CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-304

PHARMACOLOGY REVIEW(S)

11/19/08

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology OND IO
NDA: 22-304
Submission date: January 23, 2007
Drug: tapentadol
Sponsor: Ortho-McNeil Pharmaceuticals
Indication: moderate to severe pain

Reviewing Division: Division of Anesthesia, Analgesia, and Rheumatology Drug Products

Introductory Comments:
The pharm/tox reviewer and supervisor found the nonclinical information submitted for tapentadol to be sufficient to support its use for the proposed indication.

Reproductive and developmental toxicity:
The reviewer and supervisor agreed with the sponsor's proposed pregnancy category of C. Studies in rats and rabbits showed that tapentadol was not teratogenic in the rat but it did induce some malformations at high maternally-toxic doses in the rabbit. The reviewer and supervisor recommended that information be deleted from the labeling since toxicokinetic data from these studies were not available, whereas toxicokinetic data were available from subcutaneous studies and since the subcutaneous study in rabbits did show some effects at high doses. The reviewer has expressed the margin of exposures for the various studies based on a comparison of AUC in the human and animals rather than on as originally proposed by the sponsor. I agree that it is preferable to use AUC comparisons.

Carcinogenicity:
The executive carcinogenicity assessment committee found no drug-related tumors in either the rat or mouse study conducted with tapentadol. Therefore, I agree that the labeling can state that no increase in tumor incidence was observed in either species.

Animal Toxicology and/or Pharmacology:
The wording proposed by the sponsor for this section of the labeling included a description of a variety of CNS effects observed in toxicology studies. The reviewer and supervisor recommend that this section be edited to emphasize the occurrence of convulsions, particularly since these were observed in dogs at plasma levels in the range of those achieved in humans at the maximum recommended human dose. I agree that it is acceptable to include this information in the labeling since this is a significant adverse effect that may be caused directly by the drug, and a description of this finding may be useful information should someone experience such an adverse effect.

Conclusions:
I concur with the Division pharm/tox conclusion that the nonclinical data support approval of this NDA. I concur with the labeling recommended by the supervisor.

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

/s/

Paul Brown
11/19/2008 05:38:19 PM
PHARMACOLOGIST

11/20/08

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Supervisory Pharmacologist Memorandum (#3)

NDA NUMBER:	**00-000**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**23-JAN-2008**
PRODUCT:	
(Proposed) Trade Name:	**Not Finalized**
Established Name:	**Tapentadol HCl**
INDICATION:	**Relief of Moderate to Severe Acute Pain**
SPONSOR:	**Ortho-McNeil-Janssen Pharmaceuticals, Inc**
DOCUMENTS REVIEWED:	**N/A**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Kathleen A. Young, Ph.D.**
PHARM/TOX SUPERVISOR:	**Adam Wasserman, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Matthew Sullivan**

Background/Purpose

This addendum to the NDA serves to correct an error in human AUC value at the maximum recommended human dose (MRHD) which was used to calculate safety margins in the nonclinical NDA review and Supervisory memo. The exposure value used to calculate safety margins in the original review was based on an AUC_{0-t} (area under the plasma concentration-time curve for a dosing interval) which was estimated to be 500 ng*h/mL at the MRHD. However, this exposure value is representative of only a single dosing period within the day. As tapentadol is administered up to 6 times per day, the $AUC_{0-24\ hr}$ is therefore approximately 6X higher (i.e. ~ 3000 ng*h/mL). C_{max}, however, remains roughly the same (~30% increase) with multiple dosing during the day.

The impact of this change does not alter the recommendation for approval from the nonclinical standpoint though an approximately — reduction in safety margins as expressed in the previously recommended nonclinical sections of the label (from Memo #2) were subsequently necessary. These margins have been negotiated with the Applicant and agreement reached in the final label. b(4)

General toxicology studies of chronic duration in the rat and dog identified NOAELs which are below the daily AUC exposure associated with the MRHD. The principal target organs identified include the liver in the rat and the CNS in the dog. For the dog the principal toxicity is convulsion, therefore the toxicokinetic parameter of importance is likely C_{max} which is not greatly affected by the change to the $AUC_{0-24\ hr}$. The original review and Supervisory memo indicated that the human exposure was not supported by the nonclinical NOAEL; however, in both species the adverse findings were reversible and clinical data has been provided to address these findings.

Reproductive toxicology sections of the label now indicate exposures associated with the NOAEL in the studies are generally below the exposures associated with the MRHD. Studies were conducted up to maximum tolerated maternal dose and were negative for direct toxicity to the fetus though findings were observed at frank maternally toxic doses and are described in the label.

Carcinogenicity studies, which were negative for drug-related tumor development in both mouse and rat, were conducted up to the maximum tolerated dose as agreed through evaluation by the Executive Carcinogenicity Assessment Committee. The re-analysis using the correct AUC comparison does not provide safety margins for exposure at the MRHD, however. This is described in the negotiated label.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.