

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**200533Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: August 24, 2011  
To: Bob A. Rappaport, M.D., Director  
**Division of Anesthesia and Analgesia Products (DAAP)**  
Thru: Claudia Karwoski, Pharm.D., Director  
**Division of Risk Management (DRISK)**  
From: **DRISK Scientific Lead**  
Doris Auth, Pharm.D., Drug Risk Management Analyst (RMA)

**DRISK Review Team**

Megan Moncur, M.S., RMA, Team Leader  
Cynthia LaCivita, Pharm.D., RMA, Team Leader  
Kate Heinrich, M.A., Health Education Reviewer  
Jodi Duckhorn, MA, Social Scientist  
Sharon Mills, Patient Labeling Reviewer

**Division of Drug Marketing, Advertising and Communications  
(DDMAC)**

Mathilda Fienkeng, Regulatory Review Officer

**Office of Compliance**

Marcia Britt Williams, Ph.D., Consumer Safety Officer

Subject: Final Review of the Proposed Risk Evaluation and Mitigation Strategy (REMS) for Nucynta ER (tapentadol) extended-release tablets

Drug Name(s): Nucynta<sup>®</sup>ER (tapentadol) Extended-Release tablets

Dosage: 50, 100, 150, 200, 250 mg tablets

Formulation:

Submission: Resubmission Class 2, Sequence 0023

Number:

Application: NDA 200-533 TSI 466

Type/Number:

Applicant: Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
OSE RCM #: 2011-921

## **1 PURPOSE**

The purpose of this review is to evaluate Ortho-McNeil-Janssen Pharmaceutical's proposed Risk Evaluation and Mitigation Strategy (REMS) for Nucynta ER (tapentadol) extended-release tablets, NDA 200-533 submitted on February 28, 2011, as a Class 2 resubmission, sequence number 0023.

## **2 BACKGROUND**

Nucynta ER (tapentadol) extended-release is a CII, centrally-acting opioid analgesic. The proposed indication for Nucynta ER is the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The drug entity, tapentadol hydrochloride, was approved in 2008 for use in an immediate-release formulation to treat moderate to severe pain.

On November 20, 2009 Ortho-McNeil-Janssen Pharmaceuticals submitted the original application and proposed REMS for Nucynta ER (tapentadol) extended-release tablets. The original proposed REMS consisted of a Medication Guide, communication plan, and a timetable for assessment of the proposed REMS.

On April 22, 2010, the sponsor received a Pre-Approval REMS notification that stated the proposed REMS must include elements to assure safe use, specifically training for healthcare providers as described under 505-1(f)(3)(A), to ensure that the benefits of the drug outweigh the risks of: abuse, misuse, addiction and overdose as well as the use of Nucynta ER in non-opioid tolerant individuals, and to prevent the occurrence of serious adverse events associated with those risks.

The sponsor submitted an amendment for the proposed REMS and REMS supporting document on June 21, 2010, sequence 0014. DRISK evaluated this submission and posted a review in DARRTS on August 6, 2010. Comments to the sponsor included in the DRISK review were communicated to the sponsor. On October 1, 2010 the sponsor received a Complete Response (CR) because the proposed in vitro in vivo correlation models did not support the bridging of the clinical study batches to the to-be-marketed tamper resistant formulation.

On February 28, 2011 the sponsor resubmitted their application as a Class 2, resubmission in response to the CR letter addressing the aforementioned issues with bioequivalency and in response to the Agency's comments, revised the proposed REMS and REMS supporting documents.

On April 18, 2011, the sponsor received a Pre-Approval REMS notification that stated 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 extended-release and long-acting (ER/LA) opioid products. The Agency is currently working with all sponsors of ER/LA opioids to develop the single shared system. Ortho-McNeil-Janssen Pharmaceuticals, and other sponsors with pending approvals, have been instructed to

develop an interim REMS that will conform with agency standards for the other interim REMS for ER/LA opioids.

### **3 METHODS AND MATERIALS**

The proposed REMS submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA), the REMS notification letter, and consistency with REMS requirements for other long-acting and extended-release opioid analgesics. The following materials were reviewed:

#### **3.1 Materials Reviewed**

- Proposed REMS for Nucynta ER, received August 24, 2011 (Sequence 0041)
- Proposed REMS and REMS supporting document, for Nucynta ER, received July 29, 2011 (Sequence 0035)
- Proposed REMS and REMS supporting document for Nucynta ER (tapentadol) extended-release tablets, received February 28, 2011.(Sequence 0023)
- Screen shots for the Nucynta ER website and the Nucynta ER REMS website, dated May 25, 2011, sequence 0028.

#### **3.2 Materials Referenced**

- Proposed labeling for Nucynta ER, received August 23, 2011 (Sequence 0040)
- Proposed labeling for Nucynta ER, provided on August 10, 2011 by Dominic Chiapperino, Regulatory Project Manager
- Proposed labeling for Nucynta ER (tapentadol) extended-release tablets, provided on May 17, 2011 by Dominic Chiapperino, Regulatory Project Manager.
- Interim REMS review, prepared by Cynthia LaCivita, Pharm.D., dated June 22, 2011
- REMS Pre-Approval Notifications, dated April 22, 2010 and April 18, 2011

### **4 PROPOSED REMS FOR NUCYNTA ER (TAPENTADOL) EXTENDED-RELEASE TABLETS**

Listed below are the goals of the proposed REMS and a summary of the elements. Appendix A contains the complete REMS.

#### **4.1 Goals**

The goals of the proposed REMS for Nucynta ER are:

- To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction to Nucynta ER.
- To inform patients and healthcare professionals about the safe use of Nucynta ER.

