CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211672Orig1s000
211673Orig1s000

Trade Name:	XENLETA tablets, 600 mg XENLETA injection, 150 mg
Generic or Proper Name:	lefamulin
Sponsor:	Nabriva Therapeutics
Approval Date:	August 19, 2019
Indication:	For the treatment of adults with Community-Acquired Bacterial Pneumonia (CABP) caused by designated susceptible microorganisms.

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211672Orig1s000
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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 211672
NDA 211673

NDA APPROVAL

Nabriva Therapeutics Ireland DAC
c/o Nabriva Therapeutics US, Inc.
Attention: Mersedeh Miraliakbari, PharmD
Vice President, Regulatory Affairs
1000 Continental Drive, Suite 600
King of Prussia, PA 19406

Dear Dr. Miraliakbari:

Please refer to your new drug applications (NDAs) dated December 19, 2018, received December 19, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for

NDA 211672 XENLETA (lefamulin) tablets, 600 mg
NDA 211673 XENLETA (lefamulin) injection, 150 mg

These new drug applications provide for the use of XENLETA (lefamulin) tablets and XENLETA (lefamulin) injection for the treatment of adults with Community-Acquired Bacterial Pneumonia (CABP) caused by designated susceptible microorganisms.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit the labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDAs 211672 and 211673**." Approval of these submissions by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Deepak Aggarwal
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6211
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** if shipping via United States Postal Service (USPS).
Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

ADVISORY COMMITTEE

Your applications were not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 2 months because necessary studies are impossible or highly impracticable. This is because CABP is infrequent in this age group.

We are deferring submission of your pediatric studies for ages 2 months to less than 18 years for these applications because these products are ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

3672-1 Conduct a single-dose study to evaluate the pharmacokinetics and safety of intravenous XENLETA (lefamulin) in children from birth to less than 18 years of age with suspected or confirmed bacterial infections receiving standard of care.

The timetable you submitted on August 15, 2019, states that you will conduct this study according to the following schedule:

Final protocol submission:	Submitted
Study completion:	06/2024
Final report submission:	12/2024

3672-2 Conduct a single-dose study to evaluate the pharmacokinetics and safety of oral XENLETA (lefamulin) in children from birth to less than 18 years of age with suspected or confirmed bacterial infections receiving standard of care.

The timetable you submitted on August 15, 2019, states that you will conduct this study according to the following schedule:

Final protocol submission:	05/2021
Study completion:	12/2024
Final report submission:	06/2025

3672-3 Conduct a randomized active-controlled study to assess the safety and pharmacokinetics of XENLETA (lefamulin) in children from 2 months to less than 18 years of age with CABP.

The timetable you submitted on August 15, 2019, states that you will conduct this study according to the following schedule:

Draft protocol submission:	09/2020
Final protocol submission:	12/2020
Study completion:	12/2024
Final report submission:	06/2025

Submit the protocols to your INDs 106594 (lefamulin injection) and 125546 (lefamulin tablet), with cross-reference letters to the NDAs.

Reports of these required pediatric postmarketing studies must be submitted as new drug applications (NDAs) or as supplements to your approved NDAs with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the serious risk of development of resistance to XENLETA in microorganisms specific to the CABP indication in the label. We have also determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of serious risk of fetal harm following XENLETA exposure in pregnant women, and the genotoxic potential of lefamulin and its metabolite.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3672-4 Conduct a United States surveillance study for 5 years from the date of marketing to determine if resistance to XENLETA (lefamulin) has developed in those organisms specific to the CABP indication in the label.

The timetable you submitted on August 15, 2019, states that you will conduct this study according to the following schedule:

Final protocol submission:	09/2019
First interim study report submission:	06/2020
Second interim study report submission:	06/2021
Third interim study report submission:	06/2022
Fourth interim study report submission:	06/2023
Fifth interim study report submission:	06/2024
Study completion:	09/2024
Final report submission:	12/2024

3672-5 Conduct a pregnancy surveillance program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to XENLETA (lefamulin) during pregnancy.

The timetable you submitted on August 15, 2019, states that you will conduct this study according to the following schedule:

Final protocol submission:	Submitted
First interim study report submission:	08/2020
Second interim study report submission:	08/2021
Third interim study report submission:	08/2022
Fourth interim study report submission:	08/2023
Fifth interim study report submission:	08/2024
Sixth interim study report submission:	08/2025
Seventh interim study report submission:	08/2026
Eighth interim study report submission:	08/2027
Ninth interim study report submission:	08/2028
Study completion:	08/2029
Final report submission:	08/2030

3672-6 Conduct an *in vitro* Mouse Lymphoma Assay (MLA) that evaluates higher doses of lefamulin reaching 10-20% Relative Total Growth (RTG) and in accordance with the Organisation for Economic Co-operation and Development (OECD) Guidelines for the Testing of Chemicals #476.

The timetable you submitted on August 15, 2019, states that you will conduct this study according to the following schedule:

Draft protocol submission:	01/2020
Final protocol submission:	03/2020
Study completion:	06/2020
Final study report submission:	08/2020

3672-7 Conduct an *in vitro* Mouse Lymphoma Assay (MLA) that evaluates higher doses of the lefamulin metabolite BC-8041 reaching 10-20% Relative Total Growth (RTG) and in accordance with the OECD Guideline for the Testing of Chemicals #476.

The timetable you submitted on August 15, 2019, states that you will conduct this study according to the following schedule:

Draft protocol submission:	01/2020
Final protocol submission:	03/2020
Study completion:	06/2020
Final study report submission:	08/2020

Submit the clinical protocol(s) to your INDs 106594 (lefamulin injection) and 125546 (lefamulin tablets) with cross-reference letters to these NDAs. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDAs. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of each submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND(s) is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section

505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references and the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for these products. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[7]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Deepak Aggarwal, MSE, MSPH, Regulatory Project Manager, at 301-796-0746.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

[7] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

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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/

EDWARD M COX
08/19/2019 02:15:50 PM