

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200533Orig1s000

SUMMARY REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

Summary Review for Regulatory Action

Date	August 25, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	200533 Class 2 Resubmission
Applicant Name	Johnson & Johnson Pharmaceutical Research and Development, LLC on behalf of Janssen Pharmaceuticals, Inc.
Date of Submission	February 28, 2011
PDUFA Goal Date	August 26, 2011
Proprietary Name / Established (USAN) Name	Nucynta ER Tapentadol
Dosage Forms / Strength	50 mg, 100 mg, 150 mg, 200 mg and 250 mg extended-release tablets
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
Action:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
CDTL	Ellen Fields, MD, MPH
Medical Officer Review	Elizabeth Kilgore, MD
CSS	Alicja Lerner, MD, PhD, PhD/Michael Klein, PhD
ONDQA-Biopharmaceutics Review	Sandra Suarez-Sharp, PhD/Angelica Dorantes, PhD/Patrick J. Marroum, PhD
Clinical Pharmacology Review	David Lee, PhD/Yun Xu, PhD
DDMAC	Mathilda Fienkeng, PharmD, Twyla Thompson
OSI	(analytical site): Arindam Dasgupta, PhD/ Martin K. Yau, PhD (clinical site): Susan Liebenhaut, MD/Tejashri Purohit-Sheth, MD
Project Management	Dominic Chiapparino, PhD/Parinda Jani
OSE/DMEPA (C&C)	Jibril Abdus-Samad, PharmD/Todd Bridges, RPh/Carol Holquist, RPh
OSE/DMEPA (Trade Name)	Jibril Abdus-Samad, PharmD/Todd Bridges, RPh/Carol Holquist, RPh
OSE/DRISK	Cynthia LaCivita, PharmD / Doris Auth, PharmD/ Sharon R. Mills, BSN, RN, CCRP/ Barbara Fuller, RN, MSN, CWOCN/ LaShawn Griffiths, RN, MSHS-PH, BSN /Claudia Karwoski, Pharm.D.

OND=Office of New Drugs
 CDTL=Cross Discipline Team Leader
 CSS=Controlled Substance Staff
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 OSI=Office of Scientific Investigations

1. Introduction

Tapentadol is a centrally-acting analgesic which combines mu-receptor opioid agonist activity with inhibition of norepinephrine reuptake. It is pharmacologically similar to tramadol. Nucynta ER is an extended-release (ER) formulation of tapentadol and the proposed indication is “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 standard indication for ER opioid products. The application for immediate-release (IR) tapentadol, Nucynta, received approval for marketing “for the relief of moderate to severe acute pain in patients 18 years or older” on November 20, 2008.

2. Background

The original application for Nucynta ER was submitted on November 30, 2009. Dr. Rigoberto Roca, Deputy Director of the Division of Anesthesia, Analgesia, and Addiction Products, was the signatory authority for that submission. His review and summary basis for a complete response action is appended to this review. While the review team for the first-cycle submission found that there was substantial evidence to support the safety and efficacy of the product, a complete response action was taken due to the deficiencies described in the following excerpt from the Complete Response (CR) Letter, issued on October 1, 2010:

PRODUCT QUALITY/BIOPHARMACEUTICS

1. Your proposed in vitro in vivo correlation (IVIVC) models do not support the bridging of the clinical study batches (PR2) to the to-be-marketed tamper resistant formulation (TBM TRF).
2. The re-constructed IVIVC models using individual plasma concentrations are not acceptable for the following reasons:
 - The models submitted on July 23, 2010, still include a mathematical term that has no mechanistic foundation and, therefore, are not acceptable.
 - The models using the individual subject concentrations failed the external validation, indicating a lack of robustness.
3. The proposed dissolution acceptance criteria for TBM TRF tapentadol ER tablets were based on the proposed IVIVC models. Because these models were not accepted, these dissolution acceptance criteria will need to be revised. You may refer to our advice letter dated August 12, 2010, for additional guidance concerning these acceptance criteria.
4. Given that your proposed IVIVC models do not support the bridging of the clinical study batches to the TBM TRF, bioequivalence has not been demonstrated. Provide in vivo bioequivalence (BE) data comparing the PR2 and TBM TRF formulations. Because the compositions of your formulations are not proportional, you should provide bioequivalence (BE) data for the lowest, 50 mg, and highest, 250 mg,

