CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-304

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Date:	November 20, 2008
To:	Bob A. Rappaport, M.D., Director **Division of Anesthesia, Analgesia, and Rheumatology Products**
Through:	Claudia Karwoski, PharmD, Director (Acting) Division of Risk Management (DRISK) Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management (DRISK)
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Labeling and Education Team Division of Risk Management (DRISK)
Subject:	Review of Patient Labeling (Medication Guide) and Proposed REMS
Drug Name(s):	TRADENAME (tapentadol) immediate release oral tablets (CII)
Application Type/Number:	NDA 22-304
Applicant/sponsor:	Johnson & Johnson
OSE RCM #:	2008-1808

1 INTRODUCTION

This review is written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology (DAARP) for the Patient Labeling and Education Team to review the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS), which includes the draft Medication Guide (MG) prepared by the DAARP and the sponsor's Timetable for Submission of Assessments of the effectiveness of the REMS.

FDA has determined that tapentadol poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of tapentadol. FDA has determined that tapentadol meets two of the three triggering criteria for a Medication Guide as set forth in 21 CFR 208.1. Tapentadol is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, tapentadol. FDA has also determined that tapentadol is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- DRAFT TRADENAME (tapentadol) Professional Information (PI) as revised by the sponsor and review division throughout the review cycle, most recently versions dated November 17, 2008 and November 18, 2008
- DRAFT TRADENAME (tapentadol) Medication Guide (MG) prepared by the review division and including CSS comments, version provided to OSE on November 12, 2008.
- Proposed REMS, submitted on November 11, 2008 and the Amendment to the Proposed REMS, submitted on November 18, 2008.

3 BACKGROUND

Johnson & Johnson submitted an original New Drug Application, NDA 22-304 for TRADENAME (tapentadol) immediate-release tablets, on January 22, 2008. TRADENAME (tapentadol) is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older.

During the review of NDA 22-304 it became evident that tapentadol exhibits distinctive properties indicating high potential for abuse.

After consultations between the Office of New Drugs and the Controlled Substance Staff, the DAARP determined that a REMS is necessary to ensure that the benefits of tapentadol outweigh its risks. In reaching this determination the DAARP considered the following:

- The indication proposed for the formulation in NDA 22-304, treatment of acute moderate to severe pain, could result in millions of prescriptions each year.
- Moderate to severe pain is considered serious in that untreated pain can lead to physical and emotional disability, job loss and suicide.
- The potential benefit of tapentadol is that it represents the first novel analgesic with mu agonist activity in over a decade. Patients often do not respond to or tolerate some opioids. Having a novel option could offer pain relief to many patients unable to be treated successfully with existing therapies.

- The duration of treatment is days to months.
- This product carries all of the risks of an opioid including CNS depression, respiratory depression, nausea, vomiting, constipation, along with the possibility of an abuse potential that could be comparable or possibly exceed currently available opioid analgesics. In a human abuse liability pharmacology study, tapentadol displays an abuse potential comparable to that of hydromorphone. However, the duration of the euphoria from tapentadol lasted longer than hydromorphone. For this reason, it stands out in comparison to other immediate-release opioids and warrants a Medication Guide to ensure that patients are informed on the proper use of this product.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to provide FDA with new authorities to require sponsors of approved drugs to develop and comply with Risk Evaluation and Mitigation Strategies (REMS) section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

A teleconference took place on November 3, 2008 in which the DAARP informed the sponsor that a REMS is necessary for tapentadol. The only elements of the REMS will be a Medication Guide (MG) and a timetable of submission of assessments of the REMS.

The sponsor submitted a proposed REMS for NDA 22-304 on November 11, 2008, and following feedback from the Agency submitted an amendment to the proposed REMS on November 18, 2008.

4 DISCUSSION

4.1 MEDICATION GUIDE

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG drafted by the DAARP has a Flesch Kinkaid grade level of 8.1. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable. In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- rearranged information due to PLR labeling format
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with

low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4.2 PROPOSED REMS

The proposed REMS states that the Sponsor will include a supply of MG s to the wholesaler with each shipment of tapentadol in accordance with 21 CFR 208.24. The Sponsor will additionally supply copies of the MG to all retail and hospital pharmacies at least biannually.

The Timetable for Submission of Assessments is as follows:

- 1st assessment: 18 months after approval
- 2nd assessment: 3 years after approval
- 3rd assessment: 7 years after approval

The original proposed REMS included a section entitled [redacted] b(4)
At this time, the Agency does not consider this information to be included in the REMS document; this was appropriately removed in the amended REMS based on Agency feedback.

