APPLICATION NUMBER:

211672Orig1s000
211673Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<th>Application Type</th>
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<td>Application Number</td>
<td>211672 and 211673</td>
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<td>PDUFA Goal Date</td>
<td>August 19, 2019</td>
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<td>OSE RCM #</td>
<td>2018-2734; 2018-2736; 2018-2737; 2018-2739</td>
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<tr>
<td>Reviewer Name(s)</td>
<td>Till Olickal, Ph.D., Pharm.D.</td>
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<td>Review Completion Date</td>
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<tr>
<td>Subject</td>
<td>Review to determine if a REMS is necessary</td>
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<tr>
<td>Established Name</td>
<td>lefamulin</td>
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<td>Trade Name</td>
<td>Xenleta</td>
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<tr>
<td>Name of Applicant</td>
<td>Nabriva Therapeutics.</td>
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<tr>
<td>Therapeutic Class</td>
<td>Pleuromutilin antibacterial</td>
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<tr>
<td>Formulation(s)</td>
<td>600 mg tablet (NDA 211672) and 150mg for injection (NDA 211673)</td>
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<td>Dosing Regimen</td>
<td>150 mg IV every 12 hours; 600 mg PO every 12 hours</td>
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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity lefamulin is necessary to ensure the benefits outweigh its risks. Nabriva Therapeutics submitted a New Drug Applications (NDA) 211672 and 211673 for lefamulin with the proposed indication for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms. The serious risks associated with the use of lefamulin are QT Prolongation, embryo-fetal toxicity, Clostridium difficile-associated diarrhea (CDAD) and development of drug-resistant bacteria. The applicant did not submit a REMS with this application but proposed Prescribing Information (PI) that includes Warnings and Precautions.

DRISK and Division of Anti-Infective Products (DAIP) have determined that if approved, a REMS is not necessary to ensure the benefits of lefamulin outweigh its risks. CABP is a serious illness that is often associated with significant morbidity, mortality, and considerable costs of care. There are several antibacterial drugs that are FDA-approved for the treatment of CABP or lower respiratory tract infections or community acquired pneumonia (CAP) and are recommended by the Infectious Diseases Society of America (IDSA) as standard of care for the indication. Despite the availability and widespread adherence to recommended treatment guidelines, CABP continues to present a significant burden in adults. Newer generations of antibiotics have the benefit of decreased resistance compared to many agents such as fluoroquinolones thus providing an alternative treatment options for patients with treatment resistant organisms. Lefamulin appeared efficacious in both its primary and secondary outcomes and was found to be non-inferior to comparator. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of lefamulin for the treatment of adult patients with CABP caused by susceptible microorganisms. If approved, the serious risks associated with the use of lefamulin, including QT Prolongation, embryo-fetal toxicity, CDAD and development of drug-resistant bacteria will be communicated in the Warnings and Precautions section of the label, to communicate the safety issues and management of toxicities associated with lefamulin.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) lefamulin is necessary to ensure the benefits outweigh its risks. Nabriva Therapeutics submitted a New Drug Applications (NDA) 211672 and 211673 for lefamulin with the proposed indication for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms. The applicant did not submit a REMS with this application but proposed Prescribing Information (PI) that includes Warnings and Precautions.

2 Background

2.1 PRODUCT INFORMATION

Lefamulin is a NME NDA type 505(b)(1) pathway application. It is a semi-synthetic, pleuromutilin derivative antibacterial agent, with the proposed indication of treatment of adult patients with CABP caused by susceptible microorganisms. Lefamulin is a systemic pleuromutilin antibacterial with in vitro

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*Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.*
activity against gram-positive, fastidious gram-negative and atypical respiratory bacteria. It inhibits bacterial protein synthesis by interacting with the A- and P- sites of the peptidyl transferase center (PTC) in the central part of domain V of the 23s rRNA of the 50S ribosomal subunit, preventing correct positioning of the tRNA.\(^1\) Lefamulin is prepared as 600 mg tablet and 150 mg for intravenous (IV) injection. The recommended dose of lefamulin is 150 mg every 12 hours by intravenous infusion over 60 minutes for a total duration of 5 to 7 days or 150 mg every 12 hours by intravenous infusion over 60 minutes; then switch to 600 mg orally every 12 hours at the discretion of the physician for a total duration of 5 to 7 or 600 mg orally every 12 hours for a total duration of 5 days.\(^b\) Lefamulin was granted Fast Track and Qualified Infectious Disease Product (QIDP) designations for CABP on September 11, 2014 (for IV use) and January 21, 2016 (for the oral tablet). Lefamulin is not currently approved in any jurisdiction.

