceptible isolates of *Staphylococcus aureus*, *Haemophilus influenzae, Legionella pneumophila, Mycoplasma 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. [13,32] Due 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 *Mycobacterium genitalium* and drug-resistant *Neisseria gonorrhea*. Lefamulin demonstrated no activity against *Enterobacteriaceae* or *Pseudomonas aeruginosa*.[33]

Pharmacokinetics

Pharmacokinetic studies involving lefamulin in acutely ill patients ≥18 years of age with ≥3 CABP symptoms revealed no clinically significant differences in the pharmacokinetic parameters based on age, sex, race, weight, or renal impairment. [19,34]

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 hours in healthy subjects. Consumption of high-fat meals consisting of at least 50% fat or high-calorie meals (800-1000 calories) resulted in slightly reduced bioavailability.[19, 35] The absolute oral bioavailability is 25.8% in the fasted state and 21.0% in the fed state respectively.[36] The reported free plasma area under the concentration-time curve over 24 hours ($fAUC_{0-24}$) and the free plasma maximum concentration (Cmax) were 1500.8 mg.hr/L and 330.1 mg/L. respectively.

Distribution

Lefamulin is highly protein-bound, between 94.8-97.1%.[19,37] The mean volume of distribution was 86.1liters in patients following intravenous (IV) administration. After a single 150mg IV administration infused over 1 hour, the highest lefamulin epithelial lining fluid (ELF) concentrations were observed at the end of the infusion. The mean ELF was 3.87 mcg·h/mL.[19]

Metabolism

In vitro studies revealed that lefamulin is both a substrate and an inhibitor of the CYP3A4 isoenzyme. [19,35] Therefore, the administration of lefamulin should be avoided or administered with caution in patients taking medications that are metabolized by CYP3A isoenzyme. A reduction in the dosage of IV lefamulin to 150 mg every 24 hours in patients with severe hepatic impairment (Childs-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, 35] The mean elimination half-life is approximately 8 hours in patients with CABP.[11,38] Following IV administration of 150mg of lefamulin, 77% of the dose was excreted in the feces with approximately 4.2 to 9.1% unchanged and approximately 14.1% to15.5% was excreted unchanged in the urine. Following oral administration of 600mg, 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 I.

Lefamulin demonstrates both time and concentration-dependent killing against the pathogens *S. pneumoniae* and *S. aureus*.[31] In vitro susceptibility testing demonstrated an $MIC_{50/90}$ of 0.06/0.12 µg/ml against *S. pneumoniae* and *S. aureus.*[39] 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.[40]

The requirement for bactericidal activity against mycoplasmal infections is a minimum bactericidal concentration (MBC) ≤2 dilutions greater than the minimum inhibitory concentration (MIC).[41] Lefamulin had an MIC of ≤0.008 µg/ml against 18 macrolide-susceptible and 42 macrolide-resistant strains of *M. pneumoniae*. The MIC which inhibited 90% (MIC_{90}) of macrolide-susceptible and macrolide-resistant *M. pneumoniae* were ≤0.001 µg/ml, and 0.002 µg/ml, respectively.[42] Lefamulin underwent susceptibility testing against other atypical pathogens such as *L. pneumophila* and *C. pneumoniae*.[43] 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 those organisms such as *H. influenzae* and *M. catarrhalis* between 2015-2016.[44] Against *H. influenzae*, lefamulin has an $MIC_{50/90}$ of 0.5/1µg/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).[44] In general, lefamulin demonstrates susceptibility against commonly encountered bacterial pathogens. Table IV.

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.

Lefamulin Evaluation Against Pneumonia 1 (LEAP 1)[45]

LEAP 1 was conducted as a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study. Five hundred fifty-one participants with CABP were randomly assigned in a 1:1 to receive either lefamulin or moxifloxacin. Participants received 150 mg intravenously (IV) every 12 hours lefamulin, with the option of switching to an oral study drug after 6 doses if the pre-specified improvement criteria were met (n=276), or 400 mg IV every 24 hours every 24 hours moxifloxacin (n=275). Participants receiving moxifloxacin also received linezolid 600 mg IV every 12 hours 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. Length of therapy for the participants ranged from 5 to 10 days.

