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APPLICATION NUMBER:
200533Orig1s000

OTHER ACTION LETTER(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 200533

COMPLETE RESPONSE

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

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 for Nucynta ER (tapentadol) Extended-Release 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.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY/BIOPHARMACEUTICS

1. Your proposed in vitro in vivo correlation (IVIVC) models do not support the bridging of the clinical study batches (PR2) to the to-be-marketed tamper resistant formulation (TBM TRF).
2. The re-constructed IVIVC models using individual plasma concentrations are not acceptable for the following reasons:
 - The models submitted on July 23, 2010, still include a mathematical term that has no mechanistic foundation and, therefore, are not acceptable.
 - The models using the individual subject concentrations failed the external validation, indicating a lack of robustness.

3. The proposed dissolution acceptance criteria for TBM TRF tapentadol ER tablets were based on the proposed IVIVC models. Because these models were not accepted, these dissolution acceptance criteria will need to be revised. You may refer to our advice letter dated August 12, 2010, for additional guidance concerning these acceptance criteria.
4. Given that your proposed IVIVC models do not support the bridging of the clinical study batches to the TBM TRF, bioequivalence has not been demonstrated. Provide in vivo bioequivalence (BE) data comparing the PR2 and TBM TRF formulations. Because the compositions of your formulations are not proportional, you should provide bioequivalence (BE) data for the lowest, 50 mg, and highest, 250 mg, strengths. You may request a biowaiver for the intermediate strengths. The biowaiver request should be supported with: **1)** acceptable in vivo BE data for the lowest and highest strengths and **2)** in vitro comparative dissolution profile data and similar f₂ values (using the highest and lowest strengths as references).

CLINICAL

5. For Protocols KF5503/23 and KF5503/36, data pertaining to subject eligibility, primary endpoint, and rescue medication use were directly submitted by subjects via eDiaries to eTrials, the contract research organization (CRO) responsible for this electronic data capture. Because the clinical investigator sites did not maintain independent source documentation of the data that were transmitted directly to eTrials via eDiaries, verification of source data at the CRO, in conjunction with evaluation of findings from other completed inspections, is required before this application may be approved.

LABELING

6. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

As described in our letter dated April 22, 2010, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for Nucynta ER to ensure that the benefits of the drug outweigh the risks of abuse, misuse, and overdose.

We acknowledge the submission of your proposed REMS on November 30, 2009, and revised proposed REMS on June 21, 2010, which contains a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

We have determined that your proposed REMS does not adequately communicate the risks of abuse, misuse, and overdose. Because your application cannot be approved without an approved REMS, you must revise your proposed REMS and submit it as part of your response to the deficiencies cited in this letter and in our September 21, 2010 information request letter

concerning your REMS. We will continue review and discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also

request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, M.D.
Deputy Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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