PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**XENLETA™**

Lefamulin tablets
Tablets, 600 mg lefamulin (as lefamulin acetate), Oral

Pr**XENLETA™**

Lefamulin for Injection
Solution, 150 mg/15 mL (10 mg/mL) Lefamulin
(as lefamulin acetate), Intravenous

Antibacterial Agent

ATC Code: J01XX12

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

XENLETA (lefamulin) is indicated for the treatment of adults with:

- Community-acquired pneumonia (CAP) caused by: *Streptococcus pneumoniae* including multi-drug resistant *S. pneumoniae* (MDRSP*), *Staphylococcus aureus* (methicillin-susceptible isolates), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae.*

  *MDRSP refers to isolates resistant to two or more of the following antibiotics/antibiotic classes: Penicillins, cephalosporins, macrolides, tetracyclines, lincosamides, fluoroquinolones and folate-synthesis inhibitors.

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 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.

1.1 Pediatrics

Pediatrics (**< 18 years of age)**: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety and efficacy were observed between these patients and younger adult patients. Early clinical response (ECR) rates in the subgroup of patients ≥ 65 years of age were similar to ECR rates in patients < 65 years of age and comparable across treatment groups (XENLETA versus moxifloxacin).

2 CONTRAINDICATIONS

XENLETA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

CYP3A4 Substrates That Prolong the QT Interval: XENLETA (lefamulin tablets) is contraindicated in patients taking sensitive CYP3A4 substrates that prolong the QT interval (for example, pimozide). Concomitant administration of oral XENLETA with sensitive CYP3A4 substrates such as pimozide may result in increased plasma concentrations of these drugs, leading to QT interval prolongation and cases of torsades de pointes. See **WARNINGS AND PRECAUTIONS**.

Serious Warnings and Precautions

- XENLETA has been shown to prolong the QT interval of the electrocardiogram in some patients (see **WARNINGS AND PRECAUTIONS, Cardiovascular, *QT Interval Prolongation***)

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

XENLETA is available with two routes of administration: oral (tablets) and injectable solution for intravenous use.

- Injectable solution: lefamulin (as lefamulin acetate) 10 mg/mL, equivalent to 150 mg lefamulin in 15 mL of normal saline (0.9% sodium chloride), to be diluted to a final concentration of 0.6 mg/mL
- Tablets: lefamulin (as lefamulin acetate) equivalent to 600 mg of lefamulin

3.2 Recommended Dose and Dosage Adjustment

For treatment of adults with CAP the recommended dosage regimen of XENLETA is described below:

Table 1: Dosage of XENLETA in Adult CAP Patients

Dose	Treatment Duration
150 mg every 12 hours by intravenous infusion over 60 minutes*	5 to 7 days
600 mg orally every 12 hours**	5 days

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

** Tablets should be administered under fasted conditions; at least 1 hour before a meal or 2 hours after a meal

Health Canada has not authorized an indication for pediatric use.

No dose adjustment is necessary for geriatric patients (65 years and older).

No dose adjustment is necessary in patients with renal impairment, including those on hemodialysis. See **ACTION AND CLINICAL PHARMACOLOGY**.

3.2.1 Dosage Adjustment for Patients with Hepatic Impairment

XENLETA (lefamulin for Injection)
Reduce the dosage of XENLETA (lefamulin for Injection) to 150 mg infused intravenously over 60 minutes every 24 hours for patients with severe hepatic impairment (Child-Pugh Class C). No dosage adjustment of XENLETA (lefamulin for Injection) is needed for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. See **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Hepatic Impairment.**

XENLETA (lefamulin tablets)
XENLETA (lefamulin tablets) have not been studied in and are not recommended for patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. No dosage adjustment of XENLETA (lefamulin tablets) is needed for patients with mild hepatic impairment (Child Pugh Class A).

3.3 Administration

XENLETA (lefamulin for Injection)
XENLETA (lefamulin for injection) is administered by intravenous infusion over 60 minutes after admixture in a 250 mL solution of 10 mM citrate buffered 0.9% sodium chloride. The recommended infusion rate should not be exceeded. See **WARNINGS AND PRECAUTIONS**, **Cardiovascular, *QT Interval Prolongation*.**

General precautions:

- Each vial and infusion bag is for single use only.
- Standard aseptic techniques should be used for solution preparation and administration.
- To improve local tolerability, it is recommended to carefully follow the instructions for dilution and infusion. The recommended dose and infusion rate should not be exceeded.

XENLETA (lefamulin tablets)

- One 600 mg tablet administered at least 1 hour before a meal or 2 hours after a meal.
- Tablets should be swallowed whole with a sufficient amount of water (do not crush or divide).

3.3.1 Instructions for dilution and infusion:

Table 2: Dilution

Infusion Bag Size	Volume of Solution to be Added to Diluent	Approximate Available Volume	Nominal Concentration
250 mL	15 mL	265 mL	0.60 mg/mL

XENLETA (lefamulin for injection) must be mixed into the bag of solvent containing 250 mL solution of 10 mM citrate buffered saline and administered by infusion.

1. Dilute the entire 15 mL vial of XENLETA (lefamulin for injection) into the diluent bag supplied with XENLETA (lefamulin for injection) that contains 250 mL of 10 mM citrate buffered 0.9% sodium chloride.
2. Use aseptic technique when adding XENLETA (lefamulin for injection) into the diluent bag. Mix thoroughly.
3. The vial of solution and the bag of diluent solution is single-use only.
4. The diluted solution should be clear and colourless. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Use the diluent bag only if the solution is clear and the container is undamaged.
5. Administer by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. Do not administer rapidly or by bolus intravenous infusion.
6. Do not use the diluent bag in series connections.
7. Administer by intravenous infusion only. XENLETA is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Chemical and physical in-use stability after dilution has been demonstrated for 24 hours at room temperature and 48 hours at 2 - 8 °C. See **STORAGE, STABILITY AND DISPOSAL**.

The compatibility of reconstituted XENLETA with intravenous medications, additives, or substances other than 10 mM citrate buffered 0.9% sodium chloride intravenous infusion and 0.9% sodium chloride intravenous infusion has not been established. If a common intravenous line is being used to administer other drugs in addition to XENLETA, the line should be flushed before and after each XENLETA administration with 0.9% sodium chloride intravenous infusion. Do not add other additives to the diluent bag because their compatibilities with XENLETA Injection have not been established.

3.4 Missed Dose

If a dose is missed, the patient should take the dose as soon as possible and anytime up to 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next scheduled dose, do not take the missed dose, and resume dosing at the next scheduled dose.

4 OVERDOSAGE

Treatment of overdose with XENLETA should consist of observation and general support measures. The stomach should be emptied. Adequate hydration should be maintained, and electrolytes monitored. Electrocardiogram (ECG) monitoring is recommended. Hemodialysis will not significantly remove XENLETA from systemic circulation.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (infusion)	Solution for injection / 10 mg/mL lefamulin (as lefamulin acetate)	Sodium chloride, water for injection
	Diluent / 250 mL10 mM citrate buffered 0.9% sodium chloride diluent bag	Citric acid anhydrous, sodium chloride, trisodium citrate dihydrate, water for injection
Oral	Film-coated tablet 600 mg lefamulin (as lefamulin acetate)	Tablet core: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, povidone K30, talc Film-coating: Opadry® II Blue 85F205110 containing: FD&C Blue #2 Aluminum Lake; Macrogol/PEG; polyvinyl alcohol – part hydrolyzed; talc; titanium dioxide Printing ink: Opacode® Monogramming Ink Black containing ammonium hydroxide solution; butyl alcohol; black iron oxide; isopropyl alcohol; propylene glycol; shellac glaze

Solution for injection
XENLETA (lefamulin for injection) is a clear, colourless, sterile, nonpyrogenic solution for intravenous administration containing 150 mg of lefamulin in 15 mL 0.9% sodium chloride in a single use vial intended for dilution in 250 mL of 10 mM citrate buffered (pH 5) 0.9% sodium chloride. The drug product is provided in a clear type I glass 15 mL vial with a gray rubber stopper, aluminum seal and white polypropylene flip off cap. The diluent is provided in infusion bags containing 250 mL of sterile, nonpyrogenic 10mM citrate buffered (pH 5) 0.9% sodium chloride solution.

They are supplied as follows:
150 mg single use lefamulin vials; packed in cartons of 6.
250 mL single use citrate buffer diluent bags; packed in cartons of 6

Tablets
XENLETA (lefamulin tablets) are available as blue, oval, coated tablets containing 600 mg lefamulin (as lefamulin acetate). The tablet is printed with 'LEF 600' in black on one side.

They are supplied as follows:
HDPE bottles of 30 tablets with Child-resistant Closure
Unit dose opaque blister packs that contain 2 or 10 tablets

6 WARNINGS AND PRECAUTIONS

Cardiovascular
QT Interval Prolongation
XENLETA has been shown to cause a concentration-dependent prolongation of the QT interval of the electrocardiogram (ECG) in some patients. QTc prolongation can lead to an increased risk of ventricular arrhythmias including torsades de pointes. Generally, the risk of torsades de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsades de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsades de pointes can progress to ventricular fibrillation and sudden cardiac death. Avoid XENLETA use in the following patients:

- Patients with known prolongation of the QT interval
- Patients with ventricular arrhythmias including torsades de pointes
- Patients receiving Class IA (for example, disopyramide, 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
- Patients with hypokalemia

When intravenous therapy is initiated, patients should be appropriately monitored. If signs of cardiac arrhythmia occur during treatment with XENLETA, treatment should be stopped and an ECG should be performed.

In patients with renal failure who require dialysis, metabolic disturbances associated with renal failure may lead to QT interval prolongation.

In patients with mild, moderate, or severe hepatic impairment, metabolic disturbances associated with hepatic impairment may lead to QT interval prolongation.

The effect of XENLETA on patients with congenital prolongation of the QT interval has not been studied, but it is expected that these individuals may be more susceptible to drug-induced QT interval prolongation. XENLETA should be used with caution in patients with ongoing proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia, clinically relevant heart failure with reduced left-ventricular ejection fraction or previous history of symptomatic arrhythmias.

