ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Xenleta 600 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains lefamulin acetate equivalent to 600 mg of lefamulin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Blue, oval, film-coated tablet with 'LEF 600' printed in black on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xenleta is indicated for the treatment of community-acquired pneumonia (CAP) in adults when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of CAP or when these have failed (see section 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The recommended dosage of Xenleta is described in Table 1.
Patients may be treated throughout with oral lefamulin according to their clinical condition. Patients who commence treatment by the intravenous route (see the Summary of Product Characteristics for Xenleta solution for infusion) may be switched to the oral tablets when clinically indicated.

Table 1: Dosage of Xenleta

Dosage	**Treatment duration**
Oral lefamulin only: 600 mg Xenleta tablet orally every 12 hours	5 days
Intravenous lefamulin with option to switch to oral lefamulin: 150 mg of Xenleta every 12 hours by intravenous infusion over 60 minutes with option to switch to 600 mg Xenleta tablet orally every 12 hours	7 days total treatment by the intravenous or combined intravenous and oral routes

Special populations

Elderly
No dosage adjustment is required for the elderly (see section 5.2).

Renal impairment
No dosage adjustment is required in renally impaired patients, including those receiving haemodialysis (see sections 4.4 and 5.2).

Hepatic impairment
No dosage adjustment is required in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of lefamulin in children and adolescents less than 18 years of age have not yet been established. No data are available.

Method of administration

Oral use.
The tablets should be swallowed whole with water. Xenleta should be taken on an empty stomach.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to any other members of the pleuromutilin class.

Coadministration with moderate or strong inducers of CYP3A (e.g. efavirenz, phenytoin, rifampicin) or with strong inhibitors of CYP3A (e.gclarithromycin, itraconazole, ritonavir) (see section 4.5).

Coadministration with CYP3A substrates (e.g. antipsychotics, erythromycin, tricyclic antidepressants) that prolong the QT interval (see section 4.5).

Coadministration with medicinal products that prolong the QT interval such as Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products (see section 4.5).

Known QT prolongation.

Electrolyte disturbances, particularly uncorrected hypokalemia.

Clinically relevant bradycardia, unstable congestive heart failure, or history of symptomatic ventricular arrhythmias.

Coadministration with sensitive CYP2C8 substrates (e.g. repaglinide) (see section 4.5).

4.4 Special warnings and precautions for use

Prolongation of QTc interval and potential QTc-interval prolongation-related clinical conditions

Changes in cardiac electrophysiology have been observed in non-clinical and clinical studies with lefamulin. In clinical trials in patients with community-acquired pneumonia, the mean change in QTcF from baseline to Day 3 to 4 was 11.4 msec. Post-baseline QTcF increases >30 msec and >60msec were seen in 17.9% and in 1.7% of patients, respectively, and were more frequent following intravenous lefamulin dosing compared to oral dosing.

Lefamulin should be used with caution in patients with renal failure who require dialysis because metabolic disturbances associated with renal failure may lead to QT prolongation.

Lefamulin should be used with caution in patients with mild, moderate, or severe cirrhosis because metabolic disturbances associated with hepatic insufficiency may lead to QT prolongation.

Clostridioides (formerly known as *Clostridium*) *difficile*- associated diarrhoea

C. difficile associated diarrhoea (CDAD) has been reported with lefamulin and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea during or subsequent to the administration of lefamulin (see section 4.8). Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicinal products.

If CDAD is suspected or confirmed, ongoing antibacterial medicinal product use not directed against *C. difficile* may need to be discontinued. Appropriate supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered.

Non-susceptible microorganisms

Prolonged use may result in the overgrowth of non-susceptible organisms which may require interruption of treatment or other appropriate measures.

Effects on hepatic transaminases

Monitoring of hepatic transaminases (ALT, AST) is recommended during treatment, especially in patients whose transaminases are elevated at baseline (see section 4.8).

Hepatic impairment

Patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment have reduced lefamulin protein binding compared to healthy subjects or subjects with mild (Child-Pugh Class A) hepatic impairment. Treatment should be initiated in patients with moderate or severe hepatic impairment only after a careful benefit/risk evaluation, due to possible adverse reactions related to higher free concentrations of lefamulin, including prolongation of the QTcF interval. Patients should be monitored closely during treatment.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Co-administration of lefamulin with other medicinal products known to prolong the QT interval is contraindicated (see section 4.3).

Pharmacokinetic interactions

Effects of other products on lefamulin

Use with moderate and strong CYP3A/P-gp inducers
Medicinal products that are moderate or strong CYP3A inducers (e.g. rifampicin, St John´s wort [*Hypericum perforatum*], carbamazepine, phenytoin, bosentan, efavirenz, primidone) could significantly decrease lefamulin plasma concentration and may lead to reduced therapeutic effect of lefamulin. Co-administration of such medicinal products with lefamulin is contraindicated (see section 4.3).

Use with strong CYP3A/P-gp inhibitors
Medicinal products that are strong CYP3A and P-gp inhibitors (e.g. clarithromycin, diltiazem, itraconazole, ketoconazole, nefazodone, posaconazole, ritonavir-containing regimens, voriconazole) may alter absorption of lefamulin and therefore increase lefamulin plasma concentrations. Co-administration of such medicinal products or grapefruit juice with lefamulin is contraindicated (see section 4.3).

Potential for lefamulin to affect other medicinal products

Lefamulin is a moderate CYP3A inhibitor but has no induction potential.

Co-administration of oral lefamulin with agents metabolised by CYP3A such as alprazolam, alfentanil, ibrutinib, lovastatin, simvastatin, , triazolam, vardenafil, and verapamil may result in increased plasma concentrations of these medicinal products. See Table 2.

Co-administration of lefamulin with agents metabolised by CYP2C8 (e.g. repaglinide) may result in increased plasma concentrations of these medicinal products. Co-administration with sensitive substrates of CYP2C8 is contraindicated (see section 4.3 and Table 2).

In a clinical drug-drug interaction study, no clinically relevant interaction was observed when lefamulin was co-administered with the P-gp substrate digoxin. Clinical drug interaction studies with lefamulin and substrates of other transporters have not been performed. In vitro studies indicated that lefamulin acts as an inhibitor of OATP1B1, OATP1B3, BCRP, OCT1 and MATE1 transporters. Therefore, caution is recommended when co-administering lefamulin with sensitive substrates of these transporters, especially for those substrates with a narrow therapeutic window.

Table 2 summarises effects on plasma concentrations of lefamulin and on co-administered medicinal products expressed as least-square mean ratios (90% confidence interval). The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC), where ↑ indicates an increase more than 25%, ↓ indicates a decrease more than 25%, and ↔ indicates no change (equal to or less than 25% decrease or increase). The table below is not all inclusive.

Table 2: Interactions and dose recommendations of oral Xenleta with other medicinal products

Medicinal product by therapeutic areas/possible mechanism of interaction	**Effect on medicinal product levels**	**C_{max}**	**AUC**	**Clinical comments**
ANTIARRHYTHMICS				
Digoxin 0.5 mg single dose (Inhibition of P-gp)	— Digoxin	1.05 (0.88-1.26)	1.11 (0.98-1.27)	No dose adjustment required.
ANTIDEPRESSANTS				
Fluvoxamine* 100 mg twice daily (Mild inhibition of CYP3A)	Not studied Expected ↔ Lefamulin			No dose adjustment required.
ANTIDIABETICS				
Metformin 1000 mg singe dose (Inhibition of MATE, OCT1, OCT2)	Not studied			Caution is recommended. Co-administration with lefamulin may lead to higher exposures of metformin. Patients should be monitored.

