

The State of Opioid REMS

Update: December 2011

REMS Introduction

- > REMS (Risk Evaluation and Mitigation Strategy) background
 - As part of the ongoing evolution of managing risk, the FDA Amendments Act (FDAAA) of 2007 gave the FDA the authority to require REMS
 - REMS are FDA-mandated requirements to minimize the risks associated with certain medications
 - Starting in March 2008, the FDA could formally require manufacturers to submit a REMS with drugs or biologics that have a known or potential safety risk

 - > REMS can be mandated for any medication or class of medication, and certain opioids have been included in this mandate
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Ready For REMS

- > **Ready For REMSSM** is an educational initiative developed by leading pain management experts in collaboration with Cephalon
 - > Objective:
 - To raise awareness and prepare healthcare providers for the FDA-mandated REMS for opioids
 - > The program includes:
 - Presence at scientific meetings
 - An online portal to house information on REMS for opioids (www.ReadyForREMS.com)
 - > The **Ready For REMS** initiative was launched in 2009
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REMS and Opioids Today (I)

- > REMS for opioids: an evolving landscape
 - Some opioids have approved REMS and some do not
 - The FDA has announced its intent to have class-wide REMS for the long-acting/extended-release opioids (LAOs) and methadone
 - The dialogue continues among the stakeholders: the FDA, advisors to the FDA, physician groups, patient advocacy groups, industry, and the general public, etc.

REMS and Opioids Today (II)

- In April 2011, FDA announced that it required manufacturers of LAOs and extended-release opioids to propose a REMS plan to develop a single system for implementing strategies to increase training of prescribers and improve education for patients (including a medication guide to explain safe use and disposal) within 4 months
 - At present, individual REMS are being prepared and reviewed for each transmucosal immediate-release fentanyl (TIRF) product (also known as a rapid-onset opioid or ROO)
 - Currently, there are no requirements for REMS for short-acting opioids/ immediate-release opioids
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The Principle of Balance with Opioid Therapy



- > Both the WHO and the APS/AAPM acknowledge that opioids are an essential treatment option in the management of patients with moderate to severe pain^{1,2}
- > However, opioids are associated with significant risks including misuse, abuse, addiction, and overdose
 - According to the Centers for Disease Control and Prevention (CDC), unintentional overdose deaths involving prescription opioids increased 114% from 2001 to 2005³

1. WHO's Pain Ladder. <http://www.who.int/cancer/palliative/painladder/en/>. Accessed August 2010.

2. American Pain Society. Clinical Practical Guidelines. http://www.ampainsoc.org/pub/cp_guidelines.htm. Accessed August 2010.

3. National Drug Intelligence Center. National Prescription Drug Threat Assessment 2009, April 2009. <http://www.usdoj.gov/ndic/pubs33/33775/index.htm>. Accessed August 2010.

The Principle of Balance with Opioid Therapy



- > To maintain the balance of benefits and risks of opioids, good medical practice calls for us to:
 - Screen all patients and monitor them for signs of abuse and addiction
 - Use an opioid agreement and keep detailed prescribing records
 - Remind patients/caregivers to take their medication only as prescribed and to protect their prescriptions against accidental use, theft, and misuse

 - > REMS programs are intended to formalize ways to minimize these risks while maintaining access for patients who need opioid medications
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Opioid REMS Timeline (I)

Early 1990s

Risk Management Plans (RMPs)

2000s

Risk Minimization Action Plans (RiskMAPs)

2007

Via the FDA Amendments Act of 2007 (FDAAA), congress gives FDA the authority to require a REMS when FDA determines a REMS is necessary to ensure the benefits of a drug outweigh the risks¹

By the end of 2008 there was **one** approved opioid REMS: Nucynta

1. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm187975.htm>. Accessed August 31, 2010.

Opioid REMS Timeline (II)

February 2009

FDA sends letters to manufacturers of certain opioids requiring REMS¹

March 2009

FDA holds an industry meeting on REMS for certain opioid drugs²

April 2009

FDA opens a public docket to receive comments on relevant issues (open until end June 2009)³

May 2009

May 4-5 Stakeholders meet with FDA on opioids and REMS;
May 27-28 Public meeting on REMS for certain opioids⁴

December 2009

FDA/industry public meeting on REMS for certain opioids⁴

Three new opioid REMS were approved in 2009 (Darvon*, Embeda, and Onsolis), bringing the total at the end of 2009 to **four**

1. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm187975.htm>. Accessed August 31, 2010.

2. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163660.htm>. Accessed August 31, 2010.

3. <http://edocket.access.gpo.gov/2010/pdf/2010-8831.pdf>. Accessed August 31, 2010.

4. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>. Accessed August 31, 2010.

*FDA has informed Xanodyne to discontinue the sale of Darvon from the US market due to new data on QT prolongation.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm234389.htm>. Accessed November 19, 2010.

The trade names listed are registered trademarks of the following companies:
Darvon (Xanodyne Pharmaceuticals), Embeda (King Pharmaceuticals), Onsolis (Meda Pharmaceuticals Inc).