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the Sponsor's proposed REMS for tapentadol meets the statutory requirements outlined under 21CFR 208 and in accordance with 505-1. We have the following comments and recommendations:

1. The sponsor's proposed timetable for assessments (18 months, 3 years, and 7 years) is acceptable. The Sponsor should submit for review a detailed plan to evaluate the patient's understanding about the safe use of tapentadol. The submission should include:
   - All methodology and instruments that will be used to evaluate the patient's understanding about the safe use of tapentadol. This should include, but not be limited to:
     - Sample size and confidence associated with that sample size
     - How the sample will be determined (selection criteria)
     - The expected number of patients surveyed
     - How the participants will be recruited
     - How and how often the surveys will be administered
     - Explain controls used to minimize bias
     - Explain controls used to compensate for the limitations associated with their methodology
   - The survey instruments (questionnaires and/or moderator's guide).
   - Any background information on testing survey questions and the correlation to the messages in the Medication Guide.

2. Tapentadol is supplied in bottles of 100 and hospital unit dose blister packs of 10. Since tapentadol is not supplied in unit of use packaging, there is concern that the larger size bottles may be repackaged prior to dispensing and thus there would not be sufficient numbers of Medication Guides if bottles are repackaged and dispensed to multiple patients. Under 21CFR208.24 (b) (1) sufficient numbers of Medication Guides must be provided.

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Please let us know if you have any questions.

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

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/s/

Mary Dempsey
11/20/2008 12:43:42 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
11/20/2008 01:47:42 PM
DRUG SAFETY OFFICE REVIEWER

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

Date:	June 26, 2008
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia and Rheumatology Products
Through:	Claudia Karwoski, Pharm.D., Acting Director Division of Risk Management (DRISK)
From:	Gita Akhavan-Toyserkani, Pharm.D., MBA, Senior Drug Risk Management Analyst (DRISK) Mary Dempsey, Risk Management Coordinator (DRISK)
Subject:	Review of proposed Risk Management Plan (RMP)
Drug Name(s):	Tapentadol hydrochloride immediate-release (IR) tablets
Submission Number:	000
Application Type/Number:	NDA 22-304
Applicant/sponsor:	Johnson & Johnson Pharmaceutical Research & Development, LLC
OSE RCM #:	2008-283

1 INTRODUCTION AND BACKGROUND

This review follows the February 12, 2008 request from the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) for the Office of Surveillance and Epidemiology (OSE) to review Johnson & Johnson's (J&JPRD) January 23, 2008 proposed risk management plan.

Tapentadol hydrochloride immediate-release (IR) is a centrally acting analgesic agent. Tapentadol is both a mμ-opioid receptor agonist and an inhibitor of norepinephrine uptake. The proposed indication for tapentadol IR is the relief of moderate to severe acute pain. The recommended starting dose is 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending upon pain intensity. Daily doses greater than 700 mg for the first day of therapy and 600 mg on subsequent days have not been studied and are, therefore, not recommended. The Sponsor proposes labeling and routine pharmacovigilance to manage the risks of this Schedule II controlled product.

1.1 REGULATORY HISTORY

Tapentadol HCl is a New Molecular Entity (NME) that has not been previously marketed or approved in the US or abroad. Tapentadol is an analog of tramadol and therefore not a first in class NME. The application is filed as a 505(b)(1), non-priority NDA with 10-month review clock.

During a pre-NDA meeting, on June 5, 2007, J&JPRD discussed the requirements for a Risk Minimization Action Plan (RiskMAP) with the Agency. The Sponsor stated that they plan on conducting a pharmacovigilance program for the IR formulation [redacted] The Reviewing Division informed J&JPRD that the IR formulation would not require a RiskMAP unless there was something unusual (e.g. particularly vulnerable population, a more highly abusable dosage form, etc.); [redacted]

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2 MATERIAL REVIEWED

The following materials were reviewed:

- "Tapentadol IR Safety Surveillance plan" submitted January 23, 2008 by Johnson & Johnson Benefit Risk Management, LLC.
- Tapentadol HCL immediate-release tablets pre-NDA (IND 61,345) Meeting Minutes, dated June 5, 2007.

3 REVIEW

3.1 SPONSOR'S SAFETY CONCERNS

Tapentadol HCL is a Scheduled II controlled substance. J&JPRD states that, to date, the adverse events experienced with tapentadol IR throughout the clinical program have revealed a profile consistent with a centrally acting compound with mμ-opioid agonist activity. The following important identified and potential risks determined by J&JPRD are listed in Table 1:

[1] Guidance for Industry: Development and Use of Risk Minimization Action Plans: http://www.fda.gov/cder/guidance/6358fnl.pdf, dated March 2005

Table 1: Summary of Safety Concerns

Safety Concerns
Important identified risks:
Potential for abuse
Seizure
Important potential risks:
Overdose
Off-label use, incl. pediatric patients
Potential for medication errors (inappropriate prescribing, inappropriate dosing, inappropriate use) and patient misuse
Accidental exposure
Diversion
Important missing information:
Use in pediatrics

The potential for abuse was regarded as an important identified risk due to known class effects for substances with mμ-opioid activity. In addition, results of a Phase I abuse liability trial suggest that single doses of tapentadol IR had a similar abuse liability profile to that of calculated equianalgesic single doses of hydromorphone IR.[2] Seizure was included as well, due to known class effects for substances with mμ-opioid activity. One case of seizure was observed in a Phase 1 trial; however, the patient had a history of seizure which had been denied during screening for study. Subjects with history of seizures were excluded from Phase 2 and 3 clinical studies.

