



NDA 021217/S-002

SUPPLEMENT APPROVAL

Mallinckrodt, Inc.
675 McDonnell Blvd.
Hazelwood, MO 63042

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

Dear Ms. Noa:

Please refer to your Supplemental New Drug Application (sNDA) dated August 12, 2011, received August 12, 2011, 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 September 23, 2011, and February 15, March 22, April 26, May 11 and 25, and June 14 and 19, 2012, and your risk evaluation and mitigation strategy (REMS) assessment dated February 25, 2011.

This supplemental new drug application proposes modifications to the approved REMS for EXALGO (hydromorphone HCl) Extended-Release Tablets.

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, Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effectuated" (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 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).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your September 23, 2011, submission containing final printed carton and container labels.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

On February 18, 2009, you were notified that in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for certain long-acting and extended-release (LA/ER) opioid products, including EXALGO, to ensure that the benefits of the drugs continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The REMS for EXALGO was originally approved on March 1, 2010, and a REMS modification was approved on March 24, 2010. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

On April 18, 2011, you were also notified that in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class of ER/LA opioids. Your proposed modifications to the REMS consist of changes to conform to the single shared REMS system developed for the ER/LA opioids indicated for treatment of pain.

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.

Your proposed REMS is appended to this letter and approved.

This REMS will use a single, shared system for the elements to assure safe use and the REMS assessments. This single, shared system, known as the ER/LA Opioid REMS, currently includes the products listed in Appendix 1. Other products may be added in the future if additional NDAs or ANDAs are approved.

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.

Scheduled REMS Assessments

1. The first REMS assessment, due not later than six months from the date of REMS approval, should provide a report on the actions you have taken to implement the REMS since it was approved. The report should include the following information:
 - a. Grant Proposals: The status of the requests for proposals for grants for CE training including: 1) how many have issued and when will the next requests for proposals issue; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each of the grantees will make their CE training available; 6) a high-level description of each program (e.g., web based, live); and 7) an estimate of how many prescribers are expected to be trained under each program.
 - b. Evaluation Grants: The status of the requests for proposals for special grants to CE providers or other CE organizations with expertise in assessing CE outcomes who agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken training funded under this REMS to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS-compliant training, and 5) the dates of their follow-up evaluation.
 - c. Functional Components:
 - i. Date when the ER/LA Opioid REMS website was live and functional.
 - ii. Prescriber Letter 1: 1) Date when letter was posted on the ER/LA Opioid REMS website 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.
 - iii. Professional Organization/Licensing Board Letter 1: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.
 - iv. Date when the single number toll free call center was operational.
2. The second REMS assessment, due one year from the date of this letter, should include the following information:
 - a. Functional Components:
 - i. Training: 1) Date the first REMS-compliant training was available; 2) a high-level description of the training (e.g., web based, live); 3) the number of

- prescribers that have undergone the training, and 4) an estimate of how many prescribers will be trained under the program(s).
- ii. Prescriber Letter 2: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.
 - iii. Professional Organization/Licensing Board Letter 2: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.
- b. Grant Proposals: An update on the status of the requests for proposals for grants for REMS-compliant training, including: 1) new grant requests for proposals published; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each grantee will make or has made their REMS-compliant training available; 6) a high-level description of each program (e.g., web based, live), and 7) an estimate of how many prescribers will be trained under each program.
- c. Evaluation Grants: The status of the requests for proposals for special grants to CE providers who also agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken their ER/LA Opioid REMS-funded training to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS-compliant training, and 5) the dates of their follow-up evaluation.
3. The third REMS assessment, due two years from the date of this letter, should include the following information:
- a. Prescriber Letter 3: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.
 - b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training. Performance goals, based on the 2011 estimate that 320,000 prescribers are active prescribers of ER/LA opioids (prescribers who have prescribed an ER/LA opioid within the last 12 months), are as follows:
 - i. Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of active prescribers) are to have been trained;
 - ii. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of active prescribers) are to have been trained;

