Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Modification Set # 1

Date:	January 25, 2013
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Drug Name(s):	See table below
Therapeutic Class:	Opioid Agonist: Extended-Release and Long-Acting Opioid Analgesic Drug Products

Drug Name	Dosage and Route	Application Type/Number	Submission Number (eCTD)	Applicant/ Sponsor	TSI #
Avinza (morphine sulfate)	extended-release capsules	NDA 021260	0011	King	466
Butrans (buprenorphine)	Transdermal System	NDA 021306	0085 0087	Purdue	466 880
Dolophine (methadone hydrochloride)	tablets	NDA 006134	0015 0017	Roxanne	466 254
Duragesic (Fentanyl Transdermal System)	Transdermal system	NDA 019813	0078 0079	Ortho-McNeil	466 392 255
Embeda (morphine sulfate and naltrexone hydrochloride)	extended-release capsules	NDA 022321	0073	Alpharma/King	466 1083 1135

Exalgo (hydromorphone HCl)	extended-release capsules	NDA 021217	0104	Mallinkrodt	466
Kadian (morphine sulfate)	extended-release capsules	NDA 020616	0024 0025	Actavis	466
MS Contin (morphine sulfate)	controlled-release tablets	NDA 019516	0027 0028	Purdue	466
Nucynta ER (tapentadol)	extended-release oral tablets	NDA 200533	0080 0081	Ortho-McNeil	466 926
Opana ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 201655	0052 0060	Endo	466
Opana ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 021610	0045	Endo	466
Oxycontin (oxycodone hydrochloride	controlled-release tablets	NDA 020553	0074	Purdue	466 1136
Oxycontin (oxycodone hydrochloride	controlled-release tablets	NDA 022272	0158	Purdue	466 1072

OSE RCM # 2012-2535

*** This document contains proprietary and confidential information that should not be released to the public. ***

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1 INTRODUCTION

This is a review of the proposed Risk Evaluation and Mitigation Strategy (REMS) modification for extended-release and long-acting (ER/LA) opioid analgesics initially received between September 28, 2012 and October 31, 2012.

The ER/LA Opioid Analgesics REMS was originally approved on July 9, 2012. As described in the Final REMS Review by the Division of Risk Management (DRISK), dated July 6, 2012, the FDA determined that ER/LA opioid analgesics were required to have a REMS to ensure that the benefits of the drug outweighed the increased risks of addiction, unintentional overdose, and death resulting from inappropriate prescribing, misuse, and abuse.

2 BACKGROUND

The ER/LA opioid analgesics REMS is a single shared system (SSS) and includes the following products[1]:

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

The manufacturers of ER/LA opioid analgesics are collectively referred to as the REMS Program Companies (RPC).

[1] The ANDAs for select methadone products are listed because there is no corresponding reference listed NDA for these products.

3 REGULATORY HISTORY

On August 24, 2012, the Agency approved the Exalgo 32 mg strength, which resulted in a modification to ER/LA Opioid Analgesics REMS to revise the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (FDA Blueprint) to add the new strength. Additionally, after initial approval of the ER/LA Opioid Analgesic REMS, the Agency became aware of three modifications to the FDA Blueprint, which were incorporated into this modification. The following modifications to Section VI. Specific Drug Information for ER/LA Opioid Analgesic Products in the FDA Blueprint were identified:

1. Dolophine: Revised information regarding the effects of cytochrome P450 (CYP450) inducers and CYP450 inhibitors on Dolophine
2. Kadian: Addition of approved dosage strengths
3. Exalgo: Revised the statement regarding allergies to indicate that Exalgo is associated with a sulfa allergy instead of a sulfite allergy

On August 28, 2012, the Agency approved an efficacy supplement for a new indication for Nucynta ER for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults. The efficacy supplement only affected the Medication Guide (MG), which was revised to include the new indication. Therefore, while a REMS modification was necessary, revisions to REMS materials other than the MG were not warranted.

