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®ER (tapentadol) Extended-Release tablets
Dosage Formulation:	50, 100, 150, 200, 250 mg tablets
Submission Number:	Resubmission Class 2, Sequence 0023
Application Type/Number:	NDA 200-533 TSI 466
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® 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® 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.

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