Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Division of Risk Management (DRISK)

Review of 6-month Risk Evaluation and Mitigation Strategy (REMS) Assessment Report

Date: February 14, 2012

Reviewer: Julia Ju, Pharm.D., Ph.D.
Social Science Reviewer
Assessment team, DRISK

Team Leader: Doris Auth, Pharm. D.
Assessment Team, DRISK

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Drug Name(s): See table below

Therapeutic Class: Extended-release and long-acting opioid analgesic products

OSE RCM #: 2013-139

Drug Name	Dosage and Route	Application Type/Number	Applicant\ Sponsor	TSI #
AVINZA (morphine sulfate)	extended-release capsules	NDA 021260	King	466
BUTRANS (buprenorphine)	transdermal system	NDA 021306	Purdue	466 880
DOLOPHINE (methadone hydrochloride)	tablets	NDA 006134	Roxane	466 254
Methadone	oral solution	ANDA 087997	Roxane	--
Methadone	oral solution	ANDA 087393	Roxane	--
Methadone	oral concentrate	ANDA 089897	Roxane	--

DURAGESIC (Fentanyl Transdermal System)	transdermal system	NDA 019813	Ortho-McNeil	466 392 255
EMBEDA (morphine sulfate and naltrexone hydrochloride	extended-release capsules	NDA 022321	Alpharma/King	466 1083 1135
EXALGO (hydromorphone HCl)	extended-release capsules	NDA 021217	Mallinkrodt	466
KADIAN (morphine sulfate)	extended- release capsules	NDA 020616	Actavis	466
MS CONTIN (morphine sulfate)	controlled-release tablets	NDA 019516	Purdue	466
NUCYNTA ER (tapentadol)	extended-release oral tablets	NDA 200533	Ortho-McNeil	466 926
OPANA ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 201655	Endo	466
OPANA ER (oxymorphone hydrochloride)	extended- release oral tablets	NDA 021610	Endo	466
OXYCONTIN (oxycodone hydrochloride	controlled-release tablets	NDA 020553	Purdue	466 1136
OXYCONTIN (oxycodone hydrochloride	controlled-release tablets	NDA 022272	Purdue	466 1072

1 INTRODUCTION

This memorandum provides a review and comments to the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) from the Division of Risk Management (DRISK) in response to the Risk Evaluation and Mitigation Strategy (REMS) 6 month assessment report for ER/LA opioid analgesic drug products.

2 BACKGROUND

ER/LA opioid analgesic medicines are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The ER/LA opioid analgesics include Avinza, Butrans, Dolophine, Duragesic, Embeda, Exalgo, Kadian, MS Contin, Nucynta ER, Opana ER, Oxycontin ER, Palladone, and generic versions of any of these brands.

On April 19, 2011, the Food and Drug Administration (FDA) notified manufacturers of ER/LA opioid analgesics that a class-wide, single shared REMS was required. The sponsors of the ER/LA opioid analgesics formed an industry working group called the REMS Program Companies (RPC) to prepare the REMS proposal for FDA approval and to operationalize the REMS program once approved. On July 9, 2012, the single-shared ER/LA opioid analgesics REMS was approved.

The goal of the ER/LA opioid analgesics REMS program is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

REMS elements include a Medication Guide, Elements to Assure Safe Use (ETASU) (training will be made available to healthcare providers who prescribe ER/LA opioid analgesics), and a timetable for submission of assessments of the REMS at 6 months and 12 months after the initial approval date of the REMS, and annually thereafter. The first prescriber training must be available by March 1, 2013.

The primary communication methods to disseminate the REMS and REMS-compliant training to prescribers include Dear DEA Registered Prescriber (DDRP) letters and Letters to Professional Organizations and Licensing Boards (POLB). Performance goals established for these communications are:

- DDRP letter 1 will be sent not later than 60 days after the initial approval of the REMS
- DDRP letter 2 will be sent out not later than 30 days before the first prescriber REMS-compliant training
- At least annually from the date of initial approval of the REMS, the DEA registration database will be reviewed and DDRP letter 3 will be sent to all newly DEA registered prescribers
- POLB letter 1 will be sent not later than 60 days after REMS approval
- POLB letter 2 will be sent no later than 30 days before the first prescriber REMS-compliant training is available
- An interim single toll-free number call center must be implemented no later than July 23, 2012, and a fully operational centralized call center must be implemented no later than 90

calendar days after the approval of the REMS.

