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New Drug Evaluation: lefamulin

Date of Review: February 2020
Generic Name: lefamulin

End Date of Literature Search: 12/2019
Brand Name (Manufacturer): Xenleta™ (Nabriva Therapeutics, Inc)
Dossier Received: Yes

Research Questions:

1. Is there comparative evidence that lefamulin is more effective or safer than current standard of care in the treatment of community-acquired pneumonia (CAP) caused by susceptible bacterial organisms?
2. Are there subpopulations of patients for which lefamulin may be more effective or associated with less harm in the treatment of CAP?

Conclusions:

- There is low quality evidence based on two phase 3 double-blind, noninferiority trials that lefamulin 150 mg intravenous (IV) every 12 hours and 600 mg oral every 12 hours is non-inferior in early clinical response to moxifloxacin IV and oral in the treatment of CAP caused by common bacterial pathogens, with a risk difference of -2.9% (95% confidence interval [CI] -8.5 to 2.8) with IV therapy and 0.1% (95% CI -4.4 to 4.5%) with oral therapy.[1,2]
- There is insufficient evidence to make conclusions about the efficacy and safety of lefamulin in patients at risk or with suspected resistant organisms , in patients with significant hepatic disease, in severe CAP, or compared to other standard of care (beta-lactam in combination with a macrolide).
- There is low quality evidence of no difference in discontinuations due to adverse events or treatment emergent serious adverse events between lefamulin and moxifloxacin. [1,2] The most common adverse events include injection site reactions with IV therapy and diarrhea with oral therapy. Additional safety concerns include hepatic enzyme elevation, QT interval prolongation and drug-drug interactions through CYP3A4.
- There is insufficient evidence that lefamulin is more effective or associated with less harm in any subpopulations based on disease severity or baseline comorbidities.

Recommendations:

- Made lefamulin non-preferred in the miscellaneous antibiotic PDL class.

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Background:
Pneumonia is among the leading causes of morbidity and mortality worldwide. Community acquired pneumonia (CAP) is a lower respiratory infection acquired outside of a hospital or other acute care facility.[3] The incidence of CAP is 24.8 per 10,000 adults and is higher with older age and in those with medical comorbidities. Common causes include both respiratory viruses (influenza, rhinovirus, respiratory syncytial virus, etc.) and bacterial pathogens. The most common bacterial pathogens include *Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae, Staphylococcus aureus,* and atypical pathogens (*Mycoplasma pneumoniae, Legionella,* and *Chlamydia pneumoniae).*[4] *S. pneumoniae* and respiratory viruses are the most frequently detected pathogens in CAP. Patients with recent hospitalization and intravenous (IV) antibiotics, those who are immunosuppressed, and those with a history of respiratory infection with multidrug resistant bacteria may be at an increased risk of infection caused by gram negative bacilli, methicillin resistant *staphylococcus aureus* (MRSA), and/or *Pseudomonas aeruginosa*.[4]

Antibiotics approved by the FDA and recommened in clinical practice guidelines for the treatment of CAP include macrolides (azithromycin), fluoroquinolones, cephalosporins and other beta-lactam drugs.[3] The choice of the antibacterial drug depends on the severity of illness, underlying comorbidities, the likely pathogen, treatment setting (community vs. hospital) and the adverse event profile of the drug. First-line regimens typically include a macrolide or doxycycline in combination with a beta-lactam or a respiratory fluoroquinolone. High rates of macrolide resistant *S. pneumoniae* have limited the use of macrolide monotherapy. Other broad spectrum agents (beta-lactam/beta-lactamase inhibitor combinations) are reserved for patients with suspected resistant organisms or who are at risk for *Pseudomonas.* Overall, there are many current antibiotics that are options for the treatment of CAP. Lefamulin is a pleuromutilin antibiotic that inhibits bacterial protein synthesis and is available in both oral and intravenous (IV) formulations.[5] Lefamulin is bactericidal against *S. pneumoniae, H. influenzae and M. pneumoniae* (including macrolide-resistant strains), and bacteriostatic against *S. aureus (*methicillin-susceptible isolates) and *S. pyogenes* at clinically relevant concentrations.[6] In vitro activity has also been demonstrated against MRSA. It is not active against Enterobacteriaceae and *Pseudomonas aeruginosa.* Resistance induction is unknown but appears unaffected by several common mechanisms seen in other major antibiotic classes.