Participants were required to meet the following inclusion criteria: Adult greater than the age of 18, radiographic imaging that was indicative of pneumonia, Pneumonia Outcomes Research Team (PORT) risk class ≥ III, illness that initially presented within 7 days of enrollment, and ≥3 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 ≥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, 59.8 were male.

The FDA primary endpoint was an early clinical response (ECR) in the intention-to-treat population at 96 ± 24 hours after the first study drug dose.[14] At the conclusion of the trial, the lefamulin group had an ECR of 87.3% (241/276) to an ECR of 90.2% (248/275) in the moxifloxacin group. 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 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 group had an IACR (mITT) of 80.8% in the Lefamulin treatment group 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. Due to the small sample size (<10), the differences in ECR could not be evaluated in class II and V CABP. Lefamulin met the criteria for noninferiority. Table II.

Lefamulin Evaluation Against Pneumonia 2 (LEAP 2)[46]

LEAP 2 was a randomized, non-inferiority, double-blind, double-dummy, multicenter, parallel-group study comprised of 738 participants. 370 participants with confirmed CABP received 600 mg PO every 12 hours for 5 days in the lefamulin group and 368 participants received 400 mg PO every 24 hours 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: Adult greater than the age of 18, radiographic imaging that was indicative of pneumonia, Pneumonia Outcomes Research Team (PORT) risk class ≥ III, illness that initially presented within 7 days of enrollment, and ≥3 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 2 or more days within 90 days of the onset of 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 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 hours (± 24 hours) after receipt of the first dose of either study drug in the intention-to-treat 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 European Medicines Agency co-primary endpoints (FDA secondary endpoints) were investigator assessment of clinical response at test of cure (5-10 days after last dose) in the modified ITT population and in the clinically evaluable population. Rates of investigator assessment of clinical response success were found to be insignificant at 87.0% with lefamulin and 89.1% with moxifloxacin in the modified ITT population (difference, -2.1% (CI: -7.0, 2.8) Table III.

SAFETY CONSIDERATIONS

Adverse Events

Adverse reactions such as injection site reactions, including infusion site pain, phlebitis, elevated transaminases, nausea, hypokalemia, and headache were reported >2% of participants receiving lefamulin intravenously. In those receiving oral lefamulin, >2% of study participants experienced nausea, vomiting, diarrhea, and elevated 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. *Clostridium difficile*-associated diarrhea is a clinically significant adverse reaction that may occur following the use of oral or intravenous lefamulin, as antibacterial agents alter the colon's normal flora and can cause an overgrowth of *Clostridium difficile*.[19] In the LEAP 1 and LEAP 2 trials treatment discontinuation as a result of adverse events were 2.9% and 3.3% participants, respectively.[45,46] 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) millisecond for lefamulin and 16.4 (21.4)

millisecond for moxifloxacin. There were 8 patients (n = 3 lefamulin; n = 5 moxifloxacin) who presented with nonserious Treatment Emergent Adverse Events of prolonged QT intervals. However, in 4 patients (n = 1 lefamulin; n = 3 moxifloxacin), the event led to study drug discontinuation. [44]

Drug-Drug Interactions

The concomitant use of oral or intravenous lefamulin with strong and/or moderate CYP3A or P-glycoprotein inducers can reduce the efficacy of the drug and should be avoided. Conversely, co-administration of oral or IV 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 or 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 CYP 3A4 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 prior to starting lefamulin. Therapy with lefamulin may reduce the efficacy of oral contraceptives; therefore, females should use additional form 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: *Streptococcus pneumoniae, Staphylococcus aureus (methicillin-susceptible isolates), Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*