Opioid REMS Timeline (III)

May 2010

FDA re-opens the public docket through October 19, 2010¹

July 2010

FDA reveals a proposed REMS for long-acting and extended-release opioids, and methadone,² which an FDA advisory committee voted against 25-10³

October 2010

Dialogue continues among the stakeholders; class-wide REMS are still under review at FDA; individual REMS are being reviewed for each case

November 2010

Xanodyne Pharmaceuticals discontinues Darvon (propoxyphene)⁴

From year beginning 2010 to November 2010 **five** additional opioid REMS were approved (Exalgo, morphine sulfate, oxycodone hydrochloride oral solution, OxyContin, and Suboxone), bringing the total to **nine**

1. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>. Accessed August 31, 2010.
2. <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm214816.htm>. Accessed August 31, 2010.
3. <http://www.fdanews.com/newsletter/article?articleId=128946&issueId=13895>. Accessed August 31, 2010.
4. <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234383.pdf>. Accessed 1 March 2011.

The trade names listed are registered trademarks of the following companies: Exalgo (Mallinckrodt Inc., a Covidien company), OxyContin (Purdue Pharma), Suboxone (Reckitt Benckiser Pharmaceuticals Inc.), and Abstral (ProStraken Inc.).

Opioid REMS Timeline (IV)

January 2011

FDA approved Abstral (fentanyl) transmucosal tablets together with a REMS¹

April 2011

FDA announced that it required manufacturers of LAOs and extended-release opioids to propose a REMS plan to develop a single system for implementing strategies to increase training of prescribers and improve education for patients (including a medication guide to explain safe use and disposal) within 4 months²

September 2011

Transmucosal immediate-release fentanyl (TIRF) REMS programs opened for Actiq® (oral transmucosal fentanyl citrate) and FENTORA® (fentanyl buccal tablet).

From year beginning 2010 to January 2011 **eight** additional opioid REMS were approved (Exalgo, morphine sulfate, oxycodone hydrochloride oral solution, OxyContin, Suboxone, Abstral, Lazanda, FENTORA), bringing the total to **twelve**

1. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm239490.htm>. Accessed 1 March 2011.

2. FDA. Questions and Answers: FDA Requires a Risk Evaluation and Mitigation Strategy (REMS) for Long-Acting and Extended-Release Opioids. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251752.htm>. Accessed April 2011.

Opioid Classifications (I)

- > Opioids used for moderate-to-severe pain can be classified into various categories:
 - LAOs including extended-release opioids
 - Longer onset and longer duration of analgesia
 - Short-acting opioids (SAOs)
 - Traditional short-acting opioids have an onset of 30–45 minutes and a shorter duration of analgesia
 - TIRF products* (also known as rapid-onset opioids or ROOs) have an onset of 15 minutes or less and a shorter duration of analgesia

*TIRF products = transmucosal immediate-release fentanyl products.

Opioid Classifications (II)

- > Much of the public FDA discussion has been centered on a potential LAO class-wide REMS
 - In April 2011, FDA announced it required manufacturers of LAOs and extended-release opioids to propose a REMS plan to develop a single system for implementing strategies to increase training of prescribers and provide more comprehensive education for patients (including a medication guide to explain safe use and disposal) within 4 months¹
- > The REMS requirements for individual TIRF products* are under review
- > FDA has not required a class-wide REMS for other SAOs

1. FDA. Questions and Answers: FDA Requires a Risk Evaluation and Mitigation Strategy (REMS) for Long-Acting and Extended-Release Opioids. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251752.htm>. Accessed April 2011.

*TIRF products = transmucosal immediate-release fentanyl products.

Components of a REMS

While there are different components of REMS, an individual program does not have to include all of these:

**Medication
Guide/PPI***

Educational tools provided to each patient when drug is prescribed / dispensed

**Communication
Plan**

For example, letters to healthcare providers, communications to professional societies, professional education, etc.

**Elements to
Assure Safe Use**

Special requirements or restrictions to optimize safe use of products

**Implementation
System**

System to monitor, evaluate, and improve elements to assure safe use

**Timetable for
Assessment**

Minimum FDA requirement 18 months, 3 years, and 7 years after REMS approval (only compulsory element for all REMS programs)

*PPI: patient package insert.

Components of a REMS

Of the five components, the two that are most relevant to prescribers are the Medication Guide/Patient Package Insert and Elements to Assure Safe Use

Medication
Guide/PPI*

Educational tools provided to each patient when drug is prescribed / dispensed

Elements to
Assure Safe Use

Special requirements or restrictions to optimize safe use of products

*PPI: patient package insert.

