

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200533Orig1s000

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 200533/Nucynta ER (tapentadol) extended-release oral tablets

PMR/PMC Description: Deferred pediatric study under PREA: a pharmacokinetic, efficacy, and safety study of Nucynta ER for the treatment of chronic pain in pediatric patients ages 7 to less than 17 years

PMR/PMC Schedule Milestones: Final Protocol Submission: 05/28/2014
Study/Trial Completion: 10/31/2017
Final Report Submission: 03/26/2018
Other: N/A

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 the required pediatric study for ages 7 to less than 17 years for this application because this product 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 for the use of Nucynta ER in the pediatric population ages 7 to less than 17 to inform dosing, efficacy, and safety.

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 efficacy study must be a randomized double blind controlled superiority study of Nucynta ER in the pediatric population ages 7 to <17. Pharmacokinetic and safety data may also be obtained from this study.

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)
-

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

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.*

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/s/

DOMINIC CHIAPPERINO
08/25/2011

BOB A RAPPAPORT
08/25/2011

MEMORANDUM

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

DATE: August 04, 2011

TO: Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Addiction
Products(DAAAP)
Office of Drug Evaluation II

Chandrabhas Sahajwalla, Ph.D.
Director,
Division of Clinical Pharmacology II (DCPII)

FROM: Arindam Dasgupta, Ph.D., Staff Fellow
Division of Bioequivalence and GLP Compliance
(DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 200533, NUCYNTA[®] ER
(tapentadol hydrochloride) extended-release
tablets, 250 mg sponsored by Johnson & Johnson
Pharmaceutical Research & Development, L.L.C.(on
behalf of Ortho-McNeil-Janssen Pharmaceuticals,
Inc.)

At the request of the Division of Anesthesia and Analgesic
Products (DAAAP), Office of New Drugs (OND), DBGC audited
the clinical and analytical portions of the following
bioequivalence (BE) study.

Study Number: R331333-PAI-1061; HP5503/84

Study Title:

A Single-Dose, Open-Label, Randomized, Two-Way Crossover

Pivotal Study to Assess Bioequivalence of a New Tapentadol Extended-Release (TRF) 250-mg Tablet with Respect to a Tapentadol Extended-Release (PR2) 250-mg Tablet Under Fasted Conditions in Healthy Subjects

Audit of the clinical portion of the study was conducted at Celerion Inc., Lincoln, NE. Following the inspection of the clinical site (June 20-24, 2011), no Form FDA-483 was issued and there were no significant findings. The audit of the analytical portion of this study was conducted at

(b) (4)

Following inspection of the analytical site (July 11-15, 2011), Form FDA-483 was issued (**Attachment 1**). DBGCC received the firm's written response to the inspectional findings on August 3, 2011 (**Attachment 2**).

The 483 observations for study R331333-PAI-1061; HP5503/84 (analytical), (b) (4) response, and our evaluations follow:

Analytical Site:

(b) (4)

1. Failure to accurately report the carry-over evaluation conducted during tapentadol prestudy method validation. For example, in blank 1 sample (sample number 0352) in prestudy validation run, VA-09-1a, carry-over was determined to be 245.5% of the mean of the LLOQ. However, in source records the calculated carry-over in the blank 1 sample was actually 330% of that of the LLOQ.

In their response, (b) (4) acknowledged the observation as an oversight and indicated that the lab staff would be retrained to prevent such oversights from occurring in future. (b) (4) also indicated that the validation report would be amended to reflect the correct carryover evaluation data and the corrected validation report would be sent to the sponsor. As the carry-over peaks were small or absent compared to the analyte peaks in carry-over evaluation samples in majority of the analytical runs, the above observation is not likely to affect the outcome of the study.

2. Failed to use freshly prepared calibrators in the validation of autosampler stability during the conduct of tapentadol pre-study validations.

In their response, (b) (4) acknowledged the observation and indicated that since the study, (b) (4) has updated their procedures to use freshly prepared calibration standards for assessment of autosampler stability. (b) (4) plans to generate new data to demonstrate autosampler stability for tapentadol using freshly prepared calibrators by august 15, 2011.

The above observation is not likely to affect the outcome of the study.

3. Failed to document all aspects of the study conduct. For example:

a) In validation run VA-09-4a for tapentadol the 3rd blank sample (sample 0681) injected after the validation QCs exhibited carry-over of >20% of LLOQ. This validation run was accepted as it was determined that the carry-over had no influence on the run results. However the justification or objective criteria for this determination was not documented.

In their written response, (b) (4) acknowledged the observation and indicated that they have implemented corrective actions since the conduct of the study. (b) (4) also presented justification for accepting the results of carry-over evaluation.

(b) (4) response is adequate and the above finding is not likely to impact the outcome of the current study.

b) Failure to maintain documentation for individual calibrators and QC sets used during sample processing for tapentadol study. Calibrator and QC samples were stored as multi-use aliquots. In absence of documentation for individual calibrators or QC sets used during analysis or of their disposal, it cannot be confirmed if the calibrators and QCs used were within their validated freeze/thaw stability cycles.

(b) (4) acknowledged the observation and stated that they will implement a new labeling procedure for future studies such that individual calibrators and QCs were uniquely identified and tracked along with study samples.

The above finding is not likely to impact outcome of the current study.

4. Failure to retain the audit trail for the initial results table during data processing for tapentadol study. This did not allow complete reconstruction of events during data processing.

In their response, (b) (4) acknowledged the observation and indicated that they would implement new procedures where a single quantitation method would be created from default settings and would be used for processing each run in a study. Any changes made thereof was to be captured in the audit trail to allow complete reconstruction of events during data processing.

To address the concerns, (b) (4) reprocessed all their data using the modified procedure. The results of the reprocessed data were comparable to the original data. Hence the above observation is not likely to affect the outcome of the current study.

Conclusion:

Following the above inspection, the Division of Bioequivalence and GLP Compliance recommends that the analytical data analytical data of the study R331333-PAI-1061; HP5503/84 be accepted for Agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Arindam Dasgupta, Ph.D.

Final Classification:

Clinical

NAI- Celerion inc., Lincoln, NE

Analytical

VAI- [REDACTED] (b) (4)

cc: DARRTS
OND/ODEII/DAAAP/Rappaport/Dominic Chiapperino
OTS/OC/DCPII/Sahajwala/David Lee

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/s/

ARINDAM DASGUPTA
08/05/2011

MARTIN K YAU
08/05/2011



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

*

Date: August 3, 2011

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

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

Subject: **ADDENDUM TO MEMOs of Sept 9, 2010, and July 12, 2011 by Alicja Lerner, MD, PhD** Nucynta ER (Tapentadol HCl extended-release). **NDA 200-533**

I am writing this addendum to clarify some issues addressed by Dr. Alicja Lerner in two reviews on the Nucynta ER NDA.

The memo of July 12, 2011 concerned PK/PD issues that may affect the relative abuse potential of tapentadol extended release tablets Tamper Resistant Formulation (TRF). Possible interactions of food or alcohol with long acting opioid formulations and resultant safety and abuse potential effects are recognized. I discussed these issues in a July 29, 2011 meeting with Dr. Chandrahas Sahajwalla, Office of Clinical Pharmacology (OCP) and Dr. Lerner. Regarding Dr. Lerner's conclusions from the July 12th memo, CSS and OCP concur on the following:

1. Co-administration of tapentadol TRF with FDA recommended high fat/calorie meal resulted in increases in C_{max} and AUC that are within the confidence interval of 80-125%. Thus, OCP concludes that there is no food effect for this product. PD effects of tapentadol TRF formulation are potentiated after intake of alcohol, but such effects were not observed with food.
2. Co-administration of tapentadol TRF with alcohol resulted in increases in C_{max} and AUC. In the first review cycle of this product, the team agreed that as with other opioid labels, including the label of Nucynta immediate release product, warnings and precautions of the interaction of tapentadol TRF with alcohol should be adequately described in its product label.
3. The FDA recommended high fat/calorie meal was not used in the PK study in Japanese men with tapentadol TRF (R331333-PAI-1052). Therefore, results from this study are not pivotal for assessing the effect of food. The food effect should be labeled based on the result using the FDA recommended high fat/calorie meal.
4. The PK studies contain insufficient data to override the analyses and conclusions of the clinical studies that the drug does not exhibit a gender effect.

In her memo of Sept 9, 2010, Dr. Lerner concluded that the controlled release properties of the TRF formulation are overcome by simple physiochemical manipulations and that the drug product elicits typical mu opioid-like effects.

CSS Review: Nucynta ER.nda200533.08032011.addendum.doc

1 of 2

1. Because the recent bioequivalence study resolved that the PK and AE profiles of different formulations are similar, Dr. Lerner's first recommendation in the memo is withdrawn.
2. Dr. Lerner's second recommendation is also withdrawn because her AE analysis covered a limited area of investigation. Thus, her conclusions are insufficient to override the analyses and conclusions of the reviewer of the full range of clinical studies.

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/s/

MICHAEL KLEIN
08/03/2011

**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 and Labeling Review

Date: August 1, 2011

Reviewer(s): Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Todd Bridges, RPh, Team Leader
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Drug Name(s): Nucynta ER (Tapentadol) Extended-release Tablets
50 mg, 100 mg, 150 mg, 200 mg, and 250 mg

Application Type/Number: NDA 200533

Applicant/sponsor: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

OSE RCM #: 2009-2413

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

1 INTRODUCTION

This review evaluates the proposed container label, blister label, carton labeling, and insert labeling for Nucynta ER (NDA 200533) for areas of vulnerability that can lead to medication errors. Ortho-McNeil-Janssen Pharmaceuticals, Inc. submitted the proposed labels and labeling on December 1, 2009 and updated insert labeling on February 28, 2011.

1.1 BACKGROUND OR REGULATORY HISTORY

Nucynta (Tapentadol) is currently marketed in the United States. Nucynta tablets were approved by FDA on November 20, 2008, under NDA 022304. For this application, the Applicant is proposing an extended-release formulation of tapentadol to be marketed under the proprietary name, Nucynta ER. The original submission dated December 1, 2009, received a Complete Response on October 1, 2010. Subsequently, the Applicant submitted an amendment on February 28, 2011.

1.2 PRODUCT INFORMATION

Nucynta ER has a proposed indication of use for the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The recommended daily dose is 100 mg to 250 mg twice daily, taken approximately every 12 hours, with or without food. Patients currently not taking opioid analgesics should begin Nucynta ER therapy with 50 mg twice a day (approximately every 12 hours) and then be individually titrated to adjust to an optimal dose within the therapeutic range of 100 mg to 250 mg twice daily. Nucynta ER tablets will be available in five strengths: 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg. All five strengths will be marketed in bottles of 60 tablets and unit-dose blister packs of 10 tablets.

2 METHODS, MATERIALS REVIEWED, AND RESULTS

2.1 FAILURE MODE AND EFFECTS ANALYSIS AND POSTMARKETING MEDICATION ERROR DATA

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 1, 2009 (Appendix A)
- Carton Labeling submitted December 1, 2009 (Appendix B)
- Hospital Unit Dose Blister Labels submitted December 1, 2009 (Appendix C)
- Insert Labeling submitted February 28, 2011 (no image)

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

2.2 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The following section describes DMEPA use of FDA Adverse Event Reporting System (AERS) database to identify medication errors relevant to this review.

2.2.1 Nucynta (Tapentadol) Immediate-release Tablets

Since Nucynta (Tapentadol) is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Tapentadol. The AERS search conducted on June 27, 2011 used the following search terms: active ingredient “Tapentadol”, trade name “Nucynta”, and verbatim terms “Tape%” and “Nucy%%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. The time search was limited from July 21, 2010 to June 27, 2011. A previous OSE Review 2009-846 Nucynta (Tapentadol) NME 915 Review conducted an AERS search that searched up till July 21, 2010.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that described an intentional overdose, patients changing the frequency of administration, accidental ingestion, or cases that did not describe a medication error.