Pharmacokinetic studies between lefamulin and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants have not been performed. An additive effect of XENLETA and these drugs cannot be excluded, therefore XENLETA should be used with caution when given concurrently with these drugs.

The magnitude of QT interval prolongation may increase with the infusion rate and with increasing plasma concentrations of XENLETA. Therefore, the recommended duration of infusion (60 minutes) should not be shortened and the recommended dose should not be exceeded. See DOSAGE AND ADMINISTRATION.

QT interval prolongation may lead to an increased risk for ventricular arrhythmias including Torsades de Pointes. It has been observed with other drugs that prolong the QT interval that females may be at greater risk compared to males for developing Torsades de Pointes because women tend to have a longer baseline QT interval compared to men. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

No cardiovascular morbidity or mortality attributed to QTc prolongation occurred with XENLETA treatment in clinical trials involving 1242 patients. However, certain predisposing conditions may increase the risk for ventricular arrhythmias.

Patients considered to have or be at risk for major cardiac events or dysfunction including but not limited to known prolonged QT interval or family history of long QT syndrome, clinically unstable cardiac disease, or complete left bundle branch block were excluded from pivotal studies.

To assure safe and effective use of XENLETA, patients should be advised of the following information and instructions when appropriate:

- That XENLETA may produce changes to the electrocardiogram (QTc interval prolongation)
- That XENLETA should be avoided if they are currently receiving Class IA (e.g., procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents
- That XENLETA may add to the QTc prolonging effects of other drugs, including but not limited to, erythromycin, antipsychotics and tricyclic antidepressants
- To inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia, clinically relevant heart failure with reduced left-ventricular ejection fraction or previous history of symptomatic arrhythmias
- To contact their physician if they experience palpitations or fainting spells while taking XENLETA
- To inform their physician of any other medications being taken concurrently with XENLETA, including over-the-counter medications.

If use with XENLETA cannot be avoided in specific populations predisposed to QT interval prolongation or those receiving another drug that prolongs the QT interval, ECG monitoring is recommended during treatment. Hypokalemia should be corrected prior to initiating or continuing treatment with XENLETA.

Gastrointestinal

Clostridium difficile-Associated Disease

Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including XENLETA. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents. Therefore, careful medical history should be taken.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *C. difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C. difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases.

Hepatic

Hepatic Enzyme Elevations

In the pooled pivotal study safety population, there were 2 XENLETA-treated patients (0.3%) with post-baseline alanine aminotransferase (ALT) >10 x upper limit of normal (ULN), and 2 XENLETA-treated patients (0.3%) with post-baseline aspartate aminotransferase (AST) >10 x ULN. A positive dechallenge back to normal was observed in 3 of the 4 patients with ALT or AST >10 x ULN. No XENLETA-treated patient met the laboratory criteria for potential Hy's Law, and there were no cases of acute liver failure. See **ADVERSE REACTIONS**.

Patients with evidence of significant hepatic disease were excluded from pivotal studies, including those with AST or ALT >5 x ULN, or total bilirubin >3 x ULN; AST or ALT >3 x ULN and total bilirubin >2 x ULN; acute hepatitis; cirrhosis; and ascites or hepatic encephalopathy associated with end-stage liver disease.

A potential for hepatic injury cannot be ruled out. Serum chemistry testing that includes liver enzymes and bilirubin is recommended as clinically warranted.

Sexual Health

Reproduction

Based on findings from animal studies, lefamulin may cause fetal harm when administered to pregnant women. Animal studies indicate that administration of lefamulin resulted in an increased incidence of post-implantation fetal loss and stillbirths in rats and rabbits treated during the period of organogenesis or in rats treated from the beginning of organogenesis through the time of weaning. Additional rat pup deaths were observed during early lactation that

were likely related to maternal treatment with lefamulin. Decreased fetal body weights and ossification in rats and rabbits, and apparent delay in sexual maturation in rats may indicate treatment-related developmental delay, while other findings such as malformations in rats at systemic exposures lower than the systemic exposure in CAP patients may indicate a risk for embryo-fetal toxicity.

Fertility
The effects of lefamulin on fertility in humans have not been studied. Lefamulin caused no impairment of fertility or reproductive performance in male rats. In female rats, lefamulin at systemic exposures higher than the systemic exposure in CAP patients caused no impairment of reproductive indices including mating behavior and fertility but did cause abnormal estrous cycling and increased post-implantation loss.

Susceptibility/Resistance
Development of Drug-Resistant Bacteria
Prescribing XENLETA in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

The use of antibiotics may promote the overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

6.1 Special Populations

6.1.1 Pregnant Women

No clinical studies have been performed in pregnant women.

Animal studies indicate that administration of lefamulin resulted in an increased incidence of still birth. Malformations were also observed in rats at systemic exposures lower than the systemic exposure in CAP patients. XENLETA should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to initiating XENLETA. Advise females of reproductive potential to use effective contraception during treatment with XENLETA and for 2 days after the final dose. See **NON-CLINICAL TOXICOLOGY, Reproductive and Development Toxicology**.

6.1.2 Breast-feeding

There are no data on the presence of lefamulin in human milk, its effects on the breastfed infant, or its effects on milk production. Animal studies indicate that lefamulin was concentrated in the milk of lactating rats. Because of the potential for serious adverse reactions, including QT interval prolongation, a woman should pump and discard human milk for the duration of treatment with XENLETA and for 2 days after the final dose. See **NON-CLINICAL TOXICOLOGY, Reproductive and Development Toxicology**.

6.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

6.1.4 Females and Males of Reproductive Potential

Verify pregnancy status in females of reproductive potential. Advise females of reproductive potential to use effective contraception during treatment with XENLETA and for 2 days after the final dose. XENLETA may cause fetal harm when administered to a pregnant woman (see **WARNINGS AND PRECAUTIONS, Sexual Health, *Reproduction***).

6.1.5 Geriatrics

Of the 646 patients randomized to XENLETA in the Phase 3 CAP studies, 268 (41.5%) were ≥ 65 years of age. The adverse reaction profiles in patients ≥ 65 years and in patients < 65 years of age were similar. The percentage of patients in the XENLETA group who had at least one adverse reaction was 30% in patients ≥ 65 years and 38% in patients < 65 years.

6.1.6 Hepatic Impairment

Patients with evidence of significant hepatic disease were excluded from pivotal studies. Lefamulin is primarily metabolized by Cytochrome P450 3A4 (CYP3A4). In a hepatic impairment study in which non-infected patients with moderate or severe hepatic impairment were administered IV lefamulin, biologically active lefamulin concentrations increased with the degree of hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**).

Among XENLETA-treated patients, hepatobiliary adverse reactions were reported in 3.4% patients with elevated liver enzymes at baseline vs 0.4% patients with normal liver enzymes at baseline. Atrial fibrillation occurred in 2/119 (1.7%) XENLETA patients with elevated hepatic enzymes at baseline.

Monitor patients with hepatic impairment for adverse reactions associated with XENLETA Injection and Tablets throughout the treatment period.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The XENLETA safety database included 641 patients with CAP who received at least one (1) dose of XENLETA in Study 3101 and Study 3102 (pooled).

In the pooled analysis, the overall incidence of adverse reactions was 34.9% in the XENLETA group and 30.4% in the moxifloxacin group, irrespective of relationship to treatment. Serious adverse reactions occurred in 36/641 (5.6%) patients treated with XENLETA and 31/641 (4.8%) patients treated with moxifloxacin. Treatment was discontinued due to an adverse reaction in 20/641 (3.1%) patients treated with XENLETA and 21/641 (3.3%) patients treated with moxifloxacin. Death within 28 days occurred in 8/641 (1.2%) patients treated with XENLETA and 7/641 (1.1%) patients treated with moxifloxacin.

In the pooled analysis, gastrointestinal adverse reactions were the most frequently reported adverse reactions (13.1% versus (vs) 10.1%, XENLETA vs moxifloxacin, respectively). The most frequently reported individual reactions were diarrhea, nausea, and vomiting. The difference between groups was driven primarily by gastrointestinal adverse reactions associated with the oral administration of XENLETA in Study 3102, most notably by diarrhea which was reported in 12.2% vs 1.1%, XENLETA vs moxifloxacin, respectively (see Table 5). The median

onset of diarrhea was on Day 2 (range: Day 1 to 23) and the median duration was 2.5 days. In Study 3101, the opposite was observed, with diarrhea reported in 0.7% vs 7.7%, XENLETA vs moxifloxacin, respectively. Among XENLETA-treated patients, gastrointestinal events were more likely to start during oral treatment (7.7%) than during IV treatment (3.7%), and the largest observed difference was in nausea (4.8% vs 1.1%, oral vs IV, respectively).

Local infusion site reactions were the most frequently reported adverse reactions associated with IV administration of XENLETA in Study 3101 (7.0% vs 2.6%, XENLETA vs moxifloxacin, respectively; see Table 4).

In the pooled analysis, adverse reactions indicative of increased hepatic enzymes were reported in 2.3% of patients in the XENLETA group. Those affected were typically asymptomatic with reversible clinical laboratory findings (e.g., ALT values) that peaked within the first week of dosing, with decline to within or near normal levels within 2-4 weeks. Discontinuation of XENLETA due to non-serious hepatobiliary adverse reactions occurred in 2 patients. No XENLETA-treated patient met the laboratory criteria for potential Hy's Law.

In the pooled analysis, ECG findings reported as adverse reactions for more than 1 patient per treatment group were electrocardiogram QT prolonged (0.6% XENLETA, 0.8% moxifloxacin) and atrial fibrillation (0.5% XENLETA, 0.6% moxifloxacin).