Elements to Assure Safe Use

- > May be required if the drug is associated with a serious adverse event and the medication guide, patient package insert, or communication plan plus assessment are not sufficient to mitigate these risks
- > May require any of the following:
 1. Training / certification of prescribers
 2. Training / certification of pharmacists / pharmacies
 3. Restrictions on where the drug is dispensed
 4. Evidence of patient safe use conditions
 5. Patient monitoring
 6. Enrollment of patients in a registry

Components of Existing REMS

Examples	Medication Guide	Communication Plan	Elements to Assure Safe Use	Implementation System	Timetable for Assessment	Products (n)
Morphine sulfate, Nucynta, Oxycodone hydrochloride oral solution	●				●	35
Actemra, Dulera, Humira		●				13
Botox, Embeda, Simponi	●	●			●	26
Exalgo, OxyContin	●		●		●	5
Letairis, Promacta, Suboxone, Tracleer	●		●	●	●	11
Entereg, Extraneal (icodextrin) Intraperitoneal Solution		●	●	●	●	2
Abstral, NPlate, Onsolis, Sabril	●	●	●	●	●	11
Transmucosal Immediate-Release Fentanyl (TIRF) Products: Abstral, Actiq, FENTORA, Lazanda Onsolis	●		●	●	●	4 1
Class-wide Long-Acting Opioids and Extended-Release opioids	●		●		●	0

What We Know Now

- > FDA has defined a class-wide REMS program for LAOs
 - In April 2011, FDA announced that it required that manufacturers of LAOs and extended-release opioids propose a REMS plan to develop a single system for implementing strategies to increase training and education within 4 months

- > While class-wide REMS are under review at FDA, prescribers must be aware that there are individual product REMS approved with various requirements and work with each unique opioid REMS program
 - Prescriber education will not initially be mandatory
 - In June 2011, a Bill was proposed in the House of Representatives to amend the Controlled Substances Act to require practitioners to obtain specific training or certification¹

- > At present, individual REMS are to be launched for each TIRF product*
 - Manufacturers of TIRF products are working with FDA to develop a class-wide REMS for these products

1. Introduction of Bill at the 112th Congress House of Representatives, June 2011.

*TIRF product = transmucosal immediate-release fentanyl product.

List of LAO and Extended-Release Opioids Required to have an Opioid REMS¹



	Trade Name	Generic Name	Sponsor
1	Duragesic	Fentanyl Transdermal System	Ortho McNeill Janssen
2	*Palladone	Hydromorphone hydrochloride extended-release capsules	Purdue Pharma
3	Dolophine	Methadone hydrochloride tablets	Roxanne
4	Avinza	Morphine sulfate extended-release capsules	King Pharms
5	Kadian Capsules	Morphine sulfate extended-release capsules	Actavis
6	MS Contin	Morphine sulfate controlled-release tablets	Purdue Pharma
7	Oramorph	Morphine sulfate sustained-release tablets	Xanodyne Pharms
8	*Embeda	Morphine sulfate and naltrexone extended-release capsules	King Pharms
9	OxyContin	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma
10	Opana ER	Oxymorphone hydrochloride extended-release tablets	Endo Pharma
11	Exalgo	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt
12	Butrans	Buprenorphine Transdermal System	Purdue Pharma

*No longer being marketed, but is still approved.

1. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251735.htm>. Accessed April 2011. Some of these opioids have individual opioid REMS but will eventually have to be included within a class-wide opioid REMS when this is approved. Generic equivalents of these products will also require an opioid REMS.

How To Get Ready For REMS

> Coordinate your office/clinic/pharmacy

- Review your current standard operating procedures and staff roles to prepare for more interaction with staff, patients, and pharmacists and for potential new documentation requirements with REMS

> Ensure that you understand the federal and state regulations on prescribing opioids

- REMS are an addition to—not a replacement for—federal and state regulations
 - Visit <http://www.nascsa.org/stateProfiles.htm> (National Association for State Controlled Substances Authority) to find links to access a state's profile. The profile contains information and additional links to the state's controlled substance regulatory functions
 - Visit <http://www.justice.gov/dea/index.htm> (DEA website) for controlled substance policies
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How To Get Ready For REMS

- > Assess your current opioid prescribing patterns and likely future requirements
 - Find out about currently approved REMS, including opioid REMS (<http://1.usa.gov/Xs1f6>)
 - > Talk to colleagues and peers to find out how they are getting ready
 - > Familiarize yourself with the supplied written materials that are currently available for opioids you prescribe
 - Medication Guide
 - Patient Prescribing Information
 - Utilize resources (<http://bit.ly/mTUWAJ>) on www.ReadyForREMS.com
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How To Get Ready For REMS

> Enhance communication with your patients

- Explain that REMS are coming and that there may be new requirements with their opioid medications
- Visit www.zerodeaths.org for the six steps everyone needs to follow when using opioids:
 1. Never take a prescription painkiller unless it is prescribed to you
 2. Do not take pain medicine with alcohol
 3. Do not take more doses than prescribed
 4. Use of other sedative or anti-anxiety medications can be dangerous
 5. Avoid using prescription painkillers to facilitate sleep
 6. Lock up prescription painkillers



Opioid REMS: Ongoing Discussion

- > Discussions are ongoing regarding class-wide opioid REMS and the exact requirements of each REMS
 - > **Ready For REMS** will continue to raise awareness and prepare healthcare providers for FDA-requested opioid REMS and provide updates as new information becomes available
 - > Visit us at www.ReadyForREMS.com
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