Following exclusions, we evaluated a total of 3 cases relevant to this review. All three cases were classified as wrong technique, which involved patients cutting or splitting Nucynta tablets in half. The first case involved a patient that was told to cut Nucynta tablets in half and experienced hallucinations. There were no details explaining who told the patient to cut the tablet. The second case involved a patient that split Nucynta tablets and experienced problems breathing, throat closing, and swollen hands four days later requiring an emergency room visit. The third case involved a patient that required hospitalization due to problems breathing and hands swelling “like boxing gloves,” after cutting Nucynta tablets in half.

2.2.2 Concomitant use of Tramadol Extended- and Immediate-release

Since the proposed insert labeling states concomitant use of Tapentadol extended-release and other tapentadol and tramadol products is not recommended, DMEPA searched FDA AERS database to identify medication errors involving pharmacologically similar products, tramadol extended- and immediate-release products. DMEPA notes it is common practice to treat chronic pain with an extended-release opioid for around-the-clock pain management along with an immediate-release version of the same opioid for breakthrough pain.

The AERS search conducted on June 23, 2011 used the following search terms: trade names “Ryzolt” and “Ultram ER”, and verbatim terms “Ryz%” and “Ultr%%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues.” No time limitation was set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that described an intentional overdose, wrong drug, overdoses with no details of causality, patients changing the frequency of administration, or did not describe a medication error.

Following exclusions, we evaluated a total of 9 cases relevant to this review.

Wrong Frequency of Administration (5)

These cases involved patients taking tramadol extended-release tablets more than once daily such 1 tablet every 4 to 6 hours or three times daily. The first case involved a patient that was previously taking tramadol immediate-release and then “almost overdosed” on tramadol sustained-release tablets because she was taking them every 4 to 6 hours. The patient received charcoal in the emergency and was kept for observation. The second case involved a physician that reported a patient received Ultram ER 10 mg twice daily instead of once daily, resulting in confusion and hallucinations. The physician discontinued Ultram ER. The third case involved another patient that was prescribed Ultram ER 100 mg once daily but was taking it twice daily. The patient was hospitalized because her “liver stopped.” The fourth case involved a patient that was taking Ultram ER 200 mg twice daily instead of once daily as prescribed. The patient resumed the correct dose and did not suffer any adverse events. The fifth case involved a patient hospitalized for severe mental change after taking Ryzolt 100 mg three times daily for 2 days. The physician did not provide causality assessment.

Of these five cases, only was a prescribing error in which the physician prescribed Ultram ER twice daily. The other cases did not provide details for causality; however, in one case, the patient was previously receiving tramadol immediate-release tablets.

Wrong Dose, resulting in overdose (2)

The first case involved a patient took physician samples of Ultram ER 1 tablet every 4 to 6 hours and also twice daily because no one explained what “ER” meant and she did not read the labeling provided. She experienced a grand mal seizure. The second case involved a patient whose physician increased the dose of Ultram ER 300 mg daily to 400 mg daily resulting in auditory hallucinations, nervous breakdown and severe headache.

Monitoring Error (2)

The first case occurred in France and involved a patient taking tramadol sustained-release tablets 200 mg and tramadol immediate-release 50 mg for 3 days, resulting in hospitalization for hypoglycemia. The patient died in the hospital. The second case involved a patient taking Ultram ER 200 mg twice daily. The reporter thought Ultram ER was not working, as the patient supplemented with Ultracet (tramadol and acetaminophen) tablets which led to hospitalization for dizziness.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

3.1 PRODUCT DESIGN

The product design introduces vulnerabilities that can lead to medication errors due to the overlapping product strengths. The following sections discuss these concerns.

3.1.1 Overlapping Strengths

The Applicant developed an extended-release formulation of tapentadol with product strengths that overlap with the currently marketed strengths of Tapentadol Immediate-release tablets (See Appendix D). By choosing to develop an extended-release formulation of tapentadol with product strengths that overlap with those of the currently marketed Tapentadol Immediate-release tablets, the Applicant has eliminated a potentially valuable error-reduction strategy that has been employed in other product line extensions. The Applicant should have developed product strengths slightly different than available strengths of immediate-release Nucynta Tablets as previously discussed at the Pre-NDA Meeting on June 5, 2007.

Post-marketing experience has shown that the introduction of product line extensions result in medication errors if the modifier is omitted and product characteristics are similar or overlap. For example, if the modifier 'ER' is omitted or overlooked, the difference in strength would offer the opportunity for an error to be caught before it reaches the patient, provided it is a dose that could not be achieved with the current product strengths.

Currently, the Applicant has not sufficiently differentiated the labels and labeling of the proposed Nucynta ER extended-release tablets from the currently marketed Nucynta immediate-release tablets (see Appendix E). This is of greater concern for the 50 mg and 100 mg strengths for both Nucynta ER and Nucynta.

3.1.2 Concomitant use of Tapentadol Extended- and Immediate-release Products

Concomitant use of Tapentadol extended-release and other tapentadol and tramadol products is not recommended. This recommendation to avoid use of immediate- and extended-release tapentadol products is similar to the currently marketed tramadol immediate- and extended-release products. However, this recommendation differs from a common practice of using a long-acting opioid along with the short-acting opioid for breakthrough pain.

Our AERS database search uncovered 2 reports of concomitant use of tramadol extended- and immediate-release products. In both cases, patients were using a tramadol extended-release and tramadol immediate release products for breakthrough pain. It is not clear whether the concomitant use of extended- and immediate-release tramadol was the result of a prescribing error or a patient initiated error. However, in both cases, the patients did not realize the concomitant use of Tramadol extended- and immediate-release products was not recommended.

Nucynta ER insert labeling contains guidance to discontinue all other tapentadol and tramadol products when beginning and while taking Nucynta ER. If FDA receives reports of concomitant use tapentadol extended-release and other tapentadol or tramadol products, DMEPA will revisit this issue.

3.2 CONTAINER LABELS AND CARTON LABELING

The proposed Nucynta ER and currently marketed Nucynta container labels and carton labeling are similar in appearance, which can lead to product selection errors. The Applicant has not sufficiently differentiated the proposed Nucynta ER extended-release tablets from the currently marketed Nucynta immediate-release tablets. This is of greater concern for the overlapping 50 mg and 100 mg strengths for both Nucynta ER and Nucynta.

Additionally, statements to help ensure proper dosing (twice daily) are lacking. The proposed Nucynta ER recommended dosing interval is twice daily approximately every 12 hours. This is different from Nucynta's recommended dosing interval of every 4 to 6 hours. Our AERS search uncovered errors involving patients receiving tramadol extended-release products multiple times a day, similar to tramadol immediate-release. The labels and labeling for Nucynta ER should delineate the different dosing interval. This is especially of concern for the overlapping 50 mg and 100 mg strengths.

Furthermore, statements to help ensure proper administration (swallow tablets whole) are lacking. Our AERS search uncovered patients cutting Nucynta immediate-release tablets. The insert labeling is silent on whether Nucynta tablets can be cut. We note, there were no AERS reports of patients cutting tramadol extended-release tablets. However, physical manipulation of Nucynta ER will lead to clinically significant adverse events. Therefore, a statement on the container label and carton labeling to provide instruction to swallow the extended-release tablet whole and to avoid physical manipulation of the tablets is necessary.

3.3 BLISTER LABEL

The Applicant has not sufficiently differentiated the available strengths from one another. The blister labels of the different strengths of Nucynta ER are visually similar to one another because all of the label text appears in a black font on a white background. This can lead to wrong strength selection errors. Additionally, the Nucynta ER blister labels are visually similar to Nucynta. Since unit dose blisters may be stored apart from the cartons, the visual similarity could lead to the wrong strength or wrong product selection errors.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed product design, container and blister labels, and carton labeling introduce vulnerability that can lead to medication errors because of similarity to the currently marketed Nucynta (tapentadol) immediate-release tablets. We recommend the following:

A. General Comments for Container Label and Carton Labeling

1. The font color of the proprietary name chosen for Nucynta ER is similar to the currently marketed Nucynta immediate-release product. The use of the same color contributes to the similarity of these products. This can lead to selection errors and administration of the wrong product because these products may be stored next to each other. This is especially true for the strengths of Nucynta ER and Nucynta that overlap (50 mg and 100 mg).
2. Revise the proprietary name presentation for all UPPERCASE (NUCYNTA ER) to title case (Nucynta ER). This revision aims to improve the relative prominence of the modifier 'ER' and help distinguish Nucynta ER from Nucynta, which appears as NUCYNTA on the container labels and carton labeling.
3. Decrease the prominence of the schedule II symbol.
4. Revise the middle portion of the NDC number in a large font and prominence (xxxx-XXXX-xx) to help differentiate Nucynta ER from Nucynta NDC numbers. Pharmacists use this portion of the NDC number to ensure the correct product is dispensed.
5. Add the dosing frequency statement, *Twice daily*, to the principal display panel to minimize wrong frequency of administration errors. Additionally, this may improve differentiation from Nucynta (tapentadol) tablets, which is dosed every 4 to 6 hours.
6. Add the statement, *Swallow tablets whole. Do not chew, crush or dissolve*, to the principal display panel.
7. Revise the medication guide statement to read as follows:

Dispense the enclosed Medication Guide to each patient

B. Container Label

1. Revise the overall design to differentiate Nucynta ER containers labels from Nucynta. When compared side-by-side, these labels are visually similar. This visual similarity contributes to wrong drug and wrong strength errors. Revise accordingly.
2. Delete the blue rectangular box surrounding the proprietary name. This box appears on the container labels of Nucynta immediate-release tablets and contributes to the visual similarity between both Nucynta ER and Nucynta container labels.

3. Revise the statement: (b) (4) to read
Usual Dosage: See package insert for full prescribing information.

C. Carton Labeling

Revise the net quantity statement to read as follows:

100 tablets (10 x 10 count blister cards)

D. Hospital Unit-Dose Blister Label

1. Differentiate your product strengths with the use of color, boxing, or some other means, so that the Nucynta ER 50 mg and 100 mg are distinct from Nucynta 50 mg and 100 mg strength tablets. Additionally, the Nucynta ER strengths should be differentiated from one another. Revision of the strength differentiation may reduce the likelihood of wrong drug (Nucynta ER vs. Nucynta) and wrong strength selection errors since unit dose blisters may be stored apart from the cartons.
2. Decrease the prominence of the schedule II symbol.

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

5 REFERENCES

1. OSE Reviews

Merchant, L. OSE Review 2009-846 NME 915 Review for Nucynta

Abdus-Samad, J. OSE Review 2009-2412 Proprietary Name Review for Nucynta ER, March 9, 2010

2. AERS Database Case Number for Nucynta search

ISR
numbers
7514466
7441447
7431924
7060096
7148430
7272493
7242714
7310985
7457560
7498913
7242713
7439829
7479118
6935631
7457284
7271931
7529429
7462863

3. AERS Database Case Numbers for tramadol extended-release search

ISR
numbers
3452502
3820077
4012427
4993624
5025701
5058347
5058349
5078654
5119765
5196799
5287644
5381361
5414958
5416946
5444181
5461082
5489621
5762297
5930642
6038913
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JIBRIL ABDUS-SAMAD
08/01/2011

TODD D BRIDGES
08/01/2011

CAROL A HOLQUIST
08/01/2011

Consultative Review
DPP Consult #11282

Consultant Reviewer: Cara Alfaro, Pharm.D.
Clinical Analyst
Division of Psychiatry Products/OND/CDER

Consultation Requester: Sandra Saltz
Project Manager
Controlled Substance Staff (CSS)

Subject of Request: Tapentadol – suicidal ideation/behavior

Date of Request: 6/2/2011

Completion Date: 7/22/2011

Background

The Controlled Substances Staff posed two general questions that were indirectly related to tapentadol (NDA 200533), an investigational drug with mu-agonist activity and selective norepinephrine and serotonin uptake inhibition. This NDA is currently under review in the Division of Anesthesia and Analgesia Products (DAAP) for the management of moderate to severe chronic pain.

Questions

1. Is there any evidence that opioid medications contribute to or increase the risk of suicidality? If so, where could we search for the scientific evidence?