NDA 200533
Nucynta ER

Division Director's Review and Summary Basis for Approval
August 25, 2011

3

strengths. You may request a biowaiver for the intermediate strengths. The biowaiver request should be supported with: 1) acceptable in vivo BE data for the lowest and highest strengths and 2) in vitro comparative dissolution profile data and similar f2 values (using the highest and lowest strengths as references).

CLINICAL

5. For Protocols KF5503/23 and KF5503/36, data pertaining to subject eligibility, primary endpoint, and rescue medication use were directly submitted by subjects via eDiaries to eTrials, the contract research organization (CRO) responsible for this electronic data capture. Because the clinical investigator sites did not maintain independent source documentation of the data that were transmitted directly to eTrials via eDiaries, verification of source data at the CRO, in conjunction with evaluation of findings from other completed inspections, is required before this application may be approved.

The Applicant submitted this response to the CR Letter issued on October 1, 2010. This review will focus only on the new data and information submitted to address the deficiencies in the CR Letter. The reader is referred to Dr. Roca's first-cycle summary review, which has been appended to this review, for discussion of the data from the original submission supporting the efficacy and safety of Nucynta ER.

In this submission, rather than attempt to reconstruct their IVIVC model, the Applicant has provided the results of new bioequivalence studies between their Phase 3 PR2 tablets and the to-be-marketed formulation, to support the bridging of the strengths (150 mg and 200 mg) which they had originally proposed to cover with the IVIVC model. In addition, inspections of the CRO and the additional clinical pharmacology studies were performed by OSI during this review cycle to address the approvability issues in Item 5 of the CR Letter.

A post-action meeting was held with the Applicant on November 9, 2010. At that meeting, two additional concerns were raised by the clinical review team. First, the fact that the to-be-marketed 50 mg tablet was not bioequivalent to the 50 mg PR2 tablet had been noted upon review of the meeting package submitted by the Applicant for the post-action meeting. During the meeting, the Applicant was asked to provide data or a rationale in their response to the CR Letter to justify the use of multiple 50 mg tablets in place of a tablet of a higher dose. The information that they have submitted to address this concern is discussed in Section 5 below. Second, the formulation of the Nucynta ER tablets contains polyethylene oxide (b) (4)

However, polyethylene oxide is an excipient that, in certain approved products, has been associated with swelling and stickiness upon contact with saliva or water, at times resulting in serious adverse events including choking, some requiring medical intervention. As such, the Applicant was asked to

fully explore this concern in their response to the CR letter with appropriate analyses of their safety data. Those explorations were included in this submission.

During this review cycle, Dr. Lerner raised a number of concerns based on her review of the clinical pharmacology study results. The clinical pharmacology and clinical review teams disagreed with Dr. Lerner's conclusions and the matter was raised to the Division Director level for adjudication. Dr. Klein, Dr. Chandrahas Sahajwalla (Division Director in the Office of Clinical Pharmacology) and I discussed the issues raised by the reviewers and determined that Dr. Lerner's conclusions and recommendations were not consistent with the data, and Dr. Klein wrote a supervisory memo rescinding her recommendations. See Section 11 for further discussion.

3. CMC

See appendix.

4. Nonclinical Pharmacology/Toxicology

See appendix.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the new clinical pharmacology data submitted in this response to the CR Letter has been reproduced from pages 5 through 8 of Dr. Fields' review:

BE studies were conducted comparing all strengths of the TRF [tamper-resistant formulation] formulation (50mg, 100mg, 150mg, 200mg, and 250mg) with the PR2 formulation used in the Phase 3 studies. All strengths except the 50mg strength were demonstrated to be bioequivalent. You are referred to Dr. Lee's review for details regarding the studies of the 100mg, 150mg, 200mg, and 250mg.