Medicinal product by therapeutic areas/possible mechanism of interaction	Effect on medicinal product levels	C_{max}	AUC	Clinical comments
Repaglinide* 0.25 mg single dose (Inhibition of CYP3A4, CYP2C8)	Not studied Expected↑ Repaglinide			Co-administration with lefamulin may lead to higher exposures of repaglinide and is contraindicated (see section 4.3).
ANTIFUNGALS				
Ketoconazole 200 mg twice daily (Strong inhibiton of CYP3A4)	↑ Lefamulin	1.58 (1.38-1.81)	2.65 (2.43-2.90)	Co-administration with strong CYP3A inhibitors like ketoconazole may lead to increased exposures of lefamulin and is contraindicated (see section 4.3).
Fluconazole* 400 mg day 1 + 200 mg once daily (Moderate inhibition of CYP3A)	Not studied Expected ↑ Lefamulin			Co-administration of medicinal products known to prolong QT interval is contraindicated (see section 4.3).
ANTIMYCOBACTERIALS				
Rifampicin 600 mg once daily (Strong induction of CYP3A)	↓ Lefamulin	0.43 (0.37-0.50)	0.28 (0.25-0.31)	Co-administration of strong CYP3A inducers may result in reduced therapeutic effect of lefamulin and is contraindicated (see section 4.3).
ETHINYL-OESTRADIOL-CONTAINING PRODUCTS				
Ethinyl oestradiol*(EE) 35 µg once daily (Inhibition of CYP3A4)	Not studied			Use with caution. (see Section 4.6).
HIV-ANTIVIRAL AGENTS				
Efavirenz * 600 mg once daily (Moderate induction of CYP3A4)	Not studied Expected ↓ Lefamulin			Co-administration of moderate CYP3A inducers may result in reduced therapeutic effect of lefamulin and is contraindicated (see section 4.3).
BENZODIAZEPINE BZ1 RECEPTOR ANTAGONIST				
Zolpidem* 10 mg single dose (Inhibition of CYP3A4)	Not studied Expected ↑ Zolpidem			Monitor for adverse reactions during co-administration with lefamulin. Consider dosage adjustment of zolpidem[#].

Medicinal product by therapeutic areas/possible mechanism of interaction	Effect on medicinal product levels	C_{max}	AUC	Clinical comments
GASTRIC ACID SUPPRESSORS/NEUTRALIZERS				
Omeprazole	Not studied Expected: ↔ Lefamulin			No dose adjustment required.
HERBAL PRODUCTS				
St. John's Wort (Strong induction of CYP3A4)	Not studied Expected: ↓ Lefamulin			Co-administration of strong CYP3A inducers may result in reduced therapeutic effect of lefamulin and is contraindicated (see section 4.3).
HMG-COA REDUCTASE INHIBITORS				
Rosuvastatin 20 mg single dose Atorvastatin, Lovastatin, Pravastatin (Inhibition of CYP3A, BCRP, OATP1)	Not studied			Use with caution.
SEDATIVE AGENTS				
Midazolam 2 mg oral single dose (Inhibition of CYP3A4)	— Midazolam	2.03 (1.84-2.23)	3.07 (2.75-3.43)	Caution is recommened. when co-administered with oral lefamulin. Consider dosage adjustment of midazolam[#].

*Based on *in vitro* interaction studies, a physiological based pharmacokinetic model was developed and used for prediction.
[#]Refer to the respective SmPC.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with Xenleta. Women taking oral contraceptives should use an additional barrier method of contraception.

Pregnancy

There are no data from the use of lefamulin in pregnant women.
Studies in animals have shown increased incidence of stillbirth (see section 5.3).
Animal studies are insufficient with respect to embryo-foetal development (see section 5.3).
Xenleta is not recommended during pregnancy.

Breast-feeding

It is unknown whether lefamulin/metabolites are excreted in human milk.
Available pharmacokinetic data in animals have shown excretion of lefamulin/metabolites in milk (see section 5.3).
A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with Xenleta.

Fertility

The effects of lefamulin on fertility in humans have not been studied.
Lefamulin caused no impairment of fertility or reproductive performance in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Xenleta has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are diarrhoea (7%), nausea (4%), vomiting (2%), hepatic enzyme elevation (2%), headache (1%), hypokalaemia (1%), and insomnia (1%).

Gastrointestinal disorders were predominantly associated with the oral formulation of lefamulin and led to treatment discontinuation in <1%.

The most frequently reported serious adverse reaction is atrial fibrillation (<1%).

Tabulated list of adverse reactions

Based on pooled data from Phase 3 trials for both intravenous and oral formulations, the following adverse reactions have been identified with lefamulin. Adverse reactions are classified according to System Organ Class and frequency. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 3: Frequency of adverse reactions by system organ class from clinical trials

System organ class	Common	Uncommon
Infections and infestations		*Clostridioides difficile* colitis Oropharyngeal candidiasis Vulvovaginal mycotic infection
Blood and lymphatic system disorders		Anaemia Thrombocytopenia
Metabolism and nutrition disorders	Hypokalaemia	
Psychiatric disorders	Insomnia	Anxiety
Nervous system disorders	Headache	Dizziness Somnolence
Cardiac disorders	Electrocardiogram QT prolonged	Atrial fibrillation Palpitations
Respiratory, thoracic and mediastinal disorders		Oropharyngeal pain
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Abdominal pain Abdominal pain upper Constipation Dyspepsia Epigastric discomfort Gastritis Gastritis erosive

Hepatobiliary disorders	Alanine aminotransferase increased* Aspartate aminotransferase increased*	Alkaline phosphatase increased Gamma-glutamyltransferase increased
Renal and urinary disorders		Urinary retention
Investigations		Creatinine phosphokinase increased

*In Phase 3 trials (pooled data for intravenous and oral formulations), post-baseline alanine aminotransferase values >3x and >5x ULN occurred in 5% and 2% of Xenleta patients compared with 5% and 1% of moxifloxacin patients. Post-baseline aspartate aminotransferase values >3x and >5x ULN occurred in 4% and 1% of Xenleta patients compared with 2% and 1% of moxifloxacin patients. Those affected were asymptomatic with reversible clinical laboratory findings that typically peaked within the first week of Xenleta dosing. No Xenleta patient met Hy's Law criteria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest single doses of lefamulin administered in clinical trials were 750 mg oral in healthy subjects which were not associated with any serious adverse reactions. The QT interval may increase with increasing exposure to lefamulin. Treatment of overdose with lefamulin should consist of observation and general support measures. Haemodialysis will not significantly remove lefamulin from the systemic circulation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, pleuromutilins, ATC code: J01XX12.

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.

Resistance

Resistance to lefamulin in normally susceptible species may be due to mechanisms that include specific protection or modification of the ribosomal target by ABC-F proteins such as *vga* (A, B, E), Cfr methyl transferase, or by mutations of ribosomal proteins L3 and L4 or in domain V of 23S rRNA.

Cfr generally confers cross-resistance with oxazolidinones, lincosamides, phenicols and group A streptogramins. ABC-F proteins can confer cross-resistance with lincosamides and group A streptogramins.

Organisms resistant to other pleuromutilin class antibacterial agents are generally cross-resistant to lefamulin.

The activity of lefamulin is not affected by mechanisms that confer resistance to beta-lactams, macrolides, quinolones, tetracyclines, folate-pathway inhibitors, mupirocin and glycopeptides.

Inherent resistance to lefamulin occurs in *Enterobacterales* (e.g. *Klebsiella pneumoniae*) and non-fermenting Gram-negative aerobes (e.g. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*).

Antibacterial activity in combination with other antibacterial agents

In vitro studies demonstrated no antagonism between lefamulin and amikacin, azithromycin, aztreonam, ceftriaxone, levofloxacin, linezolid, meropenem, penicillin, tigecycline, trimethoprim/sulfamethoxazole, and vancomycin.

Susceptibility testing interpretive criteria

The Minimum Inhibitory Concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommended interpretive criteria are:

Organism	**Minimum Inhibitory Concentrations (mg/L)**	
	Susceptible (≤S)	**Resistant (>R)**
Streptococcus pneumoniae	0.5	0.5
Staphylococcus aureus	0.25	0.25

PK/PD relationship

The antimicrobial activity of lefamulin against *S. pneumoniae* and *S. aureus* correlated best with the ratio of the area under the concentration-time curve of free drug over 24 hours to the minimum inhibitory concentration (24-h AUC/MIC ratio).

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against pathogens susceptible to lefamulin *in vitro* listed under each indication:

Community-acquired Pneumonia

- Gram-positive bacteria:
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*
- Gram-negative bacteria:
  - *Haemophilus influenzae*
  - *Legionella pneumophila*
- Other bacteria:
  - *Mycoplasma pneumoniae*
  - *Chlamydophila pneumoniae*

Clinical efficacy has not been established against the following pathogens that are relevant to the approved indications although *in vitro* studies suggest that they would be susceptible to lefamulin in the absence of acquired mechanisms of resistance:

- Gram-negative bacteria:
  - *Haemophilus parainfluenzae*
  - *Moraxella catarrhalis*

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xenleta in one or more subsets of the paediatric population in community-acquired pneumonia (see section 4.2 for information on paediatric use).

