

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203794Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 203794/Nucynta (tapentadol) oral solution, 20 mg/mL

PMR Description: Deferred pediatric study under PREA: 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.

PMR Schedule Milestones:	Final Protocol Submission:	<u>05/31/2014</u>
	Study/Trial Completion:	<u>09/30/2018</u>
	Final Report Submission:	<u>03/31/2019</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

We are deferring submission of this required pediatric study (to evaluate the pharmacokinetics, efficacy, and safety of Nucynta in pediatric patients ages 6 to less than 17 years) for this application because Nucynta oral solution is ready for approval for use in adults and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To obtain adequate data to describe the dosing, efficacy, and safety of Nucynta in pediatric patients ages 6 to less than 17 years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study must evaluate the pharmacokinetics, efficacy, and safety of Nucynta (tapentadol) in pediatric patients ages 6 to less than 17 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Pharmacokinetic, efficacy, and safety study or clinical trial
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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

/s/

DOMINIC CHIAPPERINO
10/15/2012

JUDITH A RACOOSIN
10/15/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 203794/Nucynta (tapentadol) oral solution, 20 mg/mL

PMR Description: Deferred pediatric study under PREA: 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.

PMR Schedule Milestones:	Final Protocol Submission:	<u>03/31/2017</u>
	Study/Trial Completion:	<u>07/31/2021</u>
	Final Report Submission:	<u>12/31/2021</u>
	Other:	<u>N/A</u>

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- Unmet need
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To obtain adequate data to describe the dosing, efficacy, and safety of Nucynta in pediatric patients ages birth to 5 years.

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/s/

DOMINIC CHIAPPERINO
10/15/2012

JUDITH A RACOOSIN
10/15/2012

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 203794

Name of Drug: Nucynta (tapentadol) oral solution, 20 mg/mL, for proposed indication, management of moderate to severe acute pain in adults

Applicant: Janssen Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: Orig. December 15, 2011; revised labeling in July 12, 2012 amendment; revised Carton & Container labels in August 3, 2012 amendment; and final revised labeling in October 15, 2012 amendment.

Receipt Date: Submissions received December 15, 2011, and July 12, August 3, and October 15, 2012

Background and Summary Description:

NDA 203794 for Nucynta oral solution represents a new dosage form from the already-approved NDA 022304 for Nucynta (tapentadol) immediate-release tablets. The Sponsor's original NDA submission on December 15, 2011, contained their proposed package insert and Medication Guide intended to be common labeling with already-approved Nucynta immediate-release tablets. The patient labeling for the oral solution also includes Instructions for Use to provide detailed instructions for patients to describe how to accurately administer their dose of Nucynta oral solution. DMEPA, the Patient Labeling Team in DMPP, and both professional and consumer reviewers in OPDP all filed separate reviews in DARRTS for Nucynta oral solution labeling.

Review

The FDA sent a broad set of comments to the Sponsor on June 13, 2012, concerning the package insert and Medication Guide, instructing the Sponsor to submit revised labeling for Nucynta oral solution that is not based on common labeling with Nucynta IR tablets. The Sponsor was also directed to make Nucynta oral solution labeling more consistent where possible with updated labeling recently negotiated for Nucynta ER (NDA 200533). The Sponsor resubmitted the package insert, Medication Guide, and Instructions for Use on July 12, 2012.

The core review team members incorporated their recommended labeling changes to the group-edited package insert and the resulting substantially complete package insert was provided to the consulted groups, OPDP and PLT, on September 6, 2012.

The information request (email) to Sponsor dated October 10, 2012, concerning the package insert, Medication Guide, and Instructions for Use, incorporated the labeling recommendations of the core review team and of PLT and OPDP, based on their reviews in DARRTS. After an additional exchange of comments, the Sponsor submitted their final amendment on October 15, 2012, accepting all FDA revisions.

DMEPA comments about Carton & Container labeling were communicated to the Sponsor in an Information Request email on July 12, 2012. Carton & Container labeling was resubmitted on August 3, 2012, incorporating all of the changes FDA had requested.

All final labeling is appended to this labeling review.

Recommendations

The Nucynta oral solution package insert, Medication Guide, and Instructions for Use submitted on October 15, 2012, and the Carton & Container labeling submitted on August 3, 2012, represents agreed-upon labeling and can be approved.