Since the Division of Psychiatry Products does not routinely review opioid medications, we are unaware of any data suggesting an increase in suicidal ideation and/or suicidal behavior with opioids. Since there is likely a background rate of suicidal ideation/suicidal behavior in the disorders for which opioid medications may be used, it would be difficult to assess this risk unless it were studied prospectively in controlled clinical trials. Prospective assessment should include a rating scale that assesses suicidal ideation/suicidal behavior, such as the Columbia Suicide Severity Rating Scale (C-SSRS).

One could search recent NDA submissions for opioid medications to determine whether rating scales for suicidal ideation/suicidal behavior were included in the controlled clinical trials. Additionally, one could search PubMed (and similar databases) for published clinical trials that may have included scales to assess suicidal ideation/suicidal behavior for opioid medications.

2. For the drugs which have a mixed mechanism of action, such as tapentadol, which includes mu-agonist activity with selective norepinephrine and serotonin uptake inhibition, is there any way to distinguish the cases of suicidality related to SNRI/SSRI activity from the suicidality triggered by the underlying disorders of patients with cancer and other painful terminal diseases?

There are no specific elements of the suicidal ideation/suicidal behavior related to SNRI/SSRI activity that would distinguish it from the suicidal ideation/suicidal behavior related to an underlying disorder – be it cancer, other painful terminal diseases or psychiatric disorders such as depression. As outlined in the response to question 1, the only way to assess whether a medication may be associated with suicidal ideation/behavior, especially in disorders for which a significant background rate might be expected, is to evaluate suicidal ideation/behavior in controlled clinical trials with a tool for assessing suicidal ideation/behavior (e.g. C-SSRS). These studies should be fairly large in order to capture enough events for meaningful evaluation.

Cara Alfaro, Pharm.D.
Clinical Analyst
Division of Psychiatry Products
July 22, 2011

cc: HFD-130/Laughren
Mathis
Khin
Berman
Alfaro

HFD-009/Saltz

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/s/

CARA L ALFARO
07/22/2011

NI A KHIN
07/25/2011

THOMAS P LAUGHREN
08/01/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: July 12, 2011

TO: Dominic Chiapperino, Regulatory Project Manager
Elizabeth Kilgore, M.D., Medical Officer
Division of Anesthesia and Analgesia Products (DAAP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #200533

APPLICANT: Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI), Johnson &
Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD)

DRUG: NUCYNTA ER (Tapentadol ER)

THERAPEUTIC CLASSIFICATION: Resubmission

INDICATION: Management of moderate to severe chronic pain in patients 18 years or older
when a continuous, around-the-clock opioid analgesic is needed for an
extended period of time

Original CONSULTATION REQUEST DATE for first cycle review: January 21, 2010
DIVISION ACTION GOAL DATE: before August 28, 2011
PDUFA DATE: August 28, 2011

I. BACKGROUND:

Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) submitted NDA 200533 on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI) for Tapentadol extended release (NUCYNTA ER) for the indication of management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Clinical studies have been conducted in subjects with chronic pain due to knee arthritis, low back pain, and peripheral diabetic neuropathy. The sponsor received a complete response to the original submission because of deficiencies in their in-vitro in-vivo correlation (IVIVC) models to bridge clinical study batches to the to-be-marketed "tamper-resistant-formulation" (TRF) batches. The FDA requested additional bioequivalence studies comparing these two formulations, but no new clinical studies were requested. The sponsor resubmitted the application on February 28, 2011.

During the original review cycle, clinical inspections of four clinical sites and the sponsor were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. FDA inspection of the clinical site of Dr. Allan Soo documented instances where the clinical investigator failed to adequately document review of rescue medication use by subjects, as well as entry of pain scores into subjects' diaries on the eDiary website. An inspection of the contract research organizations (CRO), (b) (4) was conducted in order to shed additional light on the reliability of specific data points for some subjects enrolled at this site. This addendum to the original clinical inspection summary (CIS) contains the review of the CRO inspection and a revision of the review of the inspection of Dr. Soo's site contained in the original CIS dated September 20, 2010.

The protocols inspected included:

- A. Protocol KF5503/23 (Grünenthal) aka Protocol R331333-PAI-3011 (J&JPRD) entitled "A Randomized Double-Blind, Placebo- and Active-Control, Parallel-arm, Phase 3 Trial with Controlled Adjustment of Dose to Evaluate the Efficacy and Safety of CG5503 Extended-Release (ER) in Subjects with Moderate to Severe Chronic Low Back Pain and
- B. Protocol KF5503/36 (Grünenthal) aka Protocol R331333-PAI-3015 (J&JPRD) entitled "A Randomized-Withdrawal Phase III Study Evaluating the Safety and Efficacy of CG5503 Extended-Release (ER) in Subjects with Painful Diabetic Peripheral Neuropathy (DPN)"

II. RESULTS (by Site):

Name of Inspected entity and Location	Protocol #/ # of Subjects Enrolled/ Randomized	Inspection Dates	Final Classification
(b) (4)	KF 36/ 16 subjects KF 23/ 89 subjects	October 25, to 28, 2010	NAI
Allan Soo, M.D. Premiere Pharmaceutical Research, LLC 3316 S. McClintock Drive Tempe, AZ 85282	KF 23/ 32 subjects	May 19 to June 17, 2010	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. (b) (4)
 - a. **What was inspected:** This inspection covered responsibilities contracted by the sponsor to (b) (4) specifically, to provide eDiaries and support services for the electronic diaries for the 2 clinical trials, Protocol KF5503/23 (Grünenthal) aka Protocol R331333-PAI-3011 (J&JPRD) and Protocol KF5503/36 (Grünenthal) aka Protocol R331333-PAI-3015 (J&JPRD). The inspection of (b) (4) focused on the clinical investigators that had been chosen for inspection by the review division. In preparation for the FDA investigation, (b) (4) restored the clinical studies from their archives. The inspection covered review of firm's procedures, eDiary documentation, eDiary and database quality control, and security access practices. Pain scores in the (b) (4) database were compared with line listings and validated for a total of 24 subjects. Audit trails for these scores were reviewed.
 - b. **General observations/commentary:** During the trial, subjects were instructed to enter pain scores and use of acetaminophen rescue medication directly into the eDiaries. These data were analyzed by the review division to determine efficacy of NUCYNTA ER for the respective indications. (b) (4)

created the diary pages, provided the devices to the clinical sites, trained study personnel, provided a 24/7 HelpDesk function, and maintained the database for the eDiary data. While the trial was ongoing, clinical investigators (CIs) were instructed to view the diary entries on a webpage to confirm subject compliance with the protocol. They were advised by study monitors, but not required by the protocol, to print important web pages for their records. At the end of each trial, (b) (4) provided the sponsor with a CD containing the all the diary data. The sponsor provided a CD to each site containing the data for the site. There were no objectionable conditions at (b) (4) and no Form FDA 483 was issued.

During the inspection of (b) (4) the CRO provided a printout of information noting when the website had been viewed by personnel at a clinical site. This was not a routine report that could be generated by the “reports” section of the website. Because this feature was not requested in the contract with the sponsor, lack of this feature was not considered a violation. The report was created during the FDA inspection and on site programming was required to convert the data to human readable form. It suggested that Dr. Soo did not view the website as often as would be necessary to view the subject records. However, because this information was not a validated report from the system, it was determined that this could not be used for evidence to document whether Dr. Soo viewed the website during subject visits. Also, it could not be ruled out that Dr. Soo might have viewed the website before a subject visit.

(b) (4) appears to have executed contracted responsibilities appropriately. There were no objectionable conditions at (b) (4) and no Form FDA 483 was issued.

- c. **Assessment of data integrity:** The inspection of (b) (4) noted that adequate controls were in place to document integrity of data generated by the eDiaries. It could not definitively account for the apparent discrepancies in data found at Dr. Soo’s site. However, this was not considered a regulatory violation on the part of the CRO. The studies appear to have been conducted adequately, and the data generated by this CRO appear acceptable in support of the respective indication.
2. Allan Soo, M.D.
3316 S. McClintock Drive, Tempe, AZ 85282
 - a. **What was inspected:** At this site, 50 subjects were screened, and 32 subjects were randomized: 11 to Cg5503 (test article Tapentadol), 10 to placebo, and 11 to oxycodone. A total of 23 subjects completed the study. During the FDA inspection, an audit of all subjects’ records was conducted for adherence to informed consent practices. Additionally, a complete audit of 12 of the subjects’ records was conducted to verify the primary efficacy endpoint and adherence to

the protocol.

- b. **General observations/commentary:** In this trial, subjects entered daily values including pain scores, number of tablets of rescue medication taken, and other clinical trial data directly into an electronic device, eDiary. Clinical investigators (CI) were instructed to view the eDiary data by signing onto a website and attesting to the viewing by completing a checklist (“yes” or “no”) concerning the viewing for each data domain. However, the CI was not required to print out or provide other documentation of having viewed the website. There was agreement between the primary endpoint data contained in the listings in the NDA and on a CD of the eDiary data at the site provided by the sponsor. There was no evidence of under-reporting of AEs. However, a Form FDA 483 was issued for the regulatory violations noted below. In addition, there were data discrepancies noted in Item c below. (Note that treatment assignment is in brackets after the subject number):

1. Failure to adhere to the protocol:
 - a. Three subjects (115762 [Oxy], 115936 [Cg5503], and 115987 [Oxy]) reported taking more than 1000 mg acetaminophen during the titration and maintenance phase in the eDiary; however, Dr. Soo’s source notes did not reflect the use of this rescue medication. Because the data listings were populated from electronic data capture on the eDiary, the use of rescue medication contained on the CD was consistent with the information provided in the data listings, and considered reliable. However, Dr. Soo’s review of rescue medication use by viewing the website, as required by the protocol, could not be confirmed due to the lack of source documentation.
 - b. The protocol required that subjects be off rescue medication for the last three days of the titration period, prior to being transitioned to the maintenance phase. Six subjects (113339 [Cg5503], 114520 [Placebo], 115718 [Placebo], 115762 [Oxy], 115936 [Cg5503], and 115987 [Oxy]) were transitioned to the Maintenance Phase, even though subjects reported in the eDiary that they continued to take rescue medication within the last three days of the Titration Period.

Reviewer note: In Dr. Soo’s response of July 8, 2010, he stated that, if the subjects did not report taking rescue medication and the pill count reflected this, he did not check the website to ensure that the subject had entered this correctly in the eDiary. Therefore, he was unable to verify that the subject had entered data into the eDiary correctly. Because the protocol did not specify that the website should be viewed, this observations was changed to “maintain adequate and accurate case histories” as noted in the letter below. The review division should consider the impact of this finding, if any, on the assessment of safety and efficacy.

2. Failure to maintain adequate case histories:
 - a. Subjects 115936 [Cg5503] and 115987 [Oxy] did not complete the eDiary SOWS assessments, although this is marked as “yes” in the source documents, namely Dr. Soo’s documentation on a checklist indicating review of completion of the

- eDiary assessments. As the subjects did not complete this information, there is a discrepancy in Dr. Soo's documentation that this was completed by the subject.
- b. Subject 116091 [Oxy] is documented as taking investigational medical product (IMP) dose of 250 mg on the eCRF, but as 150 mg in the subject record.
 - c. For 5 subjects (113339 [Cg5503], 113780 [Oxy], 114535 [Oxy], 114875 [Oxy], and 115762 [Oxy]) there was no documentation for the reason for changes in dose titration.
 - d. An additional inconsistency between the eDiary and the data at Dr. Soo's site that was not cited on the Form FDA 483 was that, according to Dr. Soo's source records, Subject 115762 [Oxy] completed the study but the line listings and CD do not contain pain scores entered after titration. Source data at the site, in the form of the checklist described above, indicate that Dr. Soo reviewed the pain scores, but the actual pain scores were not printed out or documented in any form.