For the treatment of CABP, the recommended dose of lefamulin is 150 mg infused intravenously over 60 minutes every 12 hours for 5 to 7 days. Alternatively, the drug can be administered orally with 600 mg given every 12 hours for 5 days. The oral tablets should be administered at least 1 hour before or 2 hours after meals and should be swallowed whole with 6-8 ounces 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 hr. every 24 hours. 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/Pseudomonas aeruginosa. In addition, these patients should not have prior respiratory isolation of MRSA or Pseudomonas aeruginosa or recent hospitalization and receipt of parenteral antibiotics in the last 90 days. The society recommended to treat 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 *Streptococcus pneumoniae, Staphylococcus aureus (methicillin-susceptible isolates), Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydophila 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, neuropathy like the fluoroquinolones nor hepatotoxicity, and dietary/drug-drug interactions with divalent cations like doxycycline and the fluoroquinolones.

Lefamulin augments the current antimicrobial drugs to treat CABP. The high cost and prevalence of gastrointestinal side effects makes 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 the outpatient settings.

CONCLUSION

Lefamulin is a novel pleuromutilin antibiotic with a broad spectrum of activity against gram-positive 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 IV lefamulin is $205 per day, and the oral formulation will cost $275 per day, whereas older antibiotics are available at a fraction of this cost. Although it 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],[28] In a phase 2 study, lefamulin was evaluated in 210 patients with an acute bacterial skin and skin structure infection (ABSSSI) caused by a Gram-positive pathogen. Randomized patients received either intravenous lefamulin 100mg or 150 mg, or vancomycin 1 g every 12 hours. Treatment response was assessed daily and at test of cure (TOC). Baseline characteristics, including the frequency of methicillin-resistant Staphylococcus aureus (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 100-mg group, 48 (88.9%) and in the 150-mg group, and 47 (92.2%) in the vancomycin group. At day 3, the clinical response rate was similar across the three treatment groups. Lefamulin also demonstrated comparable clinical efficacy in ABSSSIs caused by a Gram-positive pathogen, 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%). [47]

Lefamulin is also undergoing several phase 1 trials for various indications, including prosthetic joint infections, sexually transmitted infections, osteomyelitis, and pediatric infections. The outcomes of these trials are forthcoming.

ACKNOWLEDGEMTNS

Funding: This review was supported by a grant from the National Institute of Minority Health and Health DisparityU54 MD 007582. The Rapid Service Fee was funded by the authors.

Authorship: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures: Nathaniel Eraikhuemen, Daniel Julien, Alandra Kelly, Taylor Lindsay and Dovena Lazaridis have nothing to disclosures.

Compliance with Ethics Guidelines: This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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*	

Table 2: Lefamulin Evaluation Against Pneumonia 1 (LEAP 1) n = 551[30]

Intervention			
Lefamulin 150mg IV Q12hr (N=276)		Moxifloxacin 400mg IV Q24hr (N=275)	
Early Clinical Response			
87.3%		90.2%	
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	38.1%	N=103	37.7%
Most Common AE			
Hypokalemia	2.9%	Diarrhea	7.7%
Nausea	2.9%	Hypokalemia	2.2%
Insomnia	2.9%	Nausea	2.2%
Infusion site pain	2.9%	Rise in ALT	2.2%
Infusion site phlebitis	2.2%	Hypertension	2.2%
ALT increase	1.8%	Insomnia	1.8%

Table 3:Lefamulin Evaluation Against Pneumonia II (LEAP 2)[41] n=738

Intervention			
Lefamulin 600mg PO Q12hr for 5d (N=370)		Moxifloxacin 400mg PO Q24hr for 7d (N=368)	
Early Clinical Response			
90.8%		90.8%	
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	32.6%	N= 92	25.0%
Most Common AE			
Diarrhea Nausea Vomiting Hypertension Viral Respiratory Tract Infection	12.2% 5.2% 3.3% 1.4% 1.4%	Nausea UTI Headache Hypertension	1.9% 1.6% 1.6% 1.4%