## 4.2 Elements of the Proposed Interim REMS

Below is a summary of the sponsor's proposed REMS.

### 4.2.1 The Medication Guide

The Medication Guide will be dispensed with each Nucynta ER prescription in accordance with 21 CFR 208.24.

### 4.2.2 Elements to Assure Safe Use

The elements to assure safe use include a training program for healthcare providers that prescribe Nucynta ER. Three weeks prior to the availability of Nucynta ER a Dear Healthcare letter will be mailed to prescribers most experienced in treating chronic pain with opioids agonists.

The training program includes educational information about: proper patient selection; appropriate dosing and administration; general principles of safe opioid use, including information about opioid abuse and how to identify patients who are at risk for addiction; potential misuse; and overdose with opioids including Nucynta ER.

The training program includes specific information about the potential for an overdose caused by exposure to an essentially immediate-release form of tapentadol by consuming tablets that are broken, chewed, crushed, dissolved or injected; and the risk of overdose in patients who have not developed tolerance to the sedating or respiratory-depressant effects of opioids, especially when the initial dose of Nucynta ER exceeds 50 mg twice daily.

Prescribers will receive training on the need to counsel patients to store opioid analgesics safely out of the reach of children and household acquaintances; to properly dispose of unused drugs when no longer needed by the patient; to not share drugs with anyone for any reason; and the importance of dispensers providing each patient a Medication Guide with each prescription, and instructing the patient to read it.

Prescribers will be re-trained every two years or following substantial changes to the NUCYNTA<sup>®</sup> ER REMS. The following materials are part of the REMS.

- Dear Healthcare Professional Letter
- Prescribing Nucynta ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe NUCYNTA<sup>®</sup> ER
- Nucynta ER Education Confirmation Form
- Nucynta ER REMS website

A copy of the full Prescribing Information (PI) will be included with the training materials. All REMS materials will be available on the Nucynta ER REMS website (NUCYNTAERREMS.COM)

### 4.2.3 Implementation System

Because Nucynta ER could be approved without the elements to assure safe use described under FDCA 505-1(f)(3)(B), (C), and (D) of the Act, an implementation system is not required.

#### 4.2.4 Timetable for Submission of Assessments

The sponsor will submit REMS Assessments to the FDA every 6 months for the first year from the date of approval of the REMS, and annually thereafter.

### **5 CONCLUSIONS**

The interim REMS for Nucynta ER will be implemented by the sponsor, and will be in effect until the single-shared REMS for all long-acting and extended-release opioid products is approved and implemented. The DRISK Review Team finds the proposed interim REMS for Nucynta ER, as submitted on August 24, 2011 and attached to this review, to be acceptable.

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/s/  
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DORIS A AUTH  
08/24/2011

CLAUDIA B KARWOSKI  
08/24/2011  
concur



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 22, 2011  
To: Bob A. Rappaport, M.D., Director  
**Division of Anesthesia and Analgesia Products (DAAP)**  
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Mathilda Fienkeng, Regulatory Review Officer

**Office of Compliance**

Marcia Britt Williams, Ph.D., Consumer Safety Officer

Subject: Interim Review of the Proposed Risk Evaluation and Mitigation Strategy (REMS) for Nucynta ER (tapentadol) extended-release tablets

Drug Name(s): Nucynta<sup>®</sup>ER (tapentadol) Extended-Release tablets

Dosage 50, 100, 150, 200, 250 mg tablets

Formulation:

Submission Resubmission Class 2, Sequence 0023

Number:

Application NDA 200-533 TSI 466

Type/Number:

Applicant: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

OSE RCM #: 2011-921

## **1 PURPOSE**

The purpose of this review is to evaluate Ortho-McNeil-Janssen Pharmaceutical's proposed Risk Evaluation and Mitigation Strategy (REMS) for Nucynta ER (tapentadol) extended-release tablets, NDA 200-533 submitted on February 28, 2011, as a Class 2 resubmission, sequence number 0023. The Medication Guide review will be provided under a separate cover.

## **2 BACKGROUND**

Nucynta ER (tapentadol) extended-release is a CII, centrally-acting opioid analgesic. The proposed indication for Nucynta ER is the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The drug entity, tapentadol hydrochloride, was approved in 2008 for use in an immediate-release formulation to treat moderate to severe pain.

On November 20, 2009 Ortho-McNeil-Janssen Pharmaceuticals submitted the original application and proposed REMS for Nucynta ER (tapentadol) extended-release tablets. The original proposed REMS consisted of a Medication Guide, communication plan, and a timetable for assessment of the proposed REMS.

On April 22, 2010, the sponsor received a Pre-Approval REMS notification that stated the proposed REMS must include elements to assure safe use, specifically training for healthcare providers as described under 505-1(f)(3)(A), to ensure that the benefits of the drug outweigh the risks of: abuse, misuse, addiction and overdose as well as the use of Nucynta ER in non-opioid tolerant individuals, and to prevent the occurrence of serious adverse events associated with those risks.

The sponsor submitted an amendment for the proposed REMS and REMS supporting document on June 21, 2010, sequence 0014. DRISK evaluated this submission and posted a review in DARRTS on August 6, 2010. Comments to the sponsor included in the DRISK review were communicated to the sponsor. On October 1, 2010 the sponsor received a Complete Response (CR) because the proposed in vitro in vivo correlation models did not support the bridging of the clinical study batches to the to-be-marketed tamper resistant formulation.

