PDL DRUG REVIEW

Proprietary Name: Xenleta® Tablets
Common Name: lefamulin acetate
PDL Category: Antibiotics

Comparable Products	Preferred Drug List Status
Levofloxacin	Preferred
Moxifloxacin	Non-Preferred

Summary

Pharmacology/Usage: Lefamulin, the active ingredient of Xenleta®, is a semi-synthetic antibacterial agent. It is a pleuromutilin derivative that inhibits bacterial protein synthesis through interactions 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.

Indication: For the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by the following susceptible microorganisms: *Streptococcus pneumoniae*, *Staphylococcus aureus* (methicillin-susceptible isolates), *Hemophilus influenzae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae.*

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 susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies, lefamulin may cause fetal harm when administered to pregnant women. There are no available data on the use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is a pregnancy pharmacovigilance program for Xenleta®. If Xenleta® is inadvertently administered during pregnancy or if a patient becomes pregnant while receiving Xenleta®, healthcare providers should report Xenleta® exposure by calling 1-855-5NABRIVA to enroll. Pregnancy status should be verified in females of reproductive potential. Advise females of reproductive potential to use effective contraception during treatment and for 2 days after the final dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Available as:

- Injection- clear, colorless solution in a single-dose vial, with each vial containing 150mg lefamulin in 15ml of 09% sodium chloride for further dilution. Must dilute in a 250ml solution of 10 mM citrate buffered 0.9%

sodium chloride for injection suppled with Xenleta® before use. After dilution, Xenleta® injection can be stored for up to 24 hours at room temperature and up to 48 hours when refrigerated.
- Film-Coated Tablets: 600mg. Swallow whole, do not crush or divide.

Recommended Dosage: The recommended dosage is 150mg Q12H by IV infusion over 60 minutes (with the option to switch to the 600mg tablets Q12H to complete the treatment course) for 5 to 7 days OR 600mg PO Q12H for 5 days. Take the tablets at least 1 hour before a meal or 2 hours after a meal and swallow with 6-8 ounces of water.

Monitor patients with hepatic impairment for adverse reactions associated with Xenleta® throughout the treatment period. With Xenleta® injection, reduce the dosage to 150mg infused IV over 60 minutes Q24H with severe hepatic impairment. Dosage adjustments are not required with mild or moderate hepatic impairment for Xenleta® injection. However, Xenleta® tablets have not been studied in and are not recommended with moderate or severe hepatic impairment. Dose adjustments of Xenleta® tablets are not required with mild hepatic impairment. Xenleta® dose adjustments are not required with renal impairment, including those on hemodialysis.

Drug Interactions: The pharmacodynamic interaction potential to prolong the QT interval of the electrocardiogram between Xenleta® and other drugs that effect cardiac conduction is not known. Thus, avoid concomitant use of Xenleta® injection and Xenleta® tablets with such drugs (for example, Class IA and III antiarrhythmics, antipsychotics, erythromycin, moxifloxacin, and tricyclic antidepressants).

Concomitant use of oral or IV Xenleta® with strong CYP3A4 inducers or P-gp inducers decreases lefamulin AUC and Cmax, which may reduce the efficacy of Xenleta®. Avoid concomitant use of oral or IV Xenleta® with strong and moderate CYP3A4 inducers or P-gp inducers unless the benefit outweighs the risk. Concomitant use of Xenleta® tablets with strong CYP3A inhibitors or P-gp inhibitors increases lefamulin AUC, which may increase the risk of adverse reactions with Xenleta® tablets. Thus, avoid concomitant use of Xenleta® tablets with strong CYP3A inhibitors or P-gp inhibitors. Monitor for adverse effects of Xenleta® tablets when administered concomitantly with moderate CYP3A inhibitors or P-gp inhibitors.

Concomitant use of Xenleta® tablets with sensitive CYP3A4 substrates increases the AUC and Cmax of CYP3A4 substrates, which may increase the risk of toxicities associated with cardiac conduction. Concomitant use with CYP3A substrates known to prolong the QT interval is contraindicated. Concomitant use of sensitive CYP3A substrates with Xenleta® tablets requires close monitoring for adverse effects of these drugs (for example alprazolam, diltiazem, verapamil, simvastatin, vardenafil). Concomitant use of Xenleta® injection with CYP3A4 substrates does not affect the exposure of CYP3A4 substrates.

Box Warning: There are no box warnings listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Xenleta®) minus reported % incidence for moxifloxacin for oral dosing of both. Please note that an incidence of 0% means the incidence was the same as or less than its active comparator.* The most frequently reported adverse events included diarrhea (11%), nausea (3%), vomiting (2%), and hepatic enzyme elevation (0%).

Xenleta® has the potential to prolong the QT interval of the electrocardiogram (ECG) in some patients. Avoid Xenleta® use in the following patients:

- Patients with known prolongation of the QT interval
- Patients with ventricular arrhythmias including torsade's de pointes
- Patients receiving Class IA (for example, quinidine, procainamide) or Class III (for example, amiodarone, sotalol) antiarrhythmic agents
- Patients receiving other drugs that prolong the QT interval, such as antipsychotics, erythromycin, pimozide, moxifloxacin, and tricyclic antidepressants

In patients with renal failure who require dialysis, metabolic disturbances associated with renal failure may lead to QT prolongation. In patients with mild, moderate, or severe hepatic impairment, metabolic disturbances associated with hepatic impairment may lead to QT prolongation.

