



NDA 021217/S-015

**SUPPLEMENT APPROVAL
REMS ASSESSMENT PLAN REVISION**

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 March 5, 2015, received March 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exalgo (hydromorphone) extended-release.

We acknowledge receipt of your amendment dated June 17, 2015.

This supplemental new drug application provides for proposed modifications to the approved risk evaluation and mitigation strategy (REMS) for Exalgo. This supplement is in response to our February 3, 2015, REMS Modification Notification letter, and our April 9, 2015, email advising you that your proposed REMS modification should also include revised titration information for Dolophine (methadone HCl tablets).

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 extended release and long-acting (ER/LA) opioid analgesics products, of which Exalgo is a member, was originally approved on July 9, 2012, and the most recent REMS modification was approved on August 19, 2014. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Exalgo outweigh its risks, we determined that you were required to make the following REMS modifications:

Changes to the ER/LA Opioid Analgesics REMS Blueprint for Prescriber Education to incorporate:

1. Product-specific information for a recently approved ER/LA opioid analgesic, Hysingla ER (hydrocodone bitartrate extended-release) tablets
2. Newly approved intermediate strengths of fentanyl transdermal systems
3. Revised titration information for Dolophine (methadone HCl tablets)

Your proposed modified REMS, submitted on June 17, 2015, 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. 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/remis>.

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 is due annually on July 9. Some aspects outlined in the original REMS assessment plan approved on July 9, 2012, are no longer applicable, as those time-specific elements (special instructions for the 6-month, 12-month, and 24-month assessments) have already been implemented. Therefore, included below is a revised assessment plan intended for all applicants, including those who currently participate in this REMS, as well as those that join the REMS in the future.

The revised REMS assessment plan must include, but is not limited to, the following:

- 1) Documentation of the dissemination of Prescriber Letter 3:
 - a) number of prescriber letters electronically sent, received, undeliverable, and opened, and
 - b) number of prescriber letters mailed and undeliverable.
- 2) Prescriber Training: Documentation of the number of prescribers of ER/LA opioid analgesics 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:
 - a) 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;
 - b) 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;

- c) 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.
- 3) 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. Audits must be conducted on a random sample of at least 10% of the training funded under the ER/LA Opioid REMS, and a random sample of 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 item 2 above and must evaluate:
 - a) whether the content of the training covers all elements of the FDA “blueprint” approved as part of the REMS;
 - b) whether the post-course knowledge assessment measures knowledge of all sections of the FDA “blueprint”; and
 - c) 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.
 - 4) Evaluation of Prescriber Understanding:
 - a) 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.
 - b) 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.
 - 5) 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.
 - 6) Surveillance Results: Results of surveillance and monitoring 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.
 - 7) Drug Utilization Patterns: An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of ER/LA opioid analgesics, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills.
 - 8) Patient Access: An evaluation of changes in patient access to ER/LA opioid analgesics.

- 9) Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.
- 10) Goals: The requirements for assessments of an approved REMS under section 505-1(g)(3) of the FDCA 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.

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

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.

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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that 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 the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: Provision of as many of the currently listed assessment plan items as is feasible.

- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

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.

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

Prominently identify any 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/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 021217/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 021217/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021217/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 021217

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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 Mark Liberatore, PharmD, Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
REMS

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
06/26/2015