Drug Monograph

Drug Name: **Xenleta™ (lefamulin) Tablets and Injection**
Drug Class: **Antibiotic, Pleuromutilin**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Xenleta is available as an oral tablet containing 600 mg of lefamulin and a single-dose 15 mL vial containing 150 mg of lefamulin for intravenous infusion (must be administered with lefamulin diluent).
Manufacturer:	Manufactured for: Nabriva Therapeutics US, Inc., King of Prussia, PA 19406.
Summary of Findings:	The efficacy of Xenleta was demonstrated in 2 randomized, double-blind, double-dummy, clinical trials in 1289 adults with community-acquired bacterial pneumonia (CABP). The primary measure of efficacy was early clinical response (ECR). ECR was defined as survival with improvement in at least 2 signs and symptoms of CABP (relative to baseline), no worsening of any CABP sign or symptom, and no use of concomitant antibiotics (other than adjunctive linezolid, as allowed by the study protocol in study 1) for the treatment of CABP through the ECR assessment. ECR was determine at 72 to 120 hours after the first dose. Lefamulin was noninferior to moxifloxacin for ECR. Study 1: (87.3% vs 90.2%; difference: -2.9% [95% CI: -8.5, 2.8]) Study 2: (90.8% vs 90.8%; difference: 0.1% [95% CI: -4.4, 4.5])
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☒ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1]

Community acquired bacterial pneumonia (CABP) is an acute infection involving the lungs which can range from mild to severe illness and affect people of all ages. Roughly 4 million cases of CABP occur annually, with about 25% requiring hospitalization. *Streptococcus pneumonia,* the main bacteria responsible for causing CABP, is on the Centers for Disease Control and Prevention as a serious threat for antibiotic resistance. The CDC estimates that drug-resistant *Streptococcus pneumonia* causes 1.2 million illnesses and approximately 7,000 deaths each year in the U.S. Symptoms of CABP include fever, a productive cough with purulent sputum, dyspnea, and pleuritic chest pain.

Dosage Form [2]

Xenleta is available as an oral tablet containing 600 mg of lefamulin and a single-dose vial containing 150 mg of lefamulin for intravenous infusion.

Manufacturer [2]

Manufactured for: Nabriva Therapeutics US, Inc., King of Prussia, PA 19406.

Indication(s) [2]

Xenleta is indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms.

Clinical Efficacy [2-4] (mechanism of action/pharmacology, comparative efficacy)

Lefamulin is a systemic pleuromutilin antibacterial agent which inhibits protein synthesis through interactions (hydrogen bonds, hydrophobic interactions and Van der Waals forces) with the A- and P-sites of the peptidyl transferase center in domain V of the 23s rRNA of the 50S subunit. Correct positioning of tRNA is prevented and is bactericidal.

Pharmacokinetics:

Absorption	Time to peak: 0.88 to 2 hours
Metabolism	Primarily metabolized by CYP3A4
Excretion	Urine: Oral: 5% IV: 15% Feces: Oral: 88% IV: 77%
Half-life	8 hours

Clinical Trials Experience:

STUDY 1 DESIGN	Randomized, multi-center, double-blind, double-dummy, non-inferiority study (n = 551)
INCLUSION CRITERIA	• Be male or female at least 18 years of age. • Provide written informed consent and be willing and able to adhere to the study-specified procedures and restrictions. • Have an acute illness (7 days duration) with at least 3 of the following symptoms consistent with a lower respiratory tract infection (new or worsening): -Dyspnea -New or increased cough -Purulent sputum production -Chest pain due to pneumonia • Have at least 2 of the following vital sign abnormalities: -Fever (body temperature >38.0°C (100.4°F) measured orally or equivalent temperature from an alternate body site) or hypothermia (body temperature <35.0°C (95.0°F) measured orally or equivalent temperature from an alternate body site) -Hypotension (systolic blood pressure <90 mmHg) -Tachycardia (heart rate >100 beats/min) -Tachypnea (respiratory rate >20 breaths/min) • Have at least 1 other clinical sign or laboratory finding of CABP: -Hypoxemia (i.e., O2 saturation <90% on room air or while receiving supplemental oxygen at subject's baseline requirement or PaO2 <60 mmHg) -Auscultatory and/or percussion findings consistent with pneumonia (e.g., crackles, egophony, dullness) -White blood cell (WBC) count >10,000 cells/mm3 or <4500 cells/mm3 or >15% immature neutrophils (bands) regardless of total WBC count • Have radiographically-documented pneumonia within 48 hours before enrollment (i.e., infiltrates in a lobar or multilobar distribution or diffuse opacities on chest x-ray or chest computed tomography scan consistent with acute bacterial pneumonia). • Have a Pneumonia Outcomes Research Team (PORT) Risk Class ≥III.
EXCLUSION CRITERIA	• Have received more than a single dose of a short-acting oral or IV antibacterial for CABP within 72 hours before randomization • Require concomitant systemic antibacterial therapy potentially effective against CABP pathogens • Have been hospitalized for 2 or more days within 90 days prior to the onset of symptoms or have resided in a nursing home or long-term healthcare facility within 30 days prior to the onset of symptoms. NOTE: Residence in an independent living facility is permitted. • Have confirmed or suspected CABP caused by a pathogen known to be resistant to any of the study drugs (e.g.,

	Pseudomonas aeruginosa, any pathogen of the Enterobacteriaceae Family) or attributable to etiologies other than community acquired bacterial pathogens (e.g., ventilator associated pneumonia, hospital acquired bacterial pneumonia, bacterial aspiration pneumonia, Pneumocystis jiroveci pneumonia or other fungal pneumonia, viral or mycobacterial infection of the lung). • Have a noninfectious cause of pulmonary infiltrates (e.g., pulmonary embolism, chemical pneumonitis from aspiration, hypersensitivity pneumonia, congestive heart failure, bronchial obstruction, lung cancer, cystic fibrosis). • Have confirmed or suspected pleural empyema (does not include sterile parapneumonic effusions). • Require mechanical ventilation.
TREATMENT REGIMEN	Patients were randomized to receive Xenleta (150 mg IV infusion over 60 minutes every 12 hours, with the option to switch to 600 mg orally every 12 hours after at least 3 days of IV treatment) (n=276), or moxifloxacin (400 mg IV every 24 hours, with the option to switch to 400 mg orally every 24 hours after at least 3 days of IV treatment (n=275). If MRSA was suspected at screening, patients randomized to moxifloxacin were to receive adjunctive linezolid (600 mg IV every 12 hours, with the option to switch to 600 mg orally every 12 hours after at least 3 days of IV treatment) and patients randomized to Xenleta were to receive linezolid placebo.
RESULTS	The primary measure of efficacy was early clinical response (ECR). ECR was defined as survival with improvement in at least 2 signs and symptoms of CABP (relative to baseline), no worsening of any CABP sign or symptom, and no use of concomitant antibiotics (other than adjunctive linezolid, as allowed by the study protocol) for the treatment of CABP through the ECR assessment. ECR was determine at 72 to 120 hours after the first dose. Xenleta was noninferior to moxifloxacin for ECR (87.3% vs 90.2%; difference: -2.9% [95% confidence interval: -8.5, 2.8])
SAFETY	Discussed in the Adverse Effects section below.

STUDY 2 DESIGN	Randomized, double-blind, double-dummy, non-inferiority study (n = 738)
INCLUSION CRITERIA	• Be male or female at least 18 years of age. • Provide written informed consent and be willing and able to adhere to the study-specified procedures and restrictions. • Have an acute illness (less than or equal to 7 days duration) with at least 3 of the following symptoms consistent with a lower respiratory tract infection (new or worsening): -Dyspnea. -New or increased cough. -Purulent sputum production. -Chest pain due to pneumonia. • Have at least 2 of the following vital sign abnormalities: -Fever (body temperature > 38.0 °C (100.4 °F) measured orally or equivalent temperature from an alternate body site) or