The REMS Assessment Plan includes the followings:

- An assessment of the number of prescribers who have completed REMS-compliant training (first due of grant reports in 6 month assessment; # of prescribers trained in 12 month assessment and annually thereafter)
- A summary of independent audits of training (first due: year 2)
- Evaluation of healthcare provider understanding of the training information using surveys (first due: year 3)
- Evaluation of patient understanding of the safe use of ER/LA opioids using surveys (first due: year 2)
- Surveillance of abuse, misuse, overdose, addiction, and death from ER/LA opioids (first due: year 2)
- Evaluation of drug utilization patterns (first due: year 2)
- Evaluation of prescribing behaviors (first due: year 2)
- Monitoring patterns of prescribing that suggest changes in patient access to ER/LA opioids (first due: year 2).

This 6-month assessment is the first assessment of the ER/LA opioid analgesics REMS, covering the time period from July 9, 2012 through November 9, 2012. This report includes an evaluation of the REMS functional components (REMS website, DDRP letter, POLB letter, and call center), and describes the progress that has been made toward addressing the eight key assessments.

Based on the REMS approval letter, 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.

3 MATERIAL REVIEWED

- July 9, 2012, ER/LA opioid analgesics REMS and REMS approval letter
- December 21, 2012, ER/LA opioid analgesics REMS 6-month assessment report

4 RESULTS

4.1 Functional Components

4.1.1 Dear DEA-Registered Prescriber Letter 1 (DDRP letter 1)

From the DEA Master Registrant file, 1,321,019 unique DEA-registered prescribers and 82,651 hospitals and pharmacies were identified as of July 18, 2012.

- Electronic distribution of the letter by email or facsimile commenced on July 24, 2012, well within the required 60 days following REMS approval.
    - Number of letters sent: 564,320
    - Number of letters received: 484,795
    - Number of letters undeliverable: 79,525
    - Number of letters opened: Unable to know
- The next wave of communication via USPS mail was completed by July 31, 2012.
    - Number of letters mailed: 756,699
    - Number of letters undeliverable: 22,910

Reviewer comments:
The distribution of the DDRP letter 1 met the performance goal that this letter be sent out no later than 60 days after the REMS approval.

4.1.2 Professional Organization/Licensing Board Letter 1 (POLB letter 1)

On August 24, 2012, 46 days after REMS approval, a letter was sent to a total of 265 relevant professional organizations and licensing boards by email and USPS.

- Number of letters electronically sent: 32
- Number of letters mailed: 233
- Number of letters undeliverable: 0
- Number of letters opened: Unable to know

Reviewer comments:
The distribution of the POLB letter 1 met the performance goal that this letter be sent out no later than 60 days after the REMS approval.

4.1.3 Call Center

A centralized call center became operational on July 23, 2012. A total of 268 calls have been received in the reporting period. A summary of frequently asked questions were in Table 1.

Table 1. Top 25 FAQs Utilized From July 23, 2012 -November 8, 2012

FAQ	Utilizations
Are there mandatory components associated with the REMS Program that I must complete (e.g., program enrollment, training), to allow me to continue prescribing ER/LA opioid analgesics to my patients?	50
How are "Prescribers" defined in the ER/LA Opioid Analgesics REMS Program?	22
Will pharmacists be required to complete education/training, enrollment, or verification to dispense these opioid analgesic products?	15
When will this REMS Program education/training be available?	13
Is it really okay to flush my unused opioid pain medicine down the toilet?	13
Are there components of this REMS Program that impact outpatient or mail-order pharmacy practice?	12
How can I find out more about the REMS-compliant education/training and when it becomes available?	11
Is there someone specific to contact if I should have questions about the grant application/process?	10
When will the education/training be available?	8
What is a REMS Program and what is this REMS Program?	7
Who can submit a grant application to support independent, accredited ER/LA Opioid Analgesics REMS prescriber education/training?	7
Are there components of this REMS Program that impact inpatient or long-term care pharmacy practice?	7
Does this REMS Program require pharmacists to counsel patients on the safe use of ER/LA opioid analgesics?	7
If I am a CE provider, what is the process for applying for grant monies?	6
What pain medicines are included in this REMS Program?	5
Where can I go to access additional copies of the Patient Counseling Document (PCD)?	5
What happens if I do NOT participate in REMS-compliant education/training?	5
Who is funding the REMS-compliant, independent, accredited education/training?	5
How can pharmacists obtain the product-specific Medication Guides?	5

FAQ	Utilizations
What extended-release/long-acting (ER/LA) opioid analgesics are involved in this REMS Program?	4
What if I have previously completed a/an [opioid, TIRF1, Butrans, Embeda, Exalgo, Opana, OxyContin] REMS training, do I still need to complete additional education/training for the REMS Program?	4
Did this REMS Program impact the Medication Guides?	4
How do I find the Website/Access this/Troubleshoot that?	3
Can you tell me more about the safety education/training intended for prescribers, such as myself?	3
What areas of education are contained in the FDA's ER/LA Opioid Analgesics REMS 'Blueprint'?	3

Reviewer comments:
The establishment of a fully operational centralized call center on July 23, 2012, exceeded the performance goals regarding the call center.

