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 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

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)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/01/2021