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

XENLETA was evaluated in two clinical trials in CAP patients (Study 3101 and Study 3102). Across the two trials, a total of 641 patients were treated with XENLETA. Study 3101 (IV to oral dosing switch trial) enrolled 551 adult patients, 276 randomized to XENLETA (273 received at least one dose of XENLETA) and 275 randomized to moxifloxacin (273 received at least one dose of moxifloxacin). Study 3102 (oral dosing only trial) enrolled 738 adult patients, 370 randomized to XENLETA (368 received at least one dose of XENLETA) and 368 randomized to moxifloxacin (all 368 received at least one dose of moxifloxacin).

Study 3101 enrolled patients with Pneumonia Outcomes Research Team (PORT) Risk Class III-V. The mean duration of intravenous treatment was 6 days; the mean total duration of treatment was 7 days. In the XENLETA group, treatment was initiated with 150 milligrams (mg) IV every 12 hours (q12h); after a minimum of 3 days of IV therapy, patients could be switched to oral therapy (600 mg PO q12h). Study 3102 enrolled patients with PORT Risk Class II-IV. The mean duration of treatment was 5 days for XENLETA and 7 days for moxifloxacin. Oral XENLETA was administered at 600 mg PO q12h.

In Study 3101 and Study 3102 (pooled), the median age of patients treated with XENLETA was 61 (range 19-97) years; 42% of patients were 65 years or older and 18% were 75 years or older. Patients were predominantly male (58%) and white (79%) and had a median body mass index (BMI) of 26.0 (range 13.0-56.8) kg/m^2. Approximately 52% of XENLETA-treated patients had creatinine clearance (CrCl) <90 mL/min.

Most Common Adverse Reactions

Table 4 and Table 5 include adverse reactions occurring in ≥1% of patients receiving XENLETA in Studies 3101 and 3102.

Table 4: Adverse Reactions Occurring in ≥1% of Patients Receiving XENLETA in Study 3101

Adverse Reaction	Study 3101 IV ± Oral Dosing	
	XENLETA N=273 (%)	Moxifloxacin N=273 (%)
Blood and Lymphatic System Disorders		
Anemia	1.1	0
Gastrointestinal Disorders		
Nausea	2.9	2.2
Vomiting	1.1	0.4
General Disorders and Administration Site Conditions		
Administration site reactions*	7.0	2.6
Investigations		
Electrocardiogram QT prolonged	1.1	1.8
Hepatic enzyme elevation**	2.9	2.6
Gamma-glutamyltransferase increased	1.5	0.4
Metabolism and Nutrition Disorders		
Hypokalemia	2.9	2.2
Nervous System Disorders		
Headache	1.8	1.8
Psychiatric Disorders		
Anxiety	1.1	0.4
Insomnia	2.9	1.8

*Administration site reactions include multiple adverse reaction related terms, such as infusion site pain, infusion site phlebitis, and injection site reaction.

**Hepatic enzyme elevation includes multiple adverse reaction related terms, such as alanine aminotransferase increased, aspartate aminotransferase increased, and liver function test increased.

Table 5: Adverse Reactions Occurring in ≥1% of Patients Receiving XENLETA in Study 3102

Adverse Reaction	Study 3102 Oral Dosing	
	XENLETA N=368 (%)	Moxifloxacin N=368 (%)
Gastrointestinal Disorders		
Diarrhea	12.2	1.1
Gastritis	1.1	0.5
Nausea	5.2	1.9
Vomiting	3.3	0.8
Investigations		
Hepatic enzyme elevation**	1.9	2.2
Nervous System Disorders		
Headache	1.1	1.6

**Hepatic enzyme elevation includes multiple adverse reaction related terms, such as alanine aminotransferase increased, aspartate aminotransferase increased, and liver function test increased.

7.3 Less Common Clinical Trial Adverse Reactions

Selected Adverse Reactions Occurring in Less Than 1% of Patients Receiving XENLETA in Studies 3101 and 3102:

Blood and Lymphatic System Disorders: thrombocytopenia

Cardiac Disorders: atrial fibrillation, palpitations

Gastrointestinal Disorders: abdominal pain, constipation, dyspepsia, epigastric discomfort, erosive gastritis

Infections and Infestations: *Clostridium difficile* colitis, oropharyngeal candidiasis, vulvovaginal candidiasis

Investigations: alkaline phosphatase increased, creatine phosphokinase increased

Nervous System Disorders: dizziness, somnolence

Renal and Urinary Disorders: urinary retention

7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other

Among XENLETA-treated patients, 34/623 (5.5%) reported ALT >3 x ULN, 23/623 (3.7%) reported AST >3 x ULN, 19/625 (3.0%) reported alkaline phosphatase (ALP) >2 x ULN, and 2/623 (0.3%) reported bilirubin >2 x ULN. Among XENLETA-treated patients, 2/623 (0.3%) reported ALT >10 x ULN and 2/623 (0.3%) reported AST >10 x ULN. The ALT/AST were usually <10 x ULN, with ALT generally higher than AST; ALP was usually <5 x ULN; and bilirubin values generally remained normal or <2 x ULN. At any time post-baseline, the proportions of patients meeting pre-defined criteria for potentially clinically significant liver chemistry parameters were 3.5% for ALT >3 x ULN and >200% increase from baseline; 2.0% for AST >3 x ULN and >200% increase from baseline; and 0.2%, for total bilirubin ≥2 x ULN and >150% increase from baseline.

7.5 Post-Market Adverse Reactions

Not applicable.

8 DRUG INTERACTIONS

8.1 Overview

The drug-drug interaction (DDI) potential of IV and orally administered XENLETA has been demonstrated in clinical trials. In addition, a physiological based pharmacokinetic model (PBPK) was applied to predict other potential DDIs. The drug interaction potential of IV XENLETA has only been observed with strong CYP3A inducers.

XENLETA is a substrate of CYP3A. Coadministration of drugs (CYP3A inducer) that can decrease the plasma concentrations of XENLETA should generally be avoided, monitor for reduced efficacy, unless the benefit outweighs the risk.

Orally administered XENLETA is a moderate inhibitor of CYP3A. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A may be increased by XENLETA. Patients should be monitored closely for adverse reactions associated with high plasma concentrations of drugs metabolized by CYP3A.

8.2 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6: Established or Potential Drug-Drug Interactions

XENLETA Co-administered medicines	Source of Evidence	Effect	Clinical comment
IV administration			
Strong and moderate CYP3A Inducers or P-gp Inducers (eg. Rifampin, carbamazepine, efavirenz, phenytoin, and St. John's wort)	CT	Lefamulin concentration will decrease, may reduce efficacy	Avoid coadministration of XENLETA (lefamulin for Injection) with strong and moderate CYP3A inducers or P-gp inducers unless the benefit outweighs the risks.
Oral administration			
Strong and moderate CYP3A Inducers or P-gp Inducers (eg. Rifampin, carbamazepine, efavirenz, phenytoin, and St. John's wort)	CT	Lefamulin concentration will decrease, may reduce efficacy	Avoid coadministration of XENLETA (lefamulin tablets) with strong and moderate CYP3A inducers or P-gp inducers unless the benefit outweighs the risks.
Strong CYP3A Inhibitors or P-gp inhibitors (eg. Ketoconazole, clarithromycin, diltiazem, nefazodone, nelfinavir, posaconazole, ritonavir-containing regimens, and voriconazole)	CT	Lefamulin concentration may increase, which may increase risk of adverse reactions	Avoid coadministration of XENLETA (lefamulin tablets) with strong CYP3A inhibitors or P-gp Inhibitors.
Moderate CYP3A Inhibitors or P-gp inhibitors eg. aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	CT	Lefamulin concentration may increase, which may increase risk of adverse reactions	Monitor for adverse effects of XENLETA (lefamulin tablets) when administered concomitantly with moderate CYP3A inhibitors or P-gp Inhibitors.
CYP3A substrates that prolong the QT interval	T	AUC and C_{max} of CYP3A4 substrates increase, may increase the risk of toxicities associated with cardiac conduction	Coadministration of XENLETA (lefamulin tablets) with CYP3A substrates known to prolong the QT interval is contraindicated.

XENLETA Co-administered medicines	Source of Evidence	Effect	Clinical comment
Sensitive CYP3A Substrates (eg. Midazolam, alprazolam, triazolam, alfentanil, darunavir, diltiazem, everolimus, ibrutinib, lovastatin, simvastatin, sirolimus, tacrolimus, tipranavir, vardenafil, and verapamil)	CT	AUC and C_{max} of CYP3A4 substrates increase, may increase the risk of toxicities associated with cardiac conduction	Coadministration of XENLETA (lefamulin tablets) with sensitive CYP3A substrates requires close monitoring for adverse effects of these drugs.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drugs that Prolong QT

The pharmacodynamic interaction potential to prolong the QT interval of the electrocardiogram between XENLETA and other drugs that affect cardiac repolarization is unknown. Therefore, avoid concomitant use of XENLETA (lefamulin for Injection) and XENLETA (lefamulin tablets) with such drugs (for example, Class IA and III antiarrhythmics, antipsychotics, erythromycin, moxifloxacin, tricyclic antidepressants). This list is not comprehensive. Current information sources should be consulted for recently updated lists of QT-prolonging drugs.

8.3 Drug-Food Interactions

Administration of XENLETA 600 mg tablets with a high fat, high calorie breakfast to healthy subjects resulted in a decrease in AUC_T and C_{max} by approximately 19.0% and 23.2%, respectively when compared to administration under fasting conditions. See **ACTION AND PHARMACOLOGY**.

Concomitant administration of oral XENLETA with grapefruit (or as juice; i.e. strong CYP3A inhibitor) should be used with caution. Monitor for adverse effects of oral XENLETA. See **ACTION AND CLINICAL PHARMACOLOGY**.

8.4 Drug-Herb Interactions

Avoid coadministration of IV or oral XENLETA with herbal preparations containing St. John's wort (*Hypericum perforatum*) unless the benefit outweighs the risks.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Lefamulin is a pleuromutilin antibacterial agent. It inhibits bacterial protein synthesis by interacting with the A- and P- sites of the peptidyl transferase centre (PTC) in the central part of domain V of the 23S rRNA of the 50S ribosomal subunit, preventing correct positioning of the tRNA. See **MICROBIOLOGY**.

