CENTER FOR DRUG EVALUATION AND RESEARCH

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 ErrorsPrevention
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 formulaton. 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 ultimatrely provided with adeqate 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 (tapendatol 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

hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 50 mg, 75 mg, or 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability. Daily doses greater than 700 mg on the first day of treatment and 600 mg on subsequent days are not recommended. This is consistent with the dosing for Nucynta immediate-release tablets. In contrast to the tablets, opioid oral solutions require additional attention to avoid medication errors. Nucynta oral solution has 20 mg of active drug in each milliliter of solution. Therefore, it is extremely important that prescribers clearly write the mg and mL when they prescribe the drug, e.g. 50 mg (2 mL) every 6 hours as needed for pain. This is to avoid the risk that either 50 mL or 2 mg are dosed improperly, the former resulting in overdose, the latter in inadequate pain management. In addition, a medication guide has been developed for oral opioid solutions to ensure that patients have adequate instruction for proper dosing.

DMEPA has recommended the following

> The recommended dosage and administration for Nucynta oral solution will be the same as Nucynta immediate release tablets. Therefore, we do not anticipate confusion will occur with the introduction of this new dosage form. However, the presentation of the strength as "20 mg/mL" is problematic given that the recommended volume per dose for Nucynta may range from 2.5 mL (50 mg) to 5 mL (100 mg). The manner in which the strength is stated is inconsistent with the recommended dosing and may lead to calculation errors. Expressing the statement of strength as 100 mg/5 mL may minimize the potential for medication errors due to miscalculations. Although this presentation would still require calculation for the lower doses, the medical community is familiar with this presentation (e.g., XX mg/5 mL) and it is consistent with the expression of other oral solutions. See our recommendations in Section 5.

While there are still some oral opioid solutions with the concentration expressed per 5 mL, this has, in the past, resulted in confusion when there were also products available with more than one concentration available. For example, morphine oral solution is available in 20 mg per 5 mL and 20 mg per one mL concentrations. This has led to medication errors where the higher concentration product was mistakenly substituted for the lower concentration product and patients were overdosed. Therefore, we have attempted to change the labeling for these products to consistently display the mg per one mL. As Nucynta will be labeled for doses of 50 mg, 75 mg or 100 mg, and only the 100 mg dose will be a 5 mL volume, there is still the opportunity for medication errors by displaying the concentration as 100 mg per 5 mL. This was discussed with DMEPA who agreed as noted in an email entered into DAARTS on October 15, 2012.

OPDP provided comments that were incorporated into the labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

The indication and dosing for Nucynta Oral Solution are the same as for the immediate-release tablet. The overall risk and benefit are expected to be similar as well, except for a higher risk for medication errors. The labeling and medication guide are intended to address this added risk.

- Recommendation for Postmarketing Risk Management Activities

None beyond routine postmarketing pharmacovigilance

- Recommendation for other Postmarketing Study Commitments

1937-1 A pharmacokinetic, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages 6 to less than 17 years.

Final Protocol Submission:	May 31, 2014
Study/Trial Completion:	September 30, 2018
Final Report Submission:	March 31, 2019

1937-2 A pharmacokinetic, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages birth to 5 years.

Final Protocol Submission:	March 31, 2017
Study/Trial Completion:	July 31, 2021
Final Report Submission:	December 31, 2021

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
10/15/2012