### 2.2 Regulatory History

The following is a summary of the regulatory history for lefamulin (NDA 211672 and 211673) relevant to this review:

- **10/17/2009:** Investigation New Drug (IND) 106594 submission for lefamulin IV formulation was received.
- **09/11/2014:** Fast Track and QIDP designation granted for IV formulation.
- **01/30/2015:** IND 125546 submission for lefamulin oral formulation was received.
- **01/21/2016:** Fast Track and QIDP designation granted for oral formulation.
- **12/19/2018:** NDA 211672 submission for lefamulin tablet and 211673 submission for lefamulin injection with the proposed indication for the treatment of adult patients with CABP, received.
- **04/11/2019:** A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for lefamulin.

### 3 Therapeutic Context and Treatment Options

#### 3.1 Description of the Medical Condition

CABP has been defined as an infection of the pulmonary parenchyma accompanied by the presence of clinical features of an acute infection (e.g., cough, fever, sputum production, and chest pain), along with the presence of an acute infiltrate on chest radiograph, in a patient not hospitalized or residing in a long-term care facility in the 14 days preceding the onset of symptoms.\(^2\) Typical bacterial pathogens that cause CABP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Atypical bacterial pathogens also can cause CABP and include *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*.\(^3\) *Staphylococcus aureus* has not traditionally been considered a typical cause of community acquired pneumonia (CAP) in otherwise healthy hosts. However, *S aureus* is well known to cause potentially severe CAP after influenza infection.\(^4\) CABP is a commonly occurring serious illness that is often associated with significant morbidity, mortality, and considerable

\(^b\) Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.
costs of care. In the United States, there were approximately 4.2 million ambulatory care visits for pneumonia in 2006. Pneumonia and influenza continue to be a common cause of death in the United States (ranked eighth) and Canada (ranked seventh). In 2005, there were > 60 000 deaths due to pneumonia in persons aged ≥ 15 years in the United States alone. The hospitalization rate for all infectious diseases increased from 1525 hospitalizations per 100 000 persons in 1998 to 1667 per 100 000 persons in 2005. Admission to an intensive care unit was required in 10% to 20% of patients hospitalized with pneumonia. The mean length of stay for pneumonia was ≥ 5 days and the 30-day rehospitalization rate was as high as 20%. Mortality was highest for CAP patients who were hospitalized; the 30-day mortality rate was as high as 23%. All-cause mortality for CAP patients was as high as 28% within 1 year. Compared to the incidence in adults 18 to 49 years old, the incidence among adults 50 to 64 years old, 65 to 79 years old, and 80 years or older were approximately 4, 9, and 25 times as high.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are several antibacterial drugs that are FDA-approved for the treatment of CABP or lower respiratory tract infections or CAP and are recommended by the Infectious Diseases Society of America (IDSA) as standard of care for the indication. They include macrolides (azithromycin and clarithromycin), respiratory fluoroquinolones (moxifloxacin, gemifloxacin, and levofloxacin), cephalosporins (cefotaxime and ceftriaxone), doxycycline, linezolid (if Methicillin-resistant Staphylococcus aureus [MRSA] is a concern), and aztreonam (for patients with penicillin allergy). If Pseudomonas is a consideration, empiric treatment for CABP could include piperacillin/tazobactam, cefepime, or imipenem. Other beta-lactam/beta-lactamase inhibitor combination drugs, cephalosporins, and carbapenems, which are not labeled for CABP, are often used to treat patients when resistant organisms are suspected to be the cause or when patients do not respond to first-line therapy. Oral antibacterial therapy is used when patients do not need hospitalization and are able to take oral medication. Hospitalized patients are started on IV antibacterial therapy and may be switched to oral medication when they are clinically improved. Overall, there are many options for clinicians to use to treat CABP. However, there are limitations of the current drugs, including lack of oral options for some drugs, antibacterial resistance, and drug safety issues. Additional options for the treatment of CABP that have oral and IV formulations and a broad-spectrum of antibacterial activity would be beneficial to patients. From a prevention perspective, the 13-valent pneumococcal conjugate vaccine is indicated for the prevention of pneumococcal pneumonia and invasive disease due to vaccine serotypes, and the 23-valent pneumococcal polysaccharide vaccine is recommended for prevention of pneumococcal disease in adults ≥65 years of age. Given the significance of the disease burden, the potential benefit of pneumococcal vaccination in adults is substantial. Although the IDSA/ATS guidelines recommend initiating treatment of CABP with macrolides, resistance among S. pneumoniae and M. pneumoniae isolates to this class of antibiotics has been increasingly reported worldwide. Macrolide resistance has been spreading for 15 years worldwide, with prevalence now ranging between 0 and 15% in Europe and the USA, approximately 30% in Israel and up to 90-100% in Asia. In addition to increasing resistance, the most frequently used CABP therapis, including β-lactams, macrolides, and fluoroquinolones, are associated with clinically important adverse effects. β-lactam antibiotic use (e.g., ceftriaxone) is