On February 28, 2011 the sponsor resubmitted their application as a Class 2, resubmission in response to the CR letter addressing the aforementioned issues with bioequivalency and in response to the Agency's comments, revised the proposed REMS and REMS supporting documents.

On April 18, 2011, the sponsor received a Pre-Approval REMS notification that stated 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 long-acting and extended-release opioid products. Implementation of the single, shared REMS is not in the imminent future. If the REMS is the only outstanding requirement for drug approval,

waiting for implementation of the shared system could cause a significant delay in the availability of this drug. Therefore, the proposed REMS and REMS supporting documents under review are for an interim REMS that is consistent with agency standards for the other interim REMS for long-acting extended-release opioids.

### **3 METHODS AND MATERIALS**

The proposed REMS submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA), the REMS notification letter, and consistency with REMS requirements for other long-acting and extended-release opioid analgesics. The following materials were reviewed:

#### **3.1 Materials Reviewed**

- Proposed REMS and REMS supporting document for Nucynta ER (tapentadol) extended-release tablets, received February 28, 2011.
- Proposed labeling for Nucynta ER (tapentadol) extended-release tablets, provided on May 17, 2011 by Dominic Chiapperino, Regulatory Project Manager.
- Screen shots for the Nucynta ER website and the Nucynta ER REMS website, dated May 25, 2011, sequence 0028.

#### **3.2 Materials Referenced**

- REMS Pre-Approval Notifications, dated April 22, 2010 and April 18, 2011

### **4 PROPOSED REMS FOR NUCYNTA ER (TAPENTADOL) EXTENDED-RELEASE TABLETS**

Listed below are the goals of the proposed REMS and a summary of the elements. Appendix A contains the complete REMS with DRISK edits in track changes.

#### **4.1 Goals**

The goals of the proposed REMS for Nucynta ER are:

- To inform patients and providers about the potential for abuse, misuse, overdose, and addiction to Nucynta ER.
- To inform patients and healthcare professionals about the safe use of Nucynta ER.

#### **4.2 Elements of the Proposed Interim REMS**

Below is a summary of the sponsor's proposed REMS. Please refer to the REMS document (Appendix A) for DRISK edits using track changes.

##### **4.2.1 The Medication Guide**

The Medication Guide will be dispensed with each Nucynta ER prescription in accordance with Federal law 21 CFR 208.24.

#### 4.2.2 Elements to Assure Safe Use

The elements to assure safe use include a training program for healthcare providers that prescribe Nucynta ER. Three weeks prior to the availability of Nucynta ER a Dear Healthcare letter will be mailed to prescribers most experienced in treating chronic pain with opioids agonists.

The training program includes educational information about: proper patient selection; appropriate dosing and administration; general principles of safe opioid use, including information about opioid abuse and how to identify patients who are at risk for addiction; potential misuse; and overdose with opioids including Nucynta ER.

The training program includes specific information about the potential for an overdose caused by exposure to an essentially immediate-release form of tapentadol by consuming tablets that are broken, chewed, crushed, dissolved or injected; and the risk of overdose in patients who have not developed tolerance to the sedating or respiratory-depressant effects of opioids, especially when the initial dose of Nucynta ER exceeds 50 mg twice daily.

Prescribers will receive training on the need to counsel patients to store opioid analgesics safely out of the reach of children and household acquaintances; to properly dispose of unused drugs when no longer needed by the patient; to not share drugs with anyone for any reason; and the importance of dispensers providing each patient a Medication Guide with each prescription, and instructing the patient to read it.

Prescribers will be offered training every two years or following substantial changes to the NUCYNTA<sup>®</sup> ER REMS. The following materials are part of the REMS.

- Dear Healthcare Professional Letter
- Nucynta ER Medication Guide
- Prescribing Nucynta ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe NUCYNTA<sup>®</sup> ER
- Nucynta ER Education Confirmation Form

A copy of the full Prescribing Information (PI) will be included with the training materials. All REMS materials will be available on the Nucynta ER REMS website (NUCYNTAERREMS.COM)

#### 4.2.3 Implementation System

Because Nucynta ER could be approved without the elements to assure safe use described under FDCA 505-1(f)(3)(B), (C), and (D) of the Act, an implementation system is not required.

#### 4.2.4 Timetable for Submission of Assessments

The sponsor will submit REMS Assessments to the FDA every 6 months for the first year from the date of approval of the REMS, and annually thereafter.

## 5 RECOMMENDATIONS

The interim REMS for Nucynta ER will be implemented by the sponsor, and will be in effect until the single-shared REMS for all long-acting and extended-release opioid products is approved and implemented. The DRISK Review Team finds the proposed interim REMS for Nucynta ER to be acceptable, provided the sponsor addresses all comments in the OCC-cleared REMS document, as well as comments listed below in Section 5.1 Comments for the Sponsor and the accompanying appendices. DRISK will perform a review of the final REMS to ensure it addresses all the identified deficiencies.

The “comments to the sponsor” are listed below. Please convey the comments provided below to the sponsor and copy DRISK on the correspondence.

The following comments and appendices address the necessary revisions for the proposed REMS and REMS Supporting Document submitted for Nucynta ER, NDA 200533.

### 5.1 Comments for the Sponsor

#### 1. REMS Document

Appendix A contains the necessary revisions to the REMS document in track changes. The following materials are part of the REMS and must be appended to the REMS:

- Medication Guide
- Dear Healthcare Professional Letter
- Prescribing Nucynta ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe Nucynta ER
- Nucynta ER Education Confirmation Form
- Nucynta ER REMS website (screen shots of the web pages)

#### 2. Dear Healthcare Professional Letter

Appendix B contains the necessary revisions to the document in track changes.

