

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200533Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 11, 2011
From	Ellen Fields, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA	200533 Class 2 Resubmission
Applicant	Johnson & Johnson Pharmaceutical
Date of Submission	February 28, 2011
PDUFA Goal Date	August 28, 2011
Proprietary Name / Established (USAN) names	Nucynta ER/ tapentadol extended release tablets
Dosage forms / Strength	Tablets 50, 100, 150, 200, and 250mg
Proposed Indication(s)	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.
Recommended:	Approval

1. Introduction

Tapentadol is a centrally-acting analgesic compound that has been developed in an extended-release tablet formulation for the management of moderate-to-severe chronic pain in adults when an around-the-clock opioid analgesic is needed for an extended period of time. It is believed to have a dual mechanism of action, involving both mu-opioid agonism and norepinephrine reuptake inhibition. Tapentadol immediate-release (IR) tablets received FDA approval for the relief of moderate-to-severe acute pain in adults (NDA 22-304, approved 20 November 2008). Of the long-acting opioids that have been approved, tapentadol is most similar to tramadol, which also has agonist activity on the mu opioid receptor and inhibits the reuptake of norepinephrine and serotonin.

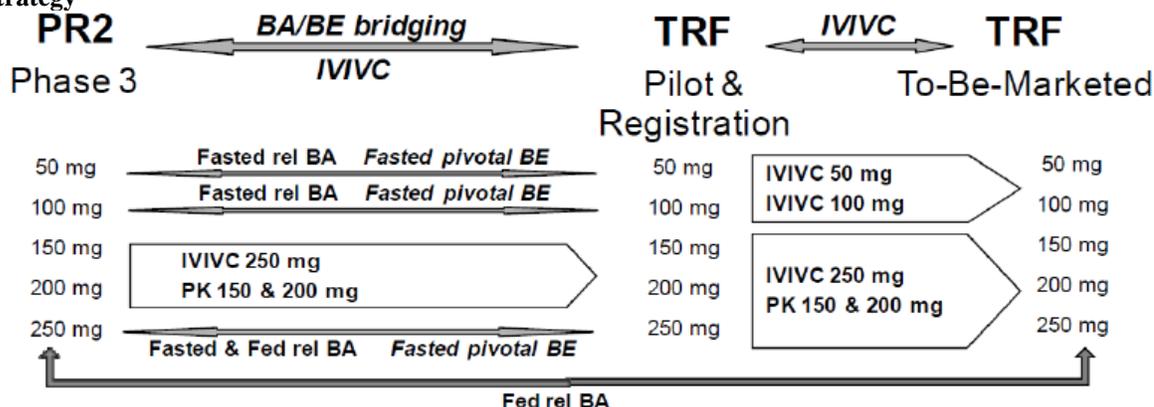
Johnson & Johnson has submitted this NDA as a response to the Complete Response (CR) action issued by the Division on October 1, 2010. The major reason for the CR action was the lack of adequate bridging between the formulation studied in the Phase 3 trials and the to-be-marketed formulation.

2. Background

The original NDA for tapentadol extended-release tablets was submitted on December 1, 2009. The basis for the NDA was four randomized, controlled Phase 3 trials, two in patients with chronic pain due to osteoarthritis of the knee, and one each in patients with chronic low back pain and painful diabetic peripheral neuropathy. Additional open-label safety data was submitted from a one-year study in patients with chronic pain, and results of multiple Phase 1 and 2 studies were also included in the NDA. All four Phase 3 trials were considered by the first cycle review team to be adequate and well-controlled. Two trials successfully demonstrated the efficacy of tapentadol ER; Study 3011 in patients with chronic low back pain, and Study 3015 in patients with painful DPN. Neither of the two OA trials demonstrated efficacy. The safety of tapentadol ER was found to be similar to that of other extended-release opioids and IR tapentadol. Details regarding the safety and efficacy reviews are available in the clinical review from the first cycle.

