

**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**

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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 C<sub>max</sub> 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<sub>0-24 hr</sub>) 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<sub>max</sub> or C<sub>ss</sub>). Clinical C<sub>max</sub> was covered by the rat though in the dog C<sub>max</sub> 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<sub>max</sub> 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

unusual toxicity for this drug relative to its class. I also note the systemic exposures with the ER tablet are similar to the IR tablet, though the increased ER product C<sub>max</sub> (130% relative to IR tablet) may result in increased incidence of CNS adverse effects. Taken together, I believe the NDA for Nucynta ER tablets may be approved.

**B. Recommendation for nonclinical studies**

None.

**C. Recommendations on labeling**

I concur with Dr. Emami's labeling recommendations. The approved immediate-release Nucynta label only needs updating with appropriate safety margins based on the slightly different exposures noted with the ER tablet.

**References**

Horvath RJ, DeLeo JA. Morphine enhances microglial migration through modulation of P2X4 receptor signaling. *J Neurosci* 2009 29(4):998-1005.

Mattioli TA, Milne B, Cahill CM. Ultra-low dose naltrexone attenuates chronic morphine-induced gliosis in rats. *Mol Pain* 2010 16(6) 22

Shimada A, Kuwamura M, Awakura T, Umemura T, Itakura C. An immunohistochemical and ultrastructural study on age-related astrocytic gliosis in the central nervous system of dogs. *J Vet Med Sci.* 1992 Feb;54(1):29-36.

Song P, Zhao ZQ. The involvement of glial cells in the development of morphine tolerance. *Neurosci Res.* 2001 Mar;39(3):281-6.

Tawfik VL, LaCroix-Fralish ML, Nutile-McMenemy N, Deleo JA. Transcriptional and translational regulation of glial activation by morphine in a rodent model of neuropathic pain *JPharmacol Exp Ther* 2005 313(3):1239-1247.

Watkins LR, Hutchinson MR, Rice KC, Maier SF. The "Toll" of Opioid-Induced Glial Activation: Improving the clinical Efficacy of Opioids by Targeting Glia. *Trends in Pharmacological Sciences* 2009 30(11):581-591.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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ADAM M WASSERMAN  
08/09/2010



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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 200533  
Supporting document/s: 000  
Applicant's letter date: November 30, 2009  
CDER stamp date: December 1, 2009  
Product: Nucynta (Tapentadol) ER Tablets  
Indication: Management of moderate to severe chronic pain  
Applicant: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD)  
Review Division: Division of Anesthesia and Analgesia Products  
Reviewer: Armaghan Emami, Ph.D.  
Supervisor/Team Leader: Adam Wasserman, Ph.D.  
Division Director: Bob Rappaport, M.D.  
Project Manager: Dominic Chiapperino, Ph.D.

*Template Version: December 7, 2009*

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## 1 Executive Summary

### 1.1 Recommendations

**1.1.1 Approvability:** The information contained in the cross-referenced NDA 22-304 submission (Tapentadol IR) indicates that the non-clinical studies of tapentadol, relied upon for this application, are not sufficient to support the maximum human exposure to tapentadol in Tapentadol Extended-Release (ER) for the clinical indication as proposed under NDA 200533.

Therefore based solely on the pharmacology and toxicology data provided Tapentadol ER should not be approved under NDA 200533.

**1.1.2 Additional Non Clinical Recommendations:** Due to intolerance of using higher doses in non-clinical studies, additional non clinical studies will not be informative.