- iii. Within four years from the time the first REMS- compliant training becomes available, 192,000 prescribers (based on 60% of active prescribers) are to have been trained.
- c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by providers to provide the REMS-compliant training. Audits must be conducted on a random sample of 1) at least 10% of the training funded under the ER/LA Opioid REMS, and 2) REMS-compliant training not funded under the ER/LA Opioid REMS that will be counted as REMS-compliant training for purposes of meeting the milestones in 3a., and must evaluate:
 - i. whether the content of the training covers all elements of the FDA “blueprint” approved as part of the REMS;
 - ii. whether the post-course knowledge assessment measures knowledge of all sections of the FDA “blueprint”; and
 - iii. whether the training was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies.
 - d. Evaluation of Patient Understanding: The results of an evaluation of patients’ understanding of the serious risks of these products and their understanding of how to use these products safely. This evaluation may include, for example, surveys of patients.
 - e. Surveillance Results: Results of surveillance for misuse, abuse, overdose, addiction, and death. Surveillance needs to include information on changes in abuse, misuse, overdose, addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency departments, addiction treatment centers, poison control call centers). The information should be drug-specific whenever possible.
 - f. Drug Utilization Patterns: An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of ER/LA opioids, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills;
 - g. Patient Access: An evaluation of changes in patients access to ER/LA Opioids.
 - h. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.
 - i. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

4. The fourth and subsequent REMS assessments should include the following information:
- a. Prescriber Letter 3: 1) number of prescriber letters electronically sent, received, undeliverable, and opened, and 2) number of prescriber letters mailed and undeliverable.
 - b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training (see 3.a above).
 - c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by the CE providers to provide the REMS-compliant training (see 3.b above).
 - d. Evaluation of Prescriber Understanding:
 - i. The results of an evaluation of ER/LA opioid prescribers' awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.
 - ii. The results of any long-term evaluation of prescribers of ER/LA opioids who have taken ER/LA Opioid REMS-funded training to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training.
 - e. Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely. (See 3.c above).
 - f. Surveillance Results: Results of surveillance and monitoring for misuse, abuse, overdose, addiction, and death (see 3.d above).
 - g. Drug Utilization Patterns: An evaluation of drug utilization patterns (see 3.e above).
 - h. Patient Access: An evaluation of changes in patient access to ER/LA opioids.
 - i. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.
 - j. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Definitions: For purposes of these REMS assessments, the following definitions apply:

1. *REMS-compliant training:* Training will be considered “REMS-compliant training” if 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA “blueprint”, 3) it includes a post-course knowledge assessment of all of the sections of the “FDA blueprint”, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.
2. *FDA Blueprint:* A document entitled, “Blueprint for Prescriber Continuing Education Programs Extended-Release and Long-Acting Opioids,” approved as part of this REMS, that contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioids.

Other REMS Assessment Requirements

All assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Submit this information, if applicable, to your individual application. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

Under section 505-1(g)(2)(C) and (D), FDA may require the submission of a REMS assessment if FDA determines that new safety or effectiveness information indicates that a REMS element should be modified or included in 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 and may propose a modification 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)**

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
REMS ASSESSMENT**

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

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Division 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 Labeling
REMS

Appendix 1 List of applications

NDA 021260	AVINZA (morphine sulfate) extended-release capsules
NDA 021306	BUTRANS (buprenorphine) Transdermal System for transdermal administration
NDA 006134	DOLOPHINE (methadone hydrochloride) tablets and its generic equivalents
ANDA 087997	Methadone Oral Solution and its generic equivalents
ANDA 087393	Methadone Oral Solution and its generic equivalents
ANDA 089897	Methadone Oral Concentrate
NDA 019813	DURAGESIC (Fentanyl Transdermal System) for transdermal administration and its generic equivalents
NDA 022321	EMBEDA (morphine sulfate and naltrexone hydrochloride) extended-release capsules
NDA 021217	EXALGO (hydromorphone HCl) Extended-Release Tablets
NDA 020616	KADIAN (morphine sulfate) extended-release capsules and its generic equivalent
NDA 019516	MS CONTIN (morphine sulfate) controlled-release tablets and its generic equivalents
NDA 200533	NUCYNTA ER (tapentadol) extended-release oral tablets
NDA 201655	OPANA ER (oxymorphone hydrochloride) Extended-Release tablets
NDA 021610	OPANA ER (oxymorphone hydrochloride) Extended-Release tablets and its generic equivalents
NDA 020553	OXYCONTIN (oxycodone hydrochloride controlled-release) Tablets
NDA 022272	OXYCONTIN (oxycodone hydrochloride controlled-release) Tablets

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

/s/

JUDITH A RACOOSIN on behalf of BOB A RAPPAPORT
07/09/2012