Dominic Chiapperino, Ph.D.
Regulatory Project Manager

10-15-12
Date

42 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DOMINIC CHIAPPERINO
10/15/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 203794 (original NDA)	
Proprietary Name: Nucynta Established/Proper Name: tapentadol Dosage Form: oral solution Strengths: 20 mg/mL	
Applicant: Janssen Pharmaceuticals, Inc. Agent for Applicant (if applicable): Janssen Research & Development, LLC	
Date of Application: December 15, 2011 Date of Receipt: December 15, 2011 Date clock started after UN: not applicable (n/a)	
PDUFA Goal Date: October 15, 2012	Action Goal Date (if different): same
Filing Date: February 13, 2012	Date of Filing Meeting: January 31, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only): 3 (new formulation)	
Proposed indication(s)/Proposed change(s):	
Type of Original NDA: AND (if applicable) Type of NDA Supplement: n/a	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? No <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): n/a				
List referenced IND Number(s): INDs 061345, 105766, and 108134				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				n/a
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				n/a
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th data-bbox="203 1446 495 1486">Application No.</th> <th data-bbox="495 1446 771 1486">Drug Name</th> <th data-bbox="771 1446 1060 1486">Exclusivity Code</th> <th data-bbox="1060 1446 1349 1486">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>	N/A			
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?		X		Due to granted biowaiver, no clinical studies, including bioequivalence studies were necessary to support approval.
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff: 12/27/11</i></p>	X			

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			PeRC notified
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Same name as approved immediate-release tablet
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to DMPP/PLT? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): n/a <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting</i>	X			Written/emailed comments for pre-NDA guidance
Any Special Protocol Assessments (SPAs)? Date(s): n/a <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 31, 2012

BLA/NDA/Supp #: NDA 203794

PROPRIETARY NAME: Nucynta

ESTABLISHED/PROPER NAME: tapentadol

DOSAGE FORM/STRENGTH: oral solution, 20 mg/mL

APPLICANT: Janssen Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): relief of moderate to severe acute pain in adults

BACKGROUND: NDA 022304 for Nucynta (tapentadol) immediate-release tablets, 25, 50, and 75 mg, was approved on Nov. 20, 2008. NDA 203794 provides for 20 mg/mL oral solution as new dosage form. Development of the oral solution was done with pediatric patients in mind, as the applicant has pending PREA-required studies to conduct that will utilize the proposed tapentadol oral solution.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dominic Chiapperino	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical	Reviewer:	No clinical studies submitted (Ellen Fields covering)	n/a
	TL:	No clinical studies submitted (Ellen Fields covering)	n/a

Clinical Pharmacology	Reviewer:	David J. Lee	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	No clinical studies submitted, no assigned reviewer	n/a
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Armaghan Emami	Y
	TL:	Adam Wasserman	Y
Product Quality (CMC)	Reviewer:	Craig Bertha	Y
	TL:	Danae Christodoulou	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Bryan Riley	N
	TL:	Stephen Langille	N
Facility Review/Inspection	Reviewer:	Zhong Li	N
	TL:	n/a	n/a
OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	Y
	TL:	Lubna Merchant	Y
OSE/DRISK (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a

Bioresearch Monitoring (OSI)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Controlled Substance Staff (CSS)	Reviewer:	Alicja Lerner	Y
	TL:	Michael Klein	N
Other reviewers	Karen Riviere, biopharm rev. Sandra Suarez, biopharm rev.		Y Y
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: none</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p><i>or efficacy issues</i></p> <ul style="list-style-type: none"> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Since biowaiver was granted and BE study, therefore, is not pivotal, no inspections will be requested</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>PRODUCT QUALITY (CMC)</p> <p>Comments: There was discussion, introduced at the filing meeting by the biopharmaceutics team in ONDQA, about whether the biowaiver granted prior to NDA submission should stand, given that the formulation contains sucrose which is thought to affect bioavailability. If FDA decided that the biowaiver should not have been granted, the application would not have been deemed fileable. The issue was resolved between DAAAP and ONDQA, and documented in the memo filed by acting Director of ONDQA, Dr. Christine Moore, PhD. As documented by Dr. Moore, the biowaiver that was granted would stand, and the bioequivalence data available for the oral solution versus the IR tablet would not be considered a pivotal BE study, although the clinical pharmacology team agreed to review the study during the review cycle. No comments would need to be included in the 74-day letter, as an information request for the available BE data had been sent prior to the filing/74-day letter issuing.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<u>Facility Inspection</u>		<input type="checkbox"/> Not Applicable
• Establishment(s) ready for inspection?		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments: none		
REGULATORY PROJECT MANAGEMENT		
Signatory Authority: Sharon Hertz or Bob Rappaport, Division sign-off		
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):		
Comments: GRMP review milestones will be followed. All primary reviews should be completed 5 weeks before Oct. 15, 2012 PDUFA date, i.e. Sep. 10, 2012.		
REGULATORY CONCLUSIONS/DEFICIENCIES		
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:	
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.	
	<u>Review Issues:</u>	
	<input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.	
	<input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):	
	<u>Review Classification:</u>	
	<input checked="" type="checkbox"/> Standard Review	
	<input type="checkbox"/> Priority Review	
ACTIONS ITEMS		
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).	
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).	
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.	

