# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-304**

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review

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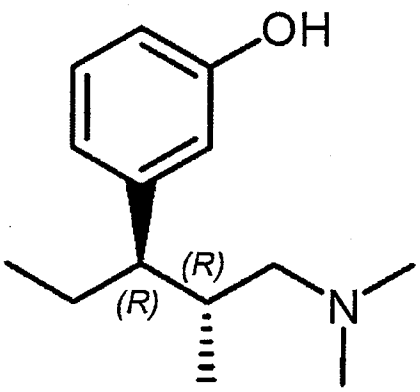
| **Date** | 23 September 2008 |
| **From** | Robert B. Shibuya, M.D., Clinical Team Leader |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA # Supplement#** | NDA [redacted] b(4) |
| **Applicant** | Johnson & Johnson Pharmaceutical Research & Development |
| **Date of Submission** | 22 January 2008 |
| **PDUFA Goal Date** | 22 October 2008 |
| | |
| **Proprietary Name / Established (USAN) names** | To be determined/Tapentadol HCl |
| **Dosage forms / Strength** | Tablet, 50, 75, 100 mg |
| **Proposed Indication** | 1. Relief of moderate to severe acute pain |
| **Recommended:** | Approval |

| **Material Reviewed/Consulted** OND Action Package, including: | |
|---|---|
| Primary Medical Officer Review | Ellen W. Fields, M.D., MPH |
| Statistical | Jonathan Norton, Ph.D.<br>Dionne Price, Ph.D.<br>Thomas Permutt, Ph.D. |
| Pharmacology Toxicology Review | Kathleen Young, Ph.D.<br>Adam Wasserman, Ph.D. |
| CMC Review | John C. Hill, Ph.D.<br>Ali Al-Hakim, Ph.D. |
| Clinical Pharmacology Review | David Lee, Ph.D.<br>Suresh Doddapaneni, Ph.D. |
| DDMAC | Michelle Safarik, PA-C |
| DSI | Antoine El-Hage, Ph.D.<br>Constance Lewin, M.D. |
| OSE/DMEDA | Laura Pincock, PharmD |
| OSE/DRISK | Gita Akhavan-Toyserkani, PharmD<br>Mary Dempsey<br>Claudia Karwoski, PharmD |

## 1. Introduction

Tapentadol is a New Molecular Entity (NME) with weak mu opioid agonist activity and norepinephrine uptake activity. It was developed under IND 61,345 for the management of acute moderate to severe pain. The chemical formula for tapentadol is $C_{14}H_{23}NO*HCl$ and the chemical structure is shown on the next page.




. HCl

For this immediate-release tablet, the applicant, Johnson & Johnson Pharmaceutical Research & Development, is seeking the indication of "the relief of moderate to severe acute pain." At this time, the applicant has not provided an acceptable tradename. Therefore, the product will be referenced as "tapentadol" throughout this review. Proposed strengths are 50, 75, and 100 mg.

At various meetings, including a Pre-IND Meeting, the End-of-Phase 2 Meeting, and the Pre-NDA Meeting, the Division described what efficacy and safety data would support approval. The Division indicated that two multiple-dose studies of at least 2-5 days duration would be required. The applicant felt that the pain in most acute pain scenarios is not of sufficient duration to demonstrate analgesia over 5 days. Therefore, the applicant proposed studying end-stage degenerative joint disease in one of the adequate and well-controlled studies. The Division agreed with this proposal.

The issue of missing data was addressed on several occasions and the Division indicated that, due to the phenomenon of differential dropout, the applicant must use a conservative imputation scheme. The applicant decided to use Last Observation Carried Forward (LOCF), a non-conservative imputation scheme, as the primary method to account for missing data. The applicant included Baseline Observation Carried Forward (BOCF), a conservative imputation scheme, in the statistical analysis plan and agreed that the BOCF analysis must confirm any positive LOCF result. In the Agency review of this NDA, the efficacy studies were carefully assessed and reanalyzed to address this issue.

Tapentadol is structurally related to tramadol (Ultram) and has similar pharmacological effects. Among typical opioid effects, tramadol, particularly in combination with monoamine oxidase inhibitors, is associated with seizures and serotonin syndrome. The safety assessment for tapentadol, in addition to the scrutiny afforded a NME, also assessed these specific areas of concern.

In addition, as an opioid, given the issues of prescription drug abuse, we have given careful consideration to risk mitigation for tapentadol. While tapentadol is likely to be classified in Schedule II, because of tapentadol's relative lack of potency and immediate-release formulation (such that an individual dosage unit is unlikely to cause significant harm to an individual), at this time, tapentadol immediate-release tablets will not be deemed to require a Risk Evaluation and Mitigation Strategy (REMS) and that routine pharmacovigilance and Schedule II controls should suffice to manage risks.