Dr. Soo did not adequately respond to the inspection findings. In his response letter dated July 8, 2010, he questioned the accuracy of the data provided on the CD provided by the sponsor at the end of the trial. He stated that he did not check the website to confirm the eDiary responses concerning use of rescue medication if the actual pill count documented the subject's report that no rescue medication was taken. While the trial was ongoing, Dr. Soo did not print out screen shots of the eDiary data to determine if the data entered into the eDiary by the subject was accurate. The CD at the clinical site and the line listings submitted to the FDA are in agreement, but appear inconsistent with source data at Dr. Soo's site. Dr. Soo's only documentation as source data of his review of entry of pain scores by the subjects in the eDiary, was a checklist ("yes", "no") in which he attests that he has reviewed the eDiary website to check the pain scores. While the trial was ongoing, Dr. Soo did not print out screen shots of the eDiary data to document the actual data entries including pain scores or medication usage.

- c. **Assessment of data integrity:** The impact that regulatory violations may have on overall efficacy conclusions reached in review of the NDA may be mitigated by the randomized, double-blind superiority design of the study allowing the data generated by this site to be used in support of the respective indication. There was no evidence of under-reporting of adverse events found during the inspection of Dr. Soo's site. The primary endpoint data contained on the CD agreed with the data found at (b) (4)

It is deferred to the review division to evaluate the impact, if any, of the finding related to the six subjects that were transitioned to the Maintenance Phase, even though subjects reported in the eDiary that they continued to take rescue medication within the last three days of the Titration Period. Additionally, it is recommended that the data from Subject 115762 not be used as the eDiary data for pain scores had no entry. Otherwise, the data appear reliable in support of the application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This Addendum is intended to capture assessment of the inspection of (b) (4), which was pending at the time of the original CIS dated September 20, 2010, as well as to capture the updated assessment of Dr. Soo's inspection based on receipt and review of the EIR. For assessment of other inspections related to this application, the reader is referred to the original CIS dated September 20, 2010.

Verification of electronically captured primary efficacy source data was performed by inspection of (b) (4). No significant regulatory violations were identified during the inspection of (b) (4) and the primary efficacy data were verified to be consistent with the NDA data listings. The data is considered reliable.

Upon further receipt and review of the EIR for Dr. Soo, as well as taking in to account the results of the inspection of (b) (4) and the fact that the data from eDiary was verified, it is unlikely that the identified regulatory violations at Dr. Soo's site would significantly impact overall data reliability. Further, the impact that the regulatory violations identified at Dr. Soo's site may have on overall efficacy conclusions reached in review of the NDA may be mitigated by the randomized, double-blind superiority design of the study allowing the data generated by this site to be used in support of the respective indication. There was no evidence of under-reporting of adverse events found during the inspection of Dr. Soo's site. The primary endpoint data contained on the CD agreed with the data found at (b) (4). It is deferred to the review division to evaluate the impact, if any, of the six subjects that were transitioned to the Maintenance Phase, even though subjects reported in the eDiary that they continued to take rescue medication within the last three days of the Titration Period. Additionally, it is recommended that the data from Subject 115762 not be used as the eDiary data for pain scores had no entry. Otherwise, the data appear reliable in support of the application.

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Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
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CONCURRENCE:

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Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
07/14/2011

TEJASHRI S PUROHIT-SHETH
07/14/2011



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

Date: July 12, 2011

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 ER (Tapentadol HCl extended-release)
NDA 200-533 (previous IND 61,345)
Indication: management of moderate to severe chronic pain in patients 18 years of age
Dosages: 50, 100, 150, 200, and 250 mg tablets for oral administration

Sponsor Ortho-McNeil c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Materials reviewed: NDA 200-533 (Dec 1, 2009) and post-CR re-submission (Feb 28, 2011)
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CSS review Sep 9 2010
Tamper Resistant Formulation Properties Report (NDA 200-533: Mod 3.2.P.2 Pharmaceutical Development)
Clin-pharm review, Nov 2009
Report of post-marketing experience with NUCYNTA (Tapentadol)
Immediate-Release from July 1, 2009 to Sep 30, 2009 (NDA 200-533: Mod 5.3.6 Postmarketing Surveillance Report)

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I. Summary

A. Background

This memo responds to the DAAAP consult regarding abuse potential of tapentadol extended release tablets tamper resistant formulation (TRF). This review supplements the previously submitted CSS review (in DARRTS, Sep 9, 2010).

The “to be marketed” formulation was called the Tamper Resistant Formulation (TRF) during clinical development. In vitro studies describing the physiochemical characteristics of the TRF formulation are summarized in Tamper Resistant Formulation Report (described in CSS review Sep 9, 2010). These studies showed that the controlled release properties of the TRF formulation can be readily overcome by multiple simple physiochemical manipulations.

During the previous review cycle, post-marketing experience with Nucynta IR (immediate-release) showed a high rate of adverse events, some of which relate to abuse and dependence liability including hallucinations (8.1%) and withdrawal syndrome (3.5 %). In addition, serotonin syndrome (3.5%) and convulsions (2.9%) were reported.

The Office of Surveillance & Epidemiology (OSE) (May 25, 2010) evaluated the AERS database for Nucynta IR (US: 169 and foreign 13), covering the period from Nov 20, 2008 to May 25, 2010. US psychiatric AEs from 81 cases (52%) included hallucinations, 39 cases (25%), serotonin syndrome, 4 cases, (2.5%), suicidal ideation, 8 cases (5.1%), one suicide attempt, and one completed suicide.

B. Conclusions for the Division (based on current and previous CSS review, Sep. 9, 2010)

1. The controlled release properties of the TRF formulation can be readily overcome by multiple simple physiochemical manipulations. See review of Sep 9, 2010.
2. The TRF formulation, in particular the dose of >150 mg, appears to exhibit an increased frequency of adverse events (e.g. euphoria) signaling abuse potential
3. A high incidence of euphoria and feeling drunk occurred in Phase 1 studies in subjects who received tapentadol TRF as compared to those who received “all tapentadol ER formulations.” Euphoria was reported in 50% of subjects who received tapentadol TRF 250 mg with water in Study R331333-PAI-1028 (HP5503/44
4. Review of the current post-CR bioequivalence studies with the TRF formulation indicates a possible gender effect, in that the majority of AEs were reported to occur in females, in particular for nervous, gastrointestinal disorders, and psychiatric AEs, such as euphoria. They occurred in females in the ratio of 8F:1M. Additionally, almost all discontinuations which were caused by vomiting occurred again mainly in females, 12:5.
5. Withdrawal symptoms, including insomnia, depressed mood, depression, suicidal ideation, disturbance in attention and restless leg syndrome, occurred after Nucynta ER administration was stopped. The occurrence of withdrawal symptoms indicates development of dependency and a need to slowly taper discontinuation of drug

6. Co-administration of tapentadol TRF with meals and alcohol resulted in increases in C_{max} and AUC's. (See discussion, below).
7. PD effects of tapentadol TRF formulation are only potentiated after intake of alcohol, and such effects were not observed with food.
8. The TRF formulation doses 100 mg and 250 mg produce increased plasma levels of tapentadol when administered with food and alcohol. A dose of 250 mg in some subjects is capable of producing levels equivalent to the dose range of 375 mg up to 575 mg. The safety of these levels is not known.¹

C. Recommendations:

1. Include appropriate warning language in the label about susceptibility of females to develop majority of AEs, sometimes of a severity that leads to discontinuation of the drug. The extent of the relation of gender differences to safe use of the drug should be further examined. One of possibilities would be to provide the data on withdrawal, and discontinuation due to AEs with respect to gender, and relationship to the dose
2. All planned clinical trials and all ongoing clinical trials (where possible) should include prospective assessment of suicidality, due to appearance of suicidality in the post-marketing phase of Nucynta.

II. DISCUSSION

Re: point 6 and 7 (above) in **Conclusions**:

Under fed conditions, approximately 25% of subjects experienced plasma levels of tapentadol at very high doses beyond which safety was not assessed. This conclusion is based on pharmacokinetic results from Studies R331333-PAI-1052 (HP5503/51) and R331333-PAI-1055 (HP5503/67). In addition, plasma concentrations from tapentadol TRF 100 mg dose and 250 mg dose were higher when taken with 40% ethanol (for 100 mg: C_{max} 38.0 ± 15.4, and for 250 mg: 104 ± 44.4) than if taken with water (for 100 mg: C_{max} 24.8 ± 8.64; and for 250 mg 77.4 ± 19.6) based on the study R331333-PAI-1028 (HP5503/44).

Study R331333-PAI-1052 (HP5503/51) (NDA, Mod. 5.3.5.4.2) evaluated the effect of food on the pharmacokinetics of tapentadol TRF 100 mg in healthy male Japanese subjects. C_{max}

¹ Definition of Dose dumping (FDA, Office of New Drugs and Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Awareness Topic: Mitigating the Risks of Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms by Robert J. Meyer, M.D. and Ajaz S. Hussain, Ph.D.; Oct 2005)

Unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form is often referred to as "dose dumping". Depending on the therapeutic indication and the therapeutic index of a drug, dose-dumping can pose a significant risk to patients, either due to safety issues or diminished efficacy or both.

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increased 153.5 % from 42.8 ± 14.0 ng/ml in fasting condition to 65.7 ± 15.9 ng/ml in the fed condition. Examination of individual subject data revealed that 25% (3 of 12) of subjects had increased ~200% C_{max} in fed conditions up to 223%. The 90% CI was 136.79-174.53 (Study report: page 39). The study was not evaluated by the Division of Clinical Pharmacology.

Study R331333-PAI-1055 (HP5503/67) (NDA, Mod. 5.3.1.2.2) evaluated the effect of food on the pharmacokinetics of tapentadol TRF 250 mg in healthy subjects. The mean C_{max} in fed condition was higher (105 ng/mL \pm 29.5) than in fasting condition (90.2 ng/mL \pm 24.2). The increase of C_{max} (relative bioavailability) in fed condition was 121% (range of 57.2% to 230%). 90% CI was 116.76 (109.91-124.04, Clin-pharm review, page 62) and was within limits established by FDA. However, the evaluation of individual subject data revealed that 25% (13 of 52) of subjects had increased C_{max} of at least 150% or more in fed vs fasted condition; this included 2 subjects with an increased C_{max} of more than 200%, with one subject reaching 230% increase of C_{max}. Twenty-five % of subjects had levels equivalent to the tapentadol dose of more than 375 mg up to 575 mg. The safety of such high doses was not yet examined. The study was evaluated by the Division of Clinical Pharmacology, page 60.

Study R331333-PAI-1028 (HP5503/44) (NDA Mod. 5.3.3.4) examined the potential for tapentadol dose dumping, in 40 healthy subjects (2 different cohorts of 19 males and 1 female in each part). PK and PD effects of 240 ml 40% ethanol intake along with administration of tapentadol extended-release TRF (100 mg and 250 mg doses) were evaluated in the 20 subjects for each dose. The increase of C_{max} (relative bioavailability) for 100 mg was 166% (range of 98.9% to 438%), and increase of C_{max} for 250 mg was 133% (range of 89.5% to 267%). These values are consistent with those cited in the Clinical Pharmacology Review (Dr. David Lee, Clin-pharm review from Nov 30, 2009, page 45, and stating that: "The increase in mean tapentadol C_{max} was most apparent in the 100-mg dose group, with individual C_{max} value increases in the range of 0.99-fold up to 4.38-fold following concomitant administration of 40% alcohol). The values for C_{max} 90% CI for alcohol effect were for tapentadol dose 100 mg: 127.53 to 172.34 (Clin-Pharm Review: page 47) and for tapentadol dose 250 mg: 115.87 to 141.84 (Clin-Pharm Review: page 48). The evaluation of individual data reveals that for the dose of 100 mg tapentadol TRF, 8 of 19 subjects had increased C_{max} >145%, including 2 subjects with increases of >400%. The evaluation of individual data for the dose of 250 mg tapentadol TRF reveals that, 4 in 20 subjects (25%) had an increased of C_{max} >157%, including 2 subjects with increases of >210%.