The primary issue that precluded the approval of tapentadol ER was the lack of adequate bridging of the Phase 3 clinical formulation (PR2) and the to-be-marketed formulation (TBM). In the original NDA, the Sponsor proposed a bridging strategy illustrated in the figure below taken from Dr. Sarah Okada's CDTL memo from the first cycle. The strategy included the use of two In-Vivo-In-Vitro Correlation (IVIVC) models and bioavailability (BA) studies to bridge the pilot batches and the clinical batches to the to-be-marketed formulation.

Figure X: Bridging Strategy



BA= bioavailability; BE= bioequivalence; pivotal BE= pivotal bioequivalence study; rel BA= relative bioavailability study.

However, during the review of the submission the ONDQA biopharmaceutics team found the proposed IVIVC models unacceptable. This was communicated to the Applicant during the review cycle at which time the Agency recommended that the Applicant reconstruct the model. In a later submission the Applicant conveyed to the Agency that they did not intend to reconstruct the IVIVC models; instead they proposed to perform additional fasted bioequivalence studies between the Phase 3 PR2 tablets and the TBM TRF (tamper-resistant formulation) tablets to support the bridging of the strengths originally proposed to be covered by the high-strength IVIVC (i.e., 150 mg and 200 mg doses). The Applicant proposed to submit the reports of these studies prior to the end of the original 10-month review cycle, however, since the composition of the 50 mg tablet was found not proportional to the 100 mg strength and these two strengths are not proportionally similar to the higher strengths, the biopharmaceutics team advised the Applicant to conduct BE studies with the highest (250 mg) and lowest (50 mg) strengths instead.

Although the biopharmaceutics team found the proposed dissolution method acceptable, the proposed dissolution specifications were not acceptable because these were based on the IVIVC models that were determined to be unacceptable. Therefore, the acceptance criteria also needed to be finalized once the results of the proposed BE studies bridging the to-be marketed formulation with the clinical trial formulation, and the dissolution profile comparisons data are submitted.

Based on the above issues, a Complete Response action was taken for NDA 200533. The following is an excerpt from the Action Letter dated October 1, 2010 listing the deficiencies that resulted in the CR action. An additional deficiency is related to verification of clinical trial source data at the Contract Research Organization (CRO).

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, 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 f_2 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.

A post-action Type A meeting was conducted between the Applicant and the Division on November 9, 2010. The discussion focused on the Applicant's pending resubmission of the NDA. The Division was in agreement with the Applicant that they had demonstrated bioequivalence for all strengths of tapentadol TRF except for the 50mg strength, and that a biowaiver for the intermediate strengths would no longer be needed as long as the BE studies were found acceptable by the review team, and that the 50mg tablet could potentially be approved after review of the Applicant's rationale, pharmacokinetic, and safety data in the

NDA resubmission. The Division also requested that the Applicant submit information to support the interchangeability of multiple 50mg tablets with one tablet of a higher dose, given the lack of bioequivalence of the 50mg tablets with the PR2 formulation. The approvability and safety of the 50mg tablets will be discussed in detail in this review.

Another issue that arose during the November meeting was that the tapentadol TRF tablets contain polyethylene oxide, an excipient that has been associated with swelling and stickiness of tablets for other drug products that contain it, and resulting adverse events of the tablet sticking in the throat and the patient experiencing choking episodes. The Applicant was asked to submit safety data to inform whether the TRF formulation represents a choking hazard.

Because tapentadol is an extended-release opioid, it will be required to adopt the class wide Risk Evaluation and Mitigation Strategy (REMS) for long-acting opioids. Until the class-wide REMS is finalized, an interim REMS for this will be part of this approval, and will be closely modeled on the recently approved interim REMS for Embeda and OxyContin.