4.1.4 ER/LA Opioid Analgesics REMS Website

The website, http://www.ER-LA-opioidREMS.com, was launched on July 23, 2012. The following materials can be access through this website:

- REMS overview
- Important safety material
- Medication guides for each of the products included in the REMS
- U.S. prescriber information for each of the products included in the REMS
- Materials for HCPs
  - ER/LA opioid analgesics REMS-compliant training
  - DDRP letters
  - Patient counseling document
  - Medication guides
  - Healthcare professional FAQs
- Materials for patients
  - Medication guides
  - Patient FAQs
- A list of all REMS-compliant CE activities (will be available when CE programs are available)

Reviewer comments:
The REMS website was launched and met the performance goal.

4.2 Assessment 1- Prescribers Training

The RPC prepared and disseminated two Requests for Grant Applications (RFA) informing organizations of the availability of grant funds to support accredited independent continuing education.

- The first RFA was posted to the ER/LA opioid analgesic REMS website on August 22, 2012, six weeks after REMS approval. The due day was September 24, 2012.
    - 36 submissions were received in response to the first RFA for CE grants.
    - One grant has been awarded at the time of this report data lock. The grantee is Trustees of Boston University, in partnership with the Federation of State Medical Boards, and joint sponsors Council of Medical Specialty Societies, and ExtendMed, Inc. The projected date of CE availability is March 1, 2013.
- The second RFA was issued on September 10, 2012. The due day was November 12, 2012.
    - 45 applications were received in response to the second RFA and 4 applications to the first grant were moved to be reviewed with the second RFA applications. These applications are currently undergoing grant evaluation.

Reviewer comments:

The projected date of CE availability of March 1, 2013 meets the established performance goal of the first REMS-compliant training becoming available by this date.

4.3 Assessment 2- Independent Audit of CE Activities

The independent audit will be done by the CE accreditors. This evaluation will be provided in the two-year assessment report.

Reviewer comments:

None.

4.4 Assessment 3a- Evaluation of Prescriber Understanding

An evaluation of prescribers' understanding of the serious risks of ER/LA opioid analgesics will be included in the three-year assessment report. The RPC has elected to conduct a baseline prescriber survey to measure prescriber understanding and behaviors prior to the availability of REMS-compliant training. Start-up activities for the baseline survey have commenced and qualitative pre-testing was conducted in December 2012.

Reviewer comments:

None.

4.5 Assessment 3b- Long-term Evaluation Grants

An RFA will be issued to solicit applications for special grants to CE providers who also agree to conduct long-term evaluation of prescribers who have completed REMS-compliant training to determine their knowledge retention and practice changes six months to one year after completing the training. Since this long-term evaluation will not begin until 6 to 12 months after REMS training, the details of the evaluation grants are in development. Additional information will be provided in the one-year assessment report.

Reviewer comments:

None.

4.6 Assessment 4- Patient Survey

An evaluation of patients' understanding of the serious risks of ER/LA opioid analgesics will be included in the two-year assessment report.

4.7 Assessment 5- Surveillance Monitoring for Misuse, Abuse, Overdose, Addiction, Death, and Intervention Taken

To be provided in future assessment reports starting from year two.

4.8 Assessment 6- Evaluation of Drug Utilization Patterns

To be provided in future assessment reports starting from year two.

4.9 Assessment item 7- Evaluation of Changes in Prescribing Behavior

To be provided in future assessment reports starting from year two.

4.10 Assessment item 8- Changes in Access to ER/LA Opioid Analgesics

To be provided in future assessment reports starting from year two.

4.11 Applicant's overall assessment of whether the REMS is meeting the goals

The applicant stated in this report that all ER/LA opioid analgesic REMS requirements have been met or exceeded for the 6-month assessment period.

5 DISCUSSION

The aim of a DRISK REMS assessment review is to determine (1) whether the report is complete, and (2) whether the REMS is meeting the goal.

This assessment report is complete and addresses all issues relevant to 6-month assessment outlined in the approved REMS assessment plan.

We concur with the sponsor that all ER/LA opioid analgesic REMS requirements have been met or exceeded for the 6-month assessment period.

7 RECOMMENDATIONS

On February 12, 2013, DRISK, DAAAP, and the Office of Compliance met to discuss this conclusion based on the data in the assessment report. We recommend that the applicants be sent a REMS complete with comments letter.

Please send the following comments to the applicants:

Please submit the detailed study protocols for FDA review at least 90 days before you conduct the evaluation of the following assessment items:

- *Evaluation of ER/LA opioid analgesics drug utilization patterns*
- *Evaluation of changes in prescribing behavior for ER/LA opioid analgesics*
- *Changes in access to ER/LA opioid analgesics*

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/s/

JING JU
02/14/2013

MARY E WILLY
02/14/2013
I concur