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other:

Dominic Chiapperino	3/9/12
Regulatory Project Manager	Date
Parinda Jani	3/9/12
Chief, Project Management Staff	Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

DOMINIC CHIAPPERINO
10/11/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion (DCDP)**

******Pre-decisional Agency Information******

Memorandum

Date: September 28, 2012

To: Dominic Chiapperino, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer, DCDP

CC: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 203794
DCDP labeling comments for NUCYNTA (tapentadol) Oral Solution, CII
Medication Guide

DCDP has reviewed the Medication Guide (Med Guide) for NUCYNTA (tapentadol) Oral Solution-CII (Nucynta) which was submitted for consult on March 23, 2012. DCDP used DMPP's tracked changes version of the Med Guide as the base document for review. DMPP's review of the Med Guide is being provided to the Reviewing Division under separate cover. We conferred with DMPP to the extent possible for consistency in our comments.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
09/28/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: September 20, 2012

To: Bob A. Rappaport, MD
Director
**Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)
and Instructions for Use (IFU)

Drug Name (established name): NUCYNTA (tapentadol)

Dosage Form and Route: oral solution

Application Type/Number: NDA 203-794

Applicant: Janssen Pharmaceuticals, Inc.

1 INTRODUCTION

On December 15, 2011, Janssen Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 203-794 for Nucynta (tapentadol) oral solution. Nucynta (tapentadol) oral solution is indicated for the relief of moderate to severe acute pain in adults. On March 23, 2012, DAAAP requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Nucynta (tapentadol) oral solution.

On June 13, 2012 the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) sent an Information Request (IR) to the Applicant by email. The IR requested that the Applicant submit an amendment to their pending application for Nucynta (tapentadol) oral solution, including revisions of the:

- Prescribing Information and Medication Guide to make both specific for Nucynta oral solution rather than as common labeling with Nucynta immediate-release oral tablets. DAAAP decided to discontinue the Medication Guide for Nucynta immediate-release oral tablets, and no longer considers it appropriate or practicable for Nucynta immediate-release oral tablets and Nucynta oral solution to have common product labeling.
- Prescribing Information to make the labeling consistent with revisions made to Nucynta ER product labeling (as submitted April 18, 2012) for such sections of the Nucynta oral solution package insert that can or should have language common for all tapentadol product labeling.
- Medication Guide for Nucynta oral solution to better address concerns of overdosage and medication errors in dispensing and administering 20 mg/mL tapentadol oral solution.

This review is written in response to a request by DAAAP for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Nucynta (tapentadol) oral solution. DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and the enclosed IFU review comments are collaborative from DMPP and DMEPA.

2 MATERIAL REVIEWED

- Draft NUCYNTA (tapentadol) oral solution Medication Guide (MG) received on December 15, 2011 and further revised on July 12, 2012, and received by DMPP on September 6, 2012.
- Draft NUCYNTA (tapentadol) oral solution Instructions for Use (IFU) received on December 15, 2011 and further revised on July 12, 2012 and received by DMPP on September 6, 2012.
- Draft Prescribing Information (PI) received on December 15, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on September 6, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 10.