3. CMC/Device

Dr. Craig Bertha completed the CMC reviews during the first cycle of this NDA. No additional CMC information was included in this submission. From the CMC perspective there were no issues precluding approval other than the unacceptable IVIVC modeling as stated in the Complete Response.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology team completed their reviews during the first cycle of this NDA. No additional pharmacology/toxicology information was included in this submission. According to the review team, there are no issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

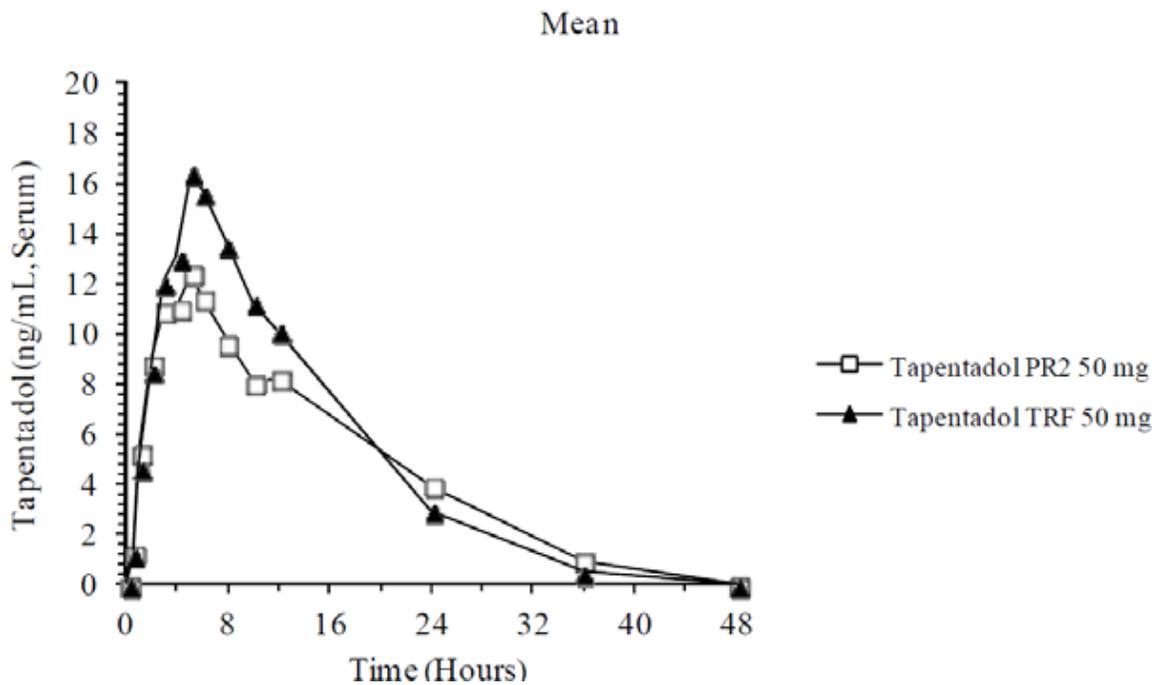
The Clinical Pharmacology review was conducted by David Lee, Ph.D., with secondary concurrence from Yun Xu, Ph.D. Their review included information submitted in the Complete Response application that consisted of the bioequivalence studies bridging the PR2 Phase 3 clinical formulation and the TRF to-be-marketed tapentadol ER formulation. In order to provide adequate information to address the issues stated in the Complete Response with respect to clinical pharmacology, the Applicant needed to submit bioequivalence information for two doses, 50 and 250 mg strengths, comparing PR2 and TRF TBM formulations along with in vitro dissolution data in support of the biowaiver request for the intermediate strengths. The Applicant submitted bioequivalence information for all available strengths to address the concerns in the current complete response submission, negating the need for the biowaiver.

BE studies were conducted comparing all strengths of the TRF 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:



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 LSM	PR2 50 mg 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 C_{max}. 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 C_{max} for the TRF formulation does not represent a safety concern because the C_{max} 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 C_{max} 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 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 Cmax increased by 6% and 17%, respectively, when TRF ER tablets were administered after a high-fat meal. The tmax was prolonged by about 1 hour with a median tmax 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. See Section 5 of this review for additional discussion of this issue.

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.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

No new efficacy trials were submitted with this Complete Response application. Details regarding efficacy findings for tapentadol ER are located in the clinical and statistical reviews of this NDA from the first cycle.

8. Safety

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.