Information from clinical trials

In a post-hoc, subgroup analysis from two Phase 3 trials in patients with community-acquired pneumonia, the clinical cure rates at a post-treatment visit in patients with any of a positive sputum culture, positive blood culture or positive urinary antigen test for *S. pneumoniae* were lower for patients treated with lefamulin compared to patients treated with moxifloxacin. When treatment commenced by the intravenous route the cure rates were 28/36 [77.8%; (95% confidence intervals (CIs) 60.8% to 89.9%)] for lefamulin vs. 26/31 [83.9%; (95% CI 66.3% to 94.6%)] for moxifloxacin. When treatment commenced by the oral route, the cure rates were 19/25 (76%; 95% CI 55.9% to 90.6%) vs. 30/32 (93.8%; 95% CI 79.2% to 99.2%), respectively.

5.2 Pharmacokinetic properties

Absorption

After oral administration of an immediate-release 600 mg tablet formulation, oral bioavailability of lefamulin under fasted conditions was 25.8%. Exposure on Day 1 ($AUC_{0\text{-}12h}$) was equivalent to the exposure obtained with lefamulin 150 mg administered intravenously.

The concomitant administration of a high-fat, high calorie breakfast with a single oral dose of 600 mg lefamulin (immediate release tablet) resulted in a slightly reduced absolute bioavailability (21.0%).

Distribution

Lefamulin is moderate to highly bound to plasma proteins (alpha-1 acid glycoprotein > human serum albumin) within a range of 88-97% at a concentration of 1 µg/mL, 83-94% at 3 µg/mL, and 73-86% at 10 µg/mL (depending on assay), demonstrating saturable, non-linear binding between 1-10 µg/mL. The steady-state volume of distribution (V_{ss}) is approximately 2.5 L/kg. Rapid tissue distribution of lefamulin into skin and soft tissues was demonstrated using microdialysis, and into the epithelial lining fluid (ELF) using bronchoalveolar lavage.

Biotransformation

In plasma, between 24 and 42% of lefamulin is metabolised primarily by CYP3A phase I reactions, leading mainly to hydroxylated metabolites devoid of antibacterial properties, most notably the main metabolite BC-8041 (2*R*-hydroxy lefamulin). BC-8041 is the only metabolite in plasma accounting for >10% (13.6% to 17.3%) of total drug related material after oral dosing while no metabolites exceeded 10% (≤6.7%) after intravenous dosing.

Elimination

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

Special populations

No clinically significant differences in the pharmacokinetics of lefamulin were observed based on gender, race, or weight.

Elderly
In CAP patients there was a trend of increasing lefamulin exposure with increasing age, with a~50% increase in AUC_{0-24} at steady-state in patients aged ≥85 years compared to patients aged <65 years.

Renal impairment
A study was conducted to compare lefamulin pharmacokinetics following intravenous administration of 150 mg in 8 subjects with severe renal impairment and 7 matched healthy control subjects. Another 8 subjects requiring haemodialysis received 150 mg lefamulin intravenously immediately before dialysis (on-dialysis) and on a non-dialysis day (off-dialysis). The AUC, C_{max}, and CL of lefamulin and its main metabolite were comparable between subjects with severe renal impairment and matched healthy subjects, and in subjects requiring haemodialysis whether on- or off-dialysis. Lefamulin and its main metabolite were not dialyzable. Renal impairment did not impact lefamulin elimination.

Hepatic impairment
A study was conducted to compare lefamulin pharmacokinetics following intravenous administration of 150 mg in 8 subjects with moderate hepatic impairment (Child-Pugh Class B), 8 subjects with severe hepatic impairment (Child-Pugh Class C), and 11 matched healthy control subjects. No clinically meaningful changes in the total AUC, C_{max}, and CL of lefamulin and its main metabolite were observed between subjects with moderate or severe hepatic impairment and matched healthy control subjects. Hepatic impairment did not meaningfully impact lefamulin elimination. Plasma protein binding decreased with increased impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, and genotoxicity.

In rats, there were no effects on male or female fertility that were considered related to lefamulin. Lefamulin/metabolites are excreted into the milk of lactating rats. Maximal concentrations of radioactivity in plasma and milk were 3.29 and 10.7 µg equivalents/g, respectively, following a single dose of 30 mg/kg radio-labelled lefamulin. Lefamulin/metabolites crossed the placenta in pregnant rats. In the plasma of suckling rat pups, lefamulin exposure was demonstrated in only 1 of 3 litters of treated dams in each of the mid and high dose groups on post-natal day 4. No test item was quantified in pup's plasma on post-natal day 20.

Adverse reactions seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

In the rat embryo-foetal development study of lefamulin during organogenesis (GD 6-17) there were 1, 0, 2, and 1 malformed foetuses in control, low, mid, and high dose groups, respectively. Findings included malformations (cleft palate, short lower jaw, vertebral and rib malformations, and a cyst in the neck region) at the mid and high doses, but the relationship to treatment is considered equivocal. Decreased or no ossification in a number of skeletal elements in all treated groups may indicate treatment-related developmental delay at all doses evaluated.

In the rabbit embryo-foetal development study of lefamulin during organogenesis (GD 6-18), low numbers of live foetuses in utero in treated groups limited the interpretation of the study. Additional findings in the high dose group included decreased foetal weight and decreased or no ossification of skeletal elements, which may be indicative of developmental delay.

In a prenatal and postnatal development study in rats the pup live birth index was reduced (87.4%) in the high dose group. In the absence of related findings at the same dose level in the rat embryo-foetal development study, stillbirth was considered to be a late stage pregnancy or delivery effect.

Evidence of dose-dependent regenerative anaemia in both species indicated lefamulin was potentially haemolytic at concentrations that are 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol (E421)
Povidone (K30)
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Talc
Colloidal silicon dioxide
Magnesium stearate

Tablet coating

Poly(vinyl alcohol) (partially hydrolysed) (E1203)
Titanium dioxide
Macrogol/PEG
Talc
Indigo carmine aluminum lake (E132)

Tablet printing

Shellac
Black iron oxide (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

One pack contains: PVC/PE/PCTFE / Aluminium blisters with 10 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Nabriva Therapeutics Ireland DAC
Alexandra House, Office 225/227
The Sweepstakes Ballsbridge
Dublin 4
D04 C7H2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1457/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 July 2020.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Xenleta 150 mg concentrate and solvent for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of concentrate contains lefamulin acetate equivalent to 150 mg of lefamulin in 15 mL of normal saline (0.9% sodium chloride), to be diluted to a final concentration of 0.6 mg/mL.

Excipients with known effect

This medicinal product contains 1,055 mg sodium per dose, equivalent to 52.75% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate and solvent for solution for infusion.
The concentrate is a colourless solution.
The solvent is a colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xenleta is indicated for the treatment of community-acquired pneumonia (CAP) in adults when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of CAP or when these have failed (see section 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The recommended dosage of Xenleta is described in Table 1.
Patients may be treated throughout with intravenous lefamulin according to their clinical condition. Patients who commence treatment by the intravenous route may be switched to the oral tablets (see the Summary of Product Characteristics for Xenleta 600 mg tablets) when clinically indicated.

Table 1: Dosage of Xenleta

Dosage	Treatment duration
Intravenous lefamulin only: 150 mg of Xenleta every 12 hours by intravenous infusion over 60 minutes	7 days
Intravenous lefamulin with option to switch to oral lefamulin:	7 days total treatment by the intravenous or combined intravenous and oral routes

Dosage	Treatment duration
150 mg of Xenleta every 12 hours by intravenous infusion over 60 minutes with option to switch to 600 mg Xenleta tablet orally every 12 hours	

Special populations

Elderly
No dosage adjustment is required for the elderly (see section 5.2).

Renal impairment
No dosage adjustment is required in renally impaired patients, including those receiving haemodialysis (see sections 4.4 and 5.2).

Hepatic impairment
No dosage adjustment is required in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of lefamulin in children and adolescents less than 18 years of age have not yet been established. No data are available.

Method of administration

Intravenous use.
Xenleta is administered by intravenous infusion over 60 minutes in an infusion volume of 250 mL. The recommended infusion rate should not be exceeded.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to any other members of the pleuromutilin class.