On September 21, 2012, the Office of New Drugs (OND) sent an email to the RPC, requesting each Sponsor to submit a proposed REMS modification to their respective application in order to reflect the recent modifications and to ensure all members of the SSS were approved with the current version of the REMS. The Agency requested all Sponsors to submit a REMS modification with the following revisions to the FDA Blueprint:

1. Section entitled “Dolophine: Specific Drug Interactions” (page 10) incorrectly states that:
    - CYP 450 inducers may increase methadone levels
    - CYP 450 inhibitors may decrease methadone levels

    The proposed modification should revise this section to state the following:
    - CYP 450 inducers may decrease methadone levels
    - CYP 450 inhibitors may increase methadone levels

2. Addition of 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 to Section entitled “Kadian” (page 11).

3. 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 modification should revise these sections to state:

- Do not use in patients with sulfite allergy—contains sodium metabisulfite.
- Allergic manifestations to sulfite component

4. Addition of the newly approved 32 mg dosage strength for Exalgo (Hydromorphone Hydrochloride Extended-Release) tablets that was approved on August 24, 2012 to the section entitled "Exalgo" (page 11).

On December 20, 2012, the Agency received notification via email of changes the RPC implemented to the REMS website after the REMS modification submission on October 10, 2012. Changes/revisions were indicated by red boxes encapsulating text or graphics. In many instances, the red boxes were not very informative as to the nature of the specific changes implemented. On December 21, 2012, DRISK asked the RPC to provide a detailed summary of all the changes to the website that have been implemented without prior Agency review. On December 21, the RPC emailed a document outlining the revision history for the REMS website. On January 2, 2013, DRISK requested further follow-up due to lingering questions about changes on the page listing covered brand and generic products under the REMS program. On January 4, 2013, the RPC responded to the Agency's inquiry indicating that:

1. The changes to the website relative to Medication Guides and U.S. Prescribing Information only include addition of or changes to the hyperlink URLs linking to Medication Guides maintained by individual member companies.
2. Changes to the REMS website were made per email correspondence from the Regulatory Project Manager received on July 13, 2012 stating the following:

> "The Opioid REMS Steering Committee met today and discussed how to handle REMS modifications. We recognize how time consuming it would be for the RPC companies to have to submit a REMS modification every time there is a minor change made to the website, the blueprint, and so forth. We are trying to develop a process to make these modifications as simple as possible, but we anticipate that this will take some time. In the mean time, we ask that you notify us by letter whenever you make a change."

4 MATERIALS REVIEWED

4.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed for the proposed ER/LA Opioid Analgesics REMS Modification[2]:

[2] On October 10, 2012, the RPC representative emailed Mark Liberatore, the OSE Project Manager, the proposed REMS modification. These documents were stated as the gold standard documents submitted by NDA/ANDA holders. DRISK reviewed and provided comments on the gold standard documents only.

Drug Name	Application Type/Number	Submission Number	FDA Receive Date
AVINZA (morphine sulfate)	NDA 021260	0011	10/23/2012
BUTRANS (buprenorphine)	NDA 021306	0085 0087	10/19/2012 12/13/2012
DOLOPHINE (methadone hydrochloride)	NDA 006134	0015 0017	09/28/2012 10/25/2012
DURAGESIC (Fentanyl Transdermal System)	NDA 019813	0078 0079	10/22/2012 11/20/2012
EMBEDA (morphine sulfate and naltrexone hydrochloride)	NDA 022321	0073	10/23/2012
EXALGO (hydromorphone HCl)	NDA 021217	0104	10/23/2012
KADIAN (morphine sulfate)	NDA 020616	0024 0025	10/19/2012 12/12/2012
MS CONTIN (morphine sulfate)	NDA 019516	0027 0028	10/19/2012 12/13/2012
NUCYNTA ER (tapentadol)	NDA 200533	0080 0081	10/31/2012 11/26/2012
OPANA ER (oxymorphone hydrochloride)	NDA 201655	0052 0060	10/19/2012 11/26/2012
OPANA ER (oxymorphone hydrochloride)	NDA 021610	0045	10/19/2012
OXYCONTIN (oxycodone hydrochloride	NDA 020553	0074	10/19/2012
OXYCONTIN (oxycodone hydrochloride	NDA 022272	0158	10/19/2012