Severity of infection and a decision to treat in the hospital or outpatient is assessed using the pneumonia severity index or pneumonia outcomes research team (PORT) score which uses 20 variables and assigned patients to 1 of 5 categories which estimates the risk of mortality (**Table 1**).[5] The PORT trial uses data from demographics, comorbidities, physical exam, laboratory and radiographic results.

Table 1: Pneumonia Outcomes Research Team Scoring and Classification[5]

PORT Score	Risk Class	Predicted Mortality (%)	Recommended Treatment Setting
≤ 70	II	0.6	Outpatient
71-90	III	0.9	Outpatient vs. Observation Admission
91-130	IV	9.3	Hospital
130	V	27	Hospital
No risk factor is Risk Class I (low risk of mortality)			

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

FDA approval of lefamulin was based upon two, phase 3, multicenter, multinational, double-blind, active-control, double-dummy, non-inferiority trials.[1,2] These trials demonstrated noninferiority of lefamulin to moxifloxacin in the treatment of CAP due to common bacterial pathogens (*S. pneumoniae, S. aureus, H. influenzae, etc.).* The primary efficacy endpoint in both trials was early clinical response (ECR) responder rate in the intent-to-treat (ITT) population. Early clinical response was defined as an improvement in at least 2 CAP signs/symptoms, no worsening of any signs/symptoms, and no concomitant antibiotic for CAP administered at 96 hours (within a 24-hour window) after receipt of first dose of study drug.[5]

The Lefamulin Evaluation Against Pneumonia 1 (LEAP 1) trial included subjects with Pneumoniae Outcome Research Team (PORT) scores of ≥3 and compared IV lefamulin 150 mg every 12 hours to IV moxifloxacin 400 mg every 24 hours.[2] Patients were able to switch to oral therapy after 3 days. Moxifloxacin patients who met criteria for suspected methicillin-resistant *S. aureus* (MRSA) also received linezolid 600 mg IV every 12 hours, which was discontinued upon confirmation of a negative MRSA baseline culture and lefamulin treated patients received a linezolid placebo.[2] Patients in the lefamulin group initially received 5 days of treatment for CAP (but received 7 days after a protocol amendment), while moxifloxacin patients were given 7 days. Prior to protocol amendment, patients with MRSA, *L. pneumophila*, or bacteremia secondary to *S. pneumoniae* received 10 days of antibiotics in either group; post-amendment, only patients with MRSA were extended to 10 days. Approximately 25% of the study population was enrolled prior to protocol amendment.[2] The LEAP 2 trial included those with PORT scores of 2-4 who were candidates for oral therapy and compared oral lefamulin 600 mg twice daily for 5 days to oral moxifloxacin 400 mg daily for 7 days.[1] Confirmed or suspected MRSA was an exclusion criteria in LEAP 2.

The ECR rates for lefamulin were noninferior to moxifloxacin in both studies, and the difference between the treatment groups met the predefined noninferiority margin (**Table 5**). In LEAP 1, non-inferiority was achieved with a -2.9% (95% CI, -8.5 to 2.8%) difference in ECR responder rate between lefamulin and moxifloxacin.[2] In LEAP 2, the difference was 0.1% (95% CI, -4.4 to 4.5%).[1] Lefamulin had similar ECR rates compared to moxifloxacin in various demographic and baseline health status subgroups (history of heart and lung disease, moderate renal impairment, and severe CAP) in both trials. Additionally, clinical response rates in the population with confirmed pathogens did not reveal any meaningful differences between the treatment arms for any particular baseline pathogen, noting that some pathogens were isolated from relatively small numbers of subjects. The most common bacterial pathogens isolated were consistent with current practice and included *S. pneumoniae, H. influenzae,* and atypical organisms. In addition, investigator-assessed clinical response at the test-of-cure visit, 5-10 days after completing therapy and up to 30 days after starting therapy did not show meaningful differences between the treatment groups.[1,2]

