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.

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