Coadministration with moderate or strong inducers of CYP3A (e.g. efavirenz, phenytoin, rifampicin) (see section 4.5).

Coadministration with CYP3A substrates (e.g. antipsychotics, erythromycin, tricyclic antidepressants) that prolong the QT interval (see section 4.5).

Coadministration with medicinal products that prolong the QT interval such as Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products (see section 4.5).

Known QT prolongation.

Electrolyte disturbances, particularly uncorrected hypokalemia.

Clinically relevant bradycardia, unstable congestive heart failure, or history of symptomatic ventricular arrhythmias.

Coadministration with sensitive CYP2C8 substrates (e.g. repaglinide) (see section 4.5).

4.4 Special warnings and precautions for use

Prolongation of QTc interval and potential QTc-interval prolongation-related clinical conditions

Changes in cardiac electrophysiology have been observed in nonclinical and clinical studies with lefamulin. In clinical trials in patients with community-acquired pneumonia, the mean change in QTcF from baseline to Day 3 to 4 was 11.4 msec. Post-baseline QTcF increases >30 msec and >60msec were seen in 17.9% and in 1.7% of patients, respectively, and were more frequent following intravenous lefamulin dosing compared to oral dosing.

The magnitude of QT prolongation may increase with increasing concentrations of lefamulin or increasing the rate of infusion of the intravenous formulation. Therefore, the recommended dose and infusion rate should not be exceeded.

Lefamulin should be used with caution in patients with renal failure who require dialysis because metabolic disturbances associated with renal failure may lead to QT prolongation.

Lefamulin should be used with caution in patients with mild, moderate, or severe cirrhosis because metabolic disturbances associated with hepatic insufficiency may lead to QT prolongation.

Clostridioides (formerly known as *Clostridium*) *difficile*- associated diarrhoea

C. difficile associated diarrhoea (CDAD) has been reported with lefamulin and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea during or subsequent to the administration of lefamulin (see section 4.8). Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicinal products.

If CDAD is suspected or confirmed, ongoing antibacterial medicinal product use not directed against *C. difficile* may need to be discontinued. Appropriate supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered.

Non-susceptible microorganisms

Prolonged use may result in the overgrowth of non-susceptible organisms which may require interruption of treatment or other appropriate measures.

Effects on hepatic transaminases

Monitoring of hepatic transaminases (ALT, AST) is recommended during treatment, especially in patients whose transaminases are elevated at baseline (see section 4.8).

Hepatic impairment

Patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment have reduced lefamulin protein binding compared to healthy subjects or subjects with mild (Child-Pugh Class A) hepatic impairment. Treatment should be initiated in patients with moderate or severe hepatic impairment only after a careful benefit/risk evaluation, due to possible adverse reactions related to higher free concentrations of lefamulin, including prolongation of the QTcF interval. Patients should be monitored closely during treatment.

Excipients

This medicinal product contains 1,055 mg sodium per dose, equivalent to 52.75% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Co-administration with other medicinal products known to prolong the QT interval is contraindicated (see section 4.3).

Pharmacokinetic interactions

Effects of other products on lefamulin

Use with moderate and strong CYP3A/P-gp inducers
Medicinal products that are moderate or strong CYP3A inducers (e.g. rifampicin, St John´s wort [*Hypericum perforatum*], carbamazepine, phenytoin, bosentan, efavirenz, primidone) could significantly decrease lefamulin plasma concentration and may lead to reduced therapeutic effect of lefamulin. Co-administration of such medicinal products with lefamulin is contraindicated (see section 4.3).

Potential for lefamulin to affect other medicinal products

Co-administration of lefamulin with sensitive CYP2C8 substrates such as repaglinide may result in increased plasma concentrations of these medicinal products. Co-administration with sensitive substrates of CYP2C8 is contraindicated (See section 4.3 and Table 2).

In a clinical drug-drug interaction study, no clinically relevant interaction was observed when lefamulin was co-administered with the P-gp substrate digoxin. Clinical drug interaction studies with lefamulin and substrates of other transporters have not been performed. In vitro studies indicated that lefamulin acts as an inhibitor of OATP1B1, OATP1B3, BCRP, OCT2 and MATE1 transporters. Therefore, caution is recommended when co-administering lefamulin with sensitive substrates of these transporters, especially for those substrates with a narrow therapeutic window.

Table 2 summarises effects on plasma concentrations of lefamulin and on co-administered medicinal products expressed as least-square mean ratios (90% confidence interval). The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC), where ↑ indicates an increase more than 25%, ↓ indicates a decrease more than 25%, and ↔ indicates no change (equal to or less than 25% decrease or increase).The table below is not all inclusive.

Table 2: Interactions and dose recommendations of intravenous Xenleta with other medicinal products

Medicinal product by therapeutic areas/possible mechanism of interaction	**Effect on medicinal product levels**	**C_{max}**	**AUC**	**Clinical comments**
ANTIDEPRESSANTS				
Fluvoxamine* 100 mg twice daily (Mild inhibition of CYP3A)	Not studied Expected ↔ Lefamulin			No dose adjustment of intravenous lefamulin required.
ANTIDIABETICS				
Metformin 1000 mg singe dose (Inhibition of	Not studied			Caution is recommended. Co-administration with lefamulin may lead to higher exposures of

Medicinal product by therapeutic areas/possible mechanism of interaction	Effect on medicinal product levels	C_{max}	AUC	Clinical comments
MATE, OCT1, OCT2)				metformin. Patients should be monitored.
Repaglinide* 0.25 mg single dose (Inhibition of CYP3A4, CYP2C8)	Not studied Expected ↑Repaglinide			Co-administration with lefamulin may lead to higher exposures of repaglinide and is contraindicated (see section 4.3).
ANTIFUNGALS				
Ketoconazole 200 mg twice daily (Strong inhibiton of CYP3A4)	↑ Lefamulin	1.06 (0.96-1.16)	1.26 (1.14-1.41)	No dose adjustment for intravenous lefamulin.
Fluconazole* 400 mg day 1 + 200 mg once daily (Moderate inhibition of CYP3A)	Not studied Expected ↔ Lefamulin			Co-administration of medicinal products known to prolong QT interval is contraindicated (see section 4.3).
ANTIMYCOBACTERIALS				
Rifampicin 600 mg once daily (Strong induction of CYP3A)	↓ Lefamulin	0.92 (0.87-0.97)	0.73 (0.70-0.76)	Co-administration of strong CYP3A inducers may result in reduced therapeutic effect of lefamulin and is contraindicated (see section 4.3).
ETHINYL-OESTRADIOL-CONTAINING PRODUCTS				
Ethinyl oestradiol*(EE) 35 µg once daily (Inhibition of CYP3A4)	Not studied Expected ↔ EE			Use with caution. (see Section 4.6).
HIV-ANTIVIRAL AGENTS				
Efavirenz * 600 mg once daily (Moderate induction of CYP3A4)	Not studied Expected ↓ Lefamulin			Co-administration of moderate CYP3A inducers may result in reduced therapeutic effect of lefamulin and is contraindicated (see section 4.3).
BENZODIAZEPINE BZ1 RECEPTOR ANTAGONIST				
Zolpidem* 10 mg single dose (Inhibition of CYP3A4)	Not studied Expected — Zolpidem			No dose adjustment required.
HERBAL PRODUCTS				

Medicinal product by therapeutic areas/possible mechanism of interaction	Effect on medicinal product levels	C_{max}	AUC	Clinical comments
St. John's Wort (Strong induction of CYP3A4)	Not studied Expected: ↓ Lefamulin			Co-administration of strong CYP3A inducers may result in reduced therapeutic effect of lefamulin and is contraindicated (see section 4.3).
HMG-COA REDUCTASE INHIBITORS				
Rosuvastatin 20 mg single dose Atorvastatin, Lovastatin, Provastatin (Inhibition of BCRP, OATP1)	Not studied			Use with caution.
SEDATIVE AGENTS				
Midazolam 2 mg oral single dose (Inhibiton of CYP3A4)	— Midazolam	1.03 (0.82-1.3)	1.17 (0.82-1.67)	No dose adjustment required when co-administered with intravenous lefamulin.

*Based on *in vitro* interaction studies, a physiological based pharmacokinetic model was developed and used for prediction.
#Refer to the respective SmPC.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with Xenleta. Women taking oral contraceptives should use an additional barrier method of contraception.