Despite the high responder rates in LEAP 1, rescue antibacterial medication (due to insufficient therapeutic effect of study drug or due to treatment-limiting adverse events resulting in discontinuation of study drug) was administered to 36 subjects in the lefamulin arm (13.0%) and 34 subjects in the moxifloxacin arm (12.4%).[5] In LEAP 2, there was in imbalance in rescue antibiotic use (10.5% of subjects in the lefamulin arm and 7.1% in the moxifloxacin arm). The primary reason was due to insufficient therapeutic effect of study drug.[5]

Applicability to several important subgroups is limited, including elderly and patients with severe CAP (PORT class V). Overall, the study populations were much healthier with fewer comorbidities than what is seen in clinical practice. Excluded populations included those with any degree of immunosuppression, hepatic disease, severe renal disease (CrCl < 30 mL/min) and those at risk for prolonged QT interval. There were not enough patients with MRSA to draw any conclusions about efficacy, and lefamulin should not be used when MRSA is suspected until additional data are provided. It is unclear if body mass index (BMI) affects drug efficacy and oral bioavailability is poor. A beta-lactam and/or macrolide comparator arm with predetermined superiority criteria would have improved robustness of the evidence since fluoroquinolone use is declining due to safety concerns and alternative options.[4]

The methods are unclear as to the study setting (inpatient vs. outpatient) or if the setting differed for patients relative to the severity of initial PORT risk class, making it difficult to assess study care in relation to normal clinical practice. Additionally, there was risk for high selection bias in both trials trial due to unclear randomization and allocation concealment procedures and differences in baseline characteristics (details in Table 5). The majority of study sites were in Eastern Europe. In LEAP 1, less than 1% of subjects were in the United States; in LEAP 2, approximately 3% of subjects were in the United States.

Clinical Safety:
In the two Phase 3 studies, there were 36 subjects in the lefamulin group (5.6%) and 31 subjects in the moxifloxacin group (4.8%) who experienced at least one treatment-emergent serious adverse event.[5] Patients were followed up for 30 days. Side effects of concern included diarrhea (oral therapy), injection site reactions (IV therapy) and hepatic enzyme elevations. No *C. difficile* cases were reported in either group within the 30-day follow-up period. There were 6 deaths in the lefamulin arm and 5 in the moxifloxacin arm. None were considered by investigators to be related to the study drug.[5] Discontinuations due to adverse events were low and similar between lefamulin and moxifloxacin in clinical trials. The most common adverse events are included below.

Table 2: Adverse reactions in ≥ 2% of patients in LEAP 1 (IV dosing)[6]

Adverse Reaction	Lefamulin (n=273)	Moxifloxacin (n=273)
Administration site reactions	7%	3%
Hepatic enzyme elevation	3%	3%
Nausea	3%	2%
Hypokalemia	3%	2%
Insomnia	3%	2%
Headache	2%	2%

Table 3: Adverse reactions in ≥ 2% of patients in LEAP 2(oral dosing)[6]

Adverse Reaction	Lefamulin (n=368)	Moxifloxacin (n=368)
Diarrhea	12%	1%
Nausea	5%	2%
Vomiting	3%	1%
Hepatic enzyme elevation	2%	2%

In Phase 3 trials, lefamulin was associated with prolonged QT interval to a similar extent as moxifloxacin, and adverse effect was added by the FDA in the Warnings and Precautions section of the lefamulin labeling. The average increase in the corrected post-dose QTc interval on day 3 was 19.8 msec for lefamulin and 21.4 msec for moxifloxacin. Treatment was discontinued in one lefamulin-treated patient and 3 moxifloxacin-treated patients secondary to prolonged QTc intervals. However, patients at risk for or known to have QTc prolongation were excluded.

