DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020533/S-034

APPROVAL LETTER

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

Attention: Prabha Kannan
Senior Regulatory Affairs Specialist

Dear Ms. Kannan:

Please refer to your Supplemental New Drug Application (sNDA) dated June 22, 2017, received June 22, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Naropin (ropivacaine HCL Injection, USP).

This Prior Approval supplemental new drug application proposes for a change (b) (4) (b) (4)

APPROVAL

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

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.

Since Naropin was approved on September 24, 1996, we have become aware that a leachables study conducted to support the safety of a newly proposed (b) (4) for the Naropin product container closure system identified several compounds above the safety qualification threshold. A toxicological risk assessment was provided to justify the safety of these leachable compounds. However, there were not adequate data to justify the local safety of two leachable compounds that include (b) (4) Additionally, the conducted leachables study only examined one drug product batch on stability rather than multiple batches (e.g., at least three) as we generally recommend in accordance with USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical

Packaging/Delivery Systems. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 risk of genetic, general, or local tissue toxicity resulting from compounds that could leach from the container closure system into the drug product solution over the course of stability.

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 this serious risk.

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

3331-1 Conduct a new leachables study to adequately characterize the leachables profile associated with the newly proposed (b) (4) Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. The materials tested should include any secondary container closure systems, if present, and be subjected to the same (b) (4) methods, as appropriate. Establish an AET of (b) (4) mcg/day. Based on these results, provide a revised toxicological risk assessment for any leachable above (b) (4) mcg/day.

Draft Protocol Submission:	March 2018
Final Protocol Submission:	April 2018
Study/Trial Completion:	June 2020 (based on the expiry dating of Naropin PPA)
Interim /Other:	August 2019
Final Report Submission:	August 2020

3331-2 Conduct a single-dose intrathecal toxicity study with acute and delayed sacrifices in a single species to qualify the local and systemic safety of (b) (4) at the levels identified as leachables in the migration studies.

Draft Protocol Submission:	March 2018
Final Protocol Submission:	May 2018
Study/Trial Completion:	August 2018
Final Report Submission:	January 2019

Submit the protocol(s) to your IND 31121, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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)".

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.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at 301-796-1268.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia,
And Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SHARON H HERTZ
02/15/2018