4.2 OTHER MATERIALS INFORMING THE REVIEW

- Division of Risk Management REMS Review for Nucynta ER (dated August 28, 2012)

- Division of Risk Management REMS Review for Exalgo (dated August 7, 2012)

5 SUMMARY OF APPLICANT'S PROPOSED REMS MODIFICATION

5.1 GOALS

There are no recommendations for revisions to the goals of the REMS.

5.2 REMS ELEMENTS

5.2.1 Medication Guide

The respective NDA/ANDA holders have proposed changes to the Medication Guides of the following products:

- AVINZA - Change of address
- OPANA ER (NDA 21610)- Change of address
- OPANA ER (NDA 201655)- Change of address
- DOLOPHINE- Addition of a missing clause, "...and miss a dose...."
- EXALGO - Remove a "b" placed after the issue date at the bottom, as in "July 2012 b".

These revisions will not impact the Medication Guides for the generic drug products. The Medication Guides will be reviewed separately by OND.

5.2.2 Elements to Assure Safe Use

5.2.2.1 Training will be made available to healthcare providers who prescribe ER/LA opioid analgesics

FDA Blueprint

The RPC proposed all revisions to the Blueprint as requested in the REMS Modification Notification email on September 21, 2012. Additionally, the RPC proposed the following revision to the Blueprint:

The subsection entitled *Use in Opioid-Tolerant Patients* under the drug product Kadian has been revised to read as:

> Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant--patients only
>
> *Reviewer Comment:*
>
> The proposed revision is acceptable. The language has been revised to be consistent with Kadian's current approved labeling.

Prescriber Letters 1, 2, and 3

There are no recommendations for revisions to the letters.

Organization Letters 1 and 2

There are no recommendations for revisions to the letters.

Patient Counseling Document

There are no recommendations for revisions to the Patient Counseling Document.

REMS Website

The NDA/ANDA holders proposed the following changes to the REMS website:

1. Inclusion of a new page directed towards continuing education providers with details about applying for educational grants to develop REMS-compliant training programs,
2. Updates to the page listing covered products under the REMS program with newly approved products (e.g. Methadose and oxymorphone hydrochloride (sponsored by Impax) and updated links for the respective Medication Guide and U.S. Prescribing Information, and
3. Addition of new questions and responses for Patient, Prescriber, and Continuing Education and Grant Frequently Asked Questions (FAQs), and Timetable for Submission of Assessments

Reviewer's Comments:

Based on the information provided by the RPC, the majority of the revisions are within the scope authorized by the Agency in regards to modifying the REMS website. The only significant area of concern identified was on the page of the website title "Products covered under the ER/LA Opioid Analgesic REMS Program," where a small number of the products listed do not have active links to their approved Medication Guides and/or U.S. Prescribing Information, which is a requirement of the REMS.

Comments for the sponsor regarding this concern are included in Section 7.3 below. Additionally, DRISK has proposed additional modifications to improve the effectiveness of the website.

5.3 REMS ASSESSMENT PLAN

There are no recommendations for revisions to the Assessment Plan.

5.4 REMS SUPPORTING DOCUMENT

The NDA/ANDA holders proposed a revision the Supporting Document by adding Table 2 to the Table of Contents.

Reviewer Comments:

The mention of Table 2 in the Table of Contents was inadvertently deleted from the REMS Supporting Document at the time of initial REMS approval. The proposed revision is acceptable.

6 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the ER/LA opioid analgesic REMS modification proposal be sent to the applicant. Please request that the applicants respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA submission.