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/s/

ALICJA LERNER
07/12/2011

MICHAEL KLEIN
07/12/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

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

Memorandum

Date: June 23, 2011

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

From: Twyla Thompson, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Shefali Doshi, DTC Group Leader
Olga Salis, Senior Regulatory Health Project Manager
Michael Wade, Regulatory Health Project Manager
(DDMAC)

Subject: NDA 200533
DDMAC labeling comments for NUCYNTA ER (tapentadol)
extended-release oral tablets – CII Medication Guide

DDMAC has reviewed the Medication Guide (Med Guide) for NUCYNTA ER (tapentadol) extended-release oral tablets (Nucynta ER). DDMAC's comments on the Medication Guide are based on the proposed draft marked-up labeling titled, "NDA 200533-resub FDA-revised PI" sent via email on June 16, 2011 by Ellen Fields. DDMAC used DRISK's tracked changes version of the Med Guide as the base document for review. DRISK's review of the Med Guide is being provided to the Review Division under separate cover.

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

If you have any questions, please contact Twyla Thompson at (301) 796-4294 or twyla.thompson@fda.hhs.gov.

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/s/

TWYLA N THOMPSON
06/23/2011

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

PATIENT LABELING REVIEW

Date: June 23, 2011

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

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): NUCYNTA ER (tapentadol) C-II

Dosage Form and Route: Extended-release oral tablets

Application Type/Number: 200-533

Applicant: Ortho-McNeil-Janssen Pharmaceuticals, Inc. c/o Johnson & Johnson Pharmaceutical Research and Development LLC

OSE RCM #: 2011-921

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for NUCYTNA ER (tapentadol) extended-release oral tablets. The Applicant submitted a Complete Response to FDA's Complete Response letter dated October 1, 2010, as well as additional requests. The purpose of the Applicant's submission is to seek approval of their New Drug Application (NDA 200-533), for NUCYTNA ER extended-release oral tablets for the proposed indication for the management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

The proposed REMS is being reviewed by DRISK and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft NUCYNTA ER (tapentadol) Medication Guide (MG) received on February 28, 2011 and revised by the review division throughout the review cycle, and sent to DRISK on June 9, 2011.
- Draft prescribing information (PI) received February 28, 2011 revised by the Review Division throughout the current review cycle and received by DRISK on June 9, 2011, further revised and provided to DRISK on June 16, 2011.

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 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 document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with other extended release opioid product MGs, to the extent possible.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG

Please let us know if you have any questions.

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/s/

BARBARA A FULLER

06/23/2011

DRISK's review of NDA 200533 Nucynta ER (tapentadol) MG

LASHAWN M GRIFFITHS

06/23/2011

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: April 28, 2011

TO: Associate Director for Bioequivalence
 Division of Scientific Investigations, HFD-48

THROUGH: Bob A. Rappaport, M.D., Director, Division of Anesthesia, Analgesia, and Addiction
 Products (DAAAP), HFD-170

FROM: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAAAP

SUBJECT: Request for Biopharmaceutical Inspections
 NDA 200533
 Nucynta ER (tapentadol) extended-release tablets, 250 mg
 Johnson and Johnson Pharmaceutical Research & Development, L.L.C.

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
R331333-PAI-1061; HP5503/84	Principal Investigator: Scott Rasmussen, MD; Clinical Site: Celerion, Inc., 621 Rose Street, Lincoln, NE 68502; US Contact: Email: Scott.rasmussen@celerion.com Tel: (402) 437-6361 Alternate: Michele Page, QA Manager Tel: (402) 437-6216	(b) (4)

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

- X Other (please explain): All analyses to demonstrate bioequivalence were conducted at the site in the Netherlands.

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **July 28, 2011**. We intend to issue an action letter on this application by **August 28, 2011**.

Should you require any additional information, please contact Dominic Chiapperino, DAAAP, at 301-796-1183 or dominic.chiapperino@fda.hhs.gov.

Concurrence: (Optional)

David J. Lee, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCP2)

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/s/

DOMINIC CHIAPPERINO
04/28/2011

BOB A RAPPAPORT
04/28/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 20, 2010

TO: Dominic Chiapperino, Regulatory Project Manager
Eric Brodsky, M.D., Medical Officer
Division of Anesthesia and Analgesia Products (DAAP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #200533

APPLICANT: Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI), Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD)

DRUG: NUCYNTA ER (Tapentadol ER)

NME: No

THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: Management of moderate to severe chronic pain in patients 18 years or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

CONSULTATION REQUEST DATE: January 21, 2010

DIVISION ACTION GOAL DATE: October 1, 2010
PDUFA DATE: October 1, 2010

I. BACKGROUND:

Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) submitted NDA 200533 on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI) for Tapentadol extended release (NUCYNTA ER) for the indication of management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Clinical studies have been conducted in subjects with chronic pain due to knee arthritis, low back pain, and peripheral diabetic neuropathy.

Clinical inspections of four clinical sites were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. The efficacy results of the studies are important in making a regulatory decision with regard to drug approval. Selection of sites was based on numbers of subjects enrolled at the site for the studies, the inspectional history of the highest enrolling clinical investigators, and the number of INDs in the DSI clinical trials database. After the sponsor became aware of anticipated clinical site inspections, the sponsor informed FDA of potential misconduct and potential violations of good clinical practice at two clinical sites for these protocols, Dr. Allan Soo and Dr. Douglas Young. In e-mail communication with Dr. Brodsky of the review division on May 12, 2010 it was established that the efficacy result from Dr. Young's site would not change the efficacy conclusions of the review, so it was elected not to pursue an inspection of Dr. Young as a PDUFA inspection. However, a For-Cause inspection may be considered by the complaints Branch in GCP-1. The inspection of Dr. Soo was a combined PDUFA/For-Cause inspection.

Additionally, a sponsor inspection was conducted 1) to evaluate the sponsor's responsibilities with respect to the conduct of the pivotal studies and 2) (b) (4)

(b) (4)
An inspection of the CRO, (b) (4) is currently pending to evaluate the responsibilities of this CRO with respect to electronic data capture of the primary efficacy endpoint.

The protocols inspected included:

- A. Protocol KF5503/23 (Grünenthal) aka Protocol R331333-PAI-3011 (J&JPRD) entitled "A Randomized Double-Blind, Placebo- and Active-Control, Parallel-arm, Phase 3 Trial with Controlled Adjustment of Dose to Evaluate the Efficacy and Safety of CG5503 Extended-Release (ER) in Subjects with Moderate to Severe Chronic Low Back Pain and
- B. Protocol KF5503/36 (Grünenthal) aka Protocol R331333-PAI-3015 (J&JPRD) entitled "A Randomized-Withdrawal Phase III Study Evaluating the Safety and Efficacy of CG5503 Extended-Release (ER) in Subjects with Painful Diabetic Peripheral Neuropathy (DPN)"

For these protocols the primary efficacy endpoint was change from baseline to last week values of the numerical rating scale (NRS) entered twice a day in an electronic diary (eDiary). Subjects were instructed to enter the NRS and the use of rescue medication into an electronic diary. The eDiary set-up and maintenance was contracted to a CRO, (b) (4). The protocol-specific “source documents” provided by the sponsor contained instructions to “transmit eDiary data and review subject data on line” and a checklist with the following questions:

- Has the subject recorded their PI score and study medication intake twice a day? (yes, no)
- Has the subject recorded their rescue medication intake in the eDiary? (yes, no).

Although clinical investigators were requested by study monitors to print out pages of the eDiary from the web pages accessed via a secure internet site, study documents including the monitoring guidelines did not clearly require that the webviews of eDiary entries be printed. Therefore, existence of documentation of the contents of the eDiaries apart from that provided by the sponsor at the end of the trial occurred at only one of the three inspected clinical sites. The data collected on the eDiary was archived by (b) (4) and also sent to JNJ data management (JNJDM). JNJDM transferred the data to (b) (4) a CRO that prepared the CD for the clinical site. At this point, it is unclear as to the details of how JNJDM transferred the data to (b) (4).

II. RESULTS (by Site):

Name of Inspected Entity and Location	Protocol #/ # of Subjects randomized	Inspection Dates	Final Classification
CI Pamela Amador, M.D. Gables Medical Research 85 Grand Canal Dr., # 400 Miami, FL 33144	KF 36/ 16 subjects	May 18 to June 8, 2010	Pending (Preliminary classification NAI)
CI Daniel Whittington, M.D. Dolby Research LLC 8150 Jefferson Hwy, Suite B Baton Rouge, LA 70809	KF 23/ 30 subjects	June 1, to 21, 2010	VAI
CI Bret Wittmer, M.D. Commonwealth Biomedical Research 240 East Ayr Parkway Madisonville, KY 42431	KF 23/ 27 subjects	May 10 to 18, 2010	NAI

Name of Inspected Entity and Location	Protocol #/ # of Subjects randomized	Inspection Dates	Final Classification
CI Allan Soo, M.D. Premiere Pharmaceutical Research, LLC 3316 S. McClintock Drive Tempe, AZ 85282	KF 23/ 32 subjects	May 19 to June 17, 2010	Pending (Preliminary field classification VAI)
Sponsor Ortho-McNeil-Janssen-Pharmaceuticals, Inc. Johnson & Johnson Pharmaceutical Research and Development, L.L.C. 1125 Trenton-Harbourton Road Titusville, N.J. 08560-0200	KF 36 and KF 23	August 9 to August 20, 2010	Pending (Preliminary classification VAI)
CRO  (b) (4)	KF 36 and KF 23	Anticipated to begin on October 25, 2010	

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = EIR has not been received and results are based on preliminary communications with the field or post inspectional correspondence has not issued.

1. Pamela Amador, M.D.
Gables Medical Research, 85 Grand Canal Dr., # 400, Miami, FL 33144

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** For Protocol KF 36, a total of 23 subjects were screened, there were 7 screen failures, and 16 subjects completed the study. All 23 subjects' records were reviewed.
- b. **General observations/commentary:** The primary endpoint data were verified by comparing line listings submitted to the NDA with data contained on CDs at the clinical site. There was no evidence of under-reporting of adverse events (AEs). No significant deficiencies were identified during the inspection and a Form FDA 483 was not issued.

- c. **Assessment of data integrity:** Provided that source data contained on the subject CDs are verified during the pending inspection of the CRO, (b) (4) the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Daniel Whittington, M.D.

Dolby Research LLC, 8150 Jefferson Hwy, Suite B, Baton Rouge, LA 70809

- a. **What was inspected:** For Protocol KF 23, a total of 47 subjects were screened, 30 subjects were enrolled, and 13 subjects completed the study. An audit of two screen failure subjects' records and fifteen of the randomized subjects' records was conducted.
- b. **General observations/commentary:** There was no evidence of under-reporting of AEs. The primary endpoint data were verified by comparing line listings submitted to the NDA with data contained on CDs at the clinical site, however, study files documented numerous difficulties with use of eDiaries. Specifically, subjects were not compliant in capturing efficacy endpoint data because they were unable to enter data into their eDiaries or transmit data from home. Etiologies of the difficulties varied and included inability of the subjects to use the diary due to subject ineptitude, prohibition of using diary at work, or equipment failures. Although sponsor instructions were to complete paper diaries real time in the event of issues with the eDiaries, in some cases, progress notes documented that the site provided instructions to subjects to enter pain intensity scores retroactively during study visits.

At the end of the inspection, a Form FDA 483 was issued for the following violations concerning failure to conduct the investigation according to the investigational plan and failure to maintain adequate case histories:

1. The investigator enrolled seven subjects, 2 each Cg5503 and placebo and 3 oxycodone group, (112562, 114469, 114695, 1144712, 114759, 115562, and 115935) with positive drug screen test for cannabis. In his response of June 30, 2010, Dr. Whittington stated that he reviewed the positive drug screens and discussed with the subject. It was his opinion that the subjects did not meet the exclusion criteria of drug abuse in the Investigator's judgment and the protocol was not clear that a positive drug screen for cannabis was exclusionary.

Reviewer's Comments: The protocol is silent on whether a positive drug screen for cannabis is a violation. This was discussed with the review division medical officer, Dr. Brodsky, who stated that because this finding was balanced between the 3 arms, it would not confound efficacy or safety assessments.

2. Subjects (116039 [placebo] and 116046 [oxycodone]) were randomized without the required number of baseline pain intensity scores prior to randomization. Each subject completed 4 of 5 required scores, so was missing one additional pain score required for randomization.