### 1.1.3 Labeling

#### 8.1 Pregnancy

##### *Pregnancy Category C.*

Tapentadol HCl was evaluated for teratogenic effects in pregnant rats and rabbits following intravenous and subcutaneous exposure during the period of embryofetal organogenesis. When tapentadol was administered twice daily by the subcutaneous route in rats at dose levels of 10, 20, or 40 mg/kg/day [producing up to 1.36 times the plasma exposure at the maximum recommended human dose (MRHD) of 500 mg/day for NUCYNTA™ ER based on an area under the time-curve (AUC) comparison], no teratogenic effects were observed. Evidence of embryofetal toxicity included transient delays in skeletal maturation (i.e., reduced ossification) at the 40 mg/kg/day dose which was associated with significant maternal toxicity. Administration of tapentadol HCl in rabbits at doses of 4, 10, or 24 mg/kg/day by subcutaneous injection [producing [0.3](#), [0.8](#), and [2.5](#) <sup>(b) (4)</sup> times the plasma exposure at the MRHD based on an AUC comparison] revealed embryofetal toxicity at doses  $\geq 10$  mg/kg/day. Findings included reduced fetal viability, skeletal delays and other variations. In addition, there were multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate at doses  $\geq 10$  mg/kg/day and above, and ablepharia, encephalopathy, and spina bifida at the high dose of 24 mg/kg/day. Embryofetal toxicity, including malformations, may be secondary to the significant maternal toxicity observed in the study.

In a study of pre- and postnatal development in rats, oral administration of tapentadol at doses of 20, 50, 150, or 300 mg/kg/day to pregnant and lactating rats during the late gestation and early postnatal period [resulting in up to 2.28 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. Treatment-related developmental delay was observed, including incomplete ossification, and significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above). At maternal tapentadol doses  $\geq 150$  mg/kg/day, a dose-related increase in pup mortality was observed to postnatal Day 4.

There are no adequate and well controlled studies of NUCYNTA™ ER in pregnant women. NUCYNTA™ ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### 8.2 Labor and Delivery

The effect of tapentadol on labor and delivery in humans is unknown. NUCYNTA™ ER is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of NUCYNTA™ ER, neonates whose mothers have been taking NUCYNTA™ ER should be monitored for respiratory depression. A specific opioid antagonist, such as naloxone, should be available for reversal of opioid induced respiratory depression in the neonate.

### 8.3 Nursing Mothers

There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. NUCYNTA™ ER should not be used during breast-feeding.

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### *Carcinogenesis*

Tapentadol was administered to rats (diet) and mice (oral gavage) [REDACTED] (b) (4) [REDACTED] for two years.

In mice, tapentadol HCl was administered by oral gavage at dosages of 50, 100 and 200 mg/kg/day for 2 years (up to [REDACTED] (b) (4) ~~0.34 times in the male mice and 0.25 times in the female mice~~ the plasma exposure at the maximum recommended human dose [MRHD] on an area under the time-curve [AUC] basis). No increase in tumor incidence was observed at any dose level.

In rats, tapentadol HCl was administered in diet at dosages of 10, 50, 125 and 250 mg/kg/day for two years (up to 0.20 times in the male rats and 0.75 times in the female rats the MRHD on an AUC basis). No increase in tumor incidence was observed at any dose level.

### *Mutagenesis*

Tapentadol did not induce gene mutations in bacteria, but was clastogenic with metabolic activation in a chromosomal aberration test in V79 cells. The test was repeated and was negative in the presence and absence of metabolic activation. The one positive result for tapentadol was not confirmed in vivo in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis, when tested up to the maximum tolerated dose.

### *Impairment of Fertility*

Tapentadol HCl was administered intravenously to male or female rats at dosages of 3, 6, or 12 mg/kg/day (representing exposures of up to approximately 0.56 times in the male rats and 0.50 times in the female rats the exposure at the MRHD on an AUC basis, based on extrapolation from toxicokinetic analyses in a separate 4-week intravenous study in rats). Tapentadol did not alter fertility at any dose level. Maternal

toxicity and adverse effects on embryonic development, including decreased number of implantations, decreased numbers of live conceptuses, and increased pre- and post-implantation losses occurred at dosages  $\geq 6$  mg/kg/day.