Special Safety Concerns

During the post-action Type C meeting held between the Agency and Sponsor on November 9, 2010, The Division identified concerns regarding the safety of tapentadol ER TRF (the to-be-marketed) tablet that should be addressed in the Complete Response submission, as follows:

1. Because the 50mg TRF tablet did not meet bioequivalence criteria compared to the formulation used in the Phase 3 trials, the Applicant was asked to submit:
 - a. Safety and pharmacokinetic information specifically for the 50mg TRF tablet.
 - b. Supportive data for interchangeability of using different combinations of the 50-mg TRF tablets to achieve a particular dose (e.g., a patient might use four 50-mg TRF tablets during titration to reach an intended dose of 200 mg and then switch to the 200 mg TRF tablet).
2. Because the to-be-marketed formulation of tapentadol ER contains polyethylene oxide, which for other drug products has been associated with causing tablets to become sticky or expand when moist making swallowing difficult and potentially resulting in a choking hazard, the Applicant was asked to evaluate whether this has been an issue and to demonstrate the safety of the product in this regard.

I am in agreement with Dr. Kilgore's assessment that the Applicant's responses regarding these issues are acceptable.

Briefly, regarding the approvability of the 50mg TRF tablet, the Applicant provided the following rationale:

- The 50mg TRF tablet is intended to be used only during initial dose titration, and the safety profile and pharmacokinetic data from the Phase 1 studies, and the Phase 3 DPN study that utilized this formulation support the use of the 50mg TRF tablet for dose titration
- Serum tapentadol concentrations are dose-proportional, and the serum tapentadol plasma concentrations for the 50mg TRF tablets do not exceed the concentrations

- achieved with multiples of the 50mg tablets to achieve therapeutic doses of 100mg-250mg.
- A cross-study comparison of the five Phase 1 BE studies showed the PK of tapentadol TRF are linear and systemic exposures are predictable for the dose range 50mg to 250mg tested.
 - Use of the 50mg TRF tablet during titration in the open-label titration period of the DPN study produced a similar and comparable safety profile as the 50mg PR2 clinical formulation tablet used in other Phase 3 studies.

The Applicant's rationale regarding the interchangeability of a particular dose of tapentadol as multiple 50mg TRF tablets in place of a single dosage strength of a TRF tablet, in addition to the first bullet above, includes:

- Serum tapentadol concentrations following administration of a particular tapentadol dose as combinations of 50mg and 100mg TRF tablets and as an equivalent single dosage strength PR2 tablet are similar.
- The safety of taking multiple TRF tablets without any unexpected consequences is evidenced by the similar safety profiles for the 50mg PR2 tablet and the 50mg TRF tablet used in the open-label titration periods of DPN studies PAI-3015/KF36 and PAI-3027/KF56 respectively, and the data from an additional open-label safety study of the TRF formulation in patients with DPN support that the safety profile observed with tapentadol TRF is similar to that established with tapentadol PR2.

Dr. Lee commented in his review on the Applicant's rationale, as noted in Section 5 of this review, and is in general agreement that patients would not be at risk for overexposure to tapentadol if multiple 50mg tablets are administered.

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 routine 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.

3. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application.

(b) (4)

4. Pediatrics

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.

5. Other Relevant Regulatory Issues

DSI inspections

A deficiency noted in the CR letter for this NDA was that the clinical investigator sites did not maintain independent source documentation of the data that were transmitted directly to eTrials via eDiaries, therefore verification of the source data at the CRO is required before the application may be approved.

During the first review cycle, clinical inspections of four clinical sites and the Sponsor were conducted in response to a routine audit request. FDA inspection of one of the clinical sites (Dr. Alan Soo) documented instances where the clinical investigator failed to adequately document review of rescue medication use, as well as entry of pain scores in 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.

DSI filed a review addendum, dated July 14, 2011, in order to capture the assessment of the inspection of (b) (4), which was pending at the time of the first cycle review (September 20, 2010) and to include the updated assessment of Dr. Soo's inspection based on receipt and review of the EIR.