	hypothermia (body temperature < 35.0 °C (95.0 °F) measured orally or equivalent temperature from an alternate body site). -Hypotension (systolic blood pressure < 90 mmHg). -Tachycardia (heart rate > 100 beats/min). -Tachypnea (respiratory rate > 20 breaths/min). • Have at least 1 other clinical sign or laboratory finding of CABP: -Hypoxemia (i.e., O2 saturation < 90 % on room air or while receiving supplemental oxygen at subject's baseline requirement or PaO2 < 60 mmHg). -Auscultatory and/or percussion findings consistent with pneumonia (e.g., crackles, egophony, dullness). -White blood cell (WBC) count > 10 000 cells/mm3 or < 4 500 cells/mm3 or >15 % immature neutrophils (bands) regardless of total WBC count. • Have radiographically-documented pneumonia within 48 hours before enrollment (i.e., infiltrates in a lobar or multilobar distribution or diffuse opacities on chest x-ray or chest computed tomography scan consistent with acute bacterial pneumonia). • Have a Pneumonia Outcomes Research Team (PORT) Risk Class of II, III, or IV and be an appropriate candidate for oral antibiotic therapy as treatment for the current episode of CABP.
EXCLUSION CRITERIA	• Have received more than a single dose of a short-acting oral or IV antibacterial for CABP within 72 hours before randomization. • Require concomitant systemic antibacterial therapy potentially effective against CABP pathogens. • Have been hospitalized for 2 or more days within 90 days prior to the onset of symptoms or have resided in a nursing home or long-term healthcare facility within 30 days prior to the onset of symptoms. NOTE: Residence in an independent living facility is permitted. • Have confirmed or suspected CABP caused by a pathogen known to be resistant to any of the study drugs (e.g., MRSA, Pseudomonas aeruginosa, any pathogen of the Enterobacteriaceae Family) or attributable to etiologies other than community acquired bacterial pathogens (e.g., ventilator associated pneumonia, hospital acquired bacterial pneumonia, bacterial aspiration pneumonia, Pneumocystis jiroveci pneumonia or other fungal pneumonia, viral or mycobacterial infection of the lung). • Have a noninfectious cause of pulmonary infiltrates (e.g., pulmonary embolism, chemical pneumonitis from aspiration, hypersensitivity pneumonia, congestive heart failure, bronchial obstruction, lung cancer, cystic fibrosis). • Have confirmed or suspected pleural empyema (does not include sterile parapneumonic effusions).

TREATMENT REGIMEN	Patients were randomized to receive Xenleta 600 mg orally every 12 hours for 5 days (n=370) or moxifloxacin 400 mg orally every 24 hours for 7 days (n=368).
RESULTS	The primary measure of efficacy was early clinical response (ECR). ECR was defined as survival with improvement in at least 2 signs and symptoms of CABP (relative to baseline), no worsening of any CABP sign or symptom, and no use of concomitant antibiotics for the treatment of CABP through the ECR assessment. ECR was determine at 72 to 120 hours after the first dose. Xenleta was noninferior to moxifloxacin for ECR (90.8% vs 90.8%; difference: 0.1% [95% confidence interval: -4.4, 4.5])
SAFETY	Discussed in the Adverse Effects section below.

Contraindications (2)

- Known hypersensitivity to Xenleta, pleuromutilin class drugs, or any components of Xenleta
- CYP3A4 substrates that prolong the QT interval (pimozide). Concomitant administration of oral Xenleta with sensitive CYP3A4 substrates may result in increased plasma concentrations of these drugs, leading to QT prolongation and cases of torsades de points.

Warnings and Precautions (2)

- QT Prolongation:
    - Avoid in the following patients: known prolongation of the QT interval, ventricular arrhythmias including torsades de points, Class IA (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic agents, and concomitant use with other drugs that prolong the QT interval (antipsychotics, erythromycin, pimozide, moxifloxacin, and tricyclic antidepressants).
    - Renal failure patients requiring dialysis: metabolic disturbances associated renal failure may lead to QT prolongation.
    - Mild, moderate, or severe hepatic impairment: metabolic disturbances associated with hepatic impairment may lead to QT prolongation.
    - ECG monitoring is recommended during treatment if use of Xenleta cannot be avoided
    - Magnitude of QT prolongation may increase with increasing concentrations of Xenleta, or increasing the infusion rate.
- Embryo-Fetal Toxicity:
    - May cause fetal harm. Verify pregnancy status of females in reproductive potential prior to initiating Xenleta. Advise females on reproductive potential to use effective contraception during treatment and for 2 days after the final dose.
- Clostridium difficile-associated Diarrhea
- Development of drug-resistant bacteria may develop when given to patients without proven bacterial infection.