If use with Xenleta® cannot be avoided in specific populations predisposed to QT prolongation or those receiving another drug that prolongs the QT interval, ECG monitoring is recommended during treatment. In addition, the magnitude of QT prolongation may increase with increasing concentrations of Xenleta® or increasing the rate of infusion of the IV formulation. Thus, the recommended dose and infusion rate should not be exceeded.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Xenleta®. It may range in severity from mild diarrhea to fatal colitis. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile,* and surgical evaluation should be started as clinically indicated.

Contraindications: In patients with known hypersensitivity to lefamulin, pleuromutilin class drugs, or any of the components of the product; Xenleta® tablets with sensitive CYP3A4 substrates that prolong the QT interval (for example, 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 torsade's de pointes.

Manufacturer: Nabriva Therapeutics US, Inc

Analysis: The safety and efficacy of Xenleta® were assessed in 2 multicenter, randomized, double-blind, double-dummy, non-inferiority studies that included adults (N=1289) with CABP. Study 1 compared 5 to 10 days of Xenleta® to 7 to 10 days of moxifloxacin ± linezolid. Study 2 compared 5 days of Xenleta® to 7 days of moxifloxacin.

In study 1, adults were randomized to Xenleta® (150mg IV infusion Q12H, with the option to switch to 600mg Q12H after at least 3 days of IV treatment) or moxifloxacin (400mg IV Q24H, with the option to switch to 400mg PO Q24H after at least 3 days of IV treatment). If methicillin-resistant *Staphylococcus aureus* (MRSA) was suspected at screening, patients randomized to moxifloxacin were to receive adjunctive linezolid (600mg IV Q12H, with the option to switch to 600mg PO Q12H after at least 3 days of IV treatment) and patients randomized to Xenleta® were to receive linezolid placebo. In this study, adults were predominantly male (60%) and white (87%), while the median age was 62 years. Common comorbid conditions included hypertension (41%), asthma/chronic obstructive pulmonary disease (17%) and diabetes mellitus (13%).

In study 2, patients were randomized to Xenleta® 600mg PO Q12H for 5 days (N=370) or moxifloxacin 400mg PO Q24H for 7 days (N=368). In this study, adults were predominantly male (52%) and white (74%), while the median age was 59 years. Concomitant comorbid conditions included hypertension (36%), asthma/COPD (16%), and diabetes (13%).

In both studies, efficacy was determined by Early Clinical Response (ECR) at 72 to 120 hours after the first dose. Patients entered the trials with at least three of four symptoms consistent with CABP (cough, sputum production, chest pain, and/or dyspnea). Response was defined as survival with improvement of at least 2 symptoms, no worsening of any symptom, and no receipt of non-study antibacterial treatment for CABP. Results can be seen in the table below, which was adapted from the prescribing information. Reminder that trial 1 compared Xenleta® to moxifloxacin ±linezolid.

Study	Xenleta®	Moxifloxacin	Treatment difference
1	241/276 (87.3%)	248/275 (90.2%)	-2.9%
2	336/370 (90.8%)	334/368 (90.8%)	0.1%

Clinical response was also assessed by the Investigator at the Test of Cure (TOC) visit 5 to 10 days after the last dose of study drug. Response was defined as survival with improvement of signs and symptoms based on the Investigator's assessment and no receipt of non-study antibacterial treatment for CABP. The following table summarizes Investigator-assessed Clinical Response (IACR) rates at TOC. Reminder that trial 1 compared Xenleta® to moxifloxacin ±linezolid.

Study	Xenleta®	Moxifloxacin	Treatment difference
1	223/276 (80.8%)	230/275 (83.6%)	-2.8%
2	322/370 (87.0%)	328/368 (89.1%)	-2.1%

The following table summarizes IACR rates at TOC by the most common baseline pathogens across both trials in the micro ITT analysis set, which comprised all randomized patients with at least 1 baseline pathogen.

Pathogen	Xenleta®	Moxifloxacin
Streptococcus pneumoniae	184/216 (85.2%)	193/223 (86.5%)
Methicillin-susceptible *Staphylococcus aureus*	14/16 (87.5%)	5/5 (100%)
Hemophilus influenzae	95/107 (88.8%)	88/105 (83.8%)
Mycoplasma pneumoniae	35/39 (89.7%)	33/34 (97.1%)
Legionella pneumophila	27/34 (79.4%)	26/31 (83.9%)
Chlamydophila pneumoniae	20/27 (74.1%)	23/31 (74.2%)

Place in Therapy: Xenleta® is a semi-synthetic antibacterial agent indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by several susceptible microorganisms. In clinical trials, it was found to be comparable to moxifloxacin. Xenleta® does have the potential to prolong the QT interval in some patients, and thus should be avoided in certain patient populations, including patients receiving other drugs that prolong the QT interval.

There is no evidence at this time that Xenleta® is safer or more effective than the currently preferred medications. It is therefore recommended that Xenleta® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1]Xenleta [package insert]. King of Prussia, PA: Nabriva Therapeutics; 2019.