DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 200533

NDA APPROVAL

Janssen Pharmaceuticals, Inc.
c/o Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.
1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560-0200

Attention: Kathleen F. Dusek, R.Ph., RAC
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) dated November 30, 2009, received December 1, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nucynta ER (tapentadol) extended-release oral tablets 50, 100, 150, 200, and 250 mg.

We acknowledge receipt of your amendments dated December 11, 2009, and March 11, 12, 25, and 30, April 2, 21, 26(2), and 30, May 13 and 21, June 4 and 21, July 23, and August 5 and 19, 2010, and February 28, March 18 and 21, April 28, May 16 and 25, June 15, 20, and 24, July 18, 20, 26, and 29, and August 2, 12, 16, and 23(3), 2011.

The February 28, 2011, submission constituted a complete response to our October 1, 2010, action letter.

This new drug application provides for the use of Nucynta ER (tapentadol) extended-release oral tablets for 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.

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

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your August 16, 2011, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages less than 7 years, as the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. The very low medical need based upon the very low prevalence of chronic pain conditions in this age category together with the immaturity of the metabolic functions in very young children that may result in unpredictably higher exposures than in other age groups, support the justification that Nucynta ER (tapentadol) extended-release oral tablets does not provide a meaningful therapeutic benefit over existing therapies for very young children.

We are deferring submission of your pediatric study for ages 7 to less than 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1815-1 Deferred pediatric study under PREA: A pharmacokinetic, efficacy, and safety study of Nucynta ER for the management of chronic pain in pediatric patients ages 7 to <17 years.

Final Protocol Submission:	May 2014
Trial Completion:	October 2017
Final Report Submission:	March 2018

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

On April 18, 2011, you were notified that in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for certain long-acting and extended-release (LA/ER) opioid products, including Nucynta ER (tapentadol) extended-release oral tablets, to ensure that the benefits of the drugs continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse, and we notified you of the elements of the REMS that would be required. You were also notified that 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.

While the class-wide REMS, including the single shared system, is being developed, your proposed interim REMS, submitted on August 23, 2011, and appended to this letter, is approved. This interim REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. We believe this interim REMS provides for management of the risks of adverse outcomes (addiction, unintentional overdose, and death) that is comparable to the REMS that we have determined is necessary for the class of LA/ER opioid products and is designed to ensure that the benefits of Nucynta ER (tapentadol) extended-release oral tablets continue to outweigh its risks while the single shared system, class-wide REMS is being developed.

We expect you to be working with the Industry Working Group (IWG) to develop the class-wide REMS. Prior to the implementation of the class-wide REMS, we will notify you in writing and you will be required to submit a proposed modified REMS that conforms to the class-wide REMS. The assessment plan requirements for this REMS were also described in the April 18, 2011, letter, and in that letter, FDA strongly recommended that sponsors make provision in the single shared system for joint assessments of the effectiveness of the REMS.

Your interim REMS must be fully operational before you introduce Nucynta ER (tapentadol) extended-release oral tablets into interstate commerce.

The interim REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of patients' understanding of the serious risks of Nucynta ER (tapentadol) extended-release oral tablets.

2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

4. An evaluation of healthcare providers' understanding of the serious risks of Nucynta ER (tapentadol) extended-release oral tablets.

5. An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

6. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

We also remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If you plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 200533 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 200533
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 200533
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

DOCKET ALARM

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Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

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Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.