CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200533Orig1s000

PHARMACOLOGY REVIEW(S)

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

Supervisory Pharmacologist Memorandum

NDA NUMBER:	**200-533**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**12/1/2009**
PRODUCT:	
(Proposed) Trade Name:	**Nucynta ER**
Established Name:	**Tapentadol extended release oral tablets**
INDICATION:	**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**
SPONSOR:	**Ortho-McNeil-Janssen-Pharmaceuticals, Inc.**
REVIEW DIVISION:	**Division of Anesthesia and Analgesia Products (HFD-170)**
PHARM/TOX REVIEWER:	**Armaghan Emami, Ph.D.**
PHARM/TOX SUPERVISOR:	**Adam Wasserman, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Dominic Chiapperino, Ph.D.**

EXECUTIVE SUMMARY

I. BACKGROUND

A. Regulatory Summary (Pharmacology/Toxicology)

The present NDA is an extended release (ER) version of Nucynta® (tapentadol), a product approved by the Agency in 2008 for treatment of moderate to severe acute pain. The intended target population for Nucynta ER is moderate to severe chronic pain in adults who need continuous opioid management of their pain. The approved immediate release (IR) tablet is supplied in 50, 75, and 100 mg strengths to be taken six times per day (seven on first day) while the ER tablet is formulated in 50, 100, 150, 200, and 250 mg strengths to be administered BID. Pharmacokinetic studies in humans indicate AUC systemic exposure is within the approved IR product though Cmax is approximately 30% higher, likely due to the greater strength of the ER tablet (250 mg vs. 100 mg).

The Division agreed with the Applicant as part of the Pre-NDA meeting of January 23, 2009 that no additional nonclinical studies would be necessary and that cross-referencing the NDA 22-304 for the IR tablet for nonclinical support would be sufficient for the present application.

The original nonclinical review of NDA 22-304 recommending approval was conducted by Dr. Kathleen Young and a concurring Supervisory memo, as well as several memo addenda, was written by me.

II. MAJOR NONCLINICAL ISSUES IDENTIFIED IN PRIMARY REVIEW

Dr. Emami has noted in her review that the Nucynta ER formulation and drug substance/drug product specifications are acceptable. Upon review of all prior materials, however, she has re-evaluated the nonclinical toxicology package submitted in support of the original N22-304 and finds the IR tablet as well as the ER tablet is not fully supported by the nonclinical data (see Dr. Emami's table in her Executive Summary). The original primary review contained a calculation error as described in my Supervisory Memo Addendum #3 of November 2008. Dr. Emami notes the NOAELs in the chronic toxicology studies in both rat and dog do not support the clinical systemic exposure (measured as area under the curve, $AUC_{0\text{-}24\ hr}$) at the maximum recommended human dose (MRHD). The highest dose tested in the rat barely reached the MRHD exposure and the dog exposure was far below (0.15X) human. The type of toxicity observed in nonclinical studies was principally CNS-related (as will be detailed in the next section). This typically correlates better with plasma levels (i.e. C_{max} or C_{ss}). Clinical C_{max} was covered by the rat though in the dog Cmax values were below the human except for the highest dose tested (1.4X). The majority of the parent drug is directly glucuronidated, rendering it inactive in analgesic assays. This metabolite forms the major human metabolite which circulates at levels >40X higher than tapentadol based on C_{max} and AUC. This pattern holds in nonclinical models as well, though metabolism is even more extensive. Although the

NOAEL dose in the dog study does not provide support for the exposure to the glucuronidated metabolite, the highest dose used does cover this exposure and I note the rat NOAEL is 1.6X the exposure at the MRHD. Dr. Emami further correctly calculates that the NOAELs in the reproductive toxicology program as well as carcinogenicity bioassays do not cover the human clinical exposure to tapentadol at the MRHD either.

Nonclinical in vivo toxicology studies (general, reproductive, and carcinogenicity) were carried out at or in excess of the maximum tolerated doses. The principal target organ identified was the CNS, and effects were dose-limiting in all studies. Observations mostly fall under the category of "clinical signs" and included in the rat lateral recumbency, irregular respiration, straub tail, cyanosis, irritability, hyperactivity, tremor and convulsions. In dogs decreased activity, labored breathing, tachypnea, rhinorrhea, salivation, tremors, and convulsions were seen. Other possible target organs included the liver in the rat, though this appears to be more likely centrilobular hepatocellular hypertrophy as an adaptive upregulation of metabolism. In the dog cardiac effects including QTc prolongation was noted. These findings, including convulsions, are commonly seen with opioids and/or NE reuptake inhibitors in nonclinical studies.

