



NDA 021217/S-012

**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 August 23, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EXALGO (hydromorphone HCl) 8-, 12-, 16-, and 32-mg Extended-Release Tablets.

We acknowledge receipt of your amendments dated January 3, and April 18 and 30, 2014, and your risk evaluation and mitigation strategy (REMS) assessment dated August 23, 2013.

This Prior Approval supplemental new drug application proposes the addition of a REMS for the authorized generic for EXALGO (hydromorphone HCl).

**APPROVAL & LABELING**

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

In addition, we have found the REMS assessment to be adequate.

**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 Medication Guide, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, 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 titled "SPL Standard for Content of Labeling Technical Qs and As at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels 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 – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. 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 021217/S-012.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for the authorized generic for EXALGO, hydromorphone HCl extended-release tablets, to ensure the benefits of the drug continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The REMS for EXALGO (hydromorphone HCl) was originally approved on March 1, 2010, and REMS modifications were approved on July 9, 2012, and April 15, 2013.

The proposed REMS for hydromorphone HCL extended-release tablets is identical to the modified EXALGO REMS which was approved on April 15, 2013, with the exception of the Medication Guide, which is revised to substitute the authorized generic name hydromorphone hydrochloride extended-release tablets for the trade name EXALGO.

Your proposed REMS for the authorized generic, hydromorphone HCL extended-release tablets, submitted on August 23, 2013, and appended to this letter, is approved.

The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments. This single, shared system, known as the Extended-release/Long-acting (ER/LA) Opioid Analgesic REMS Program, currently includes the products listed in Appendix 1. Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS and the assessment plan for the authorized generic of EXALGO, hydromorphone HCL extended-release tablets, will be the same as that described in our REMS modification approval letter dated July 9, 2012 for EXALGO, a member of the ER/LA Opioid Analgesic REMS Program

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.

Under section 505-1(g)(2)(C), FDA may require the submission of a REMS assessment if FDA determines that that an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits of the drug outweigh the risks of the drug or minimize the burden on the health care delivery system of complying with the strategy.

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

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)**

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.

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. 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, call Diana Walker PhD, Sr. 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 Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

### ENCLOSURES:

Appendix 1: List of applications having the  
ER/LA opioid analgesics REMS  
Content of Labeling  
Carton and Container Labeling  
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  
06/17/2014