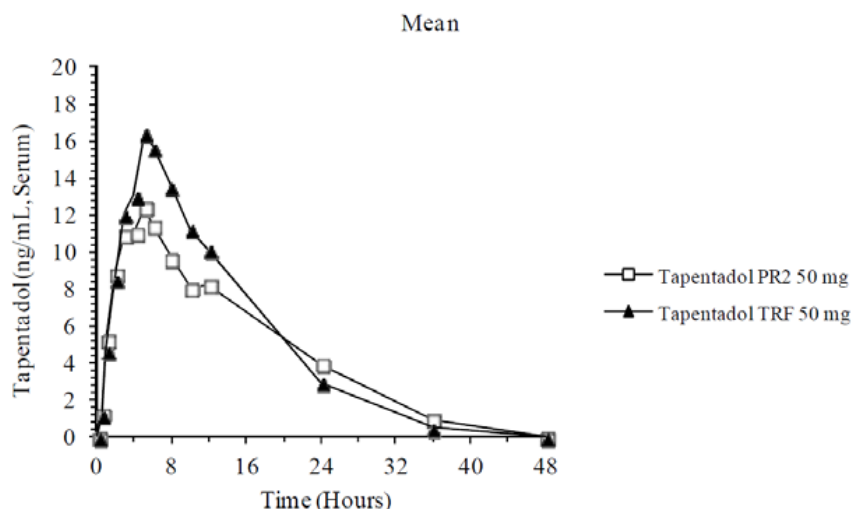
The results of the study assessing the bioequivalence of the 50mg tablet are of interest because bioequivalence was not demonstrated, and this raises concern regarding the use of the 50mg tablet. As stated in Dr. Lee's review:

“Study HP5503/82 evaluated tapentadol 50 mg tablets. Sixty-four subjects (32 men and 32 women) were enrolled for the study. The batch numbers for test (TRF 50-mg tablet) and reference (PR2 50-mg tablet) products were 9EG9279-X and PD3137, respectively. Subjects were excluded from bioequivalence analyses if they did not complete both treatments and vomited anytime during the treatments. The mean serum concentration-time profiles were somewhat dissimilar between two formulations.

The mean serum concentration-time profiles for 50 mg tablets are shown in the table below:

NDA 200533
Nucynta ER

Division Director's Review and Summary Basis for Approval
August 25, 2011



The tapentadol pharmacokinetic parameters and a summary of statistical results are presented below:

Summary Statistics on the Pharmacokinetic Parameters of Tapentadol
(Study HP5503/82: Pharmacokinetic Data Analysis Set)

PK Parameter	N	Tapentadol	Tapentadol	Ratio	90% CI	%CV
		TRF 50 mg	PR2 50 mg			
		LSM	LSM			
C_{max} , ng/mL	60	16.04	12.41	129.26	123.46 - 135.34	15.1
AUC_{last} , ng-h/mL	60	224.72	204.22	110.04	105.66 - 114.60	13.4
AUC_{∞} , ng-h/mL	59	233.41	214.32	108.91	104.42 - 113.58	13.7

CI = confidence interval, %CV = % coefficient of variation, LSM = least squares mean

N = number of subjects included in the inferential statistical analysis

TRF = tamper-resistant formulation (to-be-marketed formulation)

PR2 = prolonged release formulation 2 (used in the Phase 3 studies)

The corresponding 90% CI for AUC values were within the 80% to 125% range, but, not for the Cmax. Thus, the two formulations are not bioequivalent. However, 50 mg dose will be strictly used for a titration purpose. Therefore, the result is considered acceptable after discussion with the clinical team."

As stated in Dr. Lee's review, the lack of bioequivalence between the two formulations based on the higher Cmax for the TRF formulation does not represent a safety concern because the Cmax is only approximately 30% higher, and because the 50mg is intended to be used only during titration.