Pregnancy

There are no data from the use of lefamulin in pregnant women.
Studies in animals have shown increased incidence of stillbirth (see section 5.3).
Animal studies are insufficient with respect to embryo-foetal development (see section 5.3).
Xenleta is not recommended during pregnancy.

Breast-feeding

It is unknown whether lefamulin/metabolites are excreted in human milk.
Available pharmacokinetic data in animals have shown excretion of lefamulin/metabolites in milk (see section 5.3).
A risk to the newborns/infants cannot be excluded.
Breast-feeding should be discontinued during treatment with Xenleta.

Fertility

The effects of lefamulin on fertility in humans have not been studied.

Lefamulin caused no impairment of fertility or reproductive performance in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Xenleta has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are administration site reactions (7%), diarrhoea (7%), nausea (4%), vomiting (2%), hepatic enzyme elevation (2%), headache (1%), hypokalaemia (1%), and insomnia (1%).

Administration site reactions apply to intravenous administration and led to treatment discontinuation in <1%. Gastrointestinal disorders were predominantly associated with the oral formulation of lefamulin and led to treatment discontinuation in <1%.

The most frequently reported serious adverse reaction is atrial fibrillation (<1%).

Tabulated list of adverse reactions

Based on pooled data from Phase 3 trials for both intravenous and oral formulations, the following adverse reactions have been identified with lefamulin. Adverse reactions are classified according to System Organ Class and frequency. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 3: Frequency of adverse reactions by system organ class from clinical trials

System organ class	Common	Uncommon
Infections and infestations		*Clostridioides difficile* colitis Oropharyngeal candidiasis Vulvovaginal mycotic infection
Blood and lymphatic system disorders		Anaemia Thrombocytopenia
Metabolism and nutrition disorders	Hypokalaemia	
Psychiatric disorders	Insomnia	Anxiety
Nervous system disorders	Headache	Dizziness Somnolence
Cardiac disorders	Electrocardiogram QT prolonged	Atrial fibrillation Palpitations
Respiratory, thoracic and mediastinal disorders		Oropharyngeal pain
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Abdominal pain Abdominal pain upper Constipation Dyspepsia Epigastric discomfort Gastritis Gastritis erosive
Hepatobiliary disorders	Alanine aminotransferase increased* Aspartate aminotransferase increased*	Alkaline phosphatase increased Gamma-glutamyltransferase increased

Renal and urinary disorders		Urinary retention
General disorders and administration site conditions	Infusion site pain Infusion site phlebitis Infusion site erythema	Infusion site bruising Infusion site coldness
Investigations		Creatinine phosphokinase increased

*In Phase 3 trials (pooled data for intravenous and oral formulations), post-baseline alanine aminotransferase values >3x and >5x ULN occurred in 5% and 2% of Xenleta patients compared with 5% and 1% of moxifloxacin patients. Post-baseline aspartate aminotransferase values >3x and >5x ULN occurred in 4% and 1% of Xenleta patients compared with 2% and 1% of moxifloxacin patients. Those affected were asymptomatic with reversible clinical laboratory findings that typically peaked within the first week of Xenleta dosing. No Xenleta patient met Hy's Law criteria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest single doses of lefamulin administered in clinical trials were 400 mg intravenous in healthy subjects which were not associated with any serious adverse reactions. The QT interval may increase with increasing exposure to lefamulin. Treatment of overdose with lefamulin should consist of observation and general support measures. Haemodialysis will not significantly remove lefamulin from the systemic circulation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, pleuromutilins, ATC code: J01XX12.

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.

Resistance

Resistance to lefamulin in normally susceptible species may be due to mechanisms that include specific protection or modification of the ribosomal target by ABC-F proteins such as *vga* (A, B, E), Cfr methyl transferase, or by mutations of ribosomal proteins L3 and L4 or in domain V of 23S rRNA.

Cfr generally confers cross-resistance with oxazolidinones, lincosamides, phenicols and group A streptogramins. ABC-F proteins can confer cross-resistance with lincosamides and group A streptogramins.

Organisms resistant to other pleuromutilin class antibacterial agents are generally cross-resistant to lefamulin.

The activity of lefamulin is not affected by mechanisms that confer resistance to beta-lactams, macrolides, quinolones, tetracyclines, folate-pathway inhibitors, mupirocin and glycopeptides.

Inherent resistance to lefamulin occurs in *Enterobacterales* (e.g. *Klebsiella pneumoniae*) and non-fermenting Gram-negative aerobes (e.g. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*).

Antibacterial activity in combination with other antibacterial agents

In vitro studies demonstrated no antagonism between lefamulin and amikacin, azithromycin, aztreonam, ceftriaxone, levofloxacin, linezolid, meropenem, penicillin, tigecycline, trimethoprim/sulfamethoxazole, and vancomycin).

Susceptibility testing interpretive criteria

The Minimum Inhibitory Concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommended interpretive criteria are:

Organism	**Minimum Inhibitory Concentrations (mg/L)**	
	Susceptible (≤S)	**Resistant (>R)**
Streptococcus pneumoniae	0.5	0.5
Staphylococcus aureus	0.25	0.25

PK/PD relationship

The antimicrobial activity of lefamulin against *S. pneumoniae* and *S. aureus* correlated best with the ratio of the area under the concentration-time curve of free drug over 24 hours to the minimum inhibitory concentration (24-h AUC/MIC ratio).

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against pathogens susceptible to lefamulin *in vitro* listed under each indication:

Community-acquired Pneumonia

- Gram-positive bacteria:
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*
- Gram-negative bacteria:
  - *Haemophilus influenzae*
  - *Legionella pneumophila*
- Other bacteria:
  - *Mycoplasma pneumoniae*
  - *Chlamydophila pneumoniae*

Clinical efficacy has not been established against the following pathogens that are relevant to the approved indications although *in vitro* studies suggest that they would be susceptible to lefamulin in the absence of acquired mechanisms of resistance:

- Gram-negative bacteria:
  - *Haemophilus parainfluenzae*
  - *Moraxella catarrhalis*

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xenleta in one or more subsets of the paediatric population in community-acquired pneumonia (see section 4.2 for information on paediatric use).

Information from clinical trials

In a post-hoc, subgroup analysis from two Phase 3 trials in patients with community-acquired pneumonia, the clinical cure rates at a post-treatment visit in patients with any of a positive sputum culture, positive blood culture or positive urinary antigen test for *S. pneumoniae* were lower for patients treated with lefamulin compared to patients treated with moxifloxacin. When treatment commenced by the intravenous route the cure rates were 28/36 [77.8%; (95% confidence intervals (CIs) 60.8% to 89.9%)] for lefamulin vs. 26/31 [83.9%; (95% CI 66.3% to 94.6%)] for moxifloxacin. When treatment commenced by the oral route, the cure rates were 19/25 (76%; 95% CI 55.9% to 90.6%) vs. 30/32 (93.8%; 95% CI 79.2% to 99.2%), respectively.

5.2 Pharmacokinetic properties

Absorption

Not applicable.

Distribution

Lefamulin is moderate to highly bound to plasma proteins (alpha-1 acid glycoprotein > human serum albumin) within a range of 88-97% at a concentration of 1 µg/mL, 83-94% at 3 µg/mL, and 73-86% at 10 µg/mL (depending on assay), demonstrating saturable, non-linear binding. The steady-state volume of distribution (V_{ss}) is approximately 2.5 L/kg. Rapid tissue distribution of lefamulin into skin and soft tissues was demonstrated using microdialysis, and into the epithelial lining fluid (ELF) using bronchoalveolar lavage.

Biotransformation

In plasma, between 24 and 42% of lefamulin is metabolised primarily by CYP3A phase I reactions, leading mainly to hydroxylated metabolites devoid of antibacterial properties, most notably the main metabolite BC-8041 (2*R*-hydroxy lefamulin). BC-8041 is the only metabolite in plasma accounting for >10% (13.6% to 17.3%) of total drug related material after oral dosing while no metabolites exceeded 10% (≤6.7%) after intravenous dosing.

Elimination

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

Special populations

No clinically significant differences in the pharmacokinetics of lefamulin were observed based on gender, race or weight.

Elderly
In CAP patients there was a trend of increasing lefamulin exposure with increasing age, with a~50% increase in AUC_{0-24} at steady-state in patients aged ≥85 years compared to patients aged <65 years.