#### 3. Healthcare Professionals Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER

Appendix C contains the necessary revisions to the document in track changes.

#### 4. Education Confirmation Form

Appendix D contains the necessary revisions to the form in track changes.

#### 5. REMS Website

Make the necessary changes on the landing page of the Nucynta ER REMS website.

Second paragraph



(b) (4)

Third paragraph,

Provide the content for “click here”.

*The REMS program is designed to inform patients and healthcare professionals (HCPs) about the risks of NUCYNTA ER. To learn more about the serious risks, including potential for abuse, overdose and addiction, **click here**.*

Under step one and the REMS materials - Use the correct the name of the training program, Prescribing NUCYNTA<sup>®</sup> ER Healthcare Professional Education Program. Provide a hyperlink in step one to the program.

Include the full indication, including the limitations to the indication, and full boxed warning on the REMS website.

## **6. REMS Supporting Document**

- a.** All changes in the REMS and Prescribing Information (PI) should also be reflected in the REMS Supporting Document.
- b.** In the section titled “Background” remove reference to a reduced risk for abuse with regard to crushing or destroying the extended release property.
- c.** Correct the URL for the website for a Nucynta ER REMS.com
- d.** Assessments and Surveys
  - Add an assessment of the mailing of the Dear Healthcare Professional (HCP) Letters to your Information Needed for Assessment: including the number of mailings sent; the targeted specialties that received the Dear HCP Letter, the number of returned mailings, the date of the mailing
  - The six-month survey should include an implementation survey that identifies timelines and/or milestones identified during the initial six months after the approval of the REMS.
  - Please also refer to comments previously provided in the advice letter dated Sept 21, 2010, regarding assessments and survey methodology.

## 7. General Comments

REMS materials are not appropriate for use in a promotional manner.

All REMS materials and the REMS Supporting Document should be revised to reflect the content in the final product labeling.

Submit revisions for the proposed REMS with appended materials and the REMS Supporting Document and all other materials in **WORD** format. It is preferable that the entire REMS and appended materials be a single **WORD** document. If certain documents such as enrollment forms are only in **PDF** format, they may be submitted as such. The preference is to include as many as possible be in a single **WORD** document. Please provide a track changes and clean version of all revised materials and documents.

Appendix A - REMS Document

Appendix B - Dear Healthcare Provider Letter

Appendix C - Prescribing NUCYNTA<sup>®</sup> ER Healthcare Professional Education Program

Appendix D - NUCYNTA<sup>®</sup> ER Education Confirmation Form

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CYNTHIA L LACIVITA  
06/22/2011

CLAUDIA B KARWOSKI  
06/22/2011  
concur



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

**MEMORANDUM**

DATE: April 18, 2011

TO: File,

<b>NDA</b>	<b>Tradename</b>	<b>Established Name</b>
6134	Dolophine Tablets	(methadone hydrochloride) 5 mg and 10 mg
19516	MS CONTIN Tablets	(morphine sulfate controlled-release) 15, 30, 60, 100, 200 mg
19813	DURAGESIC	(fentanyl transdermal system) 1.25, 2.5, 5, 7.5, 10 mg
19977	Oramorph SR Tablets	(morphine sulfate sustained-release) 15, 30, 60, 100 mg
20616	KADIAN Capsules	(morphine sulfate extended-release) 10, 20, 30, 50, 60, 80, 100, 200 mg
21610	OPANA ER Tablets	(oxymorphone hydrochloride extended-release) 5, 7.5, 10, 15, 20, 30, 40 mg
21260	AVINZA Capsules	(morphine sulfate extended-release) 30, 45, 60, 75, 90, 120 mg
22324 (pending)	REMOXY Capsules	Oxycodone Hydrochloride Extended-Release, 5, 10, 20, 30 and 40 mg
200533 (pending)	Nucynta ER Tablets	(Tapentadol Extended-Release) 50, 100, 150, 200, 250 mg
201655 (between cycles)	tradename pending	Oxymorphone HCl Extended-Release Tablets, 5, 7.5, 10, 15, 20, 20, 40
20553 (discontinued)	OxyContin Tablets	(oxycodone hydrochloride controlled-release)
21044 (discontinued)	PALLADONE Capsules	(hydromorphone hydrochloride extended-release) 12, 16, 24, 32 mg

From: Laura Governale, Pharm.D., MBA  
Acting Deputy Director for Safety

Through: Bob Rappaport, M.D.  
Division Director

RE: Risk Evaluation and Mitigation Strategy (REMS) Requirements

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity.

The use of prescription opioid drug products has nearly doubled in the past decade, and with that increase in use, there has been a concordant rise in the abuse and misuse of prescription opioid drug products, resulting in increased reports of serious adverse outcomes such as death, overdose and addiction. The spectrum of behaviors contributing to these problems include inappropriate prescribing such as improper dosing, patient selection, and patient counseling, as well as inappropriate patient behaviors such as improper use, storage and disposal of prescription drug opioid products.<sup>1</sup> Extended-release (ER) and long-acting (LA) opioid products pose unique risks to patients due to their pharmacokinetic properties, duration of use, and the amount of active ingredient contained in the drug product in comparison to their immediate-release opioid counterparts. The amount of opioid contained in an extended-release tablet can be much more than the amount of opioid contained in an immediate-release tablet because extended-release tablets are designed to release the opioid over a longer period of time. Long-acting opioids can take many hours to be cleared out of the body. Improper use of any opioid can result in serious side effects including overdose and death and this risk is magnified with long-acting and extended-release opioids. As it is important that these products are prescribed and used safely among the intended population, FDA has determined that a REMS is necessary to address the issues of unintentional overdose, addiction, and death resulting from inappropriate prescribing, misuse and abuse of ER and LA opioid drug products.

