



NDA 208854

NDA APPROVAL

Shionogi Inc.
Attention: Ting Chen
Senior Director, Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated and received March 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Symproic (naldemedine), 0.2 mg oral tablets.

This new drug application provides for the use of Symproic (naldemedine), 0.2 mg tablets for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

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.

CONTROLLED SUBSTANCE SCHEDULING

The drug substance naldemedine, which is a derivative of naltrexone, is currently controlled in Schedule II under the Controlled Substances Act (CSA). A scheduling recommendation has been transmitted to the Drug Enforcement Administration (DEA) but your drug product remains a Schedule II controlled substance until the DEA has made a final scheduling decision. We further note that, when a final scheduling decision has been published in the Federal Register, you will need to make appropriate revisions to the package insert, Medication Guide, and the carton and immediate-container labels through supplementation of your NDA. This would include the statements in the labeling detailing the scheduling of naldemedine, as the scheduled substance in Symproic, as required under 21 CFR 201.57(a)(2) and (c)(10)(i).

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 package insert and Medication Guide). 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 IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels March 23, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels 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 (May 2015, Revision 3)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 208854.**” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Based on the limited available literature, few pediatric patients in all age groups receive round-the-clock opioids for greater than 4 weeks. There is also a lack of consensus on the use of opioids for the treatment of chronic non-cancer pain in pediatric patients.

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 an unexpected serious risk of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke.

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:

- 3174-1 A post-marketing, observational epidemiologic study comparing Symproic (naldemedine) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Ensure an adequate number of patients with at least 12 months of Symproic (naldemedine) exposure at the end of the study.

The timetable you submitted on February 27, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2017
Study Completion:	11/2023
Final Report Submission:	11/2025

ADDITIONAL STUDY INFORMATION

Your study protocol should specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to Symproic (naldemedine)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among Symproic (naldemedine) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the Symproic (naldemedine)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria.

Submit the protocol(s) to your IND 107475 with a cross-reference letter to this NDA. Submit all final report(s) 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 package insert, Medication Guide, and patient PI (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 package insert, 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).

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 this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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 CDR Cheronda Cherry-France, Regulatory Project Manager, at (301) 796-7295.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s):

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
03/23/2017