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APPLICATION NUMBER:

203794Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement #	203794/000
Applicant Name	Janssen Pharmaceuticals, Inc.
Date of Submission	
PDUFA Goal Date	October 15, 2012
Proprietary Name / Established (USAN) Name	Nucynta (tapentadol) Oral Solution
Dosage Forms / Strength	Oral Solution/ 20 mg per mL
Proposed Indication(s)	Moderate to severe acute pain in patients 18 years of age or older
Action/Recommended Action:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	Armaghan Emami, Ph.D., Adam Wasserman, Ph.D.
CMC Review	Craig M. Bertha, Ph.D., Prasad Peri, Ph.D.
Microbiology Review	Brian S. Riley, Ph.D., Stephen E. Languille, Ph.D.
Clinical Pharmacology Review	David Lee, Ph.D., Yun Xu, Ph.D.
OPDP	
DSI	N/A
CDTL Review	N/A
OSE/DMEPA	Denise V. Baugh, PharmD, BCPS, Lubna Merchant, PharmD, M.S.

OND=Office of New Drugs
 OPDP=Office of Professional Drug Promotion
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Errors Prevention
 DSI=Division of Scientific Investigations
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This application for Nucynta Oral Solution is a 505(b)(1) application. The formulation was developed initially for conduct of pediatric studies to fulfill the PREA PMR for Nucynta tablets, NDA 22304. No new nonclinical, clinical pharmacology, efficacy or safety data were submitted for this NDA as this oral solution is supported by a bioequivalence study with the oral tablet.

2. Background

Nucynta (Tapentadol) Tablets (NDA 022304) and Nucynta ER (Tapentadol) Extended-Release Tablets (NDA200533) were the first tapentadol products approved in the U.S., on November 20, 2008 and August 25, 2011, respectively. Tapentadol is an opioid agonist and inhibits the reuptake of norepinephrine and serotonin. In addition to adverse events consistent with mu-opioid agonist activity, tapentadol was shown to have pro-convulsant activity in rats, and induced convulsions in rats, mice, and dogs at high doses. The tapentadol-glucuronide metabolite may contribute to this effect. Notably, hallucinations, convulsions and serotonin syndrome have been reported in postmarketing experience with Nucynta IR tablets. Both seizures and serotonin syndrome risk are described in the approved Nucynta label.

This application cross-references NDA 022304 for clinical, nonclinical toxicology and clinical pharmacology information. A biowaiver for clinical pharmacology studies was granted by the FDA on June 29, 2009. This NDA contains CMC data and labeling.

3. CMC/Device

The drug substance used for this product is the same as that used for the immediate-release oral tablet formulation (NDA 22304) and the extended-release formulation (NDA 200533).

The following is from Dr. Bertha's review:

The drug substance is tapentadol hydrochloride, which is a chiral opioid compound... The (b) (4) form of the drug substance is inconsequential as it is formulated in solution. The aqueous-based solution formulation contains no co-solvents, has a target pH of 4.0, and also contains both sucralose and a proprietary flavor mixture, for taste purposes. The clear and colorless formulation is simply prepared by (b) (4). The strength of the formulation, in terms of the tapentadol base, is 20 mg/mL (equivalent to 23.3 mg of tapentadol hydrochloride), and the formulation is packaged in quantities of 100 and 200 mL in high density polyethylene bottles fitted with foil induction seals (b) (4).

A 24 month expiration dating period is supported by the stability data that have been provided in the application and the product is intended to be stored at room temperature.

The applicant was able to adequately address initial deficiencies concerning the raspberry flavor used in the formulation. The applicant was also able to provide a method validation report for the HPLC method used to for the determination of identity, assay, and degradants.

The oral dosing syringe initially provided was novel in design. Rather than have markings on the barrel of the syringe, starting at the tip and increasing along the barrel, there were markings on the plunger. An acceptable oral dosing syringe was ultimately provided with adequate acceptance testing and criteria for deliverable volume. A syringe adapter will be supplied and placed into the bottle neck prior to its first use.

A microbiology review of the drug product noted that the drug product is a non-sterile oral liquid without a specific preservative. However, during product development it was noticed that the drug substance (tapentadol HCl) had anti-microbial activity. The product meets the acceptance criteria for USP Chapter <51>. The applicant adequately addressed the product quality microbiology deficiencies by agreeing to test for microbial limits at release for each batch and by adding a specification for the absence of *B. cepacia*.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this NDA. I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology studies were submitted with this NDA. Under IND 61,345, a biowaiver was requested and granted by the Agency on June 29, 2009. In a memo dated February 24, 2012, Dr. Christine Moore, Acting Office Director of Office of New Drug Quality Assessment (ONDQA), noted that the biowaiver granted was still valid for this NDA. I concur with the conclusions reached by the Dr. Lee and Dr. Moore that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

No new clinical efficacy data were submitted in support of this application. Based on the formulation and the prior approval of Nucynta immediate-release tablets, a biowaiver was granted and the efficacy of Nucynta tablets can be extrapolated to the oral solution. There are no outstanding efficacy issues.

8. Safety

No new clinical safety data were submitted in support of this application. Oral solution formulations of opioids have been dosed in error in the past. Therefore, in contrast to the tablets, additional labeled warnings and a medication guide are included for oral solutions. This is discussed below. There are no outstanding safety issues.

9. Advisory Committee Meeting

No Advisory Committee meeting was held for this application.

10. Pediatrics

The applicant has submitted a pediatric plan and agreed to study the efficacy, safety and pharmacokinetics of Nucynta oral solution in pediatric patients ages 0 to less than 17. The proposed dates for study completion are based on the current experience with pediatric enrollment.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

The dosing for Nucynta oral solution is 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending upon pain intensity. On the first day of dosing the second dose may be given as soon as one

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