CENTER FOR DRUG EVALUATION AND RESEARCH

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

Disclaimer

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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

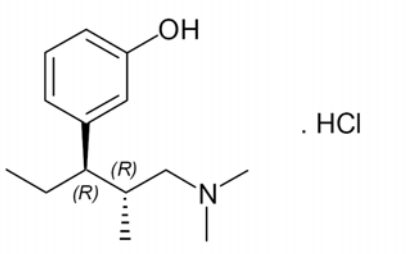
Chemical Name:

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:



Pharmacologic Class: mu-opioid receptor agonist and NE reuptake inhibitor

2.2 Relevant INDs, NDAs, and DMFs

Submission	Status/date	Sponsor	Drug	Indication	Division
IND 61,345	Active/ 12/04/2000	JRD	Tapentadol IR tablets	Moderate to severe acute pain	DAAAP
IND 105,766	Active/ 7/19/2009	JRD	Tapentadol ER tablets	Chronic diabetic peripheral neuropathy	DAAAP
IND 108,134	Active/ 3/22/2011	JRD	Tapentadol OS	Pediatric acute pain	DAAAP
(b) (4)					
NDA 22-304	approved 11/20/2008	Ortho-McNeil-Janssen	Tapentadol IR tablets (50, 75 and 100 mg)	Moderate to severe acute pain	DAAAP
NDA 200-533	approved 8/25/2011	Ortho-McNeil-Janssen	Tapentadol ER tablets (50, 100, 150, 200 and 250 mg)	Moderate to severe chronic pain	DAAAP

2.3 Drug Formulation

The drug product is an aqueous solution of tapentadol HCl. The drug product packages of 100 and 200 mL of formulation have a concentration of 20 mg/mL.

Composition of Tapentadol 20-mg/mL Oral Solution

Component	Quality Standard[a]	Function	Quantity (mg/mL)
Tapentadol HCl	Company specification	Active ingredient	23.3
Citric acid monohydrate	USP/Ph. Eur.	(b) (4)	
Sucralose	NF/Ph. Eur.		
Raspberry flavor	Company specification		
Sodium hydroxide	NF/Ph. Eur.		
Purified water	USP/Ph. Eur.		

[a] Where multiple compendia are listed, the compendium applied during testing is specific to the applicable region for commercial distribution.

2.4 Comments on Novel Excipients

All the excipients are within the IIG levels established for oral administration, except for artificial raspberry flavor. However, according to Dr. Craig Bertha (CMC reviewer), the level of this raspberry flavor is acceptable since all of the components of the flavor are GRAS and can be added to foods (see Dr. Bertha's review, DMF (b) (4), 30-Jan-2012).

2.5 Comments on Impurities/Degradants of Concern

- The maximum dose according to the proposed labeling is 600 mg of tapentadol daily, thus the qualification thresholds for degradants in the drug substance and the drug product are (b) (4) respectively. Thus the current limits of NMT (b) (4) for any individual impurity in the drug substance and NMT (b) (4) for any unspecified individual degradant in the drug product are acceptable.

Copied from the NDA submission

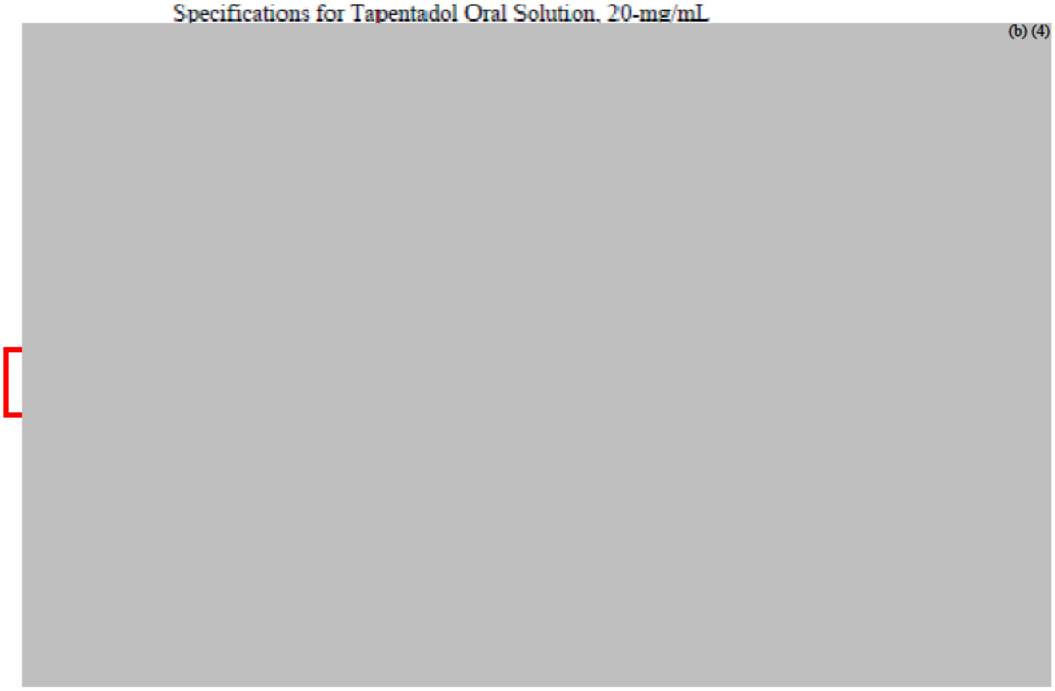
Specifications for Drug Substance

Test Parameter	Acceptance Criteria	Test Methods
1. Appearance	White to off-white powder	Visual examination
2. Identification of R331333[a]		
a. HPLC	Similar retention time for sample and reference solution peak	AD-TM-R331333-DS-HPLC-04
b. Infrared Absorption	Exhibits absorption bands at the same wavelengths as those of a similar preparation of the tapentadol hydrochloride standard	Current USP<197>
c. Chloride	Complies	Current USP <191>
3. Assay of R331333	98.0-102.0%	AD-TM-R331333-DS-HPLC-04
4. Chromatographic Purity (HPLC)		
a. Any individual impurity	Not more than (b) (4)	AD-TM-R331333-DS-HPLC-04
b. Total impurities	Not more than (b) (4)	AD-TM-R331333-DS-HPLC-04
5. Enantiomeric Purity (Chiral HPLC)[a]	Not less than	AD-TM-R331333-DS-HPLC-02
6. Water Content	Not more tha	Current USP <921> Method I
7. Heavy Metals[a]	Not more tha	Current USP <231> Method II
8. Residue on Ignition[a]	Not more tha	Current USP <281>
9. Residual Solvents[a]		
(b) (4)		

[a] This test is conducted for release only.

Copied from the NDA submission

Specifications for Tapentadol Oral Solution, 20-mg/mL



- This formulation is aqueous based for oral administration and does not contain co-solvents, and the drug is for treatment of acute pain therefore no additional extractable/leachable information would be necessary (Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Documentation, May 1999).

2.6 Proposed Clinical Population and Dosing Regimen

The drug product is to be indicated for the relief of moderate to severe acute pain in patients 18 years of age or older, as in the approved IR drug product. The drug product formulation has a concentration of 20 mg/mL corresponding to the labeled doses of 50-100 mg to be taken every 4-6 hours. Daily doses of more than 700 mg the first day and more than 600 mg on subsequent days are not recommended by the applicant in the label.

2.7 Regulatory Background

This 505 (b1) application cross-referenced NDA 022-304 for clinical, nonclinical and pharmacology information.

3 Studies Submitted

This NDA only consists of CMC data to support Nucynta oral solution, labeling and packaging components.

4 Pharmacology

N/A

5 Pharmacokinetics/ADME/Toxicokinetics

N/A

6 General Toxicology

N/A

7 Genetic Toxicology

N/A

8 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

N/A

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety Evaluation

JRD is submitting a 505 (b1) 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 (Nucynta IR tablets). JRD cross-referenced NDA 022-304 for clinical, nonclinical toxicology and pharmacology information. No nonclinical or clinical studies are provided with this application. This NDA consists of CMC information to support Nucynta oral solution, labeling and packaging components.

The indication, patient population and dosage of Nucynta oral solution are the same as approved IR product. Moreover, there is no concern about excipients and impurities/degradants in the drug product, therefore from the nonclinical perspective, this NDA may be approved.

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/s/

ARMAGHAN EMAMI
08/15/2012

ADAM M WASSERMAN
08/15/2012
I concur the NDA may be approved from the nonclinical perspective.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: 203-794	**Applicant:** Janssen Research & Development, LLC	**Stamp Date:** December 15, 2011
Drug Name: Nucynta (tapentadol) Oral Solution	**NDA Type:** 505(b)	**DAAAP/OND/CDER/FDA**

On **initial** overview of the NDA application for Refuse to File (RTF):

All non-clinical studies cross-referenced to NDA 22304

	Parameters	Yes	No	Comment
1	On its face, is the pharmacology section of the NDA/BLA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	+		
2	Is the pharmacology/toxicology section of the NDA/BLA indexed and paginated in a manner allowing substantive review to begin?	+		
3	On its face, is the pharmacology/toxicology section of the NDA/BLA legible so that substantive review can begin?	+		
4	Are all required (*) and requested BBIND studies (in accord with 505(b1) and (b2) including referenced literature) completed and submitted in this NDA/BLA (carcinogenicity*, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, acute and repeat dose adult animal studies*, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc)?	+		

5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies been conducted with the appropriate formulation?	+		
6	Is (are) the excipient(s) appropriately qualified (including interaction between the excipients if applicable)?	+		
7	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	+		
8	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	+		
9	Has the sponsor submitted all special studies/ data requested by the Division during pre-submission discussions with the sponsor?	+		
10	Are the proposed labeling sections relative to pharmacology, reproductive toxicology, and carcinogenicity appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	+		
11	Has the sponsor submitted any toxicity data to address impurities, new excipients, leachables, etc. issues.	+		

12	Has the sponsor addressed any abuse potential issues in the submission?	+		The Sponsor addressed abuse potential in NDA 22304
13	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			
14	From a pharmacology/ toxicology perspective, is the NDA/BLA fileable? If ``no`` please state below why it is not.	+		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to Sponsor: None

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/s/

ARMAGHAN EMAMI
04/19/2012

ADAM M WASSERMAN
04/19/2012