9.2 Pharmacodynamics

The 24 h AUC/MIC ratio was determined to be the most important PK/PD index associated with efficacy in animal models. Irrespective of the site of infection (lung, thigh, or bloodstream), the absence of neutrophils did not diminish the efficacy of XENLETA.

Cardiac Electrophysiology
The QTcF interval prolongation risk of XENLETA was evaluated using 2 randomized, double-blind, double-dummy, active controlled (moxifloxacin 400 mg once daily), parallel group, trials (Studies 3101 and 3102) in adult patients with CAP. A concentration dependent QTc prolongation effect of XENLETA was observed. The mean change from baseline QTcF (90% two-sided confidence interval) values were 13.6 ms (11.7, 15.5 ms) on day 3 within 15 minutes of the end of the 60-minute infusion for the 150 mg injection administered twice daily and 9.3 ms (7.6, 10.9 ms) at 1-3 hours post-dose on day 4 for the 600 mg tablet administered twice daily. The mean change from baseline QTcF (90% two-sided confidence interval) values for the moxifloxacin randomized comparison arm were 16.4 ms (14.5, 18.3 ms) on day 3 within 15 minutes of the end of the 60-minute infusion for the 400 mg injection administered once daily and 11.6 ms (10.0, 13.2ms) at 1-3 hours post-dose on day 4 for the 400 mg tablet administered once daily.

9.3 Pharmacokinetics

The pharmacokinetic parameters of XENLETA following single- and multiple-dose (every 12 hours) intravenous (150 mg) and oral (600 mg) administration are shown in Table 7. After repeated q12 h dosing, either IV or orally, steady-state was achieved after two days. Table 8 shows the pharmacokinetic parameters after population PK modelling of lefamulin plasma levels following treatment for CAP (150 mg IV q12h and 600 mg PO q12h). In CAP patients, exposure and peak plasma concentrations are higher compared to healthy subjects.

Table 7: Summary of XENLETA Pharmacokinetic Parameters after IV and Oral Administration to Healthy Adult Subjects

	150 mg IV 1 hour infusion		**600 mg PO**	
	SD	MD q12h	SD	MD q12h
	Arithmetic Mean ± Standard Deviation			
t_{max} (h)	1.0	1.0	0.88	2.00
C_{max} (µg/mL)	2.42 ± 0.52	2.77 ± 0.52	1.46 ± 0.44	1.85 ± 0.61
$t_{1/2}$ (h)	10.6 ± 0.7	14.6 ± 1.1	9.00 ± 0.68	12.0 ± 2.8
AUC_{0-12} [µg·h/mL]	5.75 ± 1.26	8.25 ± 2.00	6.35 ± 1.67	10.8 ± 4.2

AUC_{0-12h}=AUC from time zero to 12 h; C_{max}=maximum observed plasma concentration; MD=multiple dose; q12h=every 12 hours; $t_{1/2}$=elimination half-life; t_{max}=time after administration of a drug when C_{max} is observed; SD=single dose

Table 8: Pharmacokinetic (PK) Parameters of XENLETA Following Single or Multiple Dose (every 12 hours) XENLETA Administered as 150 mg (infused over 1 hour) Intravenously or 600 mg Orally in patients with CAP[a]

PK Parameters	Administration Route	Arithmetic Mean (% CV)	
		Day 1	Steady State
C_{max} (mcg/mL)	IV	3.50 (11.7)	3.60 (14.6)
	Oral[b]	2.24 (36.4)	2.24 (37.1)
C_{min} (mcg/mL)	IV	0.398 (68.1)	0.573 (89.4)
	Oral[b]	0.593 (67.3)	0.765 (75.7)
AUC_{0-24h} (mcg·h/mL)	IV	27.0 (31.8)	28.6 (46.9)
	Oral[b]	30.7 (45.0)	32.7 (49.2)

[a] Based on population PK modeling (Studies 3101 for IV administration and 3102 for PO administration)
[b] Dose administered under fasting conditions (1 hour before or 2 hours after a meal)
C_{max}=maximum plasma concentration; C_{min}=trough plasma levels; $AUC_{0–24h}$=area under the plasma concentration-time curve from time zero to 24 hours

Absorption:
The mean oral bioavailability of XENLETA (lefamulin tablets) is approximately 25% and peak lefamulin plasma concentration occurred 0.88 to 2 hours after administration to healthy subjects.

Effect of Food
Following concomitant administration of a single 600 mg oral dose of XENLETA (lefamulin tablets) with a high fat (approximately 50% of total calories from fat), high calorie breakfast (approximately 800-1000 calories), there was a decrease in AUC_T and C_{max} by approximately 19.0% and 23.2%, respectively when compared to administration under fasting conditions.

Distribution: Mean plasma protein binding of lefamulin ranges from 94.8% at 2.35 mcg/mL to 97.1% at 0.25 mcg/mL in healthy adults.

The mean (min to max) steady state volume of distribution of lefamulin is 86.1 L (34.2 to 153 L) in patients with CAP after administration of XENLETA (lefamulin for Injection).

Metabolism: XENLETA is primarily metabolized by CYP3A4.

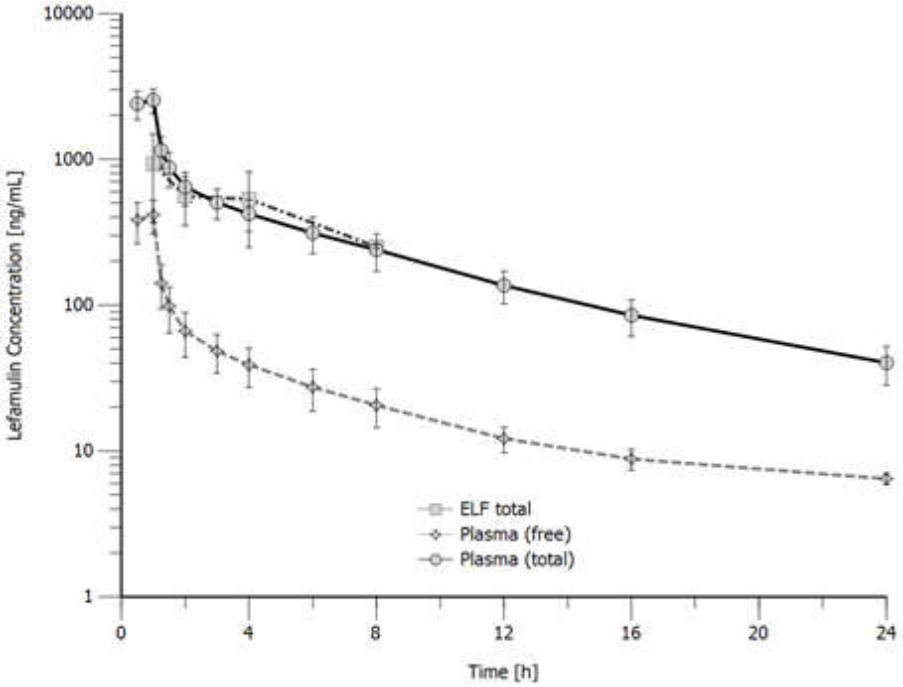
Elimination: Elimination was multiphasic and the terminal $t_{1/2}$ ranged between 9-10 hours after a single oral or IV administration. Overall, XENLETA was primarily eliminated via the non-renal route. Between 9.6%-14.1% of an intravenous dose of XENLETA was excreted as unchanged drug in the urine. The total body clearance and the renal clearance following 150 mg IV infusion were approximately 20 L/h and 1.6 L/h, respectively.

The mean (min to max) total body clearance of lefamulin is 90.1 L/h (18.8 to 227 L/h) in patients with CAP after XENLETA (lefamulin for Injection) administration. The mean (min to max) elimination half-life of lefamulin is approximately 8 hours (3 to 20 h) in patients with CAP.

Lung Penetration: Following a single IV administration of lefamulin 150 mg to healthy subjects, the highest lefamulin epithelial lining fluid (ELF) concentrations were observed at the end of infusion as shown in Figure 1. The mean ELF and plasma AUC_{0-8} was 3.87 mcg·h/mL and 5.27

mcg·h/mL, respectively. The estimated ratio of ELF AUC to unbound plasma AUC is approximately 15.

Figure 1: Mean ± Standard Deviation Concentration-time Curves of XENLETA in Plasma* and ELF after a Single Intravenous Administration of 150 mg Over 1 Hour



*For free plasma concentrations, a protein-unbound fraction of 13% was estimated and used for calculations.

Drug Interaction Studies

Clinical Studies

Effect of Other Drugs on the Pharmacokinetics of Lefamulin

Strong CYP3A inducers or P-gp inducers: oral rifampin (strong inducer) reduced the mean lefamulin $AUC_{0\text{-}inf}$ and C_{max} by 28% and 8%, respectively, when administered concomitantly with XENLETA Injection. Additionally, oral rifampin reduced the mean lefamulin $AUC_{0\text{-}inf}$ and C_{max} by 72% and 57%, respectively, when administered concomitantly with XENLETA (lefamulin tablets).
Strong CYP3A inhibitors or P-gp inhibitors: oral ketoconazole (strong inhibitor) increased the mean lefamulin $AUC_{0\text{-}inf}$ and C_{max} by 31% and 6%, respectively, when administered concomitantly with XENLETA (lefamulin for Injection). Additionally, oral ketoconazole (strong inhibitor) increased the lefamulin $AUC_{0\text{-}inf}$ and C_{max} by 165% and 58%, respectively, when administered concomitantly with XENLETA (lefamulin tablets).

Effect of Lefamulin on the Pharmacokinetics of Other Drugs

CYP3A Substrates: No clinically significant differences in the pharmacokinetics of midazolam were observed when administered concomitantly with XENLETA (lefamulin for Injection). Mean $AUC_{0\text{-}inf}$ and C_{max} of midazolam were increased by approximately 200% and 100%, respectively, when oral midazolam (CYP3A substrate) was administered concomitantly with and at 2 or 4 hours after administration of XENLETA (lefamulin tablets).