Dr. Lee also addressed the issue of the interchangeability of the 50mg tablets if they are administered as multiple units to achieve a particular dose instead of administering the higher dose unit. The following is taken from Dr. Lee's review:

The cross-study dose linearity assessment indicated that tapentadol 50 mg Cmax and AUC∞ values are in line with higher doses and do not expect to provide greater exposure when a smaller-dose unit is administered as multiple units. The observed serum tapentadol concentrations following administration of a particular dose as combinations of 50-mg and 100-mg TRF tablets, e.g., 200 mg: two 100 mg tablets or two 50 mg and one 100 mg tablets, in a Phase 3 study PAI-3027/KF56 were within the 90 percent confidence interval established by the population pharmacokinetic model. However, the

NDA 200533

Nucynta ER

Division Director's Review and Summary Basis for Approval

August 25, 2011

observed data do not provide a robust comparison, e.g., five units of 50 mg tablets compared to a single unit of 250 mg tablet, and can not be used as a strong supportive argument in the comparability discussion. In all, the results from the linearity assessment and the supportive information from the observed Phase 3 trial indicate that patients would not be at risk for over-exposure to tapentadol if multiple tablets are administered.

Food Effect

The determination regarding a food effect for tapentadol ER was made during the first cycle review, and the conclusion was that there is not a food effect for the to-be-marketed formulation based on a standard food effect study conducted in the United States. During her review of the complete response application, Dr. Alicja Lerner of the Controlled Substance Staff reviewed another food effect study conducted in Japan that was included in the complete response submission, and concluded that there is a food effect. Dr. Lee had the following comments in his clinical pharmacology review relative to the Japanese study:

“.....a cursory review was conducted for Study HP5503/51, a food effect study (with a ‘standard Japanese meal - total calories are approximately 700 - 800 kcal; percentages of energy of contents of meal are: carbohydrate 50-70%, protein less than 20%, lipid 20-30%) with 100 mg TRF ER formulation Japanese healthy men (n=12). (b) (4)

This study was reviewed briefly since TRF ER formulation was utilized. The results indicated that the geometric means for C_{max} and AUC of tapentadol under fed conditions were approximately 54 and 12% higher compared to under fasted conditions. The observed arithmetic mean C_{max} and AUC values for fed and fasted conditions were 65.7 and 42.8 ng/mL, and, 585 and 520 ng-h/mL, respectively. The provided information was considered not to be critical for this application simply because this study utilized a ‘standard Japanese meal’, not an Agency’s recommended high-fat meal, and, the fact that the studied population does not represent the population majority in the US. Additionally, the high-fat food effect information was assessed in the original NDA submission, and, that study was considered as a pivotal food effect study; in that assessment, the AUC and C_{max} increased by 6% and 17%, respectively, when TRF ER tablets were administered after a high-fat meal. The t_{max} was prolonged by about 1 hour with a median t_{max} of 6.00 hours (range: 2.98-12.0 hours) in the fed state and 5 hours (range: 2.00-12.0 hours) in the fasted state. In Phase 3 studies, tapentadol ER tablets were also administered without restriction to food. Therefore, we recommend that tapentadol ER tablets may be taken without restriction to food.”

The Division’s conclusion regarding the food effect studies is that the results of the standard food effect study reviewed by the Clinical Pharmacology team provide adequate evidence of a lack of food effect for tapentadol ER, and that while the study conducted in Japan did show an effect of food, the interpretation of the study is limited due to the fact that the meal administered during the study was not the standard meal for US studies, and the study population did not represent the US population as a whole. The clinical studies demonstrated that taking tapentadol ER without regard to food did not result in safety concerns. The labeling for tapentadol ER will reflect that it may be taken without regard to food intake.

Biopharmaceutics

Since the Applicant conducted five BE studies linking all of the proposed strengths, the biowaiver request for the intermediate strengths was no longer required. The Applicant did submit dissolution specifications for all strengths of tapentadol ER tablets which were agreed upon with the biopharmaceutics team. The dissolution specifications were based on the mean dissolution profiles for data from registration stability batches, commercial

site stability batches, and clinical (pivotal BE) batches, and were deemed acceptable from the biopharmaceutics perspective.

According to the Clinical Pharmacology and Biopharmaceutics review teams, there are no issues that preclude approval for tapentadol ER tablets at this time.

