DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021217/S-004

SUPPLEMENT APPROVAL

Mallinckrodt, Inc.
675 McDonnell Boulevard
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 January 31, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EXALGO (hydromorphone HCl) 8-, 12-, and 16-mg Extended-Release Tablets.

We acknowledge receipt of your amendments dated March 30, May 18, May 25, June 29, July 3, 6, 11, and 13, and August 1 and 6, 2012, and your risk evaluation and mitigation strategy (REMS) assessment dated February 25, 2011.

This "Prior Approval" supplemental new drug application proposes the following changes: 1) addition of the 32 mg strength EXALGO (hydromorphone HCl) extended-release tablet, and 2) a proposed modification to the approved REMS for EXALGO, which is part of the single, shared system REMS for Extended Release and Long-Acting Opioid Analgesics.

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.

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, 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 & 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 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

We acknowledge your July 13, 2012, submission containing final printed carton and container labels.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for EXALGO (hydromorphone HCl) Extended-Release Tablets was originally approved on March 1, 2010, and REMS modifications were approved on March 24, 2010 and July 9, 2012. 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. Your proposed modification to the REMS consists of the addition of the 32 mg strength to the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting (ER/LA) Opioid Analgesics (FDA Blueprint).

Your proposed modification also includes the following technical changes to the FDA Blueprint:

1) Corrections to the section entitled “Dolophine: Specific Drug Interactions” (page 10), which, as approved on July 9, 2012, incorrectly states that:
    - CYP 450 inducers may increase methadone levels
    - CYP 450 inhibitors may decrease methadone levels

    The proposed modification revises this section to state that:
    - CYP 450 inducers may decrease methadone levels
    - CYP 450 inhibitors may increase methadone levels

2) Corrections to the section entitled "Kadian" (page 11), to add the intermediate dosage strengths 40 mg, 70 mg, 130 mg, and 150 mg of Kadian (morphine sulfate extended release) capsules that FDA approved on July 9, 2012.

3) Corrections to the sections entitled "Exalgo: Key Instructions" and "Exalgo: Drug Specific Adverse Reactions" (page 11), which, as approved on July 9, 2012, incorrectly state:
    - Do not use in patients with sulfa allergy—contains sodium metabisulfite.
    - Allergic manifestations to sulfa component

    The proposed modifications revise these sections to state:
    - Do not use in patients with sulfite allergy—contains sodium metabisulfite.
    - Allergic manifestations to sulfite component

Your proposed modified REMS, submitted on August 6, 2012, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on July 9, 2012.

There are no changes to the REMS assessment plan described in our July 9, 2012, letter.

In addition to the assessments submitted according to the timetable included 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) of FDCA.

We remind you that section 505-1(f)(8) of the 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.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

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/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. 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 L. Walker, Ph.D., Sr. Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Sharon H. Hertz, M.D.
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labels
REMS

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
08/24/2012