P-gp substrates: No clinically significant differences in the pharmacokinetics of digoxin (P-gp substrate) were observed when administered concomitantly with XENLETA (lefamulin tablets).

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

Lefamulin inhibited CYP2C8 (IC_{50}=37.0 mcg/mL), BCRP (Breast Cancer Resistance Protein) (IC_{50}=21.4 mcg/mL), and MATE1 (IC_{50}=0.15 mcg/mL).

Special Populations and Conditions

Hepatic Insufficiency: The disposition of lefamulin was evaluated in non-infected subjects with normal hepatic function and with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment following administration of XENLETA (lefamulin for Injection). The half-life of lefamulin is prolonged in subjects with severe hepatic impairment compared to that in subjects with normal hepatic function (17.5 h versus 11.5 h). Protein binding of lefamulin is reduced in subjects with hepatic impairment. Therefore, unbound (biologically active) lefamulin concentrations increased with the degree of hepatic impairment. On average, unbound lefamulin plasma $AUC_{0\text{-}inf}$ was increased 3-fold in subjects with severe hepatic impairment compared to that in subjects with normal hepatic function. There is no information to evaluate the effect of hepatic impairment on the disposition of lefamulin following administration of XENLETA (lefamulin tablets). Thus, XENLETA (lefamulin tablets) are not recommended in patients with moderate or severe hepatic impairment.

Renal Insufficiency: A study was conducted to compare XENLETA pharmacokinetics following administration of 150 mg IV in 8 subjects with severe renal impairment, 8 subjects requiring hemodialysis and 7 matched healthy control subjects. Subjects requiring hemodialysis were administered XENLETA on two separate occasions, once immediately before dialysis (on-dialysis) and once on a non-dialysis day (off-dialysis). The AUC, C_{max}, and CL of XENLETA and its primary metabolite were comparable between subjects with severe renal impairment and matched healthy subjects, and in subjects requiring hemodialysis whether on- or off-dialysis. XENLETA and its primary metabolite were not dialyzable. Renal impairment did not impact XENLETA elimination.

10 STORAGE, STABILITY AND DISPOSAL

Keep out of reach and sight of children.

<u>XENLETA (lefamulin for Injection</u>
Store in a refrigerator (2 to 8°C). Do not freeze.

<u>Diluent bag</u>
Store at 2 to 30°C. Do not freeze.

<u>Diluted solution for infusion</u>
The chemical and physical in-use stability has been demonstrated for up to 24 hours at room temperature and up to 48 hours when refrigerated (2 to 8°C).

For single use only.
Any unused product or waste material should be disposed as biohazardous waste.

<u>XENLETA (lefamulin tablets)</u>
Store at 15 to 30°C.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

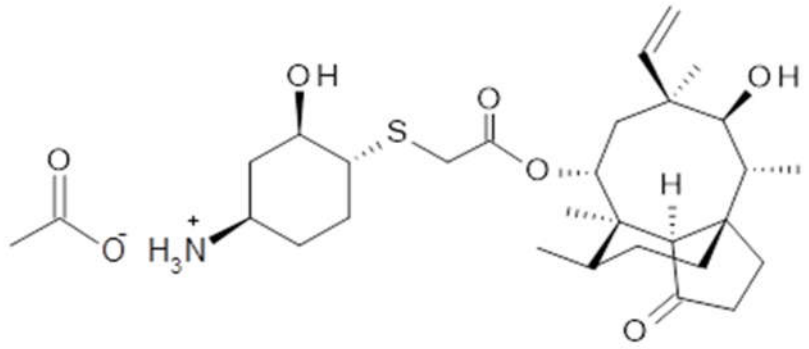
Drug Substance

Proper name: lefamulin acetate

Chemical name: 14-O-{[(1*R*,2*R*,4*R*)-4-Amino-2-hydroxy-cyclohexylsulfanyl]-acetyl}-mutilin acetate

Molecular formula and molecular mass: $C_{30}H_{49}NO_7S$ and 567.79 grams per mole

Structural formula:



Physicochemical properties: White to off-white solid with a pKa of 9.41 that is soluble in various organic solvents and is highly soluble in water and 0.9 % sodium chloride solution (> 300 mg/mL). The solubility of lefamulin acetate is ≥100 mg/mL in 0.1 N HCl and 300 mM phosphate buffers at pH 6.8 and pH 7.4.

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

The trial design and study demographics of the CAP studies are presented in Table 9.

Table 9: Summary of trial design and patient demographics for clinical trials in CAP (ITT Analysis Set)

Study #	Trial design	Dosage, route of administration and duration	Number of patients (n)	Median age (Range)	Sex
3101	Multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group, non-inferiority trial	XENLETA: 150 mg by IV infusion over 60 minutes q12h for 5 to 10 days depending on the baseline pathogen identified and the approved protocol version at the time of Screening; if pre-defined clinical criteria were met, patients could be switched to 600 mg PO q12h at the discretion of the Investigator after 3 full days (6 doses) of IV treatment Moxifloxacin with or without (±) adjunctive linezolid (600 mg IV/PO): 400 mg IV q24h for 7 to 10 days depending on the baseline pathogen identified and the approved protocol version at the time of Screening; if pre-defined clinical criteria were met, patients could be switched to 400 mg PO q24h at the discretion of the Investigator after 3 full days (6 doses) of IV treatment	N = 551 Xenleta: 276 Moxifloxacin: 275	62.0 years (19 – 91 years)	M: 330 F: 221
3102	Multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group, non-inferiority trial	XENLETA: 600 mg PO q12h for 5 days Moxifloxacin: 400 mg PO q24h for 7 days	N = 738 Xenleta: 370 Moxifloxacin: 368	59.0 years (19 – 97 years)	M: 387 F: 351

F = Female, IV = intravenous; M = Male; mg = milligrams; PO = by mouth; q12h = every 12 hours

In Study 3101, 276 patients were randomized to XENLETA and 275 patients were randomized to moxifloxacin. If methicillin-resistant *Staphylococcus aureus* (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 PO every 12 hours after at least 3 days of IV treatment), and patients randomized to XENLETA were to receive linezolid placebo. In XENLETA patients, approximately 75% received treatment for 7 days and 25% received treatment for 5 days; all moxifloxacin patients received treatment for 7 days. Approximately 72% of patients were Pneumonia Outcomes Research Team (PORT) Risk Class III, 27% PORT Risk

Class IV, and 1% were PORT Risk Class V. Median body mass index (BMI) was 25.8 (range 11-58.4) kilogram per square metre (kg/m^2). Approximately 53% of patients had creatinine clearance (CrCl) <90 millilitres per minute (mL/min). Common comorbid conditions included hypertension (41%), asthma/chronic obstructive pulmonary disease (COPD) (18%), and diabetes mellitus (13%).

In Study 3102, 370 patients were randomized to XENLETA and 368 patients were randomized to moxifloxacin. Approximately 50% of patients were PORT Risk Class II, 38% were PORT Risk Class III and 11% were PORT Risk Class IV. Median BMI was 26.0 (range 13-63.9) kg/m^2. Approximately 50% of patients had CrCl <90 mL/min. Common comorbid conditions included hypertension (36%), asthma/COPD (18%), and diabetes mellitus (13%).

In both studies, the primary efficacy endpoint was the percentage of patients with an Early Clinical Response (ECR) of responder at 72 to 120 hours after the first dose of study drug in the Intent-to-treat (ITT) Analysis Set, which comprised all randomized patients. Both studies enrolled adult patients with clinical signs and symptoms of CAP, accompanying laboratory/vital sign or physical examination abnormalities, and confirmatory pulmonary imaging. Patients entered the studies with at least three of four symptoms consistent with CAP (new or increased cough, purulent sputum production, chest pain due to pneumonia, and/or dyspnea). In Study 3101, patients required IV antibiotic therapy as initial treatment and were expected (but not required) to be hospitalized, while in Study 3102, patients were appropriate candidates for oral antibiotic therapy and did not require hospitalization. Response was defined as survival with improvement of at least two signs and symptoms the patient presented with at baseline, no worsening of any sign or symptom, and no receipt of non-study antibacterial treatment for CAP.

12.2 Study Results

In Study 3101, the ECR responder rate was 87.3% in the XENLETA group and 90.2% in the moxifloxacin group [treatment difference -2.9%; 95% confidence interval (CI): -8.5, 2.8]; XENLETA was non-inferior [12.5% non-inferiority (NI) margin] compared to moxifloxacin in the treatment of adult patients with CAP. In Study 3102, the ECR responder rate was 90.8% in the XENLETA group and 90.8% in the moxifloxacin group (treatment difference 0.1%; 95% CI: -4.4, 4.5); XENLETA was non-inferior (10% NI margin) compared to moxifloxacin. Table 10 summarizes ECR rates in the two studies. The proportion of patients meeting ECR responder criteria by visit was similar between pooled treatment groups, with approximately 60% of patients in both groups meeting ECR responder criteria by Day 3, and approximately 91% by Day 5.

Table 10: Early Clinical Response Rate in Study 3101 and Study 3102 (ITT Analysis Set)

Study	XENLETA n/N (%)	Moxifloxacin n/N (%)*	Treatment Difference (95% CI)**
3101	241/276 (87.3)	248/275 (90.2)	-2.9 (-8.5, 2.8)
3102	336/370 (90.8)	334/368 (90.8)	0.1 (-4.4, 4.5)

*Study 3101 compared XENLETA to moxifloxacin ± linezolid
**95% confidence interval for the treatment difference

In both studies, clinical response was also assessed by the Investigator at the Test of Cure (TOC) Visit (i.e., 5 to 10 days after the last dose of study drug) in the modified ITT (mITT) Analysis Set and in the Clinically Evaluable at TOC (CE-TOC) Analysis Set (key secondary

endpoints). The mITT Analysis Set included all randomized patients who received any amount of study drug. The Clinically Evaluable (CE) Analysis Set included all randomized patients who met pre-defined key inclusion/exclusion criteria, minimum dosing criteria, and had no confounding use of prohibited antibiotics. Response was defined as survival with resolution or improvement of signs and symptoms based on the Investigator's assessment and no receipt of non-study antibacterial treatment for CAP. Table 11 summarizes Investigator-assessed Clinical Response (IACR) rates at the TOC Visit in the mITT and CE-TOC Analysis Sets, which support the findings with the primary endpoint (ECR Responder rate).