During the preclinical development of tapentadol IR, subjects below 18 years of age were not studied. Therefore, knowledge of exposure in the pediatric population does not exist and the use of tapentadol IR in this population is not recommended.

3.2 SPONSOR'S RISK MANAGEMENT PROPOSAL

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4 DISCUSSION

J&JPRD states that, to date, the adverse events experienced with tapentadol IR throughout the clinical program have revealed a profile consistent with a centrally acting compound with mμ-opioid agonist activity. Specific adverse events of interest for tapentadol IR include identified risks (drug abuse, and seizures) and potential risks based on adverse events seen with product in the mμ-opioid receptor class (overdose, addiction, diversion, intentional misuse, medication

[2] Clinical Study Report (Mod 5.3.4.1): A Single-Center, Single-Dose, Double-Blind, Double-Dummy, Placebo-Controlled, Randomized Cross-Over Study to Evaluate the Abuse Potential of Three Doses of CG5503 Compared to Immediate Release Hydromorphone in Opiate-Experienced Non-Dependent Subjects.

errors, and accidental exposure). The sponsor states that while the drug possesses norepinephrine reuptake inhibitory activity, no specific safety issues arising from this mechanism has become evident during the clinical trials.

Based on the clinical experience, tapentadol IR (50 mg to 100 mg) provides analgesia similar to oxycodone IR at doses of 10 mg and 15 mg. We note that other immediate-release opioids indicated for the treatment of pain, with potency similar to morphine or oxycodone, do not have RiskMAPs in place. We further note that tapentadol is an analog of tramadol. Unlike tramadol, which is not scheduled under the Controlled Substances Act in the U.S., tapentadol will be a schedule II controlled product and therefore subject to inherent restrictions on supply and distribution.

The Sponsor's proposal is consistent with a routine pharmacovigilance program. The Sponsor states that all the safety risks can be adequately monitored and addressed by the planned surveillance activities and label. The Sponsor states that they agree with the recommendation of the Agency in that a RiskMAP is not needed for tapentadol IR.

5 CONCLUSION

We agree with the Sponsor and the Reviewing Division. The risks associated with the use of tapentadol HCL IR are similar to the risks of other immediate-release opiate products indicated for the treatment of pain with potency similar to morphine IR and oxycodone IR. It is appropriate to manage the risks of tapentadol HCL IR with labeling and routine pharmacovigilance. At this time, we do not recommend establishing a risk evaluation and mitigation strategy (REMS) for this product.

Should the safety data in the NDA show unanticipated risks associated with the use of tapentadol HCL IR, we ask that you consult OSE again to reconsider the risk management plan.

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Mary Dempsey
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DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
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DRUG SAFETY OFFICE REVIEWER

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

MEMORANDUM

DATE: November 6, 2008

TO: File, NDA 22-304, Tapentadol

From: Ellen Fields, M.D., M.P.H
Clinical Team Leader

Through: Curtis Rosebraugh, M.D.
Director, Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

RE: Risk Evaluation and Mitigation Strategy (REMS) Requirements

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Controlled Substance Staff, we have determined that a REMS is necessary to ensure that the benefits of tapentadol outweigh its risk of high potential for abuse due to distinctive properties that became evident during the application review. In reaching this determination we considered the following:

A. The indication proposed for the formulation in NDA 22-304, treatment of acute moderate to severe pain, could result in millions of prescriptions each year.

B. Moderate to severe pain is considered serious in that untreated pain can lead to physical and emotional disability, job loss and suicide.

C. The potential benefit of tapentadol is that it represents the first novel analgesic with mu agonist activity in over a decade. Patients often do not respond to or tolerate some opioids. Having a novel option could offer pain relief to many patients unable to be treated successfully with existing therapies.

D. The potential duration of treatment is days to months.

E. This product carries all of the risks of an opioid including CNS depression, respiratory depression, nausea, vomiting, constipation, along with the possibility of an abuse potential that could be comparable or possibly exceed currently available opioid analgesics. In a human abuse liability pharmacology study, tapentadol displays an abuse potential comparable to that of hydromorphone. However, the duration of the euphoria from tapentadol lasted longer than hydromorphone. For this reason, it stands out in comparison to other immediate-release opioids and warrants a Medication Guide to ensure that patients are informed on the proper use of this product.

F. Tapentadol is a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that tapentadol poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of tapentadol. FDA has determined that tapentadol is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, tapentadol. FDA has also determined that tapentadol is a product for which patient labeling could help prevent serious adverse events.

The only elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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Sharon Hertz
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MEDICAL OFFICER
signing for Curtis Rosebraugh