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Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
commonly associated with adverse events (AEs) including allergic reactions and gastrointestinal, hematologic, hepatobiliary, and neurological effects.\textsuperscript{11} Fluoroquinolone use has recently become more restricted due to the emergence of fluoroquinolone-associated disability (FQAD), which includes tiredness, concentration problems, neuropathies, tendinopathies, and other symptoms. In 2016, the US Food and Drug Administration (FDA) updated safety warnings for oral and injectable fluoroquinolones with respect to FQAD.\textsuperscript{12} In July 2018, the FDA introduced further safety labelling changes to strengthen warnings about the risk of mental health side effects and serious blood sugar disturbances (leading to coma).\textsuperscript{13}

Despite the availability and widespread adherence to recommended treatment guidelines, CABP continues to present a significant burden in adults. Newer generations of antibiotics have the benefit of decreased resistance compared to many agents such as fluoroquinolones thus opening the door as treatment options for patients with treatment resistant organisms.

4 Benefit Assessment

The efficacy of lefamulin for the treatment of CABP was evaluated in two Phase 3 clinical trials (Trial 3101 [NCT02559310] and Trial 3102 [NCT02813694]). A total of 1289 adults with CABP were randomized in two multi-center, multi-national, double-blind, double-dummy trials. Trial 3101 compared 5 to 10 days of lefamulin to 7 to 10 days of moxifloxacin ± linezolid. Trial 3102 compared 5 days of lefamulin to 7 days of moxifloxacin.

In Trial 3101, 276 patients were randomized to lefamulin (150 mg IV every 12 hours, with the option to switch to 600 mg PO every 12 hours after at least 3 days of IV treatment) and 275 patients were randomized to moxifloxacin (400 mg intravenously every 24 hours, with the option to switch to 400 mg PO every 24 hours after at least 3 days of IV treatment). If MRSA was suspected at screening, patients randomized to moxifloxacin were to receive adjunctive linezolid (600 mg IV every 12 hours, with the option to switch to 600 mg PO every 12 hours after at least 3 days of IV treatment), and patients randomized to lefamulin were to receive linezolid placebo. In Trial 3102, 370 patients were randomized to lefamulin (600 mg PO every 12 hours for 5 days) and 368 patients were randomized to moxifloxacin (400 mg PO every 24 hours for 7 days).

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for lefamulin. The efficacy was determined by Early Clinical Response (ECR) at 72 to 120 hours after the first dose in the Intent-to-treat (ITT) Analysis Set, which comprised all randomized patients, in both trials. Patients were entered the trials with at least three of four symptoms consistent with CABP (cough, sputum production, chest pain, and/or dyspnea). Response was defined as survival with improvement of at least two symptoms, no worsening of any symptom, and no receipt of non-study antibacterial treatment for CABP. Table 1 summarizes ECR rates in the two trials.\textsuperscript{e,1}

\textsuperscript{e} Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
Table 1: Clinical Response Rates at ECR Time Point in Trial 3101 and Trial 3102 (ITT Analysis Set)\textsuperscript{1,e}

<table>
<thead>
<tr>
<th>Study</th>
<th>Lefamulin n/N (%)</th>
<th>Moxifloxacin n/N (%)\textsuperscript{*}</th>
<th>Treatment Difference (95% CI)\textsuperscript{**}</th>
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<tbody>
<tr>
<td>Trial 1</td>
<td>241/276 (87.3)</td>
<td>248/275 (90.2)</td>
<td>-2.9 (-8.5, 2.8)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>336/370 (90.8)</td>
<td>334/368 (90.8)</td>
<td>0.0 (-4.4, 4.5)</td>
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\textsuperscript{*}Trial 1 compared lefamulin to moxifloxacin ± linezolid.