(b) (4) was contracted to provide eDiaries and support services for the electronic diaries for the two Phase 3 clinical trials (Protocol KF5503/23 and Protocol KF5503/36). Although minor discrepancies in data were noted at one study site, these were not considered a regulatory violation on the part of the CRO. The conclusion of the DSI inspection of the CRO was that the studies appear to have been conducted adequately, and the data generated by this CRO appear acceptable in support of the application.

Regarding Dr. Soo's site, the July, 2011 DSI addendum stated that it is unlikely that the identified regulatory violations at this site would significantly impact overall data reliability. Also, there was no evidence of under-reporting of adverse events found during the inspection of this site, and the primary endpoint data from the site agreed with the data at (b) (4). DSI deferred to the review Division to evaluate the impact, if any, of six subjects that were transitioned to the Maintenance Phase of the study, even though the subjects reported that they continued to take rescue medication within the last three days of the Titration Period, which was a protocol violation. In order to verify that this violation would not have an impact on the final efficacy determination, the Division requested that the statistical review team re-analyze the efficacy data excluding the six subjects who were subject of the protocol violation, and an additional analysis excluding the entire study site (32 subjects). In both cases, there were no changes in the overall treatment effect of tapentadol ER compared to placebo.

DAAAP also requested that the Division of Bioequivalence and GLP Compliance, Office of Scientific Investigations (DBGC) inspect the clinical and analytical portions of study HP5503/84, the pivotal study to assess bioequivalence of tapentadol TRF 250mg in fasted

healthy subjects. An audit of the clinical portion of the study was conducted at Celerion Inc., Lincoln, NE, and an audit of the analytical portion of the study was conducted at (b) (4). There were no significant findings at the clinical site; however a Form-483 was issued to the analytical site that included a number of concerns regarding the documentation and analyses of the samples. (b) (4) responded to all of the inspection concerns satisfactorily, and DBGC recommended that the analytical data be accepted for Agency review. Details regarding the inspection may be found in the DBGC review dated August 5, 2011.

CSS consult:

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. It is therefore not necessary that the Applicant provide an explanation for this finding.

3. Co-administration of tapentadol TRF with meals and alcohol resulted in increases in Cmax 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:

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.

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.

(b) (4)

Risk Evaluation and Mitigation Strategy (REMS)

As an extended-release opioid analgesic, tapentadol ER is required to have a REMS as part of the approval, and to ultimately become part of the class-wide, long-acting opioid REMS. During the first review cycle, the Applicant received a Pre-Approval REMS notification that stated that the proposed REMS must include elements to assure safe use, specifically training

for healthcare providers, to ensure that the benefits of the drug outweigh the risks of abuse, misuse, addiction, and overdose, as well as safe use of tapentadol ER, and to prevent the occurrence of serious adverse events associated with the product's risks. DRISK reviewed the Applicant's proposed REMS during the initial review cycle and provided comments.

During the current review cycle, the Applicant received a second Pre-Approval REMS notification informing them that they are to be included in the class-wide, long-acting opioid REMS. The letter stated "in the interest of public health, and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class."

Since the implementation of the single, shared REMS is not in the imminent future, and waiting for implementation of the shared system could cause a significant delay in the availability of this drug, the proposed interim REMS and REMS supporting documents have been reviewed by DRISK in order to ensure that this interim REMS is consistent with Agency standards for the other interim REMS for long-acting extended-release opioids. The following is a brief description of the interim REMS submitted by the Sponsor.

The stated goals of the proposed REMS are:

- To inform patients and providers about the potential for abuse, misuse, overdose, and addiction to Nucynta ER.
- To inform patients and healthcare professionals about the safe use of Nucynta ER.

The elements of the proposed interim REMS include the following:

- Medication guide
- Elements to assure safe use
 - Training program for healthcare providers to educate prescribers regarding proper patient selection, appropriate dosing and administration, general principles of safe opioid use, and information regarding abuse, misuse and overdose; also to educate prescribers regarding patient counseling for safe storage and disposal of Nucynta ER
 - Dear healthcare provider letter
 - Training will be offered every two years or following substantial changes to the Nucynta ER REMS.
- Implementation system
- Timetable for Submission of Assessments
 - Sponsor will submit REMS assessments to FDA every 6 months for the first year and annually thereafter

DRISK provided comments to the Applicant regarding the interim REMS (see DRISK review dated June 22, 2011), and found the proposed interim REMS acceptable providing the Sponsor addresses all comments satisfactorily. Subsequently the Applicant has provided responses DRISK's comments that were found to be acceptable. The interim REMS will be implemented by the Applicant and will be in effect until the single shared REMS for all long-acting and extended-release opioid products is approved and implemented.