Adverse Effects [2-4]

Most common, ≥ 2%; IV + Oral dosing	Xenleta (n = 273) %
Administration site reactions*	7
Hepatic enzyme elevation	3
Nausea	3
Hypokalemia	3
Insomnia	3
Headache	2

*Administration site reactions include infusion site pain, infusion site phlebitis and injection site reaction

Most common, ≥ 2%; Oral dosing only	Xenleta (n = 368) %
Diarrhea	12
Nausea	5
Vomiting	3
Hepatic enzyme elevation	2

Drug Interactions [2]

- Strong – moderate CYP3A4 inducers or P-gp Inducers: Avoid Xenleta unless the benefit outweighs the risk. Monitor for reduced efficacy of Xenleta. Strong 3A4 inducers include carbamazepine, rifampin, phenytoin, St. John's wort.
- Strong CYP3A inhibitors or P-gp Inhibitors: Avoid Xenleta. Strong 3A4 inhibitors include ketoconazole, itraconazole, clarithromycin.
- Moderate CYP3A inhibitors or P-gp inhibitors: Monitor for adverse reactions
- QT prolongation: Avoid concomitant use of Xenleta with drugs that prolong the QT interval such as class IA and III antiarrhythmics, antipsychotics, erythromycin, moxifloxacin, and tricyclic antidepressants.
- Midazolam or other sensitive CYP3A substrates: Monitor for adverse reactions.

Dosage and Administration [2]

- Injection: 150 mg every 12 hours by intravenous infusion over 60 minutes for 5 - 7 days.
- Tablets: 600 mg orally every 12 hours for 5 days
- Hepatic Impairment:
  - IV: Reduce the dosage of Xenleta to 150 mg IV every 24 hours with severe hepatic impairment. No dosage adjustment for mild to moderate impairment.
  - Tablets: No dosage adjustment for mild impairment. Not studied in moderate- to severe impairment.
- Xenleta injection must be diluted before injection. Xenleta injection is good for 24 hours at room temperature, or 48-hour when refrigerated.
- Xenleta tablets should be taken 1 hour before or 2 hours after a meal.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
lefamulin	Xenleta	Nabriva	150 mg vial 600 mg tablet	$103.50/vial $137.50/tablet

** Wholesale Acquisition Cost

Conclusion

Xenleta is indicated for the treatment of adults with CABP caused by susceptible microorganisms. The safety and efficacy of Xenleta was demonstrated in two randomized, double-blind clinical trials that enrolled 1,289 adults with qualifying CABP. All studies met FDA-specified primary endpoints of statistical non-inferiority in the intent-to-treat population compared to active comparator population. The most common adverse reactions in patients taking Xenleta injection (>2%) were administration site reactions, hepatic enzyme elevation, hypokalemia, and insomnia. The most common adverse reactions in patients taking Xenleta tablets (>2%) were diarrhea, nausea, and vomiting.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) Antibiotic / Antimicrobial Resistance (AR / AMR). Centers for Disease Control and Prevention. https://www.cdc.gov/drugresistance/biggest-threats.html#pne. Accessed November 2, 2019.
2) Product Information: Xenleta™ (lefamulin) 2019. Nabriva Therapeutics US, Inc, King of Prussia, PA 19406.
3) A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Lefamulin (BC 3781) Versus Moxifloxacin (With or Without Adjunctive Linezolid) in Adults With Community-Acquired Bacterial Pneumonia. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT02559310?term=02559310&draw=2&rank=1. Accessed November 2, 2019.
4) A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Oral Lefamulin (BC 3781) Versus Oral Moxifloxacin in Adults With Community-Acquired Bacterial Pneumonia. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02813694?term=02813694&draw=2&rank=1. Accessed November 2, 2019.

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Date: November 2, 2019.

