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.

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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:				

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