Reviewer's Comments: The above violations are unlikely to impact data integrity as they represent isolated findings with respect to data point capture and are not systemic in nature; therefore, they are unlikely to impact overall data reliability.

3. Five subjects, 2 each placebo and oxycodone group and one Cg5503 treatment group (112991, 113252, 113627, 114621, and 114690) were transitioned to the Maintenance Phase although they had not refrained from taking rescue medication within the last three days of the Titration Period as required by the protocol. This is documented in paper printouts from the webview, is contained in the CD at the site, and is in the data listings submitted by the sponsor to the NDA.

Reviewer's Comments: These protocol violations were appropriately documented in webview printouts from the clinical site, the eDiary CD, and the data listings submitted to the NDA. The data are considered reliable as the data submitted in the application is consistent with source documentation at the site; however, the review division should evaluate the clinical relevance of these protocol violations in their evaluation of study outcome.

4. Not all of the baseline pain intensity scores used to support the decision to randomize Subjects 113627, 115787, and 115971 (Cg5503), 114695(oxycodone), 114698 and 115562 (placebo), were recorded concurrently due to technological issues with the eDiaries. For approximately half of the required values, pain scores were recalled retrospectively by the subjects and entered into the source notes.

Reviewer's Comments: For 6 of the 30 enrolled subjects, baseline pain scores were recalled and not recorded contemporaneously. This finding has the potential to impact data reliability as subjects were enrolled based on recall of pain scores and not contemporaneous recording, as specified in the protocol; therefore, the efficacy value of change from baseline is based on recall values for these subjects.

5. Not all of the pain intensity scores reported within the last seven days of the maintenance period for Subjects 113555 (oxycodone), and 114754 (Cg5503) were recorded concurrently due to technological issues with the eDiaries. Subject 113555 recorded contemporaneous values on a paper diary, but Subject 114754 recalled them retrospectively.

Reviewer's Comments: The reliability of pain scores reported for Subject 114754 may be of some concern due to the retrospective collection of the data, but the exact impact can not be determined. With the exception of data for Subject 114754, the impact on data reliability is likely minimal as these represent isolated findings that were not systemic in nature.

- c. **Assessment of data integrity:** Although regulatory violations were noted, these are not considered pervasive in nature. However, the review division will need to consider the impact of enrollment of seven subjects who screened positive for cannabis use (2 each Cg5503 and placebo and 3 oxycodone group: 112562, 114469, 114695, 1144712, 114759, 115562, and 115935) in their evaluation of efficacy and safety, although based on discussion with Dr. Brodsky, this finding is unlikely to impact efficacy or safety. Additionally, the review division may consider excluding the data or treating the values as missing values in analyses, for the subjects who lacked contemporaneous capture of pain intensity scores due to technological issue with the eDiaries [Subjects 113627, 115787, and 115971 (Cg5503), 114695(oxycodone), 114698 and 115562 (placebo)].

Provided that source data contained on the subject CDs are verified during the pending inspection of the CRO, [REDACTED] (b) (4) with the exception of issues noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Bret Wittmer, M.D.

Commonwealth Biomedical Research, 240 East Ayr Parkway, Madisonville, KY 42431

- a. **What was inspected:** For Protocol KF 23, at this site there were 48 subjects screened, 27 subjects enrolled, and 14 subjects who completed the trial. A 100% of review of all subjects' signed informed consent forms and an in depth audit of the 27 enrolled subjects' records was performed.
- b. **General observations/commentary:** There was no evidence of under-reporting of AEs. The primary endpoint data were verified by comparing line listings submitted to the NDA with data contained on CDs at the clinical site. No significant regulatory violations or deficiencies were identified during the inspection. No Form FDA 483 was issued.
- c. **Assessment of data integrity:** Provided that source data contained on the subject CDs are verified during the pending inspection of the CRO, [REDACTED] (b) (4), [REDACTED], the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Allan Soo, M.D.
Premiere Pharmaceutical Research, LLC, 3316 S. McClintock Drive,
Tempe, AZ 85282
- a. **What was inspected:** For Protocol KF 23, 50 subjects were screened, 32 subjects were enrolled, and 23 subjects completed the study. An audit of 12 subjects' records was conducted.
- b. **General observations/commentary:** Prior to the inspection, the sponsor notified FDA of potential violations of good clinical practice at this site in the form of general correspondence. DSI discussed general allegations regarding GCP noncompliance at Dr. Soo's site with the sponsor including backdating of source documents and lack of clinical oversight regarding dose adjustments. The fact that the site had a low number of adverse events reported was also discussed, but there were no specifics that the sponsor could provide of an AE that was not reported. The FDA inspection did not identify any evidence of under-reporting of AEs and there was agreement between the primary endpoint data contained in the listings in the NDA and on a CD of the eDiary data at the site provided by the sponsor.

A Form FDA 483 was issued for 1) not adhering to the protocol and 2) not maintaining adequate and accurate records. Specifically, the Form FDA 483 noted the following regulatory violations:

1. Failure to adhere to the protocol:
- a) Three subjects (115762, 115936, and 115987) reported taking more than 1000 mg acetaminophen during the titration and maintenance phase in the eDiary; however, Dr. Soo's source notes did not reflect the use of this rescue medication. Because the data listings were populated from electronic data capture on the eDiary, the use of rescue medication contained on the CD was consistent with the information provided in the data listings. However, Dr. Soo's review of rescue medication use by viewing the website, as required by the protocol, could not be confirmed due to the lack of source documentation.
- b) The protocol required that subjects be off rescue medication for the last three days of the titration period, prior to being transitioned to the maintenance phase. Six subjects (113339, 114520, 115718, 115762, 115936, and 115987) were transitioned to the Maintenance Phase, even though subjects reported in the eDiary that they continued to take rescue medication within the last three days of the Titration Period. During the inspection, Dr. Soo accounted for these discrepancies to the FDA investigator by explaining that, when the subject denied the use of pain medication in response to his question, he did not review the website with the subjects' eDiary information regarding the continued use of rescue medication. Therefore, he

was unable to verify that the subject had entered data into the eDiary correctly.

Reviewer's Comments: Because Dr. Soo did not document that he checked the website as required by the protocol, it appears that subjects were transitioned inappropriately to the maintenance phase. The review division will need to consider the clinical relevance of this finding to their evaluation of safety and efficacy.

- c) Study personnel who were not medically trained gave verbal approval for subjects to titrate investigational medical product.
2. Failure to maintain adequate case histories:
- a) Subjects 115936 and 115987 did not complete the eDiary SOWS assessments, although this is marked as "yes" in the source documents.
 - b) Subject 116091 is documented as taking investigational medical product (IMP) dose of 250 mg on the eCRF, but as 150 mg in the subject record.
 - c) For 5 subjects (113339, 113780, 114535, 114875, and 115762) there was no documentation for the reason for changes in dose titration.

Reviewer's Comments: Dr. Soo's only documentation of his review based on subject history, of the use of rescue medication and entry of pain scores by the subjects in the eDiary, was a checklist ("yes", "no") in which he attests that he has reviewed the eDiary website to check the pain scores. While the trial was ongoing, Dr. Soo did not print out screen shots of the eDiary data to document the actual data entries including pain scores or medication usage.

Additional Issues not Cited on the Form FDA 483

The following issues were not cited on the Form FDA 483, but appear to be inconsistencies between the eDiary and the source data for subjects at Dr. Soo's site based on DSI's review of the Establishment Inspection Report and associated exhibits:

1. Subject 115762 had documented study visits and completed the study but no pain scores were noted in the data listings documenting eDiary entry of pain scores after titration. Source data at the site in the form of a checklist described above, note that Dr. Soo reviewed the pain scores, but the pain scores are not contained in the CD from the sponsor. As Dr. Soo did not print out the pain scores from the webpage when the trial was ongoing, it is difficult to determine the reason for this discrepancy. It is difficult to determine whether this discrepancy was an error on Dr. Soo's part where he documented viewing pain scores on the web, but in fact did not; or whether subjects failed to enter the data into the eDiary; and or whether the data was entered correctly and viewed by Dr. Soo, however, there was a technological issue with the eDiary data transmission.

2. For Subject 115987, the eDiary documented that this subject used up to 7 tablets of acetaminophen at once as rescue medication; however, source documents at Dr. Soo's site indicated that the subject responded negatively when questioned about the use of rescue medication. At the end of the trial, Subject 115987 stated that she may have entered pain scores in the field for rescue medication for all her pain scores, and this may be the basis for this discrepancy. Because Dr. Soo apparently never checked the website to determine what was actually entered into the eDiary for rescue medication, and there is no documentation of the actual pain scores at the site, the data for pain scores and rescue medication for this subject are not reliable.

Issues Noted During Review of Monitoring Reports at the Sponsor's Inspection

In addition to the observations made during the FDA inspection of Dr. Soo's site, a review of monitoring records and copies of additional source documents reviewed during the sponsor inspection (see review of sponsor inspection below) have raised significant concerns with good clinical practice procedures and the integrity of data generated by this site. Particularly concerning are:

- issues related to recurring backdating of study documents by the CI and site staff, including on at least one occasion the dating of a document by the CI when he was out of the country
 - the completion of dose titrations for multiple subjects by site personnel who were not qualified by experience or training to perform this function
 - absence of source records to support the rationale for dose titrations for multiple subjects, or completion of these documents at a time remote from when the actual assessments purportedly occurred.
- c. **Assessment of data integrity:** FDA inspection of the clinical site documented instances where the clinical investigator failed to adequately document review of rescue medication use by subjects, as well as entry of pain scores into subjects' diaries on the eDiary website. Potentially six subjects of twelve for whom records were reviewed during the FDA inspection were inappropriately transitioned to the maintenance phase of the study. In addition, sponsor findings related to GCP noncompliance have raised significant concerns with data integrity at this site, which may require additional inspectional follow-up at the site. While the pending inspection of the CRO, [REDACTED] (b) (4), may shed additional light on the reliability of specific data points for some subjects enrolled at this site, given that significant concerns related to overall GCP noncompliance and data integrity have been raised, DSI recommends that data from this site be considered unreliable pending further investigation.

5. Ortho-McNeil-Janssen-Pharmaceuticals, Inc. Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
1125 Trenton-Harbourton Road, Titusville, N.J. 08560-0200

- a. **What was inspected:** This sponsor inspection was conducted to evaluate adequacy of the sponsor's regulatory compliance in the conduct of Protocol KF5503/23 (Grünenthal) aka Protocol R331333-PAI-3011 (J&JPRD) and Protocol KF5503/36 (Grünenthal) aka Protocol R331333-PAI-3015 (J&JPRD), studies submitted in support of this NDA application. The inspection reviewed the monitoring program, training program, sponsor-clinical site correspondence, IRB/informed consent, and drug accountability.

(b) (4)

- b. **General observations/commentary:** A Form FDA 483 was issued to the sponsor for violations concerning Protocol R331333-PAI-3011 (J&JPRD) including:
1. Failure to ensure proper monitoring of the study. Specifically for failing to ensure that post inspection correspondence was provided to sites that communicated outstanding issues that required resolution and failing to ensure that monitoring visit reports were completed according to the investigational plan.
 2. The sponsor did not ensure that investigators who were noncompliant with the investigational plan were brought promptly into compliance or terminated. Specifically, the sponsor did not ensure compliance of study conduct at the following sites:
 - a) Site #1460 (Soo)

For example, sponsor documents noted multiple concerns at Dr. Soo's site that were ongoing throughout the time the site was enrolling and that remained unresolved at site closure, including:

 - i. Lack of source documentation and lack of rationale for dose adjustments at the site.
 - a) Monitoring visit reports (MVR) described telephone notes without a contemporaneous date, that were found to have been added to the file with "backdating" to the date of the telephone conversation that occurred between the study coordinators and subjects. Examples of backdating were provided for Subjects 114520, 112969, 112876, 114798, and 114774.
 - b) MVRs document that there were no source records for dosing titrations for Subjects 115041, 115310, 115936, and 115987.
 - ii. Subjects that did not have a mean pain score of 5 or more based on pain scores 3 days prior to T1 were included in the maintenance phase of the study (Subjects 114377, 114643, 114774, 115731 and 115936).