REFERENCES

1. American Thoracic Society - Patient Resources. https://www.thoracic.org/patients/patient-resources/. Accessed January 31, 2020

2. Sattar SBA, Sharma S. Bacterial Pneumonia. [Updated 2020 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513321/

3. Agency for Healthcare Research and Quality. Community-Acquired Pneumonia in the Emergency Department Setting. AHRQ Pub; 2018. http://www.ahrq.gov/sites/default/files/wysiwyg/professionals/quality-patient-safety/quality-resources/tools/cap-toolkit/cap_ed-pamphlet.pdf

4. Ramirez J. Adults Hospitalized with Pneumonia in the United States: Incidence, Epidemiology and Mortality. Open Forum Infectious Diseases. 2017;4(suppl_1). doi:10.1093/ofid/ofx163.1493

5. File TM, Marrie TJ. Burden of Community-Acquired Pneumonia in North American Adults. Postgrad Med. 2010;122(2):130-141. doi:10.3810/pgm.2010.03.2130

6. Brown JD, Harnett J, Chambers R, Sato R. The relative burden of community-acquired pneumonia hospitalizations in older adults: a retrospective observational study in the United States. BMC Geriatr. 2018;18(1):92. doi:10.1186/s12877-018-0787-2

7. Kolditz M, Ewig S. Community-acquired pneumonia in adults. Dtsch Arztebl Int. 2017;114(49):838-848. doi:10.3238/arztebl.2017.0838

8. Pneumococcal Disease | Transmission and Those at High Risk | CDC. https://www.cdc.gov/pneumococcal/about/risk-transmission.html. Accessed January 28, 2020

9. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: A literature review. Thorax. 2013;68(11):1057-1065. doi:10.1136/thoraxjnl-2013-204282

10 Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. Am J Respir Crit Care Med Vol 17. pp 388–416, 2005 DOI: 10.1164**)**

11. Regunath H, Oba Y. Community-Acquired Pneumonia. [Updated 2019 Feb 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430749/

12. Brown JS. Community-acquired pneumonia. Clin Med (Lond). 2012;12(6):538-543. doi:10.7861/clinmedicine.12-6-538

13. Metlay J, Waterer G, Long A et. al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45-e67. doi:10.1164/rccm.201908-1581st

14. Ahdal J, Nayar S, Hasan A, Waghray P, Ramananthan S, Jain R. Management of community-acquired bacterial pneumonia in adults: Limitations of current antibiotics and future therapies. Lung India. 2019;36(6):525. doi:10.4103/lungindia.lungindia_38_19

15. Jeffres MN, Narayanan PP, Shuster JE, Schramm GE. Consequences of avoiding β-lactams in patients with β-lactam allergies. Journal of Allergy and Clinical Immunology. 2016;137(4):1148-1153. doi:10.1016/j.jaci.2015.10.026

16. Hermanides J, Lemkes BA, Prins JM, Hollmann MW, Terreehorst I. Presumed β-Lactam Allergy and Cross-reactivity in the Operating Theater. Anesthesiology. 2018;129(2):335-342. doi:10.1097/aln.0000000000002252

17. Shaeer KM, Chahine EB, Varghese Gupta S, Cho JC. Macrolide Allergic Reactions. Pharmacy (Basel). 2019;7(3):135. Published 2019 Sep 18. doi:10.3390/pharmacy7030135

18. Centers for Disease Control and Prevention. 2016. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae, 2016. Available via the internet: http://www.cdc.gov/abcs/reportsfindings/survreports/spneu16.pdf

19. XENLETA™ (lefamulin) [package insert]. King of Prussia, PA: Nabriva Therapeutics; 2019

20. Brun-Buisson C, Lemaire F. Administration of Antibiotics for Pneumonia during Respiratory Failure: Reaching the Target. American Journal of Respiratory and Critical Care Medicine. 2001;164(9):1554-1555. doi:10.1164/ajrccm.164.9.2108099b