Lefamulin is metabolized by CYP3A4. Concomitant administration of lefamulin with CYP3A4 or p-glycoprotein (P-gp) inducers or inhibitors could affect serum concentrations.[6]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Clinical Cure
2) Symptom Relief
3) Mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Early clinical response rate at 96 hours

Table 4. Pharmacology and Pharmacokinetic Properties[6]

Parameter	
Mechanism of Action	Lefamulin is a systemic pleuromutilin antibacterial. It inhibits bacterial protein synthesis through interactions (hydrogen bonds, hydrophobic interactions, and Van der Waals forces) with the A- and P-sites of the peptidyl transferase center (PTC) in domain V of the 23s rRNA of the 50S subunit. The binding pocket of the bacterial ribosome closes around the mutilin core for an induced fit that prevents correct positioning of tRNA
Oral Bioavailability	25%
Distribution and Protein Binding	Protein binding 94.8% to 97.1%, volume of distribution of 86.1 L
Elimination	IV: 77.3% in feces and 15.5% in urine. Oral: 88.5% in feces and 5.3% in urine
Half-Life	8 hours
Metabolism	CYP3A4

Abbreviations: IV: intravenous; L: liter; CYP: cytochrome P450 enzyme

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. LEAP 1 Phase 3, MC, DB, AC, noninferiority RCT	1. Lefamulin 150 mg IV Q12H 2. Moxifloxacin 400 mg IV Q24H +/- Linezolid 600 mg IV Q12h Duration 5-10 days *Patients could be switched from IV to oral at the discretion of the investigator*	Demographics: -Mean age 60 y -~60% male -86% white -72% PORT risk class 2 -60% *S. pneumoniae* Key Inclusion Criteria: - Age ≥ 18 y - LRTI with ≥3 of the following: dyspnea, cough, purulent sputum chest pain, and ≥2 vital sign abnormalities - radiographically documented pneumonia - PORT class ≥3 and requires IV therapy Key Exclusion Criteria: - Concomitant antibiotics - hospitalized for ≥2 days within past 90 or resides in a nursing home or LTCF - suspected resistant pathogens - prolonged QT interval or risk factors for TdP (hypokalemia, cardiac disease), strong P-gp or CYP3A4 inhibitor or inducer - CNS disorders - CrCl < 30mL/min - hepatic disease	ITT: 1. 276 2. 275 PP: 1. 247 2. 248 Attrition: 1. 29 (10.5%) 2. 27 (9.8%)	ECR (responder rate at 96H): 1. 241 (87.3%) 2. 248 (90.2%) RD -2.9%; (95% CI -8.5 to 2.8%)* Investigator-assessed clinical response (5-10 days after last dose): 1. 223 (81.7%) 2. 230 (84.2%) RD -2.6%; (95% CI -8.9 to 3.9&)* *met noninferiority margins	NA NA	Discontinuations due to adverse event(s): 1. 8 (3.9%) 2. 11 (4%) Infusion site pain or phlebitis: 1. 14 (5.1%) 2. 3 (1.1%)	NS NA	**Risk of Bias (low/high/unclear)**: Selection Bias: high: unclear randomization procedures; baseline differences noted in age, mean procalcitonin, and rates of bacteremia Performance Bias: low: double-dummy design Detection Bias: unclear: unclear blinding of outcome assessors Attrition Bias: unclear: attrition similar between groups but slightly high (>10%) for a short-term study. Several treatment discontinuations not adequately explained. Reporting Bias: high: low rate of IV to oral transition in lefamulin group (38%) and moxifloxacin (44%) not explained. The FDA primary endpoint was only analyzed in the ITT group, rather than both ITT and per protocol for a non-inferiority trial. Other Bias: high: All manuscript authors are Nabriva employees or consultants; trial funded by Nabriva. The protocol amendment complicates interpretation of results. Over 50% of subjects had a documented protocol deviation. **Applicability**: Patient: Significant exclusion criteria limits generalizability of patient population. Less than 1% of patients were from North America Intervention: FDA-approved dose/frequency Comparator: Beta-lactam +/- macrolide recommended first-line therapy Outcomes: ECR is an appropriate outcome, though these short-term surrogate indicators use subjective criteria. Information regarding results of late follow-up visit were not reported or listed as an endpoint. Setting: 66 study sites in 18 countries. 79% Eastern Europe, few sites in North America (<1%)