### 13.2 Animal Toxicology and/or Pharmacology

In toxicological studies with tapentadol, the most common systemic effects of tapentadol were related to the mu-opioid receptor agonist and norepinephrine reuptake inhibition pharmacodynamic properties of the compound. Transient, dose-dependent and predominantly CNS-related findings were observed, including impaired respiratory function and convulsions, the latter occurring in the dog at plasma levels ( $C_{max}$ ), which are in the range associated with the maximum recommended human dose (MRHD).

## 1.2 Brief Discussion of Nonclinical Findings

Nucynta® (Tapentadol) is an analgesic compound that is being developed in an Extended-Release (ER) tablet formulation for the management of moderate to severe chronic pain in patients 18 years of age or older. Tapentadol pharmacology suggests a dual mechanism of action, involving both mu-opioid agonism and norepinephrine reuptake inhibition. Tapentadol is a centrally active stereoisomer; no metabolites with analgesic activity are known.

A tapentadol immediate release (IR) tablet formulation received FDA approval for the relief of moderate to severe acute pain in patients 18 years of age or older (NDA 22-304, approved 20 November 2008). The Sponsor (J&JPRD on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc.) is cross-referencing to the IND 61,345, 105,766 and NDA 22-304 for nonclinical support of the safety of Tapentadol ER formulation. No new nonclinical studies for tapentadol were submitted with this NDA.

Tapentadol IR is administered up to 100 mg 6 times per day (700 mg on the first day and 600 mg/day thereafter) while the proposed ER formulation is up to 250 mg twice a day. While ER  $AUC_{0-24}$  is approximately 40% lower than IR  $AUC_{0-24}$ , the ER  $C_{max}$  is approximately 30% greater than the IR  $C_{max}$  at the MHRD.

Tapentadol has been evaluated in a comprehensive preclinical program including pharmacological characterization, preclinical safety (safety pharmacology and toxicology), pharmacokinetics, and ADME. Non-clinical studies were reviewed by Dr. Kathy Young under NDA 22-304.

The major toxicity findings of tapentadol were consistent with its mu-opioid receptor agonist activity (ie, effects on the gastrointestinal, central nervous, respiratory, and cardiovascular systems). At high doses of tapentadol, transient, dose dependent and predominantly CNS-related findings, e.g. fearfulness, sedation or excited behavior, recumbency and hunched posture, impaired respiratory function, rarely convulsions, were observed. In dogs, salivation, vomiting and retching were additionally observed. Tapentadol was shown to have pro-convulsant activity in rats, and induced convulsions in rats, mice, and dogs at high doses. The tapentadol-O-glucuronide metabolite may contribute to this effect. Changes of the liver and cardiovascular system (e.g. QT prolongation) were seen in rats and dogs respectively. Of note, toxicities observed in

non-clinical (rats and dogs) studies were associated with exposure levels that do not support human exposures.

Overall, this reviewer believes that the non-clinical studies of Tapentadol are not sufficient to support the maximum human exposure to tapentadol in either the Tapentadol ER or IR product. In addition to the lack of supportive NOAEL exposures, the highest dose used in the chronic toxicology study in the dog was unable to reach the human exposure associated with the MRHD for the ER product, and neither chronic toxicology study reached AUC levels that support the MRHD exposure for the IR product. See the safety margin tables below for IR and ER formulations. The Safety margins for tapentadol IR are revised to utilize AUC<sub>0-24</sub> hr.