After consultations with the Office of New Drugs, the Office of Surveillance and Epidemiology, and members of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management committees on July 2010, we have determined that a class-wide REMS is necessary to ensure that the benefits of ER and LA opioid drug products outweigh their risks. In reaching this determination, we considered the following:

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<sup>1</sup><http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM217510.pdf>

- A. Approximately 24-33% of Americans suffer from chronic, non-cancer pain such as arthritis, lower back pain, and fibromyalgia.<sup>2</sup> In year 2009, an estimated (b) (4) unique patients received a dispensed prescription for an ER/LA opioid product from outpatient retail pharmacies.<sup>3</sup>
- B. ER and LA opioid products 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 majority of use for ER/LA opioid products is associated with “diseases of the musculoskeletal system and connective tissue” (ICD-9 codes 710-739) which include chronic pain conditions such as arthritis and back pain.<sup>4</sup>
- C. ER and LA opioid products are an important part of the armamentarium of drugs used to treat chronic pain. Some advantages of these types of formulations over the short-acting opioids are: 1) less frequent dosing; 2) better control of pain achieved through more stable drug levels; 3) improved patient compliance; and 4) less opioid side-effects.<sup>5</sup> It is important to note that patients respond differently to different opioid drug substances and some patients develop tolerance to an opioid after chronic exposure. Physicians use a technique known as “opioid rotation” whereby they switch patients from one opioid to another if patients develop tolerance and cannot get adequate pain relief from any given opioid. Therefore, having different opioids available as modified-release formulations provides important pain relief options for these patients.
- D. The expected duration of treatment with ER and LA opioids will be from weeks to months or longer. Data from outpatient prescription claims databases suggest that ER and LA opioid products are typically prescribed for approximately 30-days at a time, whereas immediate-release opioid products are prescribed for 13-21 days at a time.<sup>6</sup>
- E. ER and LA opioid drug products such as OxyContin have distinguished themselves among the class of opioid pain medications with their disproportionately high rate of serious adverse outcomes including deaths, unintentional overdose and addiction, in comparison to immediate-release opioid products.<sup>1</sup> The goal of the REMS would be to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER and LA opioids while maintaining patient access to these medications. Serious adverse outcomes of concern including addiction, unintentional overdose, and death have been reported for each of the currently marketed products listed in the table above and in association with approved formulations of the drug substances in the products under review.

<sup>2</sup> Nelson, R. *Lancet* 362(9390); 1129, 2003.

<sup>3</sup> SDI, Total Patient Tracker. Year 2009, Extracted, June 2010.

<sup>4</sup> SDI, Physician Drug and Diagnosis Audit, Year 2009, Extracted June 2010

<sup>5</sup> Balch RJ, et al. Extended-release morphine sulfate in treatment of severe acute and chronic pain. *Journal of Pain Research* 2010;3:191–200.

<sup>6</sup> SDI, Vector One®: National. Years 2000 – 2009, Extracted June 2010.

- F. ER and LA opioid products contain one of the following active drug substances such as oxycodone, morphine, fentanyl, buprenorphine, methadone, and hydromorphone; none of these active drug substances are new molecular entities.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that ER/LA opioid products pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of ER/LA opioid products. FDA has determined that ER/LA opioid products are products that have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, ER/LA opioid products for which patient labeling could help prevent serious adverse events related to the use of these products.

The elements of the REMS will be a Medication Guide, Elements to Assure Safe Use, an implementation plan, and a timetable for submission of assessments of the REMS.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHERINE S WON  
04/18/2011

SHARON H HERTZ on behalf of BOB A RAPPAPORT  
04/18/2011  
Signing for Bob Rappaport, M.D.



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: August 6, 2010

To: Bob A. Rappaport, M.D., Director  
**Division of Anesthesia and Analgesia Products (DAAP)**

Thru: Claudia Karwoski, Pharm.D., Director  
**Division of Risk Management (DRISK)**

From: **DRISK Scientific Lead**  
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Subject: Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): **Nucynta<sup>®</sup> ER** (tapentadol)

Submission Number: Original-1

Application Type/Number: 200533

Applicant/sponsor: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

OSE RCM #: 2009-2414

## **1 INTRODUCTION & BACKGROUND**

On December 28, 2009, DRISK was consulted by Division of Anesthesia and Analgesia Products (DAAP) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) for Nucynta ER (tapentadol) submitted by Ortho-McNeil-Janssen Pharmaceuticals, Inc., on December 1, 2009. The original proposed REMS consisted of a Medication Guide, communication plan, and a timetable for assessment of the proposed REMS.

Nucynta ER (tapentadol) CII is a centrally-acting opioid analgesic. The proposed indication for Nucynta ER is the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The drug entity, tapentadol hydrochloride, has already been approved for use in an immediate release formulation to treat moderate to severe pain.

The Agency has been considering a class REMS for long-acting and extended release opioid products, to address the risks of abuse, misuse, and overdose. Until the Agency has determined the elements of the class opioid REMS, DAAP with input from OSE, has decided that an interim REMS for these opioids will be required as these products are approved.