Table 11: Investigator-assessed Clinical Response Rates at TOC in Study 3101 and Study 3102 (mITT and CE-TOC Analysis Sets)

Study	XENLETA n/N (%)	Moxifloxacin n/N (%)*	Treatment Difference (95% CI)**
mITT Analysis Set			
3101	223/273 (81.7)	230/273 (84.2)	-2.6 (-8.9, 3.9)
3102	322/368 (87.5)	328/368 (89.1)	-1.6 (-6.3, 3.1)
CE-TOC Analysis Set			
3101	205/236 (86.9)	219/245 (89.4)	-2.5 (-8.4, 3.4)
3102	296/330 (89.7)	305/326 (93.6)	-3.9 (-8.2, 0.5)

*Study 3101 compared XENLETA to moxifloxacin ± linezolid.
**95% confidence interval for the treatment difference.

The ECR at 72 to 120 hours after the first dose of study drug in the Microbiological Intent-to-treat (microITT) Analysis Set, a secondary efficacy endpoint, was 87.4% in the XENLETA group and 93.1% in the moxifloxacin group in Study 3101; and 90.7% in the XENLETA group and 93.0% in the moxifloxacin group in Study 3102. The microITT Analysis Set comprised all randomized patients with at least 1 baseline pathogen.

Table 12 summarizes IACR rates at TOC by the most common baseline pathogens across both studies in the microITT Analysis Set, a secondary efficacy endpoint.

Table 12: Investigator-assessed Clinical Response Rates at TOC by Baseline Pathogen in Study 3101 and 3102 (microITT Analysis Set)

Pathogen	XENLETA n/N (%)	Moxifloxacin n/N (%)*
Streptococcus pneumoniae	184/216 (85.2)	193/223 (86.5)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	14/16 (87.5)	5/5 (100.0)
Haemophilus influenzae	95/107 (88.8)	88/105 (83.8)
Haemophilus parainfluenzae	9/9 (100.0)	4/4 (100.0)
Moraxella catarrhalis	37/46 (80.4)	22/22 (100.0)
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)

*Study 3101 compared XENLETA to moxifloxacin ± linezolid

While the IACR success rates at TOC for *Streptococcus pneumoniae* in the microITT Analysis Set were 184/216 (85.2%) in the XENLETA group versus 193/223 (86.5%) in the moxifloxacin group, a numerically lower response rate was seen in the XENLETA group among the

subpopulation with a baseline pathogen of penicillin-susceptible *Streptococcus pneumoniae* (PSSP), with rates of 35/47 (74.5%) in the XENLETA group versus 55/56 (98.2%) in the moxifloxacin group. An imbalance across treatment groups in baseline characteristics among patients with PSSP (i.e., higher rate of concomitant bacteremia and more patients meeting severity index criteria in the XENLETA group) was observed.

13 MICROBIOLOGY

Mechanism of Action

XENLETA 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.

XENLETA is bactericidal *in vitro* against *S. pneumoniae*, *H. influenzae* and *M. pneumoniae* (including macrolide-resistant strains), and bacteriostatic against *S. aureus* and *S. pyogenes* at clinically relevant concentrations.

XENLETA is not active against *Enterobacteriaceae* and *Pseudomonas aeruginosa*.

Resistance

The resistance frequency to XENLETA due to spontaneous mutations *in vitro* at 2-8 times the MIC was 2×10^{-9} to $<2 \times 10^{-11}$ for *S. aureus*, $<1 \times 10^{-9}$ to $<3 \times 10^{-10}$ for *S. pneumoniae*, and $<4 \times 10^{-9}$ to $<2 \times 10^{-10}$ for *S. pyogenes.* Resistance development at sub-MIC concentrations required greater than 1 mutational step with no resistant clones detected at ≥4-times MIC.

Resistance mechanisms that affect XENLETA include specific protection or modification of the ribosomal target by ABC-F proteins such as *vga* (A, B, E), *lsa*(E), *sal*(A), Cfr methyl transferase, or by mutations of ribosomal proteins L3 and L4. Cfr methyl transferase has the potential to mediate cross-resistance between lefamulin and phenicols, lincosamides, oxazolidinones, and streptogramin A antibacterials.

Some isolates resistant to ß-lactams, glycopeptides, macrolides, mupirocin, quinolones, tetracyclines, and trimethoprim-sulfamethoxazole may be susceptible to XENLETA.

Interaction with Other Antimicrobials

In vitro studies demonstrated no antagonism between XENLETA and other antibacterial drugs (eg, amikacin, azithromycin, aztreonam, ceftriaxone, levofloxacin, linezolid, meropenem, penicillin, tigecycline, trimethoprim/sulfamethoxazole, and vancomycin).

XENLETA has demonstrated synergy *in vitro* with doxycycline against *S. aureus*.

Antimicrobial Activity

XENLETA has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.

Gram-positive Bacteria
Streptococcus pneumoniae including multi-drug resistant isolates [MDRSP]*
*MDRSP refers to isolates resistant to two or more of the following antibiotics/antibiotic classes: Penicillins, cephalosporins, macrolides, tetracyclines, lincosamides, fluoroquinolones and folate-synthesis inhibitors.
Staphylococcus aureus (methicillin-susceptible isolates)

Gram-negative Bacteria

Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Legionella pneumophila

Other Bacteria

Mycoplasma pneumoniae
Chlamydophila pneumoniae

At least 90% of the following bacteria exhibit an *in vitro* MIC less than or equal to the susceptible breakpoints for XENLETA against isolates of similar genus or organism group. However, the safety and efficacy of XENLETA in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive Bacteria

Staphylococcus aureus (methicillin-resistant [MRSA] isolates)
Streptococcus agalactiae
Streptococcus anginosus group
Streptococcus mitis group
Streptococcus pyogenes
Streptococcus salivarius group

Susceptibility Test Methods

When available, the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (CLSI MIC assay conditions CLSI M7) or equivalent with standardized inoculum concentration and standardized concentration of lefamulin powder.

Broth microdilution and disk diffusion reference methods have been established to determine the *in vitro* activity of lefamulin according to Clinical Laboratory Standards Institute (CLSI) methodology. Standard CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC assay conditions produced reproducible MIC results. For broth microdilution testing, frozen or freshly prepared panels of isolates were used and Sensititre® panels were validated. The equivalency of broth microdilution testing methods according to CLSI and EUCAST and agar dilution has been demonstrated for the majority of relevant organisms. The MIC values should be interpreted according to criteria provided in

Table 13.

Table 13: MIC Susceptibility Test Interpretive Criteria

Organism	MIC (µg/mL) STIC (Breakpoints)			
	S	I	R	NS
S. pneumoniae	≤1	-	-	≥2
S. aureus	≤0.5	1	≥2	-
Coagulase-negative *Staphylococcus* spp.	≤0.5[a]	1	≥2	-
H. influenzae	≤4	-	-	≥8
H. parainfluenzae	≤8	-	-	≥16
M. catarrhalis	≤0.5	-	-	≥1
β-hemolytic *Streptococcus* spp.	≤0.25	-	≥0.5	-
Viridans *Streptococcus* spp.	≤0.5	1	≥2	-

I=intermediate; MIC=minimum inhibitory concentration; NS = non-susceptible; R=resistant; S=susceptible; STIC=susceptibility test interpretive criteria

[a] Proposed STIC for CoNS is based on *S. aureus* nonclinical PK/PD cut-off.

Diffusion Techniques

Quantitative methods (Kirby-Bauer disk testing, disk diffusion testing) that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. Standardized procedures (CLSI methodology M02) require the use of standardized inoculum concentrations and disks impregnated with lefamulin. Disk load studies determined that 20 µg lefamulin disks were optimal for diagnostic use of potentially susceptible CAP pathogens and a good correlation of MIC values and disk diffusion testing has been shown in various studies. The disk diffusion interpretive criteria are provided in Table 14.

Table 14: Disc Diffusion Zone Diameter and MIC Susceptibility Test Interpretive Criteria

Organism	Susceptible MIC Value (µg/mL)				Susceptible Zone Diameter (mm)			
	S	I	R	NS	S	I	R	NS
S. pneumoniae	≤1	-	-	≥2	≥17	-	-	≤16
Staphylococcus spp.	≤0.5[a]	1	≥2	-	≥22	19-21	≤18	-
H. influenzae	≤4	-	-	≥8	≥15	-	-	≤14
H. parainfluenzae	≤8	-	-	≥16	-	-	-	-
M. catarrhalis	≤0.5	-	-	≥1	≥20	-	-	≤19
β-hemolytic *Streptococcus* spp.	≤0.25	-	≥0.5	-	≥20	-	≤19	-
Viridans *Streptococcus* spp.	≤0.5	1	≥2	-	≥18	15-17	≤14	-

I=intermediate; MIC=minimum inhibitory concentration; NS=non-susceptible; R=resistant; S=susceptible.

Quality Control

Quality Control (QC) limits for broth microdilution testing (Table 15) and disk diffusion using the 20µg disks (Table 16) have been established with CLSI.