2.LEAP 2 Phase 3, MC, DB, AC, noninferiority RCT	1. Lefamulin 600 mg oral Q12H for 5 days 2. Moxifloxacin 400 mg oral Q24H for 7 days	Demographics: -Mean age 57 y -~52% male -86% white -50% PORT risk class 2 -37% PORT class 3 -63.7% *S. pneumoniae* Key Inclusion Criteria: - Age ≥ 18 y - LRTI with ≥3 of the following: dyspnea, cough, purulent sputum chest pain, and ≥2 vital sign abnormalities, - radiographically documented pneumonia - PORT class of 2-4 and a candidate for oral therapy Key Exclusion Criteria: See LEAP 1	ITT: 1. 370 2. 368 PP: 1. 345 2. 340 Attrition: 1. 23 (6.2%) 2. 28 (7.6%)	ECR (responder rate at 96H): 1. 336 (90.8%) 2. 334 (90.8%) RD 0.1%; (95% CI -4.4 to 4.5%)* Investigator-assessed clinical response (5-10 days after last study dose): 1. 322 (87.5%) 2. 328 (89.1%) RD -1.6%; (95% CI -6.3 to 3.3%)* *met noninferiority margin	 NA NA	Discontinuations due to adverse event(s): 1. 11 (3%) 2. 8 (2.2%) NS 28-day mortality 1. 3 (0.8%) 2. 3 (0.8%) NS	 NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: high: unclear randomization/allocation concealment procedures; baseline differences noted in sex, and enrollment region. Race/ethnicity designation may have been misclassified, given methods to collect these data may not have been consistent across sites Performance Bias: low: double-dummy design Detection Bias: unclear: unknown blinding of outcome assessors Attrition Bias: low: attrition similar between groups and overall low Reporting Bias: high: The FDA primary endpoint was only analyzed in the ITT group, rather than both ITT and per protocol for a non-inferiority trial. Other Bias: unclear: All manuscript authors are Nabriva employees or consultants and the trial was funded by Nabriva, presenting potential for conflicts of interest. **Applicability**: Patient: Significant exclusion criteria limits generalizability of patient population to those with common comorbidities and only 3% of patients from United States. Patients with suspected MRSA excluded Intervention: See LEAP 1 Comparator: See LEAP 1 Outcomes: See LEAP 1 Setting: 66 study sites in 18 countries. 60% Eastern Europe, limited sites in United States (3%)

Abbreviations [alphabetical order]: AC = active control; ARR = absolute risk reduction; CI = confidence interval; CNS = central nervous system; CrCl = creatinine clearance; DB = double blind; ECR = early clinical response; H = hours; ITT = intention to treat; IV = intravenous; LRTI = lower respiratory tract infection; LTCF = long-term care facility; mITT = modified intention to treat; MC = multicenter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; PORT = pneumonia outcomes research team; PP = per protocol; RCT = randomized controlled trial; RD = risk difference; TdP = Torsades de pointes; y = years.

References:

1. 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. *Jama.* 2019.
2. File 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. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2019;69(11):1856-1867.
3. Lanks CW, Musani AI, Hsia DW. Community-acquired Pneumonia and Hospital-acquired Pneumonia. *The Medical clinics of North America.* 2019;103(3):487-501.
4. Metlay JP, Waterer GW, Long AC, 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. *American journal of respiratory and critical care medicine.* 2019;200(7):e45-e67.
5. FDA Center for Drug Evaluation and Research. Lefamulin: Multi-Discipline Review. Application Number 211672Orig1s000. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=211673.
6. XENLETA (lefamulin) Precribing Information. Nabriva Therapeutics. Ireland DAC. 8/2019.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XENLETA™ safely and effectively. See full prescribing information for XENLETA.

