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APPLICATION NUMBER:

200533Orig1s000

SUMMARY REVIEW

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Summary Review for Regulatory Action

Date	August 25, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	200533 Class 2 Resubmission
Applicant Name	Johnson & Johnson Pharmaceutical Research and Development, LLC on behalf of Janssen Pharmaceuticals, Inc.
Date of Submission	February 28, 2011
PDUFA Goal Date	August 26, 2011
Proprietary Name / Established (USAN) Name	Nucynta ER Tapentadol
Dosage Forms / Strength	50 mg, 100 mg, 150 mg, 200 mg and 250 mg extended-release tablets
Proposed Indication	For 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
Action:	Approval

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Material Reviewed/Consulted OND Action Package, including:	
CDTL	Ellen Fields, MD, MPH
Medical Officer Review	Elizabeth Kilgore, MD
CSS	Alicja Lerner, MD, PhD, PhD/Michael Klein, PhD
ONDQA-Biopharmaceutics Review	Sandra Suarez-Sharp, PhD/Angelica Dorantes, PhD/Patrick J. Marroum, PhD
Clinical Pharmacology Review	David Lee, PhD/Yun Xu, PhD
DDMAC	Mathilda Fienkeng, PharmD, Twyla Thompson
OSI	(analytical site): Arindam Dasgupta,PhD/ Martin K. Yau, PhD (clinical site): Susan Liebenhaut, MD/Tejashri Purohit-Sheth, MD
Project Management	Dominic Chiapparino, PhD/Parinda Jani
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OND=Office of New Drugs
CDTL=Cross Discipline Team Leader
CSS=Controlled Substance Staff
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
OSI=Office of Scientific Investigations

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1. Introduction

Tapentadol is a centrally-acting analgesic which combines mu-receptor opioid agonist activity with inhibition of norepinephrine reuptake. It is pharmacologically similar to tramadol. Nucynta ER is an extended-release (ER) formulation of tapentadol and the proposed indication is "for 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 standard indication for ER opioid products. The application for immediate-release (IR) tapentadol, Nucynta, received approval for marketing "for the relief of moderate to severe acute pain in patients 18 years or older" on November 20, 2008.

2. Background

The original application for Nucynta ER was submitted on November 30, 2009. Dr. Rigoberto Roca, Deputy Director of the Division of Anesthesia, Analgesia, and Addiction Products, was the signatory authority for that submission. His review and summary basis for a complete response action is appended to this review. While the review team for the first-cycle submission found that there was substantial evidence to support the safety and efficacy of the product, a complete response action was taken due to the deficiencies described in the following excerpt from the Complete Response (CR) Letter, issued on October 1, 2010:

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,

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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.

The Applicant submitted this response to the CR Letter issued on October 1, 2010. This review will focus only on the new data and information submitted to address the deficiencies in the CR Letter. The reader is referred to Dr. Roca's first-cycle summary review, which has been appended to this review, for discussion of the data from the original submission supporting the efficacy and safety of Nucynta ER.

In this submission, rather than attempt to reconstruct their IVIVC model, the Applicant has provided the results of new bioequivalence studies between their Phase 3 PR2 tablets and the to-be-marketed formulation, to support the bridging of the strengths (150 mg and 200 mg) which they had originally proposed to cover with the IVIVC model. In addition, inspections of the CRO and the additional clinical pharmacology studies were performed by OSI during this review cycle to address the approvability issues in Item 5 of the CR Letter.

A post-action meeting was held with the Applicant on November 9, 2010. At that meeting, two additional concerns were raised by the clinical review team. First, the fact that the to-be-marketed 50 mg tablet was not bioequivalent to the 50 mg PR2 tablet had been noted upon review of the meeting package submitted by the Applicant for the post-action meeting. During the meeting, the Applicant was asked to provide data or a rationale in their response to the CR Letter to justify the use of multiple 50 mg tablets in place of a tablet of a higher dose. The information that they have submitted to address this concern is discussed in Section 5 below. Second, the formulation of the Nucynta ER tablets contains polyethylene oxide (b) (4) [redacted] However, polyethylene oxide is an excipient that, in certain approved products, has been associated with swelling and stickiness upon contact with saliva or water, at times resulting in serious adverse events including choking, some requiring medical intervention. As such, the Applicant was asked to

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