In our review of the MG and IFU we have:

- revised the MG and ensured to the extent possible that it is consistent with the approved extended-release and long-acting opioid analgesics class MG
- removed the Patient Instructions for Use from the end of the DRAFT MG and created a separate document titled “Instructions for Use”
- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG and IFU are appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
09/20/2012

BARBARA A FULLER
09/20/2012

LASHAWN M GRIFFITHS
09/20/2012

*****Pre-decisional Agency Information*****

Memorandum

Date: September 20, 2012

To: Dominic Chiapperino
Senior Regulatory Project Manager
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

CC: L. Shenee' Toombs, Pharm.D., Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

Subject: NDA 203794
OPDP labeling comments for NUCYNTA[®] (tapentadol) oral solution (CII)

In response to DAAAP's March 23, 2012, consult request, OPDP has reviewed the draft Prescribing Information (PI) for NUCYNTA[®] (tapentadol) oral solution (CII) (Nucynta). OPDP notes that this new NDA proposes an addition of an oral solution dosage form. The labeling consists of updates to various sections of the PI to be more consistent with the Nucynta ER PI.

Comments on the proposed PI are based on the proposed draft marked-up labeling titled "Nucynta oral solu Label subm 8-29-12 tracked FDA-revised.doc" that was sent via email from Dominic Chiapperino (RPM) on September 6, 2012. Please note that OPDP's comments on the proposed PI are provided directly on the marked up version below.

Comments on the proposed patient labeling will follow under separate cover.

If you have any questions regarding the package insert, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov.

Enclosure: Marked up PI

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/s/

EUNICE H CHUNG-DAVIES
09/20/2012



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Sep 7 2012

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **Name:** Nucynta oral solution (Tapentadol HCl)
NDA 203794 (previous IND108134 for oral solution)
Indication: management of moderate to severe acute pain in patients 18 years of age or older
Dosages: 20 mg/ml oral solution at doses of 50 mg, 75 mg, or 100 mg every 4 to 6 hours prn

Sponsor Janssen Research & Development, LLC

Materials reviewed: NDA 203794 (Dec 15 2011) is in EDR
Clin-Pharm review Aug 21 2012
OSE New Molecular Entity (NME) postmarketing evaluation background document Nov 22 2010 (for Nucynta IR NDA 22-304)

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I. Summary

A. Background

This memorandum responds to a consultation from the DAAAP concerning evaluation of abuse potential information for Nucynta oral solution (tapentadol HCl) indicated for the management of moderate to severe acute pain in patients 18 year of age or older, which is the same as

approved IR product. Tapentadol displays high affinity and selectivity for the μ opioid receptor, and additionally inhibits the reuptake of norepinephrine. It is an atypical μ opioid agonist in that it does not structurally resemble other opioids such as morphine. The sponsor submitted this NDA as a 505(b)(2) application. The Reference Listed Drug is NDA 022-304 Nucynta IR (tapentadol immediate-release) which was approved on Nov 20, 2008, for treatment of moderate to severe acute pain in patients age 18 or older.

The NDA consists of CMC data to support Nucynta ® oral solution, labeling and packaging components and also references IND 108,134. In this NDA, there were no non-clinical studies submitted. In Vivo Bioavailability study was the sole clinical study submitted¹, however was not considered a pivotal study and was not reviewed by Clin-Pharm.

B. Conclusions as for review Nucynta ER NDA 200533 Aug 1 2012:

1. A significant number of abuse-related AEs for Nucynta IR was reported post-marketing: hallucinations, the second major AE, and withdrawal syndromes were reported. Additionally, there is an increase of life-threatening AEs for Nucynta IR in post-marketing reports, in particular suicidality and serotonin syndrome.
2. Following consultation with OSE, OSE will monitor for events of suicidality, serotonin syndrome, and hallucinations. Monitoring for these events will entail periodic review of various epidemiological data bases and AERS data bases, though these data bases have serious limitations. Pending results from OSE monitoring, appropriate language highlighting suicide risk, hallucinations and withdrawal symptoms may be considered for future product labeling

C. Recommendations (to be conveyed to the Sponsor) as for review Nucynta ER NDA 200533 Aug 1 2012:

1. As a Schedule II drug under the CSA, all Schedule II narcotic regulations and procedures regarding manufacture, distribution, dispensing, storage, recordkeeping, labeling and disposal of Nucynta ER should be in place and strictly followed.
2. Sponsor should be informed of CSS Conclusions #2, above.

¹ Clin-Pharm review states: “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”..... 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.”