- iii. For Subject 116091, the follow-up visit source was signed with the date of March 3, 2008, but Dr. Soo was out of the country on vacation at this time.
- iv. Backdating of documentation related to obtaining informed consents
- v. Discordant stop dates of concomitant medications.

Reviewer's Comments: Dr. Soo's site appears to have had significant GCP violations, including backdating of study documents, while the study was ongoing that were not resolved at the time of study closure.

b) Site #1478 (Whittington)

For example, sponsor documents note concerns at Dr. Whittington's site that were ongoing throughout the time the site was enrolling but appear to have been resolved at the time of study closure:

- i. eCRF and data entries were not being completed in a timely manner.
- ii. Issues with eDiary malfunctions leading to multiple delays by site staff in recording of pain scores and other efficacy endpoints into eDiaries. The extent of these issues and the significance is discussed in the Clinical Investigator section above.
- iii. Study drug administration source documentation was not completed in a timely manner.
- iv. Source documentation and CRF inconsistencies. These appear to have been resolved at the close of the study, including 2 adverse events of headache that were discovered during a site audit by the sponsor and submitted to the NDA in a "Post Issuing Note" to the clinical study report.

Reviewer's Comments: Although Dr. Whittington's site appears to have had several GCP violations while the study was ongoing, it appears that data integrity issues, except the issue of retrospective recall for pain scores, that, by its nature, cannot be resolved, were resolved at the time of study closure and that, with the exception of issues identified previously, data from this site may be considered reliable.

c) Site #1276 (Young)

For example, sponsor documents noted the following concerns at Dr. Young's site that appear to have been resolved at the time of study closure:

- i. Source documents were not reviewed by the clinical investigator.
- ii. Source documentation was lacking for dose titration.
- iii. Lack of documentation of review of adverse events and concomitant medications.

Reviewer's Comments: The monitoring reports indicated that these issues concerning Protocol KF5503/23 (R331333-PAI-3011) were resolved before the study was closed at this site. Although Dr. Young's site had numerous GCP violations while Protocol

KF5503/23 (R331333-PAI-3011) was ongoing, it appears that these were resolved at the time of study closure. However, as an inspection of Dr. Young's site was not conducted to evaluate the conduct of this pivotal study, data integrity recommendations cannot be made.

Note that DSI's complaint branch has been forwarded information related to information provided by the sponsor where they had substantial concerns with reliability of data for other studies that were not considered pivotal to the evaluation of this application and/or studies for other drug products. Their investigation is still pending.

3. Although not included as a Form FDA 483 observation, an additional concern based on the Applicant's response to an information request is that the data collected on the eDiary and archived by (b) (4) was sent to JNJ data management (JNJDM) rather than being sent directly to the clinical sites. JNJDM transferred the data to (b) (4) a CRO that prepared the CD for the clinical site. At this point, it is unclear as to the details of how JNJDM transferred the data to (b) (4), so the integrity of the data located at the clinical sites cannot be verified until an inspection of (b) (4) is conducted.
- c. **Assessment of data integrity:** Based on review of the Establishment Inspection Report for Protocol R331333-PAI-3011 (J&JPRD), it appears that the sponsor did not bring three sites into compliance in a timely manner or discontinue their participation in the study when indicated. This is most apparent at Dr. Soo's site. While the Applicant notified DSI of GCP issues at this site after submission of the NDA, based on the nature of the alleged violations at the site, DSI concurs that this site should have been closed during the course of the study when noncompliance persisted despite the study sponsor's attempts to implement corrective actions at the site. Regarding Dr. Whittington's site, multiple issues at the site were documented in monitoring reports while the study was ongoing, but it appears that monitors were able to successfully resolve issues prior to study closure (with the exception of issues related to retrospective recall for pain scores forced by technological problems with eDiary use, which by their nature cannot be resolved). At Dr. Young's site, issues identified by the sponsor monitors concerning lack of review of source documents, lack of review of adverse events, and lack of documentation for dose titration appear to have been resolved by the close of this study; however, without an onsite inspection by FDA, the sponsor's determination that the issues were resolved cannot be confirmed, and recommendations on data reliability cannot be made.

Because of concerns related to overall GCP noncompliance and data integrity that have been raised at Dr. Soo's site, DSI recommends that data from this site be considered unreliable pending further investigation. In respect to the data collected on the eDiaries, there are concerns that the CDs supplied to the

clinical site were not sent directly from (b) (4), but were sent from (b) (4) to the sponsor before being provided to the sites. The data will be inspected at (b) (4). At this juncture, definitive recommendations on the integrity of the data cannot be verified until the inspection of (b) (4) is conducted.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigator sites and a sponsor inspection were conducted in support of this NDA. A CRO inspection of (b) (4) is pending for verification of electronically captured primary efficacy source data.

For 1 of 4 clinical sites inspected, data reliability cannot be confirmed. The specific inspectional findings at Dr. Soo's site as well as inspection of documents related to his conduct of the study reviewed during the J&J inspection raise concerns as to the reliability of the data from this site. DSI recommends that the data from his site be removed from the efficacy analysis.

In general, for the remaining 3 clinical sites inspected (Drs. Amador, Whittington, and Wittmer), the studies appeared to have been conducted adequately. No pervasive issues were identified to significantly impact data reliability based on documents available at the 3 clinical sites and at J&J, the sponsor. However, for Dr. Whittington's site, the review division may wish to consider excluding the data or treating the values as missing where retrospective recall for pain scores occurred in a few subjects as described earlier.

Verification of electronically captured primary efficacy source data could not be performed at the CI sites and will be evaluated during the inspection of (b) (4). Final recommendations on data reliability are pending inspection of (b) (4) as primary efficacy data was directly transmitted to (b) (4).

Note:

The final classification for the inspection of Drs. Soo and the sponsor, Johnson and Johnson are pending as well as the inspection of (b) (4). An addendum to this clinical inspection summary will be forwarded to the review division when results for these inspections are available.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
09/28/2010

TEJASHRI S PUROHIT-SHETH
09/28/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: September 22, 2010

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

From: Mathilda Fienkeng – Regulatory Review Officer
Twyla Thompson – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 200553 NUCYNTA™ ER (tapentadol) extended-release tablets C-II

DDMAC has reviewed the proposed product labeling (PI), and Medication Guide for NUCYNTA™ ER (tapentadol) extended-release tablets (Nucynta), submitted for DDMAC review on January 22, 2010.

The following comments are provided using the updated proposed PI and Medication Guide sent via email on August 25, 2010 by Dominic Chiapperino. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

MATHILDA K FIENKENG
09/22/2010



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

Date: September 9, 2010

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

Through: Michael Klein, Ph.D., Director
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

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

Subject: **Name:** Nucynta ER (Tapentadol HCl extended-release)
NDA 200-533 (previous IND 61,345)
Indication: management of moderate to severe chronic pain in patients 18 years of age
Dosages: 50, 100, 150, 200, and 250 mg tablets for oral administration

Sponsor Ortho-McNeil c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Materials reviewed: NDA 200-533 (Dec 1, 2009) \\CDSESUB1\EVSPROD\NDA200533\200533.enx
CSS Consult: Sep 8, 2008
<http://darrrts.fda.gov:7777/darrrts/ViewDocument?documentId=090140af80106a0f>
NDA 022-304 <http://darrrts.fda.gov:7777/darrrts/viewEDR.do?suppDocId=3175759>
Tamper Resistant Formulation Properties Report (NDA 200-533: Mod 3.2.P.2 Pharmaceutical Development)
Report of post-marketing experience with NUCYNTA (Tapentadol) Immediate-Release from July 1, 2009 to Sep 30, 2009 (NDA 200-533: Mod 5.3.6 Postmarketing Surveillance Report)
Response to 09 March 2010 Clinical Review Team and the Controlled Substance Staff Request for Information
[\\CDSESUB1\EVSPROD\NDA200533\0005](http://CDSESUB1\EVSPROD\NDA200533\0005)
Consult OSE (May 25, 2010)
<http://darrrts.fda.gov:7777/darrrts/ViewDocument?documentId=090140af801d9178>
Biopharmaceutics Review (July 29, 2010)
<http://darrrts.fda.gov:7777/darrrts/ViewDocument?documentId=090140af801e6ae7>
Clin-Pharm Review (Aug 9, 2010)
<http://darrrts.fda.gov:7777/darrrts/ViewDocument?documentId=090140af801e9a57>
Discipline Review (Aug 5 2010)

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I. Summary

A. Background

This is our response to the DAAP consult regarding the abuse related safety issues, including overdose, withdrawal, misuse and abuse of Nucynta ER (Tapentadol Extended Release).

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 is not structurally similar to other opioids, such as morphine. Tapentadol immediate-release (NDA 022-304) was approved on Nov 20, 2008 for the indication of moderate to severe acute pain in patients age 18 or older. Tapentadol, the active pharmaceutical ingredient (API), is controlled in Schedule II of the Controlled Substances Act (CSA).

During drug development which consisted of 38 clinical studies (28 Phase 1 studies and 10 Phase 2/3 studies, including two in vitro in vivo correlation (IVIVC) models) three different formulations were used: PR1 was used in early Phase 1 and Phase 2 studies, PR2 was used in Phase 1 and Phase 3 studies, and the to-be-marketed product (TRF) was used in Phase 1 studies. Additionally, the TRF had two formulations 1) the pilot batches manufactured by GRT in Aachen, Germany, and 2) the TRF registered batches produced by J&JPRD in Beerse, Belgium, **(b4)**

→ The sponsor bridged the PR2 formulation (from Phase 3) to pilot, registration and the to-be-marketed batches of the TRF formulation using relative bioavailability and bioequivalence studies, as well as an in vitro/in vivo correlation (IVIVC). However, biopharmaceutics review found this bridging inadequate due to unacceptable re-constructed IVIVC models and requested in vivo BE studies (TBM TRF to Phase 3 PR2) for doses 50 mg and 250 mg and dissolution profiles for all doses in at least three media (Discipline Review from Aug 5 2010 and General Advice Letter from Aug 10 2010).

The to-be-marketed formulation was called the Tamper Resistant Formulation (TRF) during clinical development. In vitro studies describing the physiochemical characteristics of the TRF formulation are summarized in the Tamper Resistant Formulation Report. These studies show that the controlled release properties of the TRF formulation can be readily overcome by multiple simple physiochemical manipulations.

The sponsor analyzed abuse related terms in major/pivotal studies. Our review of this analysis suggests that the percentage of some withdrawal AEs, especially neuropsychiatric AEs such as insomnia, depressed mood, depression, suicidal ideation, disturbance in attention and restless leg syndrome, was higher in the Nucynta ER population than in the oxycodone CR population. This AE profile presumably reflects a partially different mechanism of action of Nucynta, in particular its activity as the reuptake inhibitor of norepinephrine. However, it raises some concerns regarding safety of the drug, and indicates the need for slow tapering of Nucynta ER after chronic use.

During this review cycle, post-marketing experience with Nucynta immediate-release showed an unexpectedly high rate of certain adverse events, such as hallucinations (8.1%), serotonin syndrome (3.5%), withdrawal syndrome (3.5 %) and convulsions (2.9%). [

_____] OSE is performing an ongoing review of the safety of Nucynta IR. (b4)

This AE profile was confirmed by OSE review (May 25, 2010) which evaluated the AERS database for Tapentadol IR (US: 169 and foreign 13) for the time period (Nov 20, 2008-May 25, 2010). For the US, psychiatric AEs comprised 81 cases (52%), including: hallucinations, 39 cases (25%), serotonin syndrome, 4 cases, (2.5%), suicidal ideation, 8 cases (5.1%), one suicide attempt, and one completed suicide.