On April 22, 2010 DAAP notified the sponsor that the proposed REMS must include elements to assure safe use, specifically training for healthcare providers as described under 505-1(f)(3)(A), to ensure that the benefits of the drug outweigh the risks of: abuse, misuse, and overdose, use of Nucynta ER in non-opioid tolerant individuals, and to prevent the occurrence of serious adverse events associated with those risks. The amended proposed REMS and amended REMS supporting document, here after referred to as the proposed REMS and REMS supporting document, was submitted on June 21, 2010.

This evaluation is DRISK's preliminary review of the proposed REMS for Nucynta ER. The recommendations in this review are consistent with agency standards for REMS associated with extended-release opioids. The proposed REMS will require revisions and DRISK requests that DAAP convey the comments on the proposed REMS and REMS supporting document for Nucynta ER provided below to the sponsor.

If a Complete Response (CR) letter is issued due to outstanding bioequivalence deficiencies identified, DRISK will defer final REMS comments until the Sponsor submits a satisfactory response to the CR letter.

## **2 METHODS AND MATERIALS**

The proposed REMS submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA), the REMS notification letter, and consistency with REMS requirements for other extended-release opioid analgesics.

The following materials were reviewed:

- a. Proposed REMS for Nucynta ER (tapentadol), document dated 17 June 2010
- b. Nucynta ER (tapentadol) REMS supporting document, document dated 18 June 2010
- c. Proposed full Prescriber Information for Nucynta ER (tapentadol)

- d. Approved REMs for Butrans (buprenorphine) Transdermal System
- e. Approved REMs for Oxycontin (oxycodone hydrochloride controlled-release)
- f. Approved REMs for Exalago (hydromorphone hydrochloride) Extended Release Tablets

### **3 RESULTS OF REVIEW**

#### **3.1 Safety Concerns**

Safety concerns identified are the potential for abuse, misuse, overdose, and addiction to Nucynta ER, as well as the risk of use of Nucynta ER greater than 100mg per day in non-opioid tolerant individuals. The decision to require a REMS was based on consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology. The following factors were considered and support this determination:

- The proposed indication for Nucynta ER is for the management of moderate to severe chronic pain in patients 18 year of age and older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Millions of patients use extended-release opioid analgesics and it is likely that Nucynta ER will be prescribed to a large population of patients.
- Nucynta ER will be prescribed and used in patients that have moderate to severe chronic pain.
- In the clinical trials the efficacy of Nucynta ER used to treat moderate to severe chronic pain was similar to oxycodone CR. Having another extended-release opioid on the market would provide an alternate treatment option for patient that become opioid tolerant or develop adverse events to other opioid analgesics.
- Extended duration of treatment is likely to be weeks, to months or longer.
- Extended-release opioid products have been associated with serious adverse events that can be caused by including death, respiratory depression, CNS depression, seizures, and abuse.
- The occurrence of potentially life-threatening drug interactions with drugs that have selective norepinephrine reuptake inhibitor (SNRI) activity, tricyclic antidepressants, monoamine oxidase inhibitors, and triptans.
- Nucynta ER is not a new molecular entity.

#### **3.2 Proposed REMS**

##### **3.2.1 Goals**

The goals of the proposed REMS for Nucynta ER are:

- To inform patients and providers about the potential for abuse, misuse, overdose, and addiction to Nucynta ER.
- To inform patients and healthcare professionals about the safe use of Nucynta ER.

##### **3.2.2 Elements of the Proposed REMS**

###### **3.2.2.1 The Medication Guide**

The Medication Guide will be dispensed with each Nucynta ER prescription in accordance with Federal law 21CFR208.24.

### 3.2.2.2 Elements to Assure Safe Use

The elements to assure safe use include a training program for health care providers that prescribe Nucynta ER. The training program includes educational information about: proper patient selection, appropriate dosing and administration, the risks of abuse, misuse, overdose and addiction from exposure to Nucynta ER, general information about opioid use, and risk of overdose caused by exposure to an essentially immediate-release form of tapentadol due to broken, crushed, or dissolved Nucynta ER tablets.

The educational program also includes information; regarding counseling patients, providing each patient a Medication Guide with each prescription, instructing the patient to read the Medication Guide, and safe storage and disposal of Nucynta ER.

The proposed REMS states, 60 days after approval, a Dear Healthcare Professional letter will be mailed to prescribers who are most experienced in treating chronic pain (e.g., pain specialists, psychiatrists, and primary care physicians). The letter will inform prescribers of the existence and goals of the REMS for Nucynta ER, convey information about the potential risks, and emphasize the need to complete the Nucynta ER REMS Educational Program and the questionnaire.

In addition to the Dear Healthcare Professional letter, the mailing will include the following Nucynta ER REMS training materials:

1. A copy of the full prescribing information, including the Nucynta ER Medication Guide,
2. Nucynta ER Prescribing Brochure, Healthcare professional training program: A guide for healthcare professionals who prescribe or dispense Nucynta ER, and
3. Nucynta ER Prescribing Information Questionnaire.

### 3.2.2.3 Implementation System

Because Nucynta ER could be approved without the elements to assure safe use described under FDCA 505-1(f)(3)(B), (C), and (D) of the Act, an implementation system was not submitted.

### 3.2.2.4 Timetable for Submission of Assessments

Sponsor proposes to submit REMS Assessments to the FDA every 6 months for the first year from the date of approval of the REMS, and annually thereafter. The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Ortho-McNeil-Janssen Pharmaceuticals, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

## **4 RECOMMENATIONS**

The proposed REMS for Nucynta ER and REMS supporting documents need substantial revisions to meet the agency's standards for REMS of extended-release opioids. The "comments to the sponsor" are listed below. Please convey the comments provided below to the sponsor and copy DRISK on the correspondence.