21. Lodise TP, Drusano GL, Butterfield JM, Scoville J, Gotfried M, Rodvold KA. Penetration of Vancomycin into Epithelial Lining Fluid in Healthy Volunteers. Antimicrobial Agents and Chemotherapy. 2011;55(12):5507-5511. doi:10.1128/aac.00712-11

22. Wicha WW, Strickmann DB, Paukner S. Pharmacokinetics/pharmacodynamics of lefamulin in a neutropenic murine pneumonia model withStaphylococcus aureusandStreptococcus pneumoniae. Journal of Antimicrobial Chemotherapy. 2019;74(Supplement_3):iii11-iii18. doi:10.1093/jac/dkz086

23. U.S Food and Drug Administration. FDA Drug Safety Communication FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. July 2018.

24. Center for Drug Evaluation and Research. Serious low blood sugar, new mental health effects with fluoroquinolones. U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-reinforces-safety-information-about-serious-low-blood-sugar-levels-and-mental-health-side. Published October 7, 2018. Accessed July 2, 2020

25. Center for Drug Evaluation and Research. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics Published December 21, 2018

26. FDA Drug Safety Communication. FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. https://www.fda.gov/media/114192/download. Retrieved November 15, 2019.

27 Center for Drug Evaluation and Research. Serious low blood sugar, new mental health effects with fluoroquinolon. U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-reinforces-safety-information-about-serious-low-blood-sugar-levels-and-mental-health-side. Published October 7, 2018. Accessed July 2, 2020

28 Nabriva Therapeutics Receives U.S. FDA Approval of Xenleta™ (lefamulin) to Treat Community-Acquired Bacterial Pneumonia (CABP).; 2019. Available at: http://https://investors.nabriva.com/news-releases/news-release-details/nabriva-therapeutics-receives-us-fda-approval-xenleta. Accessed July 03, 2020

29. Rodvold KA. Introduction: lefamulin and pharmacokinetic/pharmacodynamic rationale to support the dose selection of lefamulin. J Antimicrob Chemother. 2019;74(Supplement_3):iii2-iii4. doi:10.1093/jac/dkz084

30 van Duijkeren E, Greko C, Pringle M, Keith Edward Baptiste KE. Et. al. Pleuromutilins: use in food-producing animals in the European Union, development of resistance and impact on human and animal health. J Antimicrob Chemother 2014; 69: 2022–2031doi:10.1093

31. Paukner S, Riedl R. Pleuromutilins: Potent Drugs for Resistant Bugs-Mode of Action and Resistance. Cold Spring Harb Perspect Med. 2017;7(1):a027110. doi:10.1101/cshperspect.a027110

32. Eyal Z, Matzov D, Krupkin M, et al. A novel pleuromutilin antibacterial compound, its binding mode and selectivity mechanism. Sci Rep. 2016;6(1):39004. doi:10.1038/srep39004

33. Veve MP, Wagner JL. Lefamulin: Review of a Promising Novel Pleuromutilin Antibiotic. Pharmacother J Hum Pharmacol Drug Ther. 2018;38(9):935-946. doi:10.1002/phar.2166

34. File Jr TM, Goldberg L, Das A, et al. Efficacy and Safety of Intravenous-to-oral Lefamulin, a Pleuromutilin Antibiotic, for the Treatment of Community-acquired Bacterial Pneumonia: The Phase III Lefamulin Evaluation Against Pneumonia (LEAP 1) Trial. Clin Infect Dis. 2019;69(11):1856-1867. doi:10.1093/cid/ciz090

35. Wicha WW, Prince WT, Lell C, Heilmayer W, Gelone SP. Pharmacokinetics and tolerability of lefamulin following intravenous and oral dosing. J Antimicrob Chemother. 2019;74(Supplement_3):iii19-iii26. doi:10.1093/jac/dkz087