Table 15: Lefamulin QC Ranges for Broth Microdilution

QC Organism	Proposed MIC QC Ranges	
	MIC Range (µg/mL)	% in Range
S. aureus ATCC 29213	0.06-0.25	100
S. pneumoniae ATCC 49619	0.06-0.5	98.6[a]
H. influenzae ATCC 49247[b]	0.5-2	94.3[a]
H. influenzae ATCC 49766[c]	0.5-2	100

QC=quality control; MIC=minimum inhibitory concentration.
[a] QC range based on values obtained from 7 laboratories instead of 8.
[b] Trailing of the endpoint was observed.
[c] not approved by CLSI

Table 16:CLSI-Approved QC Disk Diffusion Zone Diameters for Lefamulin According to CLSI Methodology

QC Organism	Disk Diffusion Zone Diameters for Lefamulin	
	Range (mm)[a]	% in Range[a]
S. pneumoniae ATCC 49619	19-27 (19-28)	99.3 (100)
S. aureus ATCC 25923	26-32 (26-33)	97.4 (99.3)
H. influenzae ATCC 49247	22-28 (21-28)	96.0 (98.9)

QC=quality control;
[a] Proposed ranges calculated by the "Range Finder" method are shown in parentheses.

14 NON-CLINICAL TOXICOLOGY

General Toxicity

Following IV administration of lefamulin to rats for 4 or 13 weeks, anemia (all doses), increased coagulation times, and lower organ weights and histopathological changes in spleen (decreased peri-arteriolar lymphoid sheath, decreased size of the marginal zone) and thymus (cortical atrophy) were seen in rats at exposures greater than approximately 0.7 times exposure in CAP patients after IV administration in the 4-week study and greater than approximately 0.3 times exposure in CAP patients in the 13-week study.

In cynomolgus monkeys administered IV lefamulin, anemia and pancreatic microvesicular vacuolization of acinar cells were noted at exposures greater than approximately 1.6 times exposure in CAP patients in a 4-week study. In a 13-week study, pancreatic microvesicular vacuolization of acinar cells and minimal alveolar macrophage infiltrates in the lung were observed at all doses, and anemia was noted at exposures greater than approximately 1.0 times clinical exposure.

Lefamulin was evaluated in 4-week oral toxicology studies in rats and cynomolgus monkeys. Findings included partially reversible degenerative changes in the stomach and evidence of lymphoid depletion and hematopoietic cell depletion in rats at exposures greater than approximately 0.6 times exposure following oral administration to CAP patients. Findings in cynomolgus monkeys included myocardial vacuolation and fibrosis at exposures equal to or greater than 0.3 times that in CAP patients.

Evidence of dose-dependent regenerative anemia in both species may indicate that XENLETA was potentially hemolytic at a concentration that is approximately ten times higher than the concentration of the infusion solution which will be used clinically. This effect was not apparent from an *in vitro* evaluation of blood compatibility using human blood at a concentration of 0.6 mg/mL.

Long-term carcinogenicity studies have not been conducted with lefamulin.

Genotoxicity

Lefamulin did not elicit genotoxic potential in an *in vivo* clastogenicity assay. Valid *in vitro* mutagenicity assays have not been performed for lefamulin or the main human metabolite of lefamulin (2*R*-hydroxy lefamulin). At least six impurities have been identified to be possibly genotoxic based on chemical structure, while two others were positive in mutagenicity testing and may contribute to a total amount of genotoxic impurities that exceed the acceptable total daily intake of mutagenic impurities. However, since the duration of clinical dosing is limited to 5-7 days, the clinical implications are unknown.

Reproductive and Development Toxicology

In rats, there were no effects on male fertility that were considered to be related to lefamulin. Reproductive indices including mating behavior and fertility were not changed in any group in either gender at the highest dose tested (75 mg/kg/day, approximately 0.7 times the mean exposure of CAP patients treated IV, based on $AUC_{0\text{-}24h}$); that dose was the NOAEL for fertility in male rats. In females, abnormal estrous cycling and increased post-implantation loss were observed at the high dose, making the NOAEL for fertility and early embryonic development in female rats the next highest dose, 50 mg/kg/day (approximately 0.5 times the mean exposure of CAP patients treated IV).

In a prenatal and postnatal development study in rats treated from the beginning of organogenesis through lactation (Gestation Day [GD] 6 through lactation day 21), the percent of live births was reduced (87.4% compared with the concurrent control of 98.7%) in the high dose group of 100 mg/kg/day (0.9 times the mean exposure in CAP patients treated IV). Equivocal findings in that study were indicative of early post-natal mortality and apparent developmental delay that may be related to pre-natal effects.

In the rat embryo-fetal development study of IV lefamulin during organogenesis (GD 6-17), findings included late resorptions in the high-dose group and malformations (cleft palate/jaw/ vertebral malformations at the mid and high doses and enlarged ventricular heart chamber with a thin ventricular wall at the high dose) for which the litter incidence was nonexistent in concurrent controls and rare in historical controls (0 to approximately 0.3%). Decreased or no ossification in a number of skeletal elements in all treated groups may indicate treatment-related developmental delay at all doses. The mean exposure at the lowest dose was approximately 0.4 times the mean exposure in CAP patients treated IV. The main human metabolite, 2*R*-hydroxy lefamulin, was evaluated in an embryo-fetal development study in rats after IV administration and was also associated with the same cardiac malformation seen in the above study, enlarged ventricular heart chamber with or without a thin ventricular wall (which could be associated with undetected valve or great vessel anomalies).

In the rabbit embryo-fetal development study of IV lefamulin during organogenesis (GD 6-18), low numbers of live fetuses in utero in treated groups limited evaluation of the study. Additional findings at the high dose included decreased fetal weight and decreased or no ossification of skeletal elements, which may be indicative of developmental delay. A NOAEL was not determined. The lowest dose (not fully evaluated due to fetal mortality) would correspond to a mean exposure approximately 0.1 times the mean exposure in CAP patients.

Results of animal studies indicate that lefamulin crosses the placenta and is found in fetal tissues. Following a single intravenous administration of 30 mg/kg radio-labelled lefamulin to pregnant female rats on Day 17 of gestation, radioactivity was visible in fetal tissue, with greatest concentrations measured in the placenta and fetal liver (34.3 and 8.26 mcg equivalents/g, respectively) compared to 96.6 mcg equivalents/g in the maternal liver.

Radioactivity in fetal tissues generally declined rapidly, and radioactivity associated with the fetus itself was below the limit of quantification by 12 hours post-dose. Radioactivity in the placenta declined rapidly and was below the limit of quantification by 24 hours after dosing. Concentrations of radioactivity in the amniotic sac remained measurable at the final sampling time (72 hours), peaking at 6 hours post-dose. The amniotic fluid did not contain radioactivity at any time after dose administration.

Administration of a single intravenous dose of 30 mg/kg radio-labelled lefamulin to lactating rats resulted in maximal mean concentrations of radioactivity in plasma and milk at 0.25-hour post-dose (3.29 and 10.7 mcg equivalents/g, respectively) that were markedly reduced at 24 hours post-dose (0.00663 and 0.0700 mcg equivalents/g, respectively). Milk/plasma ratios increased from 3.27 at 0.25-hour post-dose to 8.33 at 6 hours post-dose.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrXENLETA™
Lefamulin for injection (as lefamulin acetate), Solution

Read this carefully before you start taking **XENLETA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **XENLETA**.

Serious Warnings and Precautions

XENLETA can cause an irregular heartbeat (QT interval prolongation) in some patients. This can cause serious **heart problems**.

Talk to your healthcare professional to see if XENLETA is right for you.

What is XENLETA used for?
XENLETA is used:
- In adults
- To treat an infection of the lungs called Community-acquired pneumonia (CAP)
- CAP develops in adults with limited or no contact with hospitals or healthcare centers
- Adults with CAP get infected in a community setting

How does XENLETA work?
XENLETA belongs to a group of medicines called antibiotics. It works by killing a type of germ called bacteria that causes lung infections.

What are the ingredients in XENLETA?
Solution for Injection
Medicinal ingredients: lefamulin (as lefamulin acetate)
Non-medicinal ingredients: sodium chloride, water for injection

Diluent
Non-medicinal ingredients: citric acid anhydrous, sodium chloride, trisodium citrate dihydrate, water for injection

XENLETA comes in the following dosage forms:
As a solution containing 150 mg / 15 mL lefamulin (as lefamulin acetate).

Do not use XENLETA if:
- You are allergic to lefamulin acetate or any of the other ingredients in XENLETA
- You are allergic to a component of the XENLETA container

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take XENLETA. Talk about any health conditions or problems you may have, including if you:

- Have or have had certain heart problems such as:
    - An irregular heartbeat called a ventricular arrhythmia
    - A history of abnormal heart rhythms called 'torsades de pointes' where your heartbeat is irregular
    - A slow heart rate.
    - A condition called myocardial ischemia where your heart does not get enough blood.
    - A condition called heart failure where your heart doesn't pump blood as it should.
- Are taking heart medicines such as disopyramide, procainamide, amiodarone or sotalol
- Are taking any medicine that prolong the QT interval of the heart such as antipsychotic medicines like pimozide, antidepressant medicines and antibiotics like moxifloxacin and erythromycin. Talk to your healthcare professional if you are not sure if a medicine you take prolongs the QT interval.
- Have a family history of irregular heartbeat (such as QT interval prolongation)
- Have kidney failure and require dialysis
- Have liver problems
- Have low potassium levels in your blood
- Are pregnant or are planning to have a baby
- Are breastfeeding or are planning to breastfeed
- Are less than 18 years of age
- Are elderly

Other warnings you should know about:

Pregnancy

XENLETA should only be used in pregnancy if clearly necessary. This is because it may harm your unborn baby. In animals, XENLETA increased miscarriages, stillbirths and fetal defects. Before you are given this medicine, tell your healthcare professional if you are pregnant, think you may be pregnant or are planning to have a baby. You and your healthcare professional will decide if you will be given XENLETA.

Birth Control

If you become pregnant while receiving XENLETA it may harm your unborn baby. You should use effective birth control while you are receiving XENLETA. Continue using this birth control until 2 days after your last dose. Talk to your healthcare professional about effective methods of birth control.