\textsuperscript{**}95% confidence interval for the treatment difference

Clinical response was also assessed by the Investigator at the Test of Cure (TOC) Visit 5 to 10 days after the last dose of study drug. Response was defined as survival with improvement of signs and symptoms based on the Investigator’s assessment and no receipt of non-study antibacterial treatment for CABP. Table 2 summarizes Investigator-assessed Clinical Response (IACR) rates at TOC in the ITT Analysis Set, which comprised all randomized patients.\textsuperscript{1,e}

Table 2: Investigator-assessed Clinical Response Rates at TOC in Trial 3101 and Trial 3102 (ITT Analysis Set)\textsuperscript{1,e}

<table>
<thead>
<tr>
<th>Study</th>
<th>Lefamulin n/N (%)</th>
<th>Moxifloxacin n/N (%)\textsuperscript{*}</th>
<th>Treatment Difference (95% CI)\textsuperscript{**}</th>
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<tbody>
<tr>
<td>Trial 1</td>
<td>223/276 (80.8)</td>
<td>230/275 (83.6)</td>
<td>-2.8 (-9.6, 3.9)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>322/370 (87.0)</td>
<td>328/368 (89.1)</td>
<td>-2.1 (-7.0, 2.8)</td>
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</tbody>
</table>

\textsuperscript{*}Trial 1 compared lefamulin to moxifloxacin ± linezolid.

\textsuperscript{**}95% confidence interval for the treatment difference

Overall the analyses of the efficacy endpoints in both trials 3101 and 3102 support the non-inferiority of lefamulin relative to moxifloxacin.\textsuperscript{e,6}

5 Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for lefamulin. The safety analysis of lefamulin primarily focuses on 641 patients with CABP in two randomized, multi-center, multi-national, double-blind double-dummy trials. Trial 3101 (IV to oral switch trial) enrolled 551 adult patients, 276 randomized to lefamulin (273 received at least one dose of lefamulin) and 275 randomized to moxifloxacin (273 received at least one dose of moxifloxacin). Trial 3102 (oral only trial) enrolled 738 adult patients, 370 randomized to lefamulin (368 received at least one dose of lefamulin) and 368 randomized to moxifloxacin (all 368 received at least one dose of moxifloxacin).\textsuperscript{1}

The most common adverse reactions (incidence $\geq$2%) noted were diarrhea, which occurred in 7.3% of lefamulin subjects compared with 3.9% of moxifloxacin subjects; nausea, occurring in 4.2% lefamulin subjects compared with 2% of moxifloxacin subjects; administration site reactions, occurring in 7% lefamulin subjects compared with 2.6% of moxifloxacin subjects; and vomiting, occurring in 2.3% lefamulin subjects compared with 0.6% of moxifloxacin subjects. Hepatic enzyme elevation of 2.3% were seen in both lefamulin and moxifloxacin subjects.\textsuperscript{1}
Deaths

A total of 19 deaths in the lefamulin were reported in the clinical development program. In Study 3101 there were 11 deaths, 6 in the lefamulin arm and 5 in the moxifloxacin arm. In Study 3102 there were 8 deaths, 5 in the lefamulin arm and 3 in the moxifloxacin arm. In these two trials, 15 deaths occurred by Day 28: 8 deaths in the lefamulin arm (1.2%) compared to 7 deaths in the moxifloxacin arm (1.1%). Overall the deaths in the lefamulin arm in both trials 3101 and 3102 were assessed by the clinical reviewer as unrelated to study treatment drug. The clinical reviewer stated that the all-cause mortality observed in patients treated with lefamulin was balanced compared to patients treated with moxifloxacin.6

Serious Adverse Events (SAE)

In the two Phase 3 trials (3101 & 3102), there were 36 subjects in the lefamulin group (5.6%) and 31 subjects in the moxifloxacin group (4.8%) who experienced at least one treatment-emergent SAE. In the Phase 3 safety population, 42 subjects discontinued study drug due to at least one TEAE. These subjects were balanced between the treatment arms with 21 in the lefamulin arm (3.3%) and 21 in the moxifloxacin arm (3.3%). There were 14 subjects in the Phase 3 safety population with severe but not serious TEAEs; 8 in the lefamulin arm and 6 in the moxifloxacin arm. Notably 3 lefamulin subjects and 1 moxifloxacin subject had severe, but not serious administration site reactions. All 4 subjects’ reactions were resolving or had resolved at the end of the study. Two lefamulin subjects had severe, but not serious TEAEs of nausea that resolved by the end of the study. The clinical reviewer stated that the severe, but not serious TEAEs were not common in the Phase 3 safety population and overall these were balanced between the treatment groups. In the System of Organ Class (SOC) of Infections and Infestations, there were 17 subjects in the lefamulin arm with SAEs compared to 9 in the moxifloxacin arm. Of the 17 lefamulin subjects, 12 had lung infections (pneumonia, infectious pleural effusion, lung abscess, pneumonia bacterial, and empyema). Of the 9 moxifloxacin subjects, 6 had lung infections. The clinical reviewer stated that these 18 cases of SAEs related to lung infections, most were treatment failures of the study drug with a few cases of a separate infection. In addition, 8 of 12 lefamulin-treated subjects had a positive culture for enterobacteriaceae which are not covered by lefamulin. As a result, most of the treatment failures in lefamulin-treated subjects are likely a result of inadequate microbiological coverage.6