### SM for tapentadol IR

	Dose (mg/kg/d)	HED (mg/kg/d) <sup>a</sup>	Cmax (ng/mL)		AUC <sub>0-24</sub> (ng.hr/mL)		Human SM Based on Cmax		Human SM Based on AUC	
			parent	metabolite	parent	metabolite	parent	metabolite	parent	metabolite
Human IR MRHD										
100 mg/6 times a day	10		~101 <sub>c</sub>	~4206 <sub>c</sub>	~3652 <sub>c,d</sub>	~120000 <sub>c</sub>				
Rat 26 wk										
NOAEL <sup>b</sup>	75	12	386	~24227	624	~156905	3.8X	5.8X	0.2X	1.3X
	150	24	479	~30419	1260	~295075	4.7X	7.2X	0.3X	2.4X
	300	48	1181	~45066	2537	~491457	11.7X	10.7X	0.7X	4.1X
Dog 52 wk										
NOAEL	10	5.5	6.5	7563	20	28091	0.06X	1.8X	0.005X	0.2X
	30	16.7	40	26003	101	86308	0.4X	6.2X	0.03X	0.7X
	80	44.4	183	47424	355	227917	1.8X	11.3X	0.1X	1.9X

<sup>a)</sup> HED: Human Equivalent Dose (Assume 60 kg human) <sup>b)</sup> Approximate Cmax and AUC values (of metabolite) are from 13 weeks rat toxicity study. <sup>c)</sup> This is a rough estimate across different studies (see appendix 3) <sup>d)</sup> Based on Dr. David Lee's calculation (see Appendix 3)

**SM for tapentadol ER**

	Dose (mg/kg/d)	Cmax (ng/mL)		AUC <sub>0-24</sub> (ng.hr/mL)		Human SM Based on Cmax		Human SM Based on AUC	
		parent	metabolite	parent	metabolite	parent	metabolite	parent	metabolite
Human ER MRHD									
250 mg Twice a day	8.3	132 <sup>c</sup>	5714 <sup>c</sup>	2288 <sup>c</sup> (1144x2)	96492 <sup>c</sup> (48246x2)				
Rat 26 wk									
NOAEL <sup>b</sup>	75	386	~24227	624	~156905	3X	4.2X	0.3X	1.6X
	150	479	~30419	1260	~295075	3.6X	5.3X	0.5X	3X
	300	1181	~45066	2537	~491457	8.9X	7.9X	1.1X	5X
Dog 52 wk									
NOAEL	10	6.5	7563	20	28091	0.05X	1.3X	0.01X	0.3X
	30	40	26003	101	86308	0.30X	4.5X	0.04X	0.5X
	80	183	47424	355	227917	1.4X	8.3X	0.15X	2.4X

a) HED: Human Equivalent Dose (Assume 60 kg human) b) Approximate Cmax and AUC values (of metabolite) are from 13-week rat toxicity study. c) See Appendix 2

**SM for tapentadol ER for reproductive and carcinogenicity studies** (NOAELs taken from Dr. Kathleen Young's review of NDA 22-304)

Species	Study	Dose mg/kg/d	NOAEL mg/kg/d	AUC <sub>0-24</sub> ng.h/mL	Human SM based on AUC
Rat	Segment II SC	10, 20, 40	Maternal toxicity: 10	814 (407x2)	0.3X
			Embryofetal toxicity: 20	1764 (882X2)	0.8X
Rabbit	Segment II SC	4, 10, 24	4	615	0.3X
Rat (TP2772)	Segment III gavage	F <sub>0</sub> : 50,150,300	-	(300 mg/kg/d) F <sub>0</sub> : 2546 (1273X 2)	1.1X
		F <sub>1</sub> : 25,50,100	-	(100 mg/kg/d) F <sub>1</sub> : 263-513	0.1X-0.2X
Rat (TP2834)	Segment III gavage	20,50,150,300	Maternal toxicity: 50	1520	0.7X
			Pup development: 20	-	-
			F <sub>1</sub> : 300	-	-
Mouse	Carci gavage	50, 100, 200	200	698	0.3X
Rat	Carci Dietary	10, 50, 125, 250	250	458 (M) 1705 (F)	0.2X-0.7X