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/s/

ALICJA LERNER
09/07/2012

MICHAEL KLEIN
09/07/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date	July 11, 2012
Reviewer	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name and Strength	Nucynta (Tapentadol) Oral Solution 20 mg/mL
Application Type/Number	NDA 203794
Applicant	Ortho-McNeil-Janssen Pharmaceuticals, Inc., Janssen Research & Development, LLC
OSE RCM	2011-4655

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Nucynta (Tapentadol) Oral Solution (NDA 203794) for areas of vulnerability that could lead to medication errors. This NDA provides for a new formulation of Tapentadol, an oral solution, which will have the same indication, and dosing as for the immediate-release tablet (NDA 022304).

1.1 REGULATORY HISTORY

Nucynta (Tapentadol) Tablets (NDA 022304) and Nucynta ER (Tapentadol) Extended-release Tablets were approved November 20, 2008 and August 25, 2011 respectively.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 15, 2011 labeling submission.

- Active Ingredient: Tapentadol
- Indication of Use: relief of moderate to severe acute pain in patients 18 years of age or older
- Route of Administration: oral
- Dosage Form: solution
- Strength: 20 mg/mL
- Dose and Frequency: Initiate with or without food at a dose of 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.
- How Supplied: 100 mL and 200 mL bottles along with an oral syringe
- Storage: up to 25 C (77 F) excursions permitted to 15 C – 30 C (59 F -86 F); store the bottle upright after opening
- Container and Closure System: 120 mL and 235 mL HDPE bottles fitted with (b) (4) closures that have foil heat induction seals; target fills are 100 mL and 200 mL, respectively

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (AERS) database for Nucynta medication error reports. We also reviewed the Nucynta Oral Solution container labels, carton and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	June 28, 2011 (date of last AERS search in OSE Review # 2009-2413) through June 5, 2012
Drug Names	Active Ingredient: Tapentadol Trade Name: Nucynta Verbatim Term: Tapen% Verbatim Term: Nucu%
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issues NEC (HLT) Product Packaging Issues (HLT) Product Label Issues (HLT)

The aforementioned search strategy identified 27 reports. Each report was reviewed for relevancy and duplication. After individual review, all 27 reports were excluded for the following reasons:

- Adverse event not associated with a medication error
- Accidental overdose with insufficient detail to determine root cause
- Accidental multiple drug overdose which included tapentadol
- Product complaint (lack of effect)
- Intentional abuse, misuse, and overdose
- Tablet manipulation as these medication errors are unlikely to occur with the proposed oral solution dosage form.
- A report of the simultaneous use of Nucynta ER and Nucynta IR because the patient self-administered this regimen without the prescriber's approval.

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 15, 2011 (Appendix B)
- Carton Labeling submitted December 15, 2011 (Appendix B)
- Insert Labeling submitted December 15, 2011 (no image)
- Approved Container Label and Carton Labeling for NDA 200533 (Nucynta ER Tablets) and NDA 022304 (Nucynta Immediate Release Tablets) – See Appendix C
- Insert labeling for Nucynta ER and Nucynta Immediate release Tablets (no image)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed label and labeling for Nucynta Extended-release Tablets (OSE Review # 2009-2413 dated August 1, 2011 and OSE Review # 2011-4275 dated March 1, 2012). We evaluated these reviews to ensure all recommendations relevant to this new formulation are implemented.

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

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.

The net quantity of 100 mL and 200 mL is reasonable given the recommended doses. Furthermore, since dosing with Nucynta should be adjusted to maintain adequate analgesia with acceptable tolerability, this dosage form can be used to meet this objective.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

The risk of confusion within the Nucynta product line is similar to what already exists with currently marketed dosage forms. Although cases of simultaneous administration of Nucynta ER and Nucynta IR have been reported (OSE #2009-2413), it is unlikely that similar errors will occur with Nucynta oral solution, as it will be typically prescribed to patients unable to take a tablet. It is for this same reason that we do not anticipate the simultaneous prescribing of tapentadol solid oral dosage forms with Nucynta oral solution. Another possibility for confusion may occur between the extended-release product and the oral solution if the modifier 'ER' is dropped when a patient is prescribed Nucynta "twice daily". In this case, Nucynta oral solution may be dispensed or administered instead of Nucynta ER. This wrong drug error is no different from the risks which already exist within the product line.