## 2. Background

Tapentadol is an immediate-release weak mu opioid agonist with analgesic activity for which the applicant is seeking an indication of the management of acute moderate to severe pain. As will be discussed in later sections of this review, the drug appears efficacious and the safety profile appears typical for an opioid. All review disciplines are recommending approval. The Office of Surveillance and Epidemiology felt that routine pharmacovigilance was appropriate and opined that the Applicant's post-marketing safety surveillance was appropriate.

## 3. CMC/Device

The CMC review was conducted by John Hill, Ph.D. Tapentadol, immediate-release tablets are film-coated and undergo a[ ] Both the synthetic process and manufacturing process were felt to be robust by Dr. Hill. The product is[ ] Dr. Hill's initial CMC review noted several deficiencies including contact information, limit of detection/quantitation for the dissolution method, method validation for the[ ] test, and a letter of authorization to a DMF. The applicant's response to an Information Request was adequate and Dr. Hill and Dr. Ali Al-Hakim, Chief, Branch II, ONDQA, are recommending approval from the CMC perspective. The review of the Environmental Assessment was conducted by Ruth Ganunis who found the Applicant's assessment acceptable.

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## 4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review was conducted by Kathleen Young, Ph.D. with a secondary review by Adam Wasserman, Ph.D, Supervisory Pharmacologist.

Tapentadol was subjected to the required battery of nonclinical testing for a NME. Key findings in the non-clinical program are summarized below.

- Tapentadol is a mu-opioid agonist with some sigma (S2) activity and norephinephrine reuptake inhibitor activity. The molecule is structurally related to tramadol.
- Notable toxicities (beyond the expected, opioid-related CNS, GI, and respiratory effects) included:

- Tapentadol caused convulsions in rats at very high IV doses (15 mg/kg). These effects in the rat were observed after the parent drug and metabolites had cleared. This finding was not further evaluated by the applicant. Convulsions were noted in dogs, dosed subcutaneously and orally, at doses as low as 40 mg/kg/day. The convulsions were observed across several studies of various chronicities. There was no evidence of tolerance to the convulsant effect observed. Because of these nonclinical findings, humans at risk for seizure were excluded from participation in clinical trials with tapentadol.
- Dose-related, reversible hepatotoxicity was observed, manifested by elevations in transaminases, alkaline phosphatase, and liver weights with hepatocellular hypertrophy and one instance of hepatic necrosis. Rats were more sensitive to tapentadol-associated hepatotoxicity than dogs. The hepatotoxicity was noted at fairly high doses in rats (150 mg/kg/day).
- The other non-opioid-related target organ was the cardiovascular system. Tapentadol caused hERG channel inhibition at high concentrations (approximately 70-times the maximum Cmax of the maximum human dose) and it showed QT prolongation in *in vitro* and *in vivo* dog pharmacology studies, again at high doses/concentrations. This activity has been associated with norepinephrine reuptake inhibition.

- Tapentadol was negative in the Ames and mouse micronucleus test. It was equivocal in the CHO assay. It is important to note that a 2-year carcinogenicity study was negative.
- With regard to reproductive toxicity, the only finding that exceeded historical control rates was ablepharia (absence of the eyelids) in Himalayan rabbits although the remainder of the studies were negative.

Drs. Young and Wasserman have recommended approval for this product from the Pharmacology/Toxicology perspective.

## 5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology and Biopharmaceutics (CP/B) review was conducted by David Lee, Ph.D. with supervisory concurrence by Suresh Doddapaneni, Ph.D.

The applicant is seeking the approval of three strengths, 50, 75, and 100 mg. The dosing regimen is to be every 4-6 hours. The applicant wishes to add a provision for patients to take one extra dose of tapentadol one hour following the first dose ("reload").

To support this dosing and administration scheme as well as address routine clinical pharmacology issues, the applicant conducted an extensive Clinical Pharmacology and Biopharmaceutics program. In total, the applicant conducted nine biopharmaceutics studies providing information on absolute bioavailability, food effect, and dose linearity. Twenty-two clinical pharmacology studies were submitted providing data on metabolism, effects on the QT interval, special populations, drug-drug interactions, and pharmacokinetic/pharmacodynamic correlation. With regard to studies directly related to dosing and administration, there were six Phase 2 studies (single- and multiple-dose) in patients following third-molar extraction,

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