DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209321/Original 1

NDA APPROVAL

Jacobus Pharmaceutical Company, Inc.
Attention: Laura R. Jacobus
Vice President & Director of Quality Assurance
37 Cleveland Lane, P.O. Box 5290
Princeton, NJ 08540

Dear Ms. Jacobus:

Please refer to your New Drug Application (NDA) dated June 15, 2018, received June 15, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ruzurgi (amifampridine), 10 mg tablets.

We acknowledge receipt of your major amendment dated January 7, 2019, which extended the goal date by three months.

This new drug application provides for the use of Ruzurgi (amifampridine) tablets for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age. For administrative purposes, we have designated the following:

- NDA 209321/Original 1 (Treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age)
- NDA 209321/Original 2 ((b) (4)

The subject of this action letter is NDA 209321/Original 1. A separate action letter will be issued for NDA 209321/Original 2.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content

of labeling must be identical to the enclosed labeling text for the Prescribing Information, Instructions for Use, and Medication Guide 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*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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 carton and container labeling submitted on April 26, 2019, and April 4, 2019, respectively, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 209321**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Ruzurgi was not referred to an FDA advisory committee because the safety profile of amifampridine is acceptable for the intended population, the design of the clinical trials was acceptable, and the efficacy findings were clear.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 unexpected serious risks of adverse maternal, fetal, or infant outcomes, adverse effects on postnatal growth and development, or carcinogenicity resulting from the use of Ruzurgi.

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 studies:

3612-1 A pre- and postnatal development study of amifampridine in rat.

The timetable you submitted on May 1, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2019
Study Completion:	06/2020
Final Report Submission:	01/2021

3612-2 A fertility study of amifampridine in male and female rat.

The timetable you submitted on May 1, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2019
Study Completion:	03/2020
Final Report Submission:	10/2020

3612-3 An embryofetal development study of amifampridine in rat.

The timetable you submitted on May 1, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2019
Study Completion:	02/2020
Final Report Submission:	09/2020

3612-4 An embryofetal development study of amifampridine in rabbit.

The timetable you submitted on May 1, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2020
Study Completion:	05/2020
Final Report Submission:	12/2020

3612-5 A juvenile animal toxicology study of amifampridine in rat.

The timetable you submitted on April 29, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2020
Final Protocol Submission:	04/2020
Study Completion:	12/2020
Final Report Submission:	07/2021

3612-6 A carcinogenicity study of amifampridine in mouse.

The timetable you submitted on April 29, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2020
Final Protocol Submission:	06/2020
Study/Trial Completion:	01/2022
Final Report Submission:	09/2022

3612-7 A carcinogenicity study of amifampridine in rat.

The timetable you submitted on April 29, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2019
Final Protocol Submission:	01/2020
Study/Trial Completion:	01/2023
Final Report Submission:	07/2023

3612-8 Establish 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 Ruzurgi (amifampridine) during pregnancy. Provide a complete protocol that includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting.

The timetable you submitted on April 30, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2019
Final Protocol Submission:	06/2020
Study Completion:	06/2029
Final Report Submission:	12/2029

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks resulting from altered pharmacokinetics of amifampridine in patients with hepatic or renal impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3612-9 Conduct a clinical trial to evaluate the effect of hepatic impairment on the exposure of amifampridine after oral administration of Ruzurgi (amifampridine) relative to that in subjects with normal hepatic function. Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf).

The timetable you submitted on April 18, 2019, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	08/2019
Final Protocol Submission:	06/2020
Trial Completion:	07/2021
Final Report Submission:	02/2022

3612-10 Conduct a clinical trial to evaluate the effect of severe renal impairment (creatinine clearance 15-29 mL/min) on the exposure of amifampridine after oral administration of Ruzurgi (amifampridine) relative to that in subjects with normal renal function (i.e., a renal impairment study using reduced design). Please refer to the Guidance for Industry Pharmacokinetics in Patients with Impaired Renal

Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf).

The timetable you submitted on April 18, 2019, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	08/2019
Final Protocol Submission:	06/2020
Trial Completion:	07/2021
Final Report Submission:	02/2022

Submit clinical protocols to your IND 54313 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the 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 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, Medication Guide, and Patient Package Insert (as applicable) 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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see 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).

If you have any questions, contact Michelle Mathers, Regulatory Project Manager, at michelle.mathers@fda.hhs.gov or at (240) 402 2645.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Prescribing Information
Medication Guide
Instructions for Use

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/

WILLIAM H Dunn
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