DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200533/S-010

SUPPLEMENT APPROVAL
REMS MODIFICATION NOTIFICATION

Janssen Research and Development, LLC
on behalf of Janssen Pharmaceuticals Inc.
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869-0602

Attention: Tania Hillmer, MS, RAC
Associate Director, Regulatory Affairs

Dear Ms. Hillmer:

Please refer to your October 9, 2013, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NUCYNTA ER (tapentadol) extended-release tablets.

We acknowledge receipt of your amendments dated November 5, 2013, and March 17 and April 7, 2014.

We also refer to our letter dated September 10, 2013, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for the class of extended-release and long-acting (ER/LA) opioid analgesics, of which NUCYNTA ER is a member. This information pertains to the risks of misuse, abuse, hyperalgesia, addiction, overdose, death, and neonatal opioid withdrawal syndrome.

This supplemental new drug application provides for revisions to the labeling consistent with our September 10, 2013, letter.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content

of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the draft guidance for industry, *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The REMS for the ER/LA opioid analgesics was originally approved on July 9, 2012, and the most recent REMS modification was approved on April 15, 2013. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that the approved REMS for the ER/LA opioid analgesics must be modified to conform the REMS to the safety labeling changes for the ER/LA opioid analgesics class that are approved in this letter, to ensure that the benefits of the drugs outweigh their risks. Your proposed REMS modification submission must include the following changes to the REMS appended materials:

Revisions to the ER/LA Opioid Analgesics REMS Blueprint, ER/LA opioid analgesic REMS Website, and the Dear Prescriber Letter (DHCP) letter to incorporate the following safety labeling changes:

- New indication for ER/LA opioid analgesics.
- New warning for Neonatal Opioid Withdraw Syndrome (NOWS).
- Updated language for the following Warnings and Precautions:
  - Addiction, Abuse, and Misuse
  - Life-Threatening Respiratory Depression
  - Accidental Ingestion
  - Cytochrome P450 3A4 Interaction (for applicable products)
- Revisions to the Blueprint to incorporate updated product-specific titration

The timetable for submission of assessments of the proposed modified REMS may remain the same as that approved on July 9, 2012.

The proposed REMS modification submission should include a new proposed REMS that shows the complete previously approved REMS with all proposed modifications highlighted and the revised REMS materials as described above. Shortly following this letter, FDA will provide the ER/LA Opioid Analgesics REMS Program Companies with FDA's recommended changes to the REMS.

In addition, the submission should include an update to the REMS supporting document that includes the rationale for and description of all proposed modifications and any impact the proposed modifications would have on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a modified REMS with the changes described above is necessary to ensure the benefits of ER/LA opioid analgesics outweigh their risks, you must submit a proposed REMS modification within 60 days of the date of this letter, as a Prior Approval supplement to your NDA.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 200533
PROPOSED REMS MODIFICATION

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA 200533/S-XX
PROPOSED REMS MODIFICATION-AMENDMENT

If you do not submit electronically, please send 5 copies of your submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Dominic Chiapperino, Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

SHARON H HERTZ on behalf of JUDITH A RACOOSIN
04/16/2014