I concur with the review team that the Applicant has provided adequate data to resolve the concerns related to the dissolution specifications for Nucynta ER. I also concur that the small increase in C_{max} seen with the 50 mg tablets is not clinically relevant and that there are adequate data to support that the product may be taken with or without food without concern for an increased risk of toxicity.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

See appendix.

8. Safety

The following summary of the updated safety data submitted in this response to the CR Letter has been reproduced from pages 8 and 9 of Dr. Fields' review:

The original NDA submission included safety data on more than 4,000 subjects who received tapentadol ER in 38 clinical studies. In this submission the Sponsor included safety data collected since the cut-off date for the 4-month safety update in the original NDA submission, October 1, 2009. This consisted of unblinded data on 1,700 study subjects from eight completed Phase 1 studies, and three completed Phase 2 and 3 studies. Additional data was submitted for 11 ongoing Phase 2 and 3 studies that included only numbers of deaths and serious adverse events. Phase 2 and 3 studies were conducted in patients with chronic pain due to osteoarthritis, chronic low back pain, cancer, postherpetic neuralgia, and diabetic peripheral neuropathy.

The updated safety profile of tapentadol ER as reviewed by Dr. Kilgore is consistent with that noted during the first cycle review. There were no new or concerning safety signals detected during her review. The review of laboratory tests, ECG findings, and vital sign measurements did not indicate any potential clinically relevant safety concerns. There were no new deaths reported for the completed studies, and the SAEs reported in the update did not lead to concern regarding any new safety issues. The most frequently reported treatment emergent adverse events (TEAEs) in this update included gastrointestinal and nervous system disorders such as nausea, constipation, headache, and somnolence, which is consistent with the findings from the first cycle review.

The following additional summary evaluation has been reproduced from pages 10 and 11 of Dr. Fields' review:

Regarding the safety of the TRF tablets in terms of choking and sticking, the Applicant has stated that there were no Product Quality Complaints submitted for the Phase 1 and Phase 3 studies showing difficulty swallowing the TRF tablets, and there were no TEAEs that would suggest difficulty swallowing the tapentadol TRF tablets in the 845 subjects who took tapentadol TRF in the Phase 1 and Phase 3 studies. Dr. Kilgore also reviewed the adverse event data from studies utilizing the TRF formulation and did not detect any events likely associated with the tablets swelling or sticking in the throat or GI tract. This information appears adequate to address the choking/sticking issue from a premarketing perspective. The product label will include instructions to take one tablet at a time with adequate water to avoid choking or sticking, and the Applicant will be required to report to the Agency adverse events related to the stickiness of the tablets as 15-day expedited safety reports. If a safety signal appears in this regard during the postmarketing period, additional steps may be taken.

Since the CR Action for this NDA, the required New Molecular Entity Post Marketing Evaluation (915 review) for Nucynta (NDA 22-304) was completed by OSE and DAAAP on November 22, 2010. As noted in this review, a Tracked Safety Application (TSI) was opened in May, 2010 to investigate events that may represent new safety signals for Nucynta as reported in Periodic Safety Reports to the Agency. These included events of hallucination, suicidal ideation, angioedema, and headache, and a higher than expected number of reports of seizure and serotonin syndrome (SS), that were included in the class labeling for tramadol and tapentadol products, but had not occurred during the clinical trials. Of note, it appears that the reports of serotonin syndrome included concomitant medications that would increase the SS risk. The following conclusions and recommendations were made:

- Hallucination and seizure are adequately described in revised Nucynta labeling of 11/1/10.
- Reports of headache have likely been confounded by underlying medical conditions, and routing postmarketing surveillance for these events should be continued.
- Serotonin syndrome, suicidal ideation, angioedema and palpitations should be added to the Nucynta label as postmarketing events.
- The Nucynta ER label will also reflect the above issues.

9. Advisory Committee Meeting

As this was a reformulation of an approved opioid and as the Agency has already received sufficient advice from our advisory committee on the development of (b) (4) opioid formulations, this application was not taken to an advisory committee for discussion.