Breastfeeding

You should not breastfeed while you are receiving XENLETA. Talk to your healthcare professional if you are breastfeeding or are planning to breastfeed. While you are receiving XENLETA your breast milk can harm your baby. You should pump and discard your breastmilk while you are receiving XENLETA. Continue this for 2 days after your final dose. Talk to your healthcare professional about pumping and discarding your breastmilk.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with XENLETA:
- Medicines used to treat infections, such as rifampin, clarithromycin or erythromycin
- Carbamazepine or phenytoin, used to treat epilepsy
- Medicines used to treat HIV, such as efavirenz
- St. John's wort, an herbal remedy used to treat depression

How to take XENLETA:
- XENLETA will be given to you by a healthcare professional.
- It will be infused directly into your vein.
- It will be infused over a period of 60 minutes.
- Follow all instructions given to you by your healthcare professional.

Usual dose:

The usual dose of XENLETA is 150 mg every 12 hours for 5 to 7 days.

Overdose:

If you think you have been given too much XENLETA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using XENLETA?
These are not all the possible side effects you may feel when taking XENLETA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Low potassium levels in your blood (hypokalemia), which can cause muscle weakness, twitching or abnormal heart rhythm
- Reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness (anaemia)
- Reduction in blood platelets (blood cells which help the blood to clot), which increases risk of bleeding or bruising
- Difficulty sleeping (insomnia)
- Feeling anxious
- Headache
- Feeling tired or drowsy
- Feeling sick (nausea) or being sick (vomiting)
- Diarrhea
- Stomach pain, pain in the abdomen or around the stomach
- Constipation
- Indigestion, or inflammation of the stomach lining (gastritis)
- Retaining urine for longer than usual, leading to difficulty urinating or in fully emptying your bladder (urinary retention)
- Muscle problems/muscle enzyme elevation (blood tests may show changes to some of the parts of your blood)
- Fungal infection of the throat and mouth (thrush or candida infection)

Serious side effects and what to do about them

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Heart problems (irregular heartbeat due to lengthening of the QT interval): chest discomfort, fainting, feeling light-headed, fluttering or thumping in the chest, heart skips a beat, palpitations (awareness of heartbeats), sudden collapse, weakness.			X
Liver problems abdominal pain, dark urine, fatigue, loss of appetite, nausea, vomiting, yellowing of the skin or eyes (jaundice).		X	
Redness, pain or swelling at the site of injection	X		
Clostridium difficile colitis (bowel inflammation): abdominal pain or tenderness, fever, severe diarrhea (bloody or watery).			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- The healthcare professional will store the product in a refrigerator (2 to 8°C). It should not be frozen.
- Keep out of reach and sight of children.

If you want more information about XENLETA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.sunovion.ca, or by calling 1-800- 739-0565.

This leaflet was prepared by Sunovion Pharmaceutical Canada Inc., Mississauga, ON L5N 0E8

Last Revised: July 10, 2020

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrXENLETA™
Lefamulin Tablets (as lefamulin acetate), Oral

Read this carefully before you start taking **XENLETA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **XENLETA**.

Serious Warnings and Precautions

XENLETA can cause an irregular heartbeat (QT interval prolongation) in some patients. This can cause serious heart problems.

Talk to your healthcare professional to see if XENLETA is right for you.

What is XENLETA used for?
XENLETA is used:
- In adults
- To treat an infection of the lungs called Community-acquired pneumonia (CAP)
- CAP develops in adults with limited or no contact with hospitals or healthcare centers
- Adults with CAP get infected in a community setting
    - Antibacterial drugs like XENLETA treat only bacterial infections. They do not treat viral infections.

How does XENLETA work?
XENLETA belongs to a group of medicines called antibiotics. XENLETA works by killing a type of germ called bacteria that causes lung infections.

What are the ingredients in XENLETA?
Medicinal ingredients: lefamulin (as lefamulin acetate)

Non-medicinal ingredients: ammonium hydroxide solution, black iron oxide, butyl alcohol, colloidal silicon dioxide, croscarmellose sodium, FD&C Blue #2 Aluminum Lake, isopropyl alcohol, Macrogol/PEG, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol – part hydrolyzed, povidone K30, propylene glycol, shellac glaze, talc, titanium dioxide.

XENLETA comes in the following dosage forms:
As tablets containing 600 mg lefamulin (as lefamulin acetate).

Do not use XENLETA if:
- You are allergic to lefamulin acetate or any other ingredients in XENLETA tablets.
- You are taking other medicines that prolong the QT interval of the heart, like pimozide, a medicine used to treat schizophrenia. Talk to your doctor if you are not sure if a medicine you take prolongs the QT interval.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take XENLETA. Talk about any health conditions or problems you may have, including if you:

- Have or have had certain heart problems such as:
    - An irregular heartbeat called a ventricular arrhythmia
    - A history of abnormal heart rhythms called 'torsades de pointes' where your heartbeat is irregular
    - A known abnormal electrocardiogram (ECG) heart tracing which has shown that you have a longer QT interval
    - A slow heart rate.
    - A condition called myocardial ischemia where your heart does not get enough blood.
    - A condition called heart failure where your heart doesn't pump blood as it should.
- Are taking heart medicines such as disopyramide, procainamide, amiodarone or sotalol
- Have a family history of irregular heartbeat (such as QT interval prolongation)
- Have kidney failure and require dialysis
- Have liver problems
- Have low potassium levels in your blood
- Are pregnant or are planning to have a baby
- Are breastfeeding or are planning to breastfeed
- Are less than 18 years of age
- Are elderly

Other warnings you should know about:

Pregnancy

XENLETA should only be used in pregnancy if clearly necessary. This is because it may harm your unborn baby. In animals, XENLETA increased miscarriages, stillbirths and fetal defects. Before you are given this medicine, tell your healthcare professional if you are pregnant, think you may be pregnant or are planning to have a baby. You and your healthcare professional will decide if you will be given XENLETA.

Birth Control

If you become pregnant while receiving XENLETA it may harm your unborn baby. You should use effective birth control while you are receiving XENLETA. Continue using this birth control until 2 days after your last dose. Talk to your healthcare professional about effective methods of birth control.

Breastfeeding

You should not breastfeed while you are receiving XENLETA. Talk to your healthcare professional if you are breastfeeding or are planning to breastfeed. While you are receiving XENLETA your breast milk can harm your baby. You should pump and discard your breastmilk while you are receiving XENLETA. Continue this for 2 days after your final dose. Talk to your healthcare professional about pumping and discarding your breastmilk.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with XENLETA:

- Carbamazepine or phenytoin, used to treat epilepsy
- Medicines used to treat HIV, such as darunavir, efavirenz, nelfinavir, ritonavir, or tipranavir
- St. John's Wort, an herbal remedy used to treat depression
- Medicines used to treat an irregular heart rate, such as quinidine, procainamide, amiodarone or sotalol
- Medicines used to treat angina, high blood pressure, or certain types of tachycardia (fast heart beat), such as diltiazem or verapamil
- Medicines used to treat infections, such as rifampin, clarithromycin or erythromycin
- Medicines for treatment of fungal infections (anti-fungal), such as posaconazole, ketoconazole or voriconazole
- Medicines used to treat schizophrenia, such as pimozide
- Medicines used to treat depression, such as nefazodone
- Medicines used to treat anxiety, such as alprazolam, triazolam, midazolam or any benzodiazepines such as diazepam
- Opioid pain medications such as alfentanil
- Everolimus, used in the treatment of some types of cancer, or to prevent rejection of a donated organ
- Vardenafil, a medicine used to treat male erectile dysfunction
- Ibrutinib, used in the treatment of certain types of cancer
- Statins, used to help to reduce cholesterol levels such as lovastatin or simvastatin
- Grapefruit (also as grapefruit juice)

How to take XENLETA:

- Take XENLETA exactly as your healthcare professional tells you to take it.
- Swallow the XENLETA tablet whole with water.
- Take it at least 1 hour before a meal or 2 hours after a meal.
- Do not crush or divide tablets.
- Although you may feel better early in treatment, XENLETA should be taken exactly as directed.
- Misuse or overuse of XENLETA could lead to the growth of bacteria that will not be killed by XENLETA (resistance). This means that XENLETA may not work for you in the future.
- Do not share your medicine.

Usual dose:

- One 600 mg tablet by mouth every 12 hours for 5 days.

Overdose:

If you think you have taken too much XENLETA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose of this medication, take it as soon as you remember. This will help keep a constant amount of medication in your blood. But, if it is less than 8 hours until your next dose,

skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using XENLETA?

These are not all the possible side effects you may feel when taking XENLETA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Headache
- Diarrhea
- Dizziness
- Feeling anxious
- Feeling sick (nausea) or being sick (vomiting)
- Indigestion or inflammation of the stomach lining (gastritis)
- Stomach pain, pain in the abdomen or around the stomach
- Reduction in blood platelets (blood cells which help the blood to clot), which increases risk of bleeding or bruising
- Fungal infection of the throat and mouth (thrush or candida infection)
- Fungal infection of the vagina and vulva (thrush or candida infection)
- Feeling tired or drowsy
- Retaining urine for longer than usual, leading to difficulty urinating or in fully emptying your bladder (urinary retention)
- Muscle problems/muscle enzyme elevation (blood tests may show changes to some of the parts of your blood)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Heart problems (irregular heartbeat due to lengthening of the QT interval): chest discomfort, fainting, feeling light-headed, fluttering or thumping in the chest, heart skips a beat, palpitations (awareness of heartbeats), sudden collapse, weakness.			X
Liver problems abdominal pain, dark urine, fatigue, loss of appetite, nausea, vomiting, yellowing of the skin or eyes (jaundice).		X	
Redness, pain or swelling at the site of injection	X		

Clostridium difficile colitis (bowel inflammation): abdominal pain or tenderness, fever, severe diarrhea (bloody or watery).			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

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- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at 15 to 30°C.
- Keep out of reach and sight of children.

If you want more information about XENLETA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.sunovion.ca, or by calling 1-800- 739-0565.

This leaflet was prepared by Sunovion Pharmaceutical Canada Inc., Mississauga, ON L5N 0E8

Last Revised: July 10, 2020