Finally, we note that there is adequate color differentiation within the product line to minimize the risk of selection errors.

The most problematic aspect of the proposed product design concerns the dosing (b) (4). The design of the dosing (b) (4) is confusing and does not provide for dosing accuracy. Additionally, the dosing (b) (4) is error prone as it is calibrated with the highest unit of measure ("100 mg") (b) (4) the lowest unit of measure starting at the tip of the syringe, which is commonly seen with similar dosing devices. An additional area of concern is that the units of measure appear on the inside of the plunger rather than the "syringe casing". (b) (4)

Due to these concerns, an information request (IR) request was sent to the Applicant on May 15, 2012. The concerns with the dosing device were outlined in the IR letter (see Appendix D) and the Agency requested the Applicant re-design the device and re-submit the revised device for our review.

DMEPA received the revised dosing device June 25, 2012. The design of the new oral dosing device is a syringe, similar to other oral dosing syringes that are utilized in the marketplace. Specifically, the dosing scale is printed on the barrel of the syringe and it begins with the lowest dose near the tip of the syringe and the largest dose at the top. The statement "Nucynta – For Oral Use Only" appears along the length of the syringe to clearly associate the syringe with this drug product. However, it would be preferable to have "oral solution" to also appear on this syringe to highlight the fact that the syringe is for oral use. The Applicant proposes that replacement syringes will be made available to the pharmacist in the event that a patient misplaces the original syringe. However, there are no details regarding the number of replacement syringes which would be available and when they would receive them (e.g., whether the pharmacist receives them on a case by case basis or if they receive a specific number of syringes when the product is purchased).

Additionally, this device comes with a syringe adapter. Its purpose is to prevent the solution from spilling when the bottle is inverted, allows for dispensing the dose without inserting the syringe into the drug product, and prevents the syringe from being stored in the product between scheduled doses. Although our concerns regarding the dosing device are lessened, we identify further improvements that can be made. Finally, the

Applicant states that the dosing accuracy for this revised device is equivalent to the previously proposed syringe. We defer to the Division and to Chemistry, Manufacturing, and Controls (CMC) to confirm this statement.

During this review, we also noted that the presentation of the proprietary name can be improved to increase its readability and a statement on the principal display panel can be deleted because it clutters the label. See Section 5 for specific recommendations.

Additionally, the Applicant has proposed a common package insert for Nucynta IR tablets and Nucynta oral solution, however since an Instructions for Use (IFU) section is required only for the oral solution, the division has requested the Applicant revise the package insert to make the labeling consistent with revisions made to Nucynta ER product labeling. In addition, they requested the Applicant revise the IFU for Nucynta oral solution to better address concerns of over dosage and medication errors in dispensing and administering tapentadol oral solution. The revised insert labeling is pending.

4 CONCLUSIONS

DMEPA concludes that statements on the proposed container label and carton labeling can be improved to increase their readability and prominence to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

- A. Container Label and Carton Labeling (100 mL and 200 mL bottle)
 1. Revise the statement of strength from “20 mg/mL” to read “100 mg/5 mL” to maintain consistency with other approved oral solutions and to minimize the potential for medication errors due to miscalculations. Please note that there should be space between the number and the metric measurement.
 2. Revise the statement which starts with “Each 1 mL contains 20 mg of . . . “ to read “Each 5 mL contains 100 mg of . . . “ to be consistent with the above recommendation. Note that there should be space between the number and the metric measurement.
 3. To increase readability, revise the proprietary name presentation from all UPPERCASE letters (NUCYNTA) to title case (Nucynta). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape formed by words set in all upper case. Revise accordingly.
 4. Delete the “Caution: Federal law prohibits the . . . ” statement from the principal display since it is not necessary and it clutters the label.

B. Proposed Dosing Device

1. Revise the statement, (b) (4) to read “For Use Only with Nucynta Oral Solution”.
2. Provide details of the process for replacing lost syringes and syringe adaptors and how this process will be communicated to patients and pharmacists.

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

REFERENCES

OSE Review # 2009-2413. Label and Labeling Review for Nucynta ER (Tapentadol) Extended-release Tablets, Abdus-Samad, J. August 1, 2011.

OSE Review # 2011-4275. Label and Labeling Review for Nucynta ER (Tapentadol) Extended-release Tablets, Cotter, S. March 1, 2012.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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