XENLETA (lefamulin) injection, for intravenous use
XENLETA (lefamulin) tablets, for oral use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

XENLETA is a pleuromutilin antibacterial indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms. (1.1)

To reduce the development of drug resistant bacteria and maintain the effectiveness of XENLETA and other antibacterial drugs, XENLETA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.2)

DOSAGE AND ADMINISTRATION

- For treatment of adults with CABP, the recommended dosage of XENLETA is as follows:

Dosage	Treatment Duration
150 mg every 12 hours by intravenous infusion over 60 minutes* (2.1)	5 to 7 days
600 mg orally every 12 hours. (2.1)	5 days

*With the option to switch to XENLETA Tablets 600 mg every 12 hours to complete the treatment course.

- Patients with Hepatic Impairment: Reduce the dosage of XENLETA Injection to 150 mg infused over 60 minutes every 24 hours in patients with severe hepatic impairment (Child-Pugh Class C). XENLETA Tablets have not been studied in and are not recommended for patients with moderate (Child-Pugh Class B) or severe hepatic impairment (2.2).
- Administration Instruction for XENLETA Tablets: Take at least 1 hour before a meal or 2 hours after a meal. Swallow XENLETA Tablets whole with water (6 to 8 ounces). (2.3)
- Administration Instruction for XENLETA Injection: Infuse over 60 minutes. (2.3)
- See Full Prescribing Information for additional information on the administration and preparation of XENLETA Tablets and Injection. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection
- A single-dose clear glass vial containing 150 mg of lefamulin in 15 mL of 0.9% sodium chloride for further dilution prior to intravenous infusion. (3)

Tablets
- 600 mg of lefamulin. (3)

CONTRAINDICATIONS

- XENLETA is contraindicated in patients with known hypersensitivity to lefamulin, pleuromutilin class drugs, or any of the components of XENLETA. (4.1)
- Concomitant use of XENLETA tablets with CYP3A substrates that prolong the QT interval is contraindicated. (4.2)

WARNINGS AND PRECAUTIONS

- QT Prolongation: Avoid use in patients with known QT prolongation, ventricular arrhythmias including torsades de pointes, and patients receiving drugs that prolong the QT interval such as antiarrhythmic agents. (5.1)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.2, 8.1, 8.3)
- *Clostridium difficile*-associated Diarrhea (CDAD): Evaluate patients who develop diarrhea. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2%) are:
- XENLETA Injection: administration site reactions, hepatic enzyme elevation, nausea, hypokalemia, insomnia, headache. (6.1)
- XENLETA Tablets: diarrhea, nausea, vomiting, hepatic enzyme elevation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Nabriva Therapeutics US, Inc. at 1-855-5NABRIVA or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

XENLETA Injection	
Strong or moderate CYP3A inducers or P-gp inducers	Avoid XENLETA unless the benefit outweighs the risk. Monitor for reduced efficacy. (7.1)
XENLETA Tablets	
Strong or moderate CYP3A inducers or P-gp inducers	Avoid XENLETA unless the benefit outweighs the risk. Monitor for reduced efficacy. (7.1)
Strong CYP3A inhibitors or P-gp inhibitors	Avoid XENLETA. (7.1)
Moderate CYP3A inhibitors or P-gp inhibitors	Monitor for adverse reactions. (7.1)
CYP3A substrates that prolong the QT interval	Concomitant use is contraindicated. (4.2, 7.2)
Midazolam and other sensitive CYP3A substrates	Monitor for adverse reactions. (7.2)

USE IN SPECIFIC POPULATIONS

Lactation: A lactating woman should pump and discard human milk for the duration of treatment with XENLETA and for 2 days after the final dose. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2019