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 QT PROLONGATION

Nonclinical toxicity studies showed lefamulin reduced the amplitudes of the human ether-a-go-go-related gene (hERG)-mediated potassium channel currents in a concentration-dependent manner which suggested it would cause QT prolongation in humans. Analysis of all post-baseline QTcF values showed the proportion of subjects with exposure to lefamulin with any measure of QT prolongation was no higher compared to the moxifloxacin comparator. The mean maximum change in QTcF from baseline is 16.8 msec with lefamulin vs 19.3 msec with moxifloxacin. Of the 636 patients treated with lefamulin in the clinical trial, 0.3% (n=2) were found to have a QTc interval greater than 500 msec and 1.7% (n=11) of patients had an increase from baseline QTc greater than 60 msec vs in moxifloxacin group (n=636) reported 0.9% (n=6) to have a QTc interval > 500 and 2.5% (n=16) of patients had an increase from baseline QTc >60 msec. In Phase 3 safety population, there were a total of 20/636 (3.1%) has maximum
post post-baseline QTcF >480 msec in lefamulin group vs 21/636 (3.3%) in moxifloxacin group. The risk of QT prolongation will likely be communicated in the Warnings and Precautions sections of the label, along with a recommendation that ECG monitoring be considered if there is a need to administer lefamulin in patients predisposed to QT prolongation or if concurrent use with another QT prolonging drug. Further, the Contraindications section of the label will communicate that CYP3A4 substrates that prolong the QTc interval should not be used with lefamalin.1

5.2 EMBRYO-FETAL TOXICITY

Based on animal embryo-fetal toxicity studies, lefamulin can cause fetal harm when administered to a pregnant woman. In animal embryo-fetal toxicity studies, decreased fetal body weights and ossification in rats and rabbits, and apparent delay in sexual maturation in rats may indicate treatment-related developmental delay, while other findings such as rare malformations in rats at systemic exposures lower than the systemic exposure in CABP patients may indicate a risk for embryo-fetal toxicity. In the rat embryo-fetal development study of IV lefamulin during organogenesis, findings included late resorptions in the high-dose group and malformations (cleft palate/jaw/vertebral malformations at the mid and high doses, and enlarged ventricular heart chamber with a thin ventricular wall at the high dose) for which the litter incidence was rare in concurrent and historical controls (0 to approximately 0.3%).1 If approved, the risk of embryo-fetal toxicity will likely be communicated with recommended guidance to use effective contraception during treatment with lefamulin in the Warnings and Precautions and Use In Specific Populations sections of the label. Further, section of the label will communicate the recommendation to obtain a pregnancy test in females of reproductive potential prior to initiating treatment with lefamulin. Additionally, the Applicant will be required to conduct a post-marketing required (PMR) Pregnancy Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to lefamulin during pregnancy. Labeling instructs patients should be encouraged to enroll in the lefamulin pregnancy registry if they become pregnant.14

5.3 CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA (CDAD)

CDAD has been reported with the use of nearly all antibacterial agents; it may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of C. difficile. If approved, the label will advise that if CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against C. difficile may need to be discontinued. Similar to other antibacterial agents, the risk of CDAD will be included in the Warnings and Precautions section of the label.1

5.4 DEVELOPMENT OF DRUG-RESISTANT BACTERIA

Similar to other antibacterial agents, if lefamulin is approved, the label will advise in the Warnings and Precautions section that prescribing lefamulin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.1
6 Expected Postmarket Use

According to the current proposed indication, if approved, lefamulin will be used both in outpatient and inpatient settings and will be prescribed by various types of healthcare providers such as general practice physicians, internal medicine physicians, midlevel practitioners, and infectious disease specialists. The IV route or IV switch to oral route will be used in inpatient and/or outpatient settings such as infusion centers or home infusion.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for lefamulin beyond routine pharmacovigilance and labeling. The applicant proposed a PI that includes Warnings and Precautions to address the risks of QT Prolongation, embryo-fetal toxicity, CDAD and development of drug-resistant bacteria.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for lefamulin, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population. The likely prescribers for lefamulin will be various types of healthcare providers such as general practice physicians, internal medicine physicians, midlevel practitioners, and infectious disease specialists. The risks identified are risks that these providers have likely encountered in their practice experience. As described in section 3.1 of this review, community acquired pneumonia despite the availability other treatment options is still associated with significant mortality.