B. Conclusions:

1. The controlled release properties of the TRF formulation can be readily overcome by multiple simple physiochemical manipulations. It is clear that simple physiochemical manipulations, [

_____] (b4)
Table 1 below.

2. The “to be marketed” formulation [also referred to as TRF] exhibits an increased frequency of abuse related adverse events. Data was provided for a variety of different formulations and the various formulations appear to differ somewhat in regards to pharmacokinetic parameters and abuse related adverse events. Our focus is on the “to be marketed” formulations currently identified as TRF.
 - In Phase 1 study in healthy subjects (R331333-PAI-1028), 50% of the subjects exhibited euphoria at 250 mg.
 - In the pooled AE analysis of Phase 1 single-dose studies, 5.5% of subjects exhibited euphoria, and 8.1% subjects reported “feeling drunk” as compared to 1% and 0% subjects taking other ER formulations, respectively.
 - Concomitant alcohol use appears to result in increased Cmax and AUC of tapentadol. Changes in pharmacokinetic parameters in the TRF formulation could affect the abuse potential of the drug product.
3. Withdrawal symptoms, including insomnia, depressed mood, depression, suicidal ideation, and disturbance in attention, occurred after tapentadol ER was stopped. Such withdrawal symptoms are typical of all mu opioids.

C. Recommendations

1. The sponsor must provide information and explanations of the PK and AE differences noted in the clinical trials using TRF and other ER formulations, because of pooled data that encompasses all formulations that were investigated. Linkage of the PK/PD data for the various formulations is needed.
2. Because the drug product at the 250 mg dose level appears to result in a high percentage of euphoria and other Opioid like adverse events, the sponsor must provide an adequate rationale for marketing the dose, so that the benefits continue to outweigh the risks.
3. Upon approval and marketing, the drug product should continue to be monitored for abuse, misuse, overdose, and withdrawal.

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200533

ORIG-1

ORTHO MCNEIL
JANSSEN
PHARMACEUTICA
LS INC

TAPENTADOL

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/s/

ALICJA LERNER
09/09/2010

LORI A LOVE
09/09/2010

MICHAEL KLEIN
09/10/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 24, 2010

To: Bob A. Rappaport, M.D, Director
Division of Anesthesia and Analgesia Products (DAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Steve L. Morin RN, BSN
Patient Labeling Reviewer
Division of Risk Management

Subject: Deferral Memo for Review of Patient Labeling (Medication Guide),

Drug Name(s): Nucynta®ER (tapentadol)

Application Type/Number: NDA 200533

Applicant/sponsor: Ortho-McNeil-Janssen Pharmaceuticals, Inc..

OSE RCM #: 2009-2414

The Division of Anesthesia and Analgesia Products (DAAP) requested that the Division of Risk Management (DRISK) review the Applicant's proposed Medication Guide (MG) for New Drug Application NDA 200533 submitted by Ortho-McNeil-Janssen Pharmaceuticals, Inc. for Nucynta®ER (tapentadol).

This REMS was addressed by the DRISK review dated August 6, 2010; however, DAAP has determined that a Complete Response will be issued this cycle. Therefore, DRISK will defer comment on the sponsor's proposed MG at this time. A final discussion on the appropriate risk management strategy will be undertaken after the sponsor submits a satisfactory response to the Complete Response action letter.

Please send us a new consult request at that time. This memo serves to close-out the consult request for Nucynta®ER (tapentadol) NDA 200533.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

STEVE L MORIN
08/24/2010

LASHAWN M GRIFFITHS
08/24/2010

DSI CONSULT: Request for Clinical Inspections for the Original NDA for Tapentadol ER

Date: January 21, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan Leibenhaut, M.D., Medical Officer, GCP2
Division of Scientific Investigations (DSI), HFD-45, Office of Compliance/CDER

Through: Eric Brodsky, M.D., Medical Officer, Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Sarah Okada, M.D., Cross Discipline Team Leader (CDTL), DAARP

From: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAARP

Subject: **Request for 3 Clinical Site Inspections**

I. General Information

Application#: NDA 200533
Product: Tapentadol ER (NUCYNTA ER)
Sponsor: Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI),
Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD)

Sponsor contact information: Kathleen Dusek, R.Ph., RAC, Associate Director, Regulatory Affairs, (609) 730-2719 or Peggy Ferrone at (908) 704-5116

NME: No
Review Priority (Standard or Priority): Standard
Study Population: Patients with chronic pain due to knee osteoarthritis, low back pain, and peripheral diabetic neuropathy

Proposed Indication: "Management of moderate to severe chronic pain in patients 18 years or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time"

Study Population includes < 17 years of age: No
Is this for Pediatric Exclusivity: No
PDUFA Goal Date: October 1, 2010
Action Goal Date: October 1, 2010
Inspection Summary Goal Date: August 1, 2010

II. Background Information

Johnson and Johnson submitted an original NDA for tapentadol extended release tablets (NUCYNTA ER), a long-acting opioid agonist for the “management of moderate to severe **chronic pain** in patients 18 years or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.” Tapentadol (NUCYNTA), an immediate release formulation of tapentadol was approved in November 2008 and marketed in June 2009 for the treatment of “moderate to severe **acute pain** in patients 18 years of age or older.”

This application contains 38 studies of tapentadol ER including 4 Phase 3 efficacy/safety trials (Studies KF11, KF12, KF23, and KF36) shown in Table 1. Studies KF11, KF12, and KF23 were randomized, double-blind, parallel-group, placebo-controlled and active-controlled trials and the primary efficacy endpoint was the change from baseline in the mean pain intensity (based on an 11-point numerical rating scale) over the last week of the maintenance period between the tapentadol ER and placebo groups. Study KF36 was a randomized withdrawal trial and the primary efficacy endpoint was the change from baseline (start of the double-blind period) in mean pain intensity (11-point numerical rating scale) over the last week of maintenance period. In Studies KF11, KF23, and KF36, the overwhelming majority of patients were treated at U.S. sites; whereas, in Study KF12 all patients were treated at 12 European countries (see Table 1).

According to Johnson and Johnson, tapentadol ER demonstrated a statistically significant treatment effect for the primary efficacy endpoint compared to placebo in Studies KF11, KF23, and KF36 (the 3 trials with an overwhelming majority of U.S. patients). There were no sites that comprised more than 5% of the treated study population in each trial. According to Johnson and Johnson, tapentadol ER failed to demonstrate a statistically significant treatment effect for the primary efficacy endpoint compared to placebo in Study KF12 (the European trial).

Table 1: Design and clinical sites in four Phase 3 efficacy/safety trials of tapentadol ER in patients with moderate to severe chronic pain					
Study ¹	Sites ²			Population	Treatment Groups
	Country	# of Sites	# of Patients ²		
Phase 3: Parallel-Group, Placebo and Active Controlled Trials (3 weeks titration followed by 12 weeks of maintenance)					
KF11	U.S.	87	795	Knee OA	Tapentadol ER (n=344) Oxycodone CR (n=342) Placebo (n=337)
	Canada	15	176		
	New Zealand	6	28		
	Australia	4	24		
KF12	12 European countries ³			Knee OA	Tapentadol ER (n=319) Oxycodone CR (n=331) Placebo (n=337)
KF23	U.S.	86	796	Chronic LBP	Tapentadol ER (n=318) Oxycodone CR (n=328) Placebo (n=319)
	Canada	15	153		
	Australia	3	9		
Phase 3: Randomized Withdrawal Trial (3 week open-label titration then 12 week randomized, double-blind withdrawal)					
KF36 ⁴	U.S.	78	380	Diabetic Peripheral Neuropathy	Tapentadol ER (n=196) Placebo (n=193)
	Canada	5	9		

NRS = numerical rating scale

- 1 Studies KF11, KF12, KF23, and KF36 are abbreviations for Studies KF5503/11 (R331333-PAI-3008), KF5503/12 (R331333-PAI-3009), KF5503/23 (R331333-PAI-3011), and KF5503/36 (R331333-PAI-3015), respectively. Note each study has two numbers (the first number represents Grünenthal GmbH's designation and the second number represents Johnson and Johnson's designation). Grünenthal GmbH is a German pharmaceutical company that has a license agreement with Johnson and Johnson for tapentadol ER.
- 2 Sites in which patients were treated with at least one dose of study medication. The number of patients listed included only patients who were treated.
- 3 The 12 European countries were Austria, Croatia, Germany, Hungary, Latvia, Poland, Portugal, Romania, Slovakia, Spain, the Netherlands, and the United Kingdom
4. The listed sites are those that had treated patients in the randomized withdrawal period in Study K36. In Study K36, there were 578 and 13 patients who received at least one dose of study medication in the open-label, run-in phase in the U.S. and Canada, respectively,.

III. Protocol/Site Identification

See Table 2 for DAARP’s 3 requested U.S. sites to be audited.

Table 2: Requested U.S. sites to be audited in Studies KF23 and KF36¹						
Site #	Principle Investigator Contact Information	Protocol ID ¹	# of Patients			Population
			Random-ized ²	Treated with Tapentadol	U.Treated with Placebo	
Site 49	Pamela Amador, M.D., Gables Research 85 Grand Canal Drive, # 400, Miami, FL 33144, USA	KF36	16	7	9	Patients with moderate to severe chronic pain due to peripheral diabetic neuropathy
Site 1477	Bret Wittmer, M.D. Commonwealth Biomedical Research LLC 240 East Ayr Parkway Madisonville, KY 42431, USA	KF23	27	11	9	Patients with moderate to severe chronic low back pain
Site 1460	Allan Soo, M.D. Premiere Pharmaceutical Research, LLC 3316 S. McClintock Drive Tempe, AZ 85282, USA	KF23	32	9	9	Patients with moderate to severe chronic low back pain

1 Studies KF23 and KF36 are abbreviations for Studies KF5503/23 (R331333-PAI-3011) and KF5503/36 (R331333-PAI-3015), respectively.

2 Randomized patients includes patients not treated with any dose of study medication and patients treated with tapentadol ER, placebo, or the active control (i.e., oxycodone CR).

IV. Site Selection/Rationale

The purpose of this consult is to audit and verify the integrity of clinical trial data submitted to NDA 200533 to support the efficacy and safety of tapentadol ER for the management of moderate to severe chronic pain. Three U.S. sites (2 sites in Study K23 and 1 site in Study K36) are requested for inspection. No foreign sites are requested.

Site 49 in Study K36 was selected because tapentadol ER had a large treatment effect in patients at Site 49 compared to the other sites. If the efficacy data from Site 49 were disregarded, tapentadol ER would still demonstrate significant treatment effects over placebo in the treatment of chronic pain in Study K36, although the overall treatment effect of tapentadol ER compared to placebo would be reduced. Additionally, Site 49 treated the highest number of patients in the randomized withdrawal portion of Study KF36 (the portion of the trial that served as the primary support for efficacy).

Sites 1477 and 1460 in Study K23 were selected because they were high enrollers and tapentadol ER had greater treatment effects at these sites compared to the other sites. However, if the efficacy data from either of these sites were disregarded, there would be no change in the overall treatment effect of tapentadol ER in Study K23. Additionally, these sites were chosen because according to DSI these investigators have performed multiple clinical studies under INDs but have not been inspected by the FDA.

In the pivotal trials of tapentadol ER, there were no investigators — who enrolled patients — who had a potential conflict of interest. Also at this time, there is no evidence that the data in the pivotal trials is fraudulent (e.g., the efficacy appears to be similar to other chronic opioids in the treatment of chronic pain and common opioid-associated AEs were reported in the NDA).

Reasons for the 3 selected domestic (U.S.) clinical trial site inspections are the following (bolded and marked with an “X”):

Enrollment of large numbers of study subjects: Sites 49, 1477, and 1460

High treatment responders: Site 49

Significant primary efficacy results pertinent to decision-making

There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

Other (specify): Sites 1477 and 1460. According to DSI, these principle investigators have enrolled patients in several studies under IND; however, they have never been inspected before.

Should you require any additional information, please contact Eric Brodsky (the medical officer) at 301-796-0855.

Concurrence: (as needed)

Eric Brodsky, M.D., Medical Reviewer

Sarah Okada, M.D., Cross Discipline Team Leader

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	NUCYNTA ER Tablets (Tapentadol Hcl) 50mg, 100mg, 150mg, 200mg, 250mg

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/s/

DOMINIC CHIAPPERINO
01/21/2010