**Note:**

1. The systemic exposures (AUC) to the parent drug for almost all doses including the NOAEL in 26-week rats and 52-week dog repeat dose studies are below the clinical exposure associated with the MRHD for both IR and ER formulations.
2. The peak plasma tapentadol concentration ( $C_{max}$ ) at LD and MD taken from the 52-week dog study are below the clinical exposure associated with the MRHD for both IR and ER formulations, though the  $C_{max}$  from the high dose (HD) in the 52-week dog study and from the 26-week rat study (all doses) represent greater than 1-fold the  $C_{max}$  at the MRHD for both IR and ER formulation. Convulsions were seen in 2/8 HD dogs and the  $C_{max}$  exposure margin associated with this dose level for the ER and IR formulation is 1.8 and 1.4 times greater than the clinical  $C_{max}$  at the MRHD.
3. The systemic exposures (AUC) to the metabolite at LD and MD in the 52-week dog study are below the clinical exposure associated with the MRHD for both IR and ER formulations.
4. The systemic exposures (AUC) to the parent drug for the NOAEL taken from reproductive and carcinogenicity studies are below the clinical exposure associated with the MRHD.

It is noted that significant CNS findings (hallucination, convulsion and serotonin syndrome) have been reported in postmarketing experience with Tapentadol IR (Nucynta®) tablets and are being evaluated by the Office of Surveillance and Epidemiology. Also a similar drug, Tramadol (with mu-opioid and NET inhibitory activities) showed seizures in post-marketing reporting and is described in the label. Notably, both Seizures and Serotonin Syndrome Risk are described in the approved Nucynta label.

## **2 Drug Information**

### **2.1 Drug:**

Nucynta®

#### **2.1.1 CAS Registry Number (Optional)**

175591-09-0

#### **2.1.2 Generic Name**

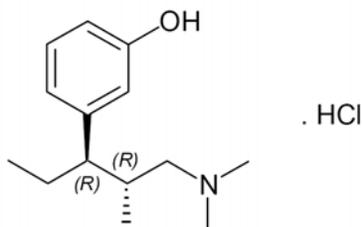
Tapentadol HCL

#### **2.1.3 Code Name**

CG5503 and R331333

#### **2.1.4 Chemical Name**

3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol

**2.1.5 Molecular Formula/Molecular Weight**C<sub>14</sub>H<sub>23</sub>NO.HCl / 257.80**2.1.6 Structure****2.1.7 Pharmacologic class**

Mu-Opioid receptor (MOR) agonist/norepinephrine (NE) re-uptake inhibitor

**2.2 Relevant IND/s, NDA/s, and DMF/s**

Submission	Status/date	Sponsor	Drug	Indication	Division
IND 61,345	Active/ 12/04/2000	J&JPRD	Tapentadol IR tablets	Moderate to severe acute pain	DAAP
IND 105,766	Active/ 7/19/2009	J&JPRD	Tapentadol ER tablets	Chronic diabetic peripheral neuropathy	DAAP
(b) (4)					
NDA 22-304	approved 11/20/2008	Ortho-McNeil-Janssen	Tapentadol IR tablets (50, 75 and 100 mg)	Moderate to severe acute pain	DAAP
This NDA 200-533	Under Review 12/01/2009	Ortho-McNeil-Janssen	Tapentadol ER tablets (50, 100, 150, 200 and 250 mg)	Moderate to severe chronic pain	DAAP
(b) (4)					

**2.3 Clinical Formulation**

Tapentadol Tamper Resistant Extended-Release tablets in strengths of 50, 100, 150, 200, and 250 mg (free base)

**2.3.1 Drug Formulation**

The compositional formulation of the Tamper Resistant Extended-Release tablets, 50-, 100-, 150-, 200-, and 250-mg proposed for commercial manufacture are presented in Table 1 and Table 2 by the Sponsor.

Table 1: Tapentadol Extended-Release Tablets Composition - Core

Component	Quality Reference	Function	Dose Strength (Free Base of Tapentadol)									
			50-mg		100-mg		150-mg		200-mg		250-mg	
			mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w
Tapentadol HCl (R331333)	Non-compendial	Active ingredient	(b) (4)									
Polyethylene Oxide	NