CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203794Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW MEMO

NDA: 203794	Submission Date: 12/15/11
Submission Type	1S
Brand/Code Name:	Nucynta™ Oral Solution
Generic Name:	Tapentadol oral solution
Primary Reviewer:	David Lee, Ph.D.
Team Leader:	Yun Xi, Ph.D.
OCP Division:	DCP 2
OND Division:	Division of Anesthesia, Analgesia and Addiction Products
Sponsor:	Janssen Pharmaceuticals, Inc.
Relevant NDA(s)	22-304
Relevant IND(s):	61,345
Formulation; Strength(s):	20 mg/mL
Proposed Indication:	• For the management of moderate to severe acute pain in patients 18 years of age or older
Proposed Dosage Regimen:	• Individualize dosing according to the severity of pain being treated; 50 mg, 75 mg, or 100 mg Q4 - 6 h depending upon pain intensity. On the first day of dosing, the second dose may be administered 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 Q 4 - 6 h and should be adjusted to maintain adequate analgesia with acceptable tolerability. Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are, therefore, not recommended.

Table of Contents

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application and found the submission acceptable from clinical pharmacology perspective. There are no Labeling related comments to be conveyed to the Applicant at this time.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of Clinical Pharmacology Findings

Janssen Research & Development, LLC, submitted a New Drug Application (NDA) for Nucynta® (tapentadol) Oral Solution, on behalf of Janssen Pharmaceuticals, Inc., in accordance with Section 505(b) of the Federal Food, Drugs, and Cosmetic Act. The indication for this NDA is for the management of moderate to severe acute pain, as in the approved NDA 22304 for Nucynta® (tapentadol) immediate-release tablets (Janssen Research). A reference is made to NDA 22304 for Clinical, Nonclinical, Toxicology, and Pharmacology information.

No clinical studies were provided with this Application, due to the fact that a biowaiver was requested and granted by the Agency on 6/29/09. In the memo dated February 24, 2012 by Dr. Christine Moore, Acting Office Director of Office of New Drug Quality Assessment (ONDQA), the suitability of a biowaiver for NDA 203794 Nucynta Oral Solution relative to the immediate release tablet was further discussed. It is stated that "Based on the information reviewed, I deem that the biowaiver granted by ONDQA for IND 61,345 on 6/29/09 is valid for NDA 203794".

In spite of the fact that biowaiver being granted, the Applicant has submitted Study HP5503/59, titled, "A relative bioavailability trial to compare a new tapentadol oral solution 100 mg with the tapentadol immediate release 100 mg tablet," on 2/7/12. According to the Applicant, Study 5503/59 utilized the same tapentadol solution formulation that is the subject to this NDA approval. The tapentadol immediate release

tablet used in study contains the equivalent formulation as the current FDA-approved NUCYNTA (tapentadol) formulation, only with the exception of the colorant used in the film-coating.

Since the Agency granted the biowaiver of the proposed tapentadol solution, this application may be approved based on the biowaiver without additional clinical or clinical pharmacology studies. From a clinical pharmacology perspective, the submitted study report HP5503/59 will be considered as non-pivotal information and will not be reviewed. No OSI inspection will be requested for this study.

2 Detailed Labeling Recommendations

There are no changes to the Label regarding Clinical Pharmacology.

3 Appendices

3.1 Proposed Package Insert - Not applicable

3.2 Individual study review – Not applicable

3.3 Consult Review (including Pharmacometric Reviews) – Not applicable

3.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**203794**	**Brand Name**	**Nucynta Oral Solution**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Tapentadol Oral Solution**
Medical Division	**DAAAP**	**Drug Class**	**Pain**
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**	**For the management of moderate to severe acute pain in patients 18 years of age or older**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**Solution 20 mg/mL**

Pharmacometrics Reviewer	-	**Dosing Regimen**	50 mg, 75 mg, or 100 mg Q4 - 6 h depending upon pain intensity. On the first day of dosing, the second dose may be administered 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 Q 4 - 6 h and should be adjusted to maintain adequate analgesia with acceptable tolerability. Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are, therefore, not recommended.
Date of Submission	**Dec 15, 2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**Sept 15, 2012**	**Sponsor**	**Janssen**
Medical Division Due Date	**Sept 15, 2012**	**Priority Classification**	**Standard**
PDUFA Due Date	**Oct 15, 2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	X	1		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			Biowaiver is granted for this product.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			x	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			x	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do			x	

	the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			x	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Janssen Research & Development, LLC, submitted a New Drug Application (NDA) for Nucynta® (tapentadol) Oral Solution, on behalf of Janssen Pharmaceuticals, Inc., in accordance with Section 505(b) of the Federal Food, Drugs, and Cosmetic Act. The indication for this NDA is for the management of moderate to severe acute pain, as in the approved NDA 22304 for Nucynta® (tapentadol) immediate-release tablets by the same Sponsor. A reference is made to NDA 22304 for Clinical, Nonclinical, Toxicology, and Pharmacology information.

No clinical studies were provided with this Application, due to the fact that a biowaiver was requested and granted by the Agency on 6/29/09. In spite of the fact that biowaiver being granted the Applicant has submitted Study HP5503/59, titled, "A relative bioavailability trial to compare a new tapentadol oral solution 100 mg with the tapentadol immediate release 100 mg tablet," on 2/7/12. According to the Applicant, Study 5503/59 utilized the same tapentadol solution formulation that is the subject to this NDA approval.

In the memo dated February 24, 2012 by Dr. Christine Moore, Acting Office Director of ONDQA, the suitability of a biowaiver for NDA 203794 Nucynta Oral Solution relative to the immediate release tablet is discussed. It is stated that "Based on the information reviewed, I deem that the biowaiver granted by ONDQA for IND 61,345 on 6/29/09 is valid for NDA 203794". Since the Agency granted the biowaiver of the proposed tapentadol solution and it is deemed valid, this application may be approved based on the biowaiver grant without additional clinical or clinical pharmacology studies. Therefore, the submitted study report HP5503/59 will be considered as non-pivotal information and no OSI inspection will be requested for this study.

From a clinical pharmacology perspective, the application is recommended for filing. We will request the Sponsor to submit the following information for completeness of the submission:

1. Regarding study HP5503/59, confirm that:

a. Tapentadol oral solution used in the study is the to-be-marketed formulation; and

b. FDA-approved Nucynta (tapentadol) immediate-release tablet was the immediate-release tablet formulation used as reference.

2. In addition to submitted Bioanalytical Analyses Study SBA_S_09040 (i.e., study PK1210A), and in order to have complete information concerning bioanalytical analyses, submit the following reports:

a. PK1134, "Complete Validation of an LC-MS/MS method for the determination of R331333 and R403347 in human serum," December 2007, including also Amendment 1 to study report PK1134, January 2009, containing long-term (24 months) stability data at -25°C (b) (4)

b. PK1070 (SBA_S_07093), "Partial validation of a method for the determination of CG5503 free base and its metabolite CG5503 glucuronide (GRTE1472) in human serum by LC-MS/MS," including also Amendment 1 to report SBA_S_07093, 2008, containing freeze/thaw stability data (-25°C/room temperature) and short-term (72 hours) stability data at room temperature (b) (4) respectively); and,

c. PK711 (SBA_S_04004), "Stability of CG5503, CG5503 glucuronide (GRTE1472), and CG5503 sulfate (GRT3793H) in human blood and human serum - investigation by LC-MS/MS," October 2007, containing post-preparative stability data, 192 hours at 8°C (conditions during autosampling) (b) (4)

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/s/

DAVID J LEE
08/21/2012

YUN XU
08/21/2012

BIOPHARMACEUTICS FILING REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 203-794	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	December 15, 2011		
Division:	Anesthesia, Analgesia, and Addiction Products	**Acting Biopharmaceutics Supervisory Lead:** Angelica Dorantes, Ph.D.	
Sponsor:	Janssen Research & Development, LLC	**Secondary Signature:** Sandra Suarez-Sharp, Ph.D.	
Trade Name:	NUCYNTA®	**Date Assigned:**	December 21, 2011
Generic Name:	Tapentadol	**Date of Review:**	February 24, 2012
Indication:	The management of moderate to severe acute pain.	**Type of Submission:** 505(b)(2) New Drug Application	
Formulation/strengths:	Solution/ 20 mg per mL		
Route of Administration:	Oral		

SUBMISSION:

This is a 505(b)(2) New Drug Application for 20 mg/mL tapentadol oral solution. The indication is for the management of moderate to severe acute pain.

BIOPHARMACEUTIC INFORMATION:

Tapentadol is currently approved as NUCYNTA® (tapentadol) immediate-release tablets 50 mg, 75 mg, and 100mg strengths (NDA 22-304). This NDA provides for an oral solution formulation to be used for the same indication as the approved indication for the immediate release tablets.

This submission includes a BA/BE waiver request. A biowaiver for the CFR BA/BE requirements was granted for this product by the FDA on June 29, 2009 on the basis that tapentadol is a BCS Class 1 compound. Tapentadol was granted BCS 1 classification by the Agency, despite its low oral absolute bioavailability (b) (4).

However, the proposed drug product does not qualify for a BA/BE waiver for the following reasons:

1. According to the BCS guidance for industry, demonstration of in vivo BA or BE may not be necessary for pharmaceutically equivalent drug products containing Class 1 drug substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients.

2. The proposed product and the reference product do not meet the definition of pharmaceutical equivalents established in 21CFR 320.1 (c):

   Pharmaceutical equivalents means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

3. The proposed product contains sucralose as an inactive ingredient. Published scientific literature indicates, although not totally conclusive, that sucralose may potentially affect the absorption and bioavailability of drugs (Abou-Donia et al. 2008, (b) (4)).

During the January 31, 2012 filing meeting for this NDA, ONDQA-Biopharmaceutics communicated to the reviewing team their concerns regarding the potential effect that the presence of sucralose could have on the bioavailability of tapentadol oral solution. Biopharmaceutics suggested that data from an acceptable in vivo bioequivalence study may be needed to support the approval of the proposed product under this NDA application and mentioned that the lack of this information may potentially preclude the filing of this NDA from a Biopharmaceutics perspective.

Subsequently, it was determined that the Applicant had already submitted, under IND 108,134, the synopsis for study No. HP5503/59, which objective was to evaluate the BA/BE of the proposed oral product (5 mL of 20 mg/mL) vs. the IR oral tablet (100 mg).

In response to the FDA's request made during the February 2, 2012 teleconference, the Applicant submitted on February 7th, an amendment to the NDA including the complete final report for BA/BE study HP5503/59. The following was stated in the Applicant's cover letter dated February 7, 2012:

> *Reference is made to New Drug Application (NDA) 203794 for NUCYNTA® (tapentadol) Oral Solution, submitted 15 December 2011. Reference is also made to a teleconference with FDA on 02 February 2012. FDA noted that during their 45 day review, they learned that the Division of Biopharmaceutics no longer issues biowaiver requests for products that contain sucralose, due to concerns about bioavailability. A biowaiver had been granted for the NUCYNTA® oral solution in 2009, but FDA said that they would now require a bioavailability study. FDA noted that a synopsis for study HP5503/59;R331333PAI1044, "A relative bioavailability trial to compare a new tapentadol oral solution 100 mg with the tapentadol immediate release 100 mg tablet", was previously submitted to the Oral Solution IND 108134. FDA agreed that if the formulation is the same in both the study and the NDA, they would consider this study to support the Oral Solution NDA and they requested that the full clinical study report be submitted to the NDA. We confirmed to the division via email that the formulation is the same, and noted additionally that the batch analysis for the batch used in the study was included in the initial submission for NDA 203794. On behalf of Janssen Pharmaceuticals Inc., Janssen Research & Development LLC (JRD) is submitting the aforementioned study report.*

The acceptability of the BA/BE study submitted to support the approval of the proposed product is a review issue. The provided BA/BE study No. HP5503/59 will be reviewed by the Clinical Pharmacology Team from OCP. Therefore, the acceptability of the waiver request is no longer a review issue for evaluation by the Biopharmaceutics Team.

RECOMMENDATION:
The ONDQA-Biopharmaceutics Team has reviewed the information provided in NDA 203-794 for filing purposes. From a Biopharmaceutics perspective, NDA 203-794 for NUCYNTA® (tapentadol) Oral Solution is **fileable**.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez-Sharp, Ph.D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

cc: Christine M.V. Moore, Ph.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAREEN RIVIERE
02/24/2012

ANGELICA DORANTES
02/24/2012