10. Pediatrics

The following summary of the pediatric study requirements has been reproduced from pages 11 and 12 of Dr. Fields' review:

NDA 200533
Nucynta ER

Division Director's Review and Summary Basis for Approval
August 25, 2011

The pediatric study requirements for drug products intended to treat chronic pain include studies in pediatric patients ages 7 to <17 years of age. Studies in patients under the age of 7 years are not required, since the population of pediatric patients with chronic pain in this age group is too small to study. The types of studies required include those assessing efficacy, safety, and pharmacokinetics. Although the Division's current policy includes extrapolation of efficacy from adults to pediatric patients two years and older for opioids, tapentadol is not a pure mu-opioid agonist, having the additional mechanism of action related to norepinephrine reuptake inhibition. For products such as this, that currently include tramadol and tapentadol, efficacy may not be extrapolated from findings in adults.

The Sponsor submitted a pediatric plan that included a waiver request for pediatric patients under 7 years, and a deferral request for pharmacokinetic, efficacy, and safety studies in patients ages 7-<17 years, with the appropriate justifications. A timeline was submitted as shown below:

- Final protocol submission to Agency: May 28, 2014
- Study completion date: October 31, 2017
- Study report submission to Agency: March 26, 2018

The Sponsor's rationale for the study start date (three years from now) is that the determination of dosing in pediatric patients for tapentadol ER is dependent in part on the results of the PK studies of the IR formulation in pediatric patients.

The pediatric plan was presented to the Pediatric Research Committee (PeRC) on July 6, 2011, and was found acceptable by the Committee.

11. Other Relevant Regulatory Issues

The following summary reproduced from pages 12 through 15 of Dr. Fields' review, addresses the concerns raised by Dr. Lerner, mentioned above in Section 2:

Dr. Alicja Lerner of the Controlled Substance Staff (CSS), with secondary concurrence from Michael Klein, Ph.D., filed two reviews for this NDA in order to address abuse-related safety issues, one during the first cycle dated September 9, 2010, and another during the current review cycle, dated July 12, 2011. The issues in the September, 2010 review were not addressed by the first cycle review team, and were deferred for internal discussion during the subsequent review cycle.

The conclusions from Dr. Lerner's first cycle review are summarized as follows:

1. The controlled-release properties of the purported tamper-resistant formulation can be readily overcome by multiple simple physiochemical manipulations.
2. The to-be-marketed formulation exhibits an increased frequency of abuse-related adverse events.
3. Withdrawal symptoms, including insomnia, depressed mood, depression, suicidal ideation, and disturbance in attention, occurred after the extended-release formulation tapentadol was stopped. They noted that such withdrawal symptoms are typical of all μ -opioid receptor agonists.

The CSS recommendations based on these conclusions are:

1. The Sponsor must provide information and explanations of the pharmacokinetic and adverse event differences noted in the clinical trials using the tamper-resistant formulation and other extended-release formulations, because of pooled data that encompasses all formulations that were investigated. Linkage of the pharmacokinetic/pharmacodynamic 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.

Additional conclusions from the current cycle CSS review are summarized here:

1. Review of the bioequivalence studies submitted during the second cycle with the TRF formulation indicates a possible gender effect, with nervous system, gastrointestinal and psychiatric adverse events occurring in females up to 8-12 times more frequently than in males.
2. Withdrawal symptoms occurred after Nucynta ER administration was stopped. The occurrence of withdrawal symptoms indicates development of dependency and a need to slowly taper when discontinuing the drug.
3. Co-administration of tapentadol TRF with meals and alcohol resulted in increases in Cmax and AUC's.
4. Pharmacodynamic effects of tapentadol TRF formulation are potentiated after intake with alcohol, not food.

CSS recommendations based on the above conclusions are:

1. Include appropriate warning language in the label regarding susceptibility of females to development of adverse events. The extent of the relation of gender to adverse events should be further examined.
2. All planned and ongoing clinical trials should include prospective assessment of suicidality, due to the appearance of suicidality in the post-marketing phase of Nucynta.

The Division conducted extensive internal discussion regarding the CSS conclusions and recommendations from the two reviews, and had concerns regarding the following issues:

1. Dr. Lerner expressed concern that the to-be-marketed formulation of tapentadol had more abuse-related adverse events than other formulations studied, and the Applicant should provide linkage for the PK/PD data for all formulations studied.