4. Labeling

- Proprietary name: Nucynta ER- accepted by DMEPA and DDMAC
- Labeling discussions with the Applicant are ongoing at this time. In general, the Nucynta ER label will be consistent with other extended-release opioids, tramadol, and tapentadol products.

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(b) (4)

- A Medication Guide is required for this product.
- DMEPA has provided comments to the sponsor regarding the carton and container related to avoiding medication errors with the immediate release Nucynta, especially since there are overlapping dosage units. These discussions are ongoing at this time.

5. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
Approval
- Risk Benefit Assessment

As stated in the first cycle Decisional Memo, “Although the Applicant has submitted sufficient data to support the efficacy and safety for the proposed indication, approval of this application is not possible during this review cycle due to the lack of adequate bridging of the Phase 3 clinical formulation (PR2) and the to-be-marketed formulation. Furthermore, verification of source data at the CRO, in conjunction with evaluation of findings from the other completed inspections, is required before this application may be approved.”

In this Complete Response submission:

1. The Applicant has adequately responded to the issues underlying the Complete Response action.
 - a. An adequate bridge was established between the clinical trial formulation and the to-be-marketed formulation of tapentadol ER by demonstrating bioequivalence for the 100mg, 150mg, 200mg, and 250mg tablets via bioequivalence studies
 - b. Although bioequivalence was not established for the 50mg tablet, based on the pharmacokinetics, safety data, and the fact that the 50mg tablet is intended for use only during titration, there appear to be no issues to preclude the approval of the 50mg strength.
 - c. DSI inspection of the CRO and clinical sites found no issues that would preclude approval of tapentadol ER.

2. The Applicant has adequately addressed the additional issues discussed at the Type A post-action meeting.
 - a. Support for the interchangeability of multiple 50mg tablets of tapentadol ER with higher dosage units was provided, and included pharmacokinetic and safety data for the to-be-marketed 50mg tablets.
 - b. Data regarding the safety of the to-be-marketed formulation regarding whether the tablets represent a choking risk due to the presence of the excipient polyethylene oxide (PEO) was included in the submission, and demonstrated no increased incidence of adverse events related to the PEO, or relevant product complaints during the clinical trials.
3. No new or unexpected safety concerns were detected during the review of the updated safety data in this submission.
 - Recommendation for Postmarketing Risk Evaluation and Management Strategies

Since Nucynta ER is a member of the class of extended-release opioids, it will require a REMS to address the risks of abuse, misuse, and overdose. An interim REMS will be part of the current approval, which will be modeled on the interim REMS for other recently approved extended-release opioids. When the class-wide REMS for long-acting opioids is finalized, Nucynta ER will be included in the drugs that will adopt the shared REMS system.

- Recommendation for other Postmarketing Requirements and Commitments

The pediatric study requirement for age's birth to 7 years is waived because the necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 7 years of age who have chronic pain and require around-the-clock opioids is so small that it is impractical to study this population.

The pediatric studies in patients ages 7-17 years have been deferred because this product is ready for approval for use in adults and the pediatric study has not been completed. In addition, the

The postmarketing requirement is as follows:

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 17 years.

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

- Recommended Comments to Applicant

The following reporting requirement should be added to the Action letter for this product in order to assess whether adverse events related to the presence of PEO, are associated with Nucynta ER:

In addition to the standard reporting requirements for an approved NDA, we request that submit as 15-day expedited 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 that you provide analyses of clinical trial and post-marketing reports of these adverse events of special interest in your periodic safety update reports.

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

/s/

ELLEN W FIELDS
08/11/2011