



NDA 021217/S-014

**SUPPLEMENT APPROVAL**

Mallinckrodt, Inc.  
675 McDonnell Boulevard (30-2)  
Hazelwood, MO 63042

Attention: Linda F. Noa, M.S., RAC  
Senior Manager, Regulatory Affairs

Dear Ms. Noa:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EXALGO (Hydromorphone HCl) extended-release tablets.

We acknowledge receipt of your amendments dated June 13, June 20, July 8, and August 7, 2014.

This supplemental new drug application provides for modifications to the approved risk evaluation and mitigation strategy (REMS) for EXALGO.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for the ER/LA Opioid Analgesics REMS, of which EXALGO is a member, was originally approved on July 9, 2012, and the most recent REMS modification was approved on April 15, 2013. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of:

Revisions to the ER/LA Opioid Analgesics REMS Blueprint, ER/LA opioid analgesic REMS Website, and the Dear Prescriber Letter (DHCP) letter to incorporate the following safety labeling changes:

- i. New indication for ER/LA opioid analgesics.
- ii. New warning for Neonatal Opioid Withdraw Syndrome (NOWS).
- iii. Updated language for the following Warnings and Precautions:
  1. Addiction, Abuse, and Misuse
  2. Life-Threatening Respiratory Depression
  3. Accidental Ingestion

4. Cytochrome P450 3A4 Interaction (for applicable products)
  - iv. Revisions to the Blueprint to incorporate updated product-specific titration language.

Changes to the ER/LA Opioid Analgesics REMS Blueprint to include product-specific information for ER/LA opioids approved after the last ER/LA REMS modification on April 15, 2013.

Your proposed modified REMS, received on August 7, 2014, and appended to this letter, is approved.

This REMS uses a single, shared system for the elements to assure safe use, and the REMS assessments are jointly completed by the ER/LA opioid analgesic application holders. This single shared system, known as the ER/LA Opioid Analgesics REMS Program, currently includes the products listed on the FDA REMS website, available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf>. Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the ER/LA Opioid Analgesic REMS Program REMS is due annually on July 9. There are no changes to the REMS assessment plan.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A).

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 021217 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY)**

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 021217 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 021217  
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 021217  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

**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 questions, call Diana Walker, Senior Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Judith A. Racoosin, MD, MPH  
Deputy Director for Safety  
Division of Anesthesia, Analgesia,  
and Addiction Drugs  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
REMS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JUDITH A RACOOSIN  
08/19/2014