36. Wicha, W., Lell, C, Seltzer, E., Prince, W.T, Gelone, S. (2017). Pharmacokinetics and Safety of an Oral, Immediate-Release (IR) Tablet Formulation of Lefamulin in Fed and Fasted Healthy Subjects, Poster presented at 27th European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria

37. Dubey A, Maggo S, Karan A, Singh N, Bhaskaran S. Lefamulin: novel pleuromutilin drug for community acquired bacterial pneumonia. Int J Basic Clin Pharmacol. 2019;8:2783. doi:10.18203/2319-2003.ijbcp20195297

38. Wicha WW, Ivezic-Schoenfeld Z, Novak R. Pre-clinical efficacy of BC-3781 in thigh and bacteremia infections caused by staphylococci. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy 2010; Abstract F1-2109.

39. Bhavnani SM, Zhang L, Hammel JP, et al. Pharmacokinetic/pharmacodynamic target attainment analyses to support intravenous and oral lefamulin dose selection for the treatment of patients with community-acquired bacterial pneumonia. J Antimicrob Chemother. 2019;74:III35-III41. doi:10.1093/jac/dkz089

40. Paukner S, Gelone SP, Arends SJR, Flamm RK, Sader HS. Antibacterial Activity of Lefamulin against Pathogens Most Commonly Causing Community-Acquired Bacterial Pneumonia: SENTRY Antimicrobial

Surveillance Program (2015-2016). Antimicrob Agents Chemother. 2019;63(4):e02161-18. doi:10.1128/AAC.02161-18

41. Waites KB, Nolte FS. Laboratory Diagnosis of Mycoplasmal Infections. Washington, DC: ASM Pr.; 2001.

42. Waites KB, Crabb DM, Duffy LB, Jensen JS, Liu Y, Paukner S. In Vitro Activities of Lefamulin and Other Antimicrobial Agents against Macrolide-Susceptible and Macrolide-Resistant Mycoplasma pneumoniae from the United States, Europe, and China. Antimicrob Agents Chemother. 2017;61(2):e02008-16. doi:10.1128/AAC.02008-16

43. Sader HS, Paukner S, Ivezic-Schoenfeld Z, Biedenbach DJ, Schmitz FJ, Jones RN. Antimicrobial activity of the novel pleuromutilin antibiotic BC-3781 against organisms responsible for community-acquired respiratory tract infections (CARTIs). J Antimicrob Chemother. 2012;67(5):1170-1175. doi:10.1093/jac/dks001

44. Paukner S, Sader HS, Ivezic-Schoenfeld Z, Jones RN. Antimicrobial Activity of the Pleuromutilin Antibiotic BC-3781 against Bacterial Pathogens Isolated in the SENTRY Antimicrobial Surveillance Program in 2010. Antimicrob Agents Chemother. 2013;57(9):4489 LP - 4495. doi:10.1128/AAC.00358-13

45. Efficacy and Safety of Intravenous-to-oral Lefamulin, a Pleuromutilin Antibiotic, for the Treatment of Community-acquired Bacterial Pneumonia: The Phase III Lefamulin Evaluation Against Pneumonia (LEAP 1) Trial. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6853694/. Accessed August 1, 2020.

46. Alexander E, Goldberg L, Das AF, et al. Oral Lefamulin vs Moxifloxacin for Early Clinical Response among Adults with Community-Acquired Bacterial Pneumonia: The LEAP 2 Randomized Clinical Trial. In: JAMA - Journal of the American Medical Association. Vol 322. American Medical Association; 2019:1661-1671. doi:10.1001/jama.2019.15468

47. Prince WT, Ivezic-Schoenfeld Z, Lell C; Tack CK, Novak R, Obermayr F; Talbota GH. Phase II Clinical Study of BC-3781, a Pleuromutilin Antibiotic, in Treatment of Patients with Acute Bacterial Skin and Skin Structure Infections. Antimicrobial Agents and Chemotherapy May 2013:57(5) p. 2087–2094