Lefamulin is a pleuromutilin antibacterial agent, with the proposed indication of treatment of adult patients with CABP caused by susceptible microorganisms. At the time of this writing, labeling negotiations were still ongoing with the Applicant. Based on the efficacy and safety information currently available, the clinical reviewers stated that lefamulin shows clinically meaningful benefit to patients with CABP, and recommends approval of lefamulin for the treatment of adult patients with CABP caused by susceptible microorganisms.6

The most concerning adverse reactions observed with the use of lefamulin are QT Prolongation, CDAD, and development of drug-resistant bacteria. Additionally, the Contradictions section of the label will communicate that CYP3A4 substrates that prolong the QTc interval should not be used concurrently with lefamulin.

Based on animal embryo-fetal toxicity studies, lefamulin can cause fetal harm when administered to a pregnant woman. For lefamulin, in the rat embryo-fetal development study findings included late resorptions in the high-dose group and malformations (cleft palate/jaw/vertebral malformations at the mid and high doses, and enlarged ventricular heart chamber with a thin ventricular wall at the high dose) for which the litter incidence was rare in concurrent and historical controls (0 to approximately 0.3%). For lefamulin, there is one fully adequate study (in rats), but not enough survival of offspring in the rabbit to do a reliable evaluation; additionally, there was not the multi-species concordance as seen with another antibiotic, Vibativ (telavancin) that might heighten the risk in humans.1,15
Similar to thalidomide, the results of an Intravenous Injection Rat Developmental Toxicity Study with Vibativ showed developmental anomalies that include brachymeila, syndactyly, and anophthalmia and there was concordance between all three tested species (rats, rabbits, and minipigs); because of these findings the division determined that a boxed warning and REMS comprised of a communication plan were warranted to communicate the risk, as well as a pregnancy registry.

If lefamulin is approved, the risk of embryo-fetal toxicity will likely be communicated with recommended guidance to use effective contraception during treatment with lefamulin in the Warnings and Precautions and Use In Specific Populations sections of the label; of the label will communicate the recommendation to obtain a pregnancy test in females of reproductive potential prior to initiating treatment with lefamulin. Additionally, the applicant will be required to conduct a PMR Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to lefamulin during pregnancy.

Lefamulin appeared efficacious in both its primary and secondary outcomes and was found to be non-inferior to comparator and its risks will be communicated through labeling. Despite the availability and widespread adherence to recommended treatment guidelines, CABP continues to present a significant burden in adults. Newer generations of antibiotics have the benefit of decreased resistance compared to many agents such as fluoroquinolones, thus opening the door as treatment options for patients with treatment resistant organisms.

DRISK and DAIP have determined that if approved, a REMS is not necessary to ensure the benefits of lefamulin outweigh its risks. If lefamulin is approved, labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with lefamulin.

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of lefamulin. The management of the risks associated with lefamulin treatment will be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

1 Draft Prescribing Information for lefamulin as currently edited by the FDA, last updated July 17, 2019.
6 Natarajan M. DAIP Multidisciplinary Clinical Review (draft) for NDA 2211672 and 211673 lefamulin, dated July 17, 2019.


8 Prevnar 13. Prescribing Information (last updated 08/2017).

9 Pneumovax 23. Prescribing Information (last updated 05/2015).


14 Late-Cycle Meeting background package, dated June 10, 2019.

15 Nostrandt AC. Nonclinical memo for NDA 211672 and NDA 211673 lefamulin, dated June 14, 2019.


17 Cox EM. Office Director Decisional Memo for NDA 22110 telavancin, dated September 11, 2009.


19 Supplement approval Release from REMS requirement for NDA 22110 telavancin, dated May 24, 2017.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TILL OLICKAL
07/19/2019 03:59:26 PM

ELIZABETH E EVERHART
07/19/2019 04:08:33 PM
I concur.

CYNTHIA L LACIVITA
07/19/2019 04:14:14 PM