The Division determined that since bioequivalence studies submitted with the Complete Response demonstrated a pharmacokinetic link between the previous formulations and the to-be-marketed formulations, this no longer represents a safety concern.

2. The Applicant should provide a rationale for marketing the 250mg dose because there was an increased incidence of euphoria seen in patients receiving 250mg.

The Division noted that the above conclusion was based on results of Phase 1 studies, where healthy study subjects are given doses of tapentadol ER without titration. It is expected that higher doses would result in more abuse and opioid-related adverse events.¹ It is therefore not necessary that the Applicant provide an explanation for this finding.

¹ Abuse potential assessments often consider responses from healthy subjects at supratherapeutic doses.

3. Co-administration of tapentadol TRF with meals and alcohol resulted in increases in C_{max} and AUC's

Dr. Lerner implied in her review that there is a significant food effect for tapentadol TRF, based on her review of a food effect study conducted in Japan, in contrast to the conclusion made by the clinical pharmacology team, that there is no food effect. This is discussed in detail in this review in Section 8, Safety, which explains why the Division agrees with the clinical pharmacology review team.

Because of the conflicting conclusions made by the review division, the Clinical Pharmacology review team, and CSS, and in order to comply with the Equal Voice initiative, additional discussions were conducted among the Division Directors of the three groups. The result of these discussions was a memo dated August 3, 2011, by Michael Klein, Ph.D. of CSS that resolved the conflicting opinions of the different review teams.

The following is taken from Dr. Klein's memorandum:

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. Chandradas 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:

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.

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.²

(b) (4)

OSI inspected the CRO for the clinical studies due to concerns regarding the fact that the investigator sites had not maintained independent source documentation of the data that were transmitted to eTrials via eDiaries. They found that the studies had been conducted appropriately and recommended that the data from the studies were acceptable for review. While the findings from one of the clinical sites initially raised some concerns based on the OSI inspection (see Dr. Field's review, page 12), when those data were reanalyzed by the statistical team with the potentially unacceptable subject data removed, there was no change in the overall treatment effect for Nucynta ER compared to placebo. OSI also inspected the clinical and analytical sites for the new pivotal bioequivalence study. Their recommendation was that the data from those sites were acceptable for review.

12. Labeling

The Agency and the Applicant have reached agreement on the product labeling. As

(b) (4)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
- Approval
- Risk Benefit Assessment

The Applicant has provided appropriate and sufficient data to address the product quality deficiencies cited in the CR Letter. In addition, the OSI inspections have resolved the data integrity concerns raised during the first cycle. In light of the previous findings of safety and efficacy during the first

² [Italics added for clarity.]

review cycle, and the absence of any new safety signals that would change the risk-benefit balance, this marketing application for Nucynta ER is now eligible for an approval action, with an appropriate REMS to address the risks associated with extended-release opioid drug products.

- Postmarketing Risk Evaluation and Management Strategies

As a member of the class of extended-release and long-acting opioid drug products, Nucynta ER will be required to have the single, shared class REMS that has been mandated by the Agency. While the single, shared system is being developed, we will approve the application with an interim REMS that was submitted on August 23, 2011, consisting of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. When the class-wide REMS is approved, the Applicant will be notified in writing and will be required to submit a modified REMS incorporating their REMS into the single, shared system. The Applicant submitted their interim REMS as part of their response to the CR Letter. It has been reviewed by the clinical and OSE review teams and found to be acceptable. In addition, the Applicant will be required to submit, as expedited 15-day reports, all post-marketing and clinical trial cases of choking, gagging, sticking, and gastrointestinal obstruction, regardless of whether these reports are classified as serious or unexpected; and they will be expected to submit analyses of clinical trial and post-marketing reports of these adverse events of special interest in their periodic safety update reports.

APPENDIX

17 pages have been Withheld in Full immediately following this page as a duplicate copy of the "Summary Review for a Complete Response Action" dated October 1, 2010 which is located in the "Medical Review Section"

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/s/

BOB A RAPPAPORT
08/25/2011