Renal impairment
A study was conducted to compare lefamulin pharmacokinetics following intravenous administration of 150 mg in 8 subjects with severe renal impairment and 7 matched healthy control subjects. Another 8 subjects requiring haemodialysis received 150 mg lefamulin intravenously immediately before dialysis (on-dialysis) and on a non-dialysis day (off-dialysis). The AUC, C_{max}, and CL of lefamulin and its main metabolite were comparable between subjects with severe renal impairment and matched

healthy subjects, and in subjects requiring haemodialysis whether on- or off-dialysis. Lefamulin and its main metabolite were not dialyzable. Renal impairment did not impact lefamulin elimination.

Hepatic impairment
A study was conducted to compare lefamulin pharmacokinetics following intravenous administration of 150 mg in 8 subjects with moderate hepatic impairment (Child-Pugh Class B), 8 subjects with severe hepatic impairment (Child-Pugh Class C), and 11 matched healthy control subjects. No clinically meaningful changes in the total AUC, C_{max}, and CL of lefamulin and its main metabolite were observed between subjects with moderate or severe hepatic impairment and matched healthy control subjects. Hepatic impairment did not meaningfully impact lefamulin elimination. Plasma protein binding decreased with increased impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, and genotoxicity.

In rats, there were no effects on male or female fertility that were considered related to lefamulin. Lefamulin/metabolites are excreted into the milk of lactating rats. Maximal concentrations of radioactivity in plasma and milk were 3.29 and 10.7 µg equivalents/g, respectively, following a single dose of 30 mg/kg radio-labelled lefamulin. Lefamulin/metabolites crossed the placenta in pregnant rats. In the plasma of suckling rat pups, lefamulin exposure was demonstrated in only 1 of 3 litters of treated dams in each of the mid and high dose groups on post-natal day 4. No test item was quantified in pup's plasma on post-natal day 20.

Adverse reactions seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

In the rat embryo-foetal development study of lefamulin during organogenesis (GD 6-17), there were 1, 0, 2, and 1 malformed foetuses in control, low, mid, and high dose groups. Findings included malformations (cleft palate, short lower jaw, vertebral and rib malformations, and a cyst in the neck region) at the mid and high doses, but the relationship to treatment is considered equivocal. Decreased or no ossification in a number of skeletal elements in all treated groups may indicate treatment-related developmental delay at all doses evaluated.

In the rabbit embryo-foetal development study of lefamulin during organogenesis (GD 6-18), low numbers of live foetuses in utero in treated groups limited the interpretation of the study. Additional findings in the high dose group included decreased foetal weight and decreased or no ossification of skeletal elements, which may be indicative of developmental delay.

In a prenatal and postnatal development study in rats the pup live birth index was reduced (87.4%) in the high dose group. In the absence of related findings at the same dose level in the rat embryo-foetal development study, stillbirth was considered to be a late stage pregnancy or delivery effect.

Evidence of dose-dependent regenerative anaemia in both species indicated lefamulin was potentially haemolytic at concentrations that are 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate

Sodium chloride
Water for injections

Solvent

Citric acid
Sodium citrate
Sodium chloride
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years.

After dilution

The chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at room temperature and 48 hours at 2°C to 8°C. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Concentrate

Store in a refrigerator (2°C to 8°C). Do not freeze.

Solvent

Store below 25°C. Do not freeze.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

One pack contains:
Type I glass, closed with a stopper (chlorobutyl rubber) and sealed with a flip off cap, 2 vials with 15 mL concentrate.
Polypropylene (PP) infusion bags, 2 bags with 250 mL solvent.

6.6 Special precautions for disposal and other handling

General precautions

Each vial and infusion bag are for single use only.
Standard aseptic techniques should be used for solution preparation and administration.

Instructions for dilution and infusion

Xenleta concentrate must be mixed into the bag of solvent containing 250 mL solution of 10mM citrate buffered saline and administered by infusion.

1. Aseptically withdraw 15 mL of Xenleta from the concentrate vial.

2. Transfer concentrate to the bag of solvent containing 250 mL solution of 10mM citrate buffered 0.9% sodium chloride injection.
3. Discard any unused portion from the concentrate vial. The vial of concentrate and the bag of solvent solution is single-use only.
4. The diluted solution should be clear and colourless. Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
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. Avoid rapid or bolus intravenous infusion.
6. Administer by intravenous infusion only.

The compatibility of reconstituted Xenleta with intravenous medicinal products, additives, or substances other than 10mM 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 medicinal products in addition to Xenleta, the line should be flushed before and after each Xenleta administration with 0.9% sodium chloride intravenous infusion.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Nabriva Therapeutics Ireland DAC
Alexandra House, Office 225/227
The Sweepstakes
Ballsbridge
Dublin 4
D04 C7H2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1457/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 July 2020.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Nabriva Therapeutics Ireland DAC
Alexandra House, Office 225/227
The Sweepstakes,
Ballsbridge
Dublin 4
D04 C7H2
Republic of Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xenleta 600 mg film-coated tablets
lefamulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains lefamulin acetate equivalent to 600 mg of lefamulin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nabriva Therapeutics Ireland DAC
Alexandra House, Office 225/227
The Sweepstakes, Ballsbridge
Dublin 4, D04 C7H2
Republic of Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1457/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xenleta

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Xenleta 600 mg film-coated tablets
lefamulin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Nabriva Therapeutics

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

KIT OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xenleta 150 mg concentrate and solvent for solution for infusion
lefamulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of concentrate contains lefamulin acetate equivalent to 150 mg of lefamulin

3. LIST OF EXCIPIENTS

Concentrate:
Sodium chloride
Water for injections

Solvent bag:
Sodium chloride
Sodium citrate
Citric acid
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate and solvent for solution for infusion
2 vials of lefamulin concentrate
2 solvent bags

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nabriva Therapeutics Ireland DAC
Alexandra House, Office 225/227
The Sweepstakes, Ballsbridge
Dublin 4, D04 C7H2
Republic of Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1457/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xenleta 150 mg concentrate for solution for infusion
lefamulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains lefamulin acetate equivalent to 150 mg of lefamulin.

3. LIST OF EXCIPIENTS

Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

2 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nabriva Therapeutics Ireland DAC
Alexandra House, Ballsbridge
D04 C7H2, Dublin, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

IV Solvent for Dilution Carton

1. NAME OF THE MEDICINAL PRODUCT

Solvent for Xenleta
Solvent for solution for infusion

2. STATEMENT OF ACTIVE SUBSTANCE

3. LIST OF EXCIPIENTS

Sodium chloride, sodium citrate, and citric acid in water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solvent for solution for infusion
2 bags 250 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nabriva Therapeutics Ireland DAC
Alexandra House, Office 225/227

The Sweepstakes, Ballsbridge
Dublin 4, D04 C7H2
Republic of Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1457/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CONCENTRATE VIAL (15 ml)

1. NAME OF THE MEDICINAL PRODUCT

Xenleta 150 mg concentrate for solution for infusion
lefamulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains lefamulin acetate equivalent to 150 mg of lefamulin

3. LIST OF EXCIPIENTS

Contains sodium chloride and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate
15 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after dilution
Single use.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nabriva Therapeutics Ireland DAC

Alexandra House, Ballsbridge
D04 C7H2, Dublin, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1457/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Label for Infusion Bag with Solvent

1. NAME OF THE MEDICINAL PRODUCT

Solvent for Xenleta
IV

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

Each bag contains: sodium chloride, sodium citrate, and citric acid in water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solvent for solution for infusion
250 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nabriva Therapeutics Ireland DAC
Alexandra House, Ballsbridge

D04 C7H2, Dublin, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1457/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Xenleta 600 mg film-coated tablets
lefamulin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xenleta is and what it is used for
2. What you need to know before you take Xenleta
3. How to take Xenleta
4. Possible side effects
5. How to store Xenleta
6. Contents of the pack and other information

1. What Xenleta is and what it is used for

Xenleta is an antibiotic medicine containing the active substance lefamulin. It belongs to a group of medicines called 'pleuromutilins'.

Lefamulin works by killing certain bacteria which cause infections.

Xenleta is used to treat adults who have bacterial infections in the lung, also known as pneumonia, when other treatments for pneumonia are not considered to be suitable.