### **4.1 Comments for the Sponsor**

The following comments and appendices address revisions that are needed for the proposed REMS and REMS supporting document submitted for Nucynta ER, NDA 200533.

**4.1.1 Proposed REMS** Please see Appendix A (Appendix B – clean version) to view revisions to the proposed REMS. These revisions are consistent with current agency standards for REMS with extended-release opioid analgesics.

**4.1.2 Goals** The goals have been reviewed and are acceptable.

**4.1.3 Medication Guide** A Medication Guide will be dispensed with each Nucynta ER prescription in accordance with 21 CFR 208.24. Detailed information on the distribution and dispensing of the Medication Guide has been deleted from the REMS document, and should be included in the REMS supporting document.

Specific comments on the Medication Guide will be provided under a separate review.

#### **4.1.4 Elements to Assure Safe Use**

4.1.4.1 See Appendix C (Appendix D for clean copy) for revisions to the Dear Healthcare Professional letter.

4.1.4.2 Rename the Nucynta ER prescribing brochure to the *Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER*. A brochure may be perceived as promotional material, it may not be readily apparent that it contains important safety information.

4.1.4.3 Include the following items under elements to assure safe use:

- Dear Healthcare Provider letter,
- Healthcare Professionals Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER and
- Nucynta ER Educational Confirmation Form.

4.1.4.4 The Dear Healthcare Provider letter should be available on the Ortho-McNeil-Janssen Pharmaceuticals, Inc. website for a time period of 1 year after the date of the ‘initial’ mailing to targeted healthcare professionals.

4.1.4.5 The Dear Healthcare Provider letter mentions a Nucynta ER Healthcare Professional Training Program Kit. To be consistent with terminology in 4.1.4.2, rename the kit to the *Healthcare Professional Educational Program Kit*. Please provide an explanation of the purpose and the educational content of the kit in the proposed REMS and REMS supporting document. Please list all the components included in the kit.

4.1.4.6 Remove the Highlights of Prescribing Information as an attachment to the Dear Healthcare Provider letter. The highlights do not provide detailed safety information. Instead, attach the prescribing information (PI), which includes a section of highlighted safety information.

4.1.4.7 The initial mailing of prescriber education material should include the following:

- Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER (formerly named Nucynta ER Prescribing Brochure),
- Nucynta ER Prescribing Information,
- Medication Guide, and
- Education confirmation form with survey questions.

4.1.4.8 Remove the Dear Pharmacist letter and the Dear State

Licensing/Authority/Professional Association letter from the REMS. If so desired, these letters can be implemented outside of the REMS.

4.1.4.9 Make the following revisions to the Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER (formerly named Nucynta ER Prescribing Brochure):

- i. Revise the guide by providing information in a more succinct manner by using bulleted text and sub headings.
- ii. Revise to include these specific sections:
  - purpose statement for the brochure,
  - indication,
  - contraindication,
  - adverse effects (risk of respiratory depression, additional side effects)
  - addictive disorder and physical dependence
  - appropriate dosing and administration
  - patient selection/patient counseling

4.1.4.10 For consistency with other extended-release opioid REMS rename the Nucynta ER Prescribing Information Questionnaire to the Nucynta ER Education Confirmation Form. See Appendix G (Appendix H for clean copy) for revisions.

#### **4.5 Implementation System**

Because Nucynta ER can be approved without elements to assure safe use, as described under FDCA 505-1(f)(3)(B), (C), and (D) of the Act, an implementation system is not required.

#### **4.6 Timetable for Submission of Assessment**

The proposed timetable for submission of assessment is acceptable.

#### **4.7 REMS Supporting Document**

All changes in the REMS should also be included in the REMS Supporting Document. In the section titled “information for assessment”, include the following:

- An evaluation of patients’ understanding of the serious risks of Nucynta ER,
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24, a
- A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance,
- A report on the status of the training program for healthcare providers,
- An evaluation of health care providers’ awareness and understanding of the serious risks associate with Nucynta ER,
- Specify measures used to increase awareness of surveys,

- An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction,
- An analysis to evaluate utilization patterns including use in non-opioid tolerant patients, and
- With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

#### **4.8. Assessments and Surveys**

Submit for review a detailed plan that will be used to evaluate patients', and prescribers' understanding about the safe use of Nucynta ER. The proposed plan **does not** need to be submitted for FDA review prior to approval of the REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodology and instruments that will be used to evaluate the knowledge about the risks associated with and safe use of Nucynta ER.

##### **4.8.1 Survey Methodology**

4.8.1.1 Recruit respondents using a multi-modal approach. For example, respondents could be recruited, through physicians' offices, pharmacies, managed care providers, or consumer panels or on-line.

Explain how often non-respondent follow-up or reminders will be performed. If an incentive or honorarium is used, please provide details on what is offered and the estimated dollar value.

Explain how recruitment sites will be selected.

4.8.1.2 Define the sample size and confidence intervals associated with that sample size.

4.8.1.3 Define the expected number of people that will be surveyed to obtain the proposed sample size, and how the sample will be determined (selection criteria).

4.8.1.4 The sample should be demographically representative of the population who use the drug (patients), and prescribe the drug (doctors).

4.8.1.5 If possible and appropriate, the sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level and geographically.

4.8.1.6 List the inclusion criteria for patients and prescribers. For example, eligible patient respondents must be:

- Age 18 years or older,
- Currently taking Nucynta ER or have taken the drug in the past 3 months,
- Not currently participating in a clinical trial involving Nucynta ER, and
- Not a healthcare provider.