The Applicant previously noted focal gliosis and perivascular mononuclear cell infiltration in the pons and medulla of mid-dose and high-dose animals in the 12-month dog toxicology studies and both the study pathologist as well as the external reviewing pathologist believed these were incidental due to the low incidence, severity, lack of dose-relatedness. The Applicant also stated they additionally did not believe these were therefore related to convulsions as they did not occur in the same animals. As part of her review of NDA 22-304 Dr. Young agreed with the Applicant that these findings did not represent a treatment-related effect. I did not remark on these observations in my original concurring Supervisory memo or addenda. Dr. Emami has pointed this observation out for further evaluation. I note one mid-dose animal with perivascular infiltration and gliosis in the pons and medulla was also an animal with convulsion noted. Although it would be most useful to have historical control data from this laboratory to rule out a treatment-related effect, several aspects temper concern the most critical of which was that it was not clearly dose-related. Although not observed in control or low-dose animals, there were 3 animals (2 males, one female) in MD while there was only 1 animal (female) in HD with these findings despite a significantly higher exposure in the HD group animals. Findings after 52-weeks of exposure were graded as minimal to slight in severity. Gliosis of the CNS is considered an age-related phenomenon in dogs (Shimanda et al., 1992) and while the dogs on the study are not considered aged, there is a continuum of development of this pathology over the lifetime with moderate to severe levels of gliosis achieved in elderly dogs. Against this argument is the recent understanding that various opioids can activate glia through enhancement of microglial migration through P2X4 (purinergic) receptor activation (Horvath and DeLeo 2009) as well as through a non-stereoselective activation of toll-like

receptor 4 (TLR4) which has been posited to underlie the development of tolerance, dependence, reward, and respiratory depression. Spinal activation of glia as measured by glial fibrillary acidic protein (GFAP) has been reported with short-term administration of morphine (Tawfik et al., 2005) An inflammatory response with gliosis has been described with chronic spinal morphine, which can be blocked by naltrexone (Mattioli et al., 2010) and a similar but widespread CNS activation of glia has been shown with morphine administered systemically over shorter time-scales as well (Song et al., 2001). A recent review summarizes the relationship between opioids, glia and pro-inflammatory response (Watkins et al., 2009). Though these argue that the findings described in the tapentadol study in dog could be treatment-related, it does not appear that this minimal response to maximal treatment presents an unusual risk relative to the mainstays of pain treatment.

In regards to exposures in the reproductive and carcinogenicity studies not being supportive of the clinical exposure at the MRHD due to reaching the maximum tolerated dose, this is not ideal but we cannot ask more of the Applicant. I note that there was no evidence of teratogenicity in reproductive toxicology studies conducted even up to exposures that met or exceeded the human exposure. In regards to the carcinogenicity study the Applicant was operating under a SPA agreement with the Agency and the studies were appropriately accepted for review.

Putting the animal data into a broader context we have by this time accumulated a fairly significant clinical database which has largely showed classic opioid-related safety issues. Dr. Emami notes that there have been some post-marketing reports of serious adverse events including seizure, serotonin syndrome, and death. These are currently being assessed along with all tapentadol-related AE reports as part of a post-marketing safety evaluation conducted by the Office of Surveillance and Epidemiology (FDAAA provision: Section 915). Although not completed, informal communication with OSE appears to indicate these reports are not at a higher rate than would be expected. It is also worth noting that the approved Nucynta (immediate release) label relays concerns of seizure and serotonin syndrome as part of the Warnings and Precautions section.

III. RECOMMENDATIONS

A. Recommendation on approvability

Although I recognize Dr. Emami's evaluation that the nonclinical data is not technically supportive of the systemic exposure at the Maximum Recommended Human Dose (MRHD) for the ER tablet, the toxicities observed are largely confined to the CNS and are common to opioid and/or NE reuptake inhibitors. Also reassuring, a significant body of clinical safety data is available which has not to this point revealed

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.