2. What you need to know before you take Xenleta

Do not take Xenleta
- if you are **allergic to lefamulin** or any of the other ingredients of this medicine (listed in section 6)
- if you are **allergic to other medicines** from the pleuromutilin class
- if you are **taking certain medicines** that might interact with Xenleta. This is because some medicines may stop Xenleta working or lead to side effects if they are given with Xenleta. See below under **Other medicines and Xenleta** for examples.
- if you are **taking medicines** that can cause changes in the heart's electrical activity seen with an ECG (see below under **Other medicines and Xenleta).** This is because lefamulin can cause a condition called QT interval prolongation i.e. abnormal electrical activity that affects the heart's rhythm.
- if you have a **salt imbalance** in the blood (especially low levels of potassium in the blood)
- if you have or have had an **irregular heart rhythm or an abnormal ECG finding called QT prolongation**
- if you have a **very slow heart beat** (bradycardia)
- if your **heart does not work well enough** (heart failure)

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before you are given Xenleta
- if you have **kidney failure** and require dialysis.
- if you have cirrhosis (**severe liver disease**.)

If any of these apply to you, or if you are not sure, tell your doctor before taking Xenleta.

If you develop severe diarrhoea during or after taking Xenleta tablets, talk to your doctor because you may need to stop your medicine, or you may need to take another medicine to treat the diarrhoea. Antibiotics can lead to excessive growth of certain bacteria in your bowel (gut) that can damage the bowel and cause severe diarrhoea.

If you develop yellow skin (jaundice) or the white of your eyes turn yellow (scleral icterus), talk to your doctor because you may need to stop taking Xenleta or other medicines.

Other infections
There is a small possibility that you may get a different infection caused by another bacteria during or after treatment with Xenleta. Your doctor will monitor you closely for any new infections and give you another treatment if necessary.

Children and adolescents
Xenleta is **not recommended** for use in children and adolescents less than 18 years old.

Other medicines and Xenleta
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, as some of them could affect or be affected by Xenleta. The lists below provide only some examples of medicines that should be avoided while taking lefamulin or for which caution is needed. Your doctor will a dvise you if lefamulin is suitable for you.

You must not take any of the following medicines with lefamulin:
- carbamazepine, phenytoin, primidone (for epilepsy)
- efavirenz, ritonavir- (for HIV)
- St. John's Wort, an herbal remedy (for depression or low mood)
- bosentan diltiazem, amiodarone, sotalol, quinidine, procainamide (for angina, high blood pressure or heart rhythm disturbances)
- rifampicin, clarithromycin, erythromycin (for bacterial infections)
- fluconazole, itraconazole, posaconazole, voriconazole (for fungal infections)
- ketoconazole (for Cushing's disease)
- repaglinide (for diabetes)
- nefazodone, amitryptylline or pimozide (for depression or other mental illness)

Your doctor may need to adjust the dose of some medicines while you are taking lefamulin. These medicines include:
* alprazolam, midazolam, triazolam or other drugs called benzodiazepines (for anxiety)
* alfentanil (an opioid for pain)
* vardenafil (for erectile dysfunction)
* ibrutinib (for certain types of cancer)
* lovastatin, rosuvastatin or simvastatin (to reduce cholesterol levels)
* metformin (for diabetes)
* zolpidem (for insomnia)
* ethinyl oestradiol (used in birth control pills)
* verapamil (for high blood pressure)

Xenleta with food and drink
Xenleta should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal. This is because food and some drinks can affect the way medicines work.

You must not eat grapefruit or drink grapefruit juice while on treatment with Xenleta as it might interact with Xenleta and increase side effects.

Pregnancy, breast-feeding
Do not take Xenleta if you are pregnant or breast-feeding. If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Taking Xenleta will not influence the ability to drive or use machines.

Xenleta contains sodium
This medicine contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially, 'sodium free'.

3. How to take Xenleta

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 600-mg Xenleta tablet taken every 12 hours for 5 days. The tablets should be swallowed whole with water.

Xenleta tablets may also be taken after starting treatment with Xenleta infusion via an intravenous drip. The number of days you then need to take Xenleta tablets will depend on how many days you had treatment by a drip.

Your doctor will tell you for how long you should take Xenleta. It is important that you complete the course.

If you take more Xenleta than you should
If you accidentally take too many tablets, contact your doctor or pharmacist.

If you forget to take Xenleta
Do not take a double dose to make up for a forgotten tablet. You should continue with your course from the next scheduled dose.

If you stop taking Xenleta
Take the complete course of tablets prescribed by your doctor, even if you begin to feel better before you have finished them all. If you stop taking the tablets too soon, the infection may return, or your condition may get worse.

Some bacteria may remain and become resistant to antibiotics if you do not complete the course or if you do not take your tablets at the right time. This can result in the infection returning or in the antibiotic not working if the infection returns.

If you get a side effect that concerns you, tell a doctor immediately to get advice before taking the next dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people

* low potassium levels in your blood (hypokalaemia), which can cause muscle weakness, twitching or abnormal heart rhythm
* difficulty sleeping (insomnia)
* headache
* change of the heart rhythm (seen on an ECG, which monitors the electrical activity of the heart)
* diarrhoea
* feeling sick (nausea) or being sick (vomiting)
* increase of a special liver enzyme in the blood (transaminases)

Uncommon: may affect up to 1 in 100 people

* inflammation of the bowel causing diarrhoea (colitis), due to an infection by a type of bacteria called *Clostridioides difficile* (previously called *Clostridium difficile*)
* fungal (yeast) infection of the throat and mouth (thrush or candida infection)
* fungal (yeast) infection of the vagina and vulva (thrush or candida infection)
* reduction in red blood cells (anaemia), which can make the skin pale and cause weakness or breathlessness
* reduction in blood platelets (blood cells which help the blood to clot), which increases your risk of bleeding or bruising
* feeling anxious
* dizziness
* feeling tired or drowsy
* irregular heartbeat or rhythm or palpitations
* pain at the back of the nose and throat
* stomach pain, pain in the abdomen or around the stomach
* constipation
* indigestion, stomach acidity (heartburn), or inflammation of the stomach lining (gastritis)
* increase of a liver enzyme in the blood (gamma-glutamyl transferase and alkaline phosphatase)
* increase in a muscle enzyme in the blood (creatine phosphokinase)
* difficulty in urinating or in fully emptying your bladder (urinary retention)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Xenleta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Xenleta contains

- The active substance is lefamulin. Each tablet contains lefamulin acetate equivalent to 600 mg of lefamulin.
- The other ingredients are colloidal silicon dioxide (E551), croscarmellose sodium (E468), magnesium stearate (E572), mannitol (E421), microcrystalline cellulose (E460), povidone K30, talc (E553b).
- Film Coating: black iron oxide (E172), indigo carmine lake (E132), macrogol, poly (vinyl alcohol) (E1203), propylene glycol, shellac (E904), talc, titanium dioxide (E171).

What Xenleta looks like and contents of the pack

Xenleta 600 mg film-coated tablets are blue, oval, film-coated tablets printed with “LEF 600” in black on one side.

Xenleta film-coated tablets are provided in blister packs of 10 tablets.

Marketing Authorisation Holder and Manufacturer

Nabriva Therapeutics Ireland DAC
Alexandra House, Office 225/227
The Sweepstakes,
Ballsbridge
Dublin 4
D04 C7H2
Republic of Ireland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient

Xenleta 150 mg concentrate and solvent for solution for infusion
lefamulin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xenleta is and what it is used for
2. What you need to know before you are given Xenleta
3. How you will be given Xenleta
4. Possible side effects
5. How to store Xenleta
6. Contents of the pack and other information

1. What Xenleta is and what it is used for

Xenleta is an antibiotic medicine that contains the active substance lefamulin. It belongs to a group of medicines called 'pleuromutilins'.

Lefamulin works by killing certain bacteria which cause infections.

Xenleta is used to treat adults who have bacterial infections in the lung, also known as pneumonia, when other treatments for pneumonia are not considered to be suitable.