The comments below are based on DRISK's preliminary review of the REMS modification proposal for ER/LA opioid analgesics. Appended to this review is the REMS modification proposal and FDA Blueprint, including our track changes. The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

7 COMMENTS FOR THE APPLICANT

7.1 REMS DOCUMENT

Revise the header of the document to read as:

Initial REMS Approval: 07/2012

Most Recent Modification: XX/2013

7.2 MEDICATION GUIDE

All NDA/ANDA holders must resubmit the final Medication Guide for their product to their respective applications with the final REMS modification submission.

7.3 ELEMENT TO ASSURE SAFE USE

FDA Blueprint

1. The proposed revisions to the FDA Blueprint are acceptable.
2. Replace the current date formatting in the header of the Blueprint with a numerical representation of MONTH and YEAR (e.g. XX/XX/XXXX is revised to XX/2013).

ER/LA Opioid Analgesics REMS Website

Landing Page (Page 1 of 45):

1. Delete the following content currently on the REMS website landing page:

> The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting (ER/LA) opioid analgesics.
>
> A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure that the benefits of a drug outweigh its risks.
>
> ER/LA opioid analgesics companies have worked with the FDA to develop materials for the REMS program to educate and inform healthcare professionals on the safe prescribing of ER/LA opioid analgesics. In addition, CE providers are developing independent CE-accredited educational activities that focus on the safe prescribing of ER/LA opioid analgesics.

2. Replace the language deleted in the comment above with:

> **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**
>
> A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks.
>
> The FDA has required a REMS for extended-release and long-acting (ER/LA) opioid analgesics.

ER/LA Opioid Analgesics REMS Education for Accredited Continuing Education Providers (Page 5 of 45):

Is the RPC going to allow for continual (or rolling) Request for Grant Applications (RFA) submissions by CE providers? If so, the current deadlines for RFA submissions should be removed (and replaced, if necessary) – as this may discourage CE providers from submitting grants.

Products covered under the ER/LA Opioid Analgesics REMS (Page 6-8 of 45)

1. In the Generic Products table, remove all listings of tentatively approved products. Revise the webpage to include only currently approved products.

2. The link(s) to the Medication Guide and/or U.S Prescribing Information for the following drug products are inactivated with "coming soon" placed to the inactivated link:

Brand Name	Company
Methadose	Mallinckrodt
Generic Name	**Company**
Fentanyl transdermal system	Aveva Drug Delivery Systems, Inc., an Apotex Company (marketed by Apotex Corp)
Fentanyl extended-release transdermal system	Mylan Technologies, Inc
Methadone hydrochloride tablets	ThePharmaNetwork, LLC
Morphine sulfate extended-release tablets	Mylan Pharmaceuticals Inc.
Morphine sulfate extended-release capsules	Par Pharmaceticals Companies, Inc.
Oxymorphone hydrochloride extended-release tablets -	Impax (marketed by Global Pharmaceuticals, division of Impax)

Provide an explanation for why active links to the current and approved Medication Guides and/or Prescribing Information for the aforementioned products are not provided.

3. Companies that have completed a transfer of ownership on an application should represent their company name on all documents as :

   Company A d/b/a Company B

   or

   Company A a subsidiary of Company B

Frequently Asked Questions

1. Page 12 of 45: "Does my doctor have to be certified to prescribe me an extended-release opioid?

   No. Unlike other programs, this REMS is a Federal program, and at this time there is no certification requirement or connection to state certification programs."

   FDA Comment: The phrase, "Unlike other programs, this REMS is a Federal program", is confusing because it may imply that other REMS programs are not

7.4 REMS SUPPORTING DOCUMENT

The revision to the REMS Supporting Document is acceptable.

7.5 GENERAL COMMENTS

Resubmission Requirements and Instructions: Submit the revised proposed REMS modification for the ER/LA opioid analgesics with attached materials. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document.

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

/s/

DANIELLE SMITH
01/25/2013

REEMA J MEHTA
01/26/2013