Submit any screener instruments, and describe if any quotas of sub-populations will be used.

4.8.1.7 Explain how surveys will be administered and the intended frequency. Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online, e-mail, in writing or by mail, over the phone, and in person.

Explain how surveyors will be trained.

4.8.1.8 Explain how you control for limitations or bias that may be associated with the methodology and survey instruments.

4.8.1.9 Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.

Potential respondents should be told that their answers will not affect their ability to receive or take (patients), and prescribe (doctors) Nucynta ER, and that their answers and personal information will be kept confidential and anonymous.

4.8.1.10 Respondents should not be eligible for more than one wave of the survey.

4.8.1.11 Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

Data may be stratified by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments that were utilized.

#### **4.8.2 Assessment of Patients' Knowledge**

4.8.2.1 The assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug, the assessment is not intended to evaluate consumer comprehension of the Medication Guide. Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed, respondents should not be offered an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

4.8.2.2 Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.

4.8.2.3 The patient knowledge survey should include questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event. Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Nucynta ER?" section of the Medication Guide.

The risk-specific questions should be not be biased or leading and multiple choice questions should include instructions to “select all that apply.” Each question should have an “I don’t know” answer option.

The order of the multiple choice responses should be randomized on each survey.

4.8.2.4 Order the patient questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

4.8.2.5 Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

4.8.2.6 Prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

Now we are going to ask you some questions about the Medication Guide you may have received with Nucynta ER. The Medication Guide is a paper handout that contains important information about the risks associated with use of Nucynta ER and how to use Nucynta ER safely. Medication Guides always include the title “Medication Guide” followed by the word Nucynta ER and its pronunciation. The Medication Guide usually has sections titled “What is the most important information I should know about Nucynta ER,” “What is Nucynta ER,” and “Who should not take Nucynta ER.”

4.8.2.7 Use the following (or similar) questions to assess receipt and use of the Medication Guide.

Who gave you the Medication Guide for Nucynta ER? (Select all that apply)

- a) My doctor or someone in my doctor’s office
- b) My pharmacist or someone at the pharmacy
- c) Someone else - please explain: \_\_\_\_\_
- d) I did not get a Medication Guide for Nucynta ER.

Did you read the Medication Guide?

- a) All,
- b) Most,
- c) Some,
- d) None

Did you understand what you read in the Medication Guide?

- a) All,
- b) Most,
- c) Some,
- d) None

Did someone offer to explain to you the information in the Medication Guide?

- a) Yes, my doctor or someone in my doctor's office
- b) Yes, my pharmacist or someone at the pharmacy
- c) Yes, someone else – please explain: \_\_\_\_\_
- d) No

Did you accept the offer? Yes or No

Did you understand the explanation that was given to you?

- a) All,
- b) Most,
- c) Some,
- d) None

Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

### **4.8.3 Assessment of Healthcare Providers' (prescribers) Knowledge**

4.8.3.1 The assessment should evaluate how effective the REMS is in achieving the goal(s), by evaluating healthcare providers' knowledge of:

- the serious risks associated with use of Nucynta ER,
- how to properly prescribe Nucynta ER, and
- how to properly monitor for the serious risks associated with the use of Nucynta ER.

The assessment is not intended to assess healthcare providers' comprehension of the educational materials.

Respondents should not be offered an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.

4.8.3.2 Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.

4.8.3.3 The healthcare provider knowledge survey should include a section with questions asking about the specific risks and safety information conveyed in the educational materials. Questions should not be biased or leading, and multiple choice questions should include instructions to "select all that apply." Each question should have an "I don't know" answer option. The order of the multiple choice responses should be randomized on each survey.

4.8.3.4 Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

4.8.3.5 Use the following (or similar) questions to assess receipt and use of the educational materials.

Prior to today, which of the following were you aware of or received with regard to Nucynta ER? (Select all that apply)

Educational Material	Aware	Received
Full Prescribing Information	<input type="checkbox"/>	<input type="checkbox"/>
Medication Guide	<input type="checkbox"/>	<input type="checkbox"/>
Dear Healthcare Provider Letter	<input type="checkbox"/>	<input type="checkbox"/>
Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER	<input type="checkbox"/>	<input type="checkbox"/>
Something else - please explain:	<input type="checkbox"/>	<input type="checkbox"/>
None of the above	<input type="checkbox"/>	<input type="checkbox"/>

Did you read the Full Prescribing Information?

- a) All,
- b) Most,
- c) Some,
- d) None
- e) I did not receive the Nucynta ER Full Prescribing Information

Did you read the Medication Guide?

- a) All,
- b) Most,
- c) Some,
- d) None
- e) I did not receive the Nucynta ER Medication Guide

Did you read the Dear Healthcare Provider Letter?

- a) All,
- b) Most,
- c) Some,
- d) None
- e) I did not receive the Nucynta ER Dear Healthcare Provider Letter

Did you read the Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER?

- a) All,
- b) Most,
- c) Some,
- d) None
- e) I did not receive the Training Educational Brochure for Nucynta ER.

Do you have any questions about any of the educational materials related to Nucynta ER? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA.

#### **4.9 General Comments**

Submit revisions for the proposed REMS with appended materials and the REMS Supporting Document and all other materials in **WORD** format. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such. The preference is to include as many as possible be in a single WORD document. Please provide a track changes and clean version of all revised materials and documents.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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

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/s/

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DOMINIC CHIAPPERINO

04/20/2010

signed off by Sharon and Bob; Bob wanted Larissa as signatory

LARISSA LAPTEVA

04/22/2010