2. What you need to know before you are given Xenleta

You must not be given Xenleta
- if you are **allergic to lefamulin** or any of the other ingredients of this medicine (listed in section 6)
- if you are **allergic to other medicines** from the pleuromutilin class
- if you are **taking certain medicines** that might interact with Xenleta. This is because some medicines may stop Xenleta working or lead to side effects if they are given with Xenleta. See below under **Other medicines and Xenleta** for examples.
- if you are **taking medicines** that can cause changes in the heart's electrical activity seen with an ECG (see below under **Other medicines and Xenleta).** This is because lefamulin can cause a condition called QT interval prolongation i.e. abnormal electrical activity that affects the heart's rhythm.
- if you have a **salt imbalance** in the blood (especially low levels of potassium in the blood)
- if you have or have had an **irregular heart rhythm or an abnormal ECG finding called QT prolongation**
- if you have a **very slow heart beat** (bradycardia)
- if your **heart does not work well enough** (heart failure)

Warnings and precautions
Talk to your doctor or nurse before you are given Xenleta
- if you have **kidney failure** and require dialysis.
- if you have cirrhosis (**severe liver disease**)

If any of these apply to you, or if you are not sure, tell your doctor before you are given Xenleta.

If you develop severe diarrhoea during or after being given Xenleta, tell your doctor immediately since it may be necessary to interrupt your treatment. Antibiotics can lead to excessive growth of certain bacteria in your bowel (gut) that can damage the bowel and cause severe diarrhoea.

If you develop yellow skin (jaundice) or the white of your eyes turn yellow (scleral icterus), talk to your doctor because you may need to stop taking Xenleta or other medicines.

Other infections
There is a small possibility that you may get a different infection caused by another bacteria during or after treatment with Xenleta. Your doctor will monitor you closely for any new infections and give you another treatment if necessary.

Children and adolescents
Xenleta is **not recommended** for use in children and adolescents under 18 years old.

Other medicines and Xenleta
Tell your doctor if you are taking, have recently taken or might take any other medicines, as some of these could affect or be affected by Xenleta. The lists below provide only some examples of medicines that should be avoided while taking lefamulin or for which caution is needed. Your doctor will a dvise you if lefamulin is suitable for you.

You must not take any of the following medicines with lefamulin:
- carbamazepine, phenytoin, primidone (for epilepsy)
- efavirenz (for HIV)
- St. John's Wort, an herbal remedy (for depression or low mood)
- bosentan, diltiazem, amiodarone, sotalol, quinidine, procainamide (for angina, high blood pressure or heart rhythm disturbances)
- rifampicin, clarithromycin, erythromycin (for bacterial infections)
- fluconazole, itraconazole, posaconazole, voriconazole (for fungal infections)
- ketoconazole (for Cushing's disease)
- repaglinide (for diabetes)
- nefazodone, amitryptylline or pimozide (for depression or other mental illness)

Your doctor may need to adjust the dose of some medicines while you are taking lefamulin. These medicines include:
* lovastatin, rosuvastatin or simvastatin (to reduce cholesterol levels)
* metformin (for diabetes)
* ethinyl oestradiol (used in birth control pills)

Pregnancy, breast-feeding
You should not be given Xenleta if you are pregnant or breast-feeding. If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before you are given this medicine.

Driving and using machines
Taking Xenleta will not influence the ability to drive or use machines.

Xenleta contains sodium
This medicine contains 1,055 mg sodium (main component of cooking/table salt) in each dosage unit. This is equivalent to 53% of the recommeded maximum daily dietary intake of sodium for an adult.

3. How you will be given Xenleta

Xenleta will be given to you **by a doctor or nurse**.

The recommended dose for adults is 150 mg every 12 hours. It will be given to you through a drip directly into a vein (intravenously) over a period of 1 hour.

A course of treatment usually lasts for 7 days, or longer if your doctor recommends it.

Your doctor may decide to switch you from having Xenleta through a drip to taking Xenleta tablets to complete your treatment for a total (drip and tablet) of 7 days of treatment.

If you are given more Xenleta than you should receive
Xenleta will be given to you in hospital by a doctor or nurse. It is, therefore, unlikely you will be given too much. Tell your doctor or nurse if you are concerned that you may have been given too much Xenleta.

If you miss a dose of Xenleta
Xenleta will be given to you in hospital by a doctor or nurse. It is therefore unlikely you will miss a dose. Tell your doctor or nurse if you are concerned that you have missed a dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
* low potassium levels in your blood (hypokalemia), which can cause muscle weakness, twitching or abnormal heart rhythm
* difficulty sleeping (insomnia)
* headache
* diarrhoea
* feeling sick (nausea), or being sick (vomiting)
* increase of a special liver enzyme in the blood (transaminases)
* redness or swelling or pain at the site of the injection
* alteration of the heart rhythm (seen on an ECG, which monitors the electrical activity of the heart)

Uncommon: may affect up to 1 in 100 people
* inflammation of the bowel causing diarrhoea (colitis), due to an infection by a type of bacteria called *Clostridioides difficile* (previously called *Clostridium difficile*)
* fungal (yeast) infection of the throat and mouth (thrush or candida infection)
* fungal (yeast) infection of the vagina and vulva (thrush or candida infection)
* reduction in red blood cells (anaemia), which can make the skin pale and cause, weakness or breathlessness
* reduction in blood platelets (blood cells which help the blood to clot), which increases risk of bleeding or bruising
* feeling anxious
* dizziness
* feeling tired or drowsy
* irregular heart beat or rhythm or palpitations
* pain at the back of the nose and throat
* stomach pain, pain in the abdomen or around the stomach
* constipation

* indigestion, stomach acidity (heartburn), or inflammation of the stomach lining (gastritis)
* increase of a liver enzyme in the blood (gamma-glutamyl transferase and alkaline phosphatase)
* increase in a muscle enzyme in the blood (creatine phosphokinase)
* difficulty urinating or in fully emptying your bladder (urinary retention)

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Xenleta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and outer carton. The expiry date refers to the last day of that month.

Concentrate: Store in a refrigerator (2°C to 8°C). Do not freeze.

Solvent: Store below 25°C. Do not freeze.

After dilution:
The stability of the diluted solution has been demonstrated for 24 hours at room temperature and 48 hours at 2°C to 8°C. Administer immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

The diluted solution should be clear and colourless and should not be used if it contains any particles or the solution is cloudy.

6. Contents of the pack and other information

What Xenleta contains
- The active substance is lefamulin. Each vial contains lefamulin acetate equivalent to 150 mg of lefamulin.
- The other ingredients are: citric acid (E330), sodium citrate dihydrate (E331), sodium chloride and water for injections.

What Xenleta looks like and contents of the pack
Xenleta is a concentrate for solution for infusion.

The concentrate is a clear colourless solution in a glass vial, closed with a rubber stopper and sealed with a lift off cap.

The solvent is a clear colourless solution in a polypropylene infusion bag.

Xenleta is supplied in a pack containing 2 vials of concentrate and 2 infusion bags with solvent.

Marketing Authorisation Holder and Manufacturer
Nabriva Therapeutics Ireland DAC
Alexandra House, Office 225/227
The Sweepstakes,
Ballsbridge
Dublin 4
D04 C7H2
Republic of Ireland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

<.....>

The following information is intended for healthcare professionals only:

Instructions for dilution prior to administration
Parenteral (intravenous) medicinal products should be inspected visually for particles or discoloration prior to administration. Only solutions which are clear, colourless, and free of visible particles should be diluted.

How to prepare Xenleta for administration

General precautions

Each vial and infusion bag is for single use only.
Standard aseptic techniques should be used for solution preparation and administration.

Instructions for dilution and infusion

Xenleta concentrate must be mixed into the bag of solvent containing 250 mL solution of 10mM citrate buffered saline and administered by infusion.

1. Aseptically withdraw 15 mL of Xenleta from the concentrate vial.
2. Transfer concentrate to the bag of solvent containing 250 mL solution of 10mM citrate buffered 0.9% sodium chloride.
3. Discard any unused portion from the concentrate vial. The vial of concentrate and the bag of solvent solution is single-use only.
4. The diluted solution should be clear and colourless. Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
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. Avoid rapid or bolus intravenous infusion.
6. Administer by intravenous infusion only.

The compatibility of reconstituted Xenleta with intravenous medicinal products, additives, or substances other than 10mM citrate buffered 0.9% sodium chloride intravenous infusion or 0.9% sodium chloride intravenous infusion has not been established. If a common intravenous line is being used to administer other medicinal products in addition to Xenleta, the line should be flushed before and after each Xenleta administration with 0.9% sodium chloride intravenous infusion.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.