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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	203-794
Supporting document/s:	001
Applicant's letter date:	December 15, 2011
CDER stamp date:	December 15, 2011
Product:	Tapentadol (Nucynta®) oral solution
Indication:	Moderate to severe acute pain in patients 18 years of age or older
Applicant:	Janssen Pharmaceuticals, Inc.
Review Division:	Division of Anesthesia, Analgesia and Addiction Products
Reviewer:	Armaghan Emami, Ph.D.
Supervisor/Team Leader:	Adam Wasserman, Ph.D.
Division Director:	Bob Rappaport, M.D.
Project Manager:	Dominic Chiapperino

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1 Executive Summary

1.1 Introduction

Janssen Research & Development, LLC (JRD) is submitting a New Drug Application for Nucynta® (tapentadol) oral solution. The indication for this NDA is for the management of moderate to severe acute pain in patients age 18 or older, as in the approved NDA 022-304 (November 2008) for Nucynta immediate-release tablets. Also, a tapentadol extend release tablet formulation received FDA approval for the management of moderate to severe chronic pain (NDA 200-533, approved 25 August 2011).

This application cross-references NDA 022-304 for clinical, nonclinical toxicology and pharmacology information. No nonclinical or clinical studies are provided with this application. A biowaiver for clinical studies was granted by the FDA on 29 June 2011. This NDA only consists of CMC data to support Nucynta oral solution, labeling and packaging components.

1.2 Brief Discussion of Nonclinical Findings

Tapentadol is an opioid agent with a dual mode of analgesic action, the inhibition of norepinephrine combined with moderate opioid agonist activity. Tapentadol has been evaluated in a comprehensive preclinical program including pharmacological characterization, preclinical safety (safety pharmacology and toxicology), pharmacokinetics, and ADME. Nonclinical studies were reviewed by Dr. Kathy Young under NDA 022-304.

The major toxicity findings of tapentadol were consistent with its mu-opioid receptor agonist activity (i.e., effects on gastrointestinal, central nervous, respiratory, and cardiovascular systems). At high doses of tapentadol, transient, dose dependent and predominantly CNS-related findings, e.g. fearfulness, sedation or excited behavior, recumbency and hunched posture, impaired respiratory function and rarely convulsions were observed in nonclinical models. In dogs, salivation, vomiting and retching were additionally observed. Tapentadol was shown to have pro-convulsant activity in rats, and induced convulsions in rats, mice, and dogs at high doses. The tapentadol-O-glucuronide metabolite may contribute to this effect. Changes of the liver (increases of liver enzymes and liver weights, and histopathology findings of hepatocellular hypertrophy), and cardiovascular system (e.g. QT prolongation) were seen in rats and dogs respectively. Of note, toxicities observed in nonclinical (rats and dogs) studies were associated with exposure levels below human exposures at maximum recommended human dose (MRHD).

It is noted that significant CNS findings (hallucination, convulsion 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.

There are no novel excipients in the proposed drug product formulation. The excipients are within the limits allowed in previously approved product as listed in the FDA's Inactive Ingredient Database (IIG) except for the artificial raspberry flavor that has not been used in any approved drug product. However, based on CMC review of DMF (b) (4) (30-Jan-2012) by Dr. Craig Bertha, all of the components of this flavor are GRAS and can be added to foods. The total daily intake of all inactive ingredients together would be 10 mg at most and does not represent an issue of toxicologic concern. Moreover, drug substance and drug product specifications for impurities/degradants are below the ICH Q3A & Q3B levels for qualification.

1.3 Recommendations

1.3.1 Approvability: From the nonclinical pharmacology toxicology perspective, this NDA may be approved. The indication, patient population and dosage of Nucynta oral solution are the same as approved IR product and the formulation is acceptable.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: Dosage is the same as approved IR product; therefore no changes to the nonclinical sections of the label are recommended.

2 Drug Information

2.1 Drug

CAS Registry Number: 175591-09-0

Generic Name: Tapentadol

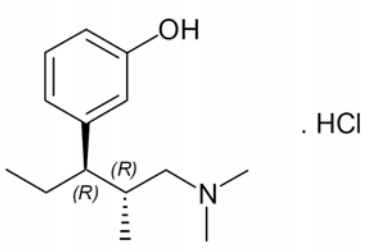
Chemical Name:

3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2- methylpropyl]phenol monohydrochloride

Molecular Formula: $C_{14}H_{23}NO \cdot HCl$

Molecular Weight: 257.81 g/mol; Free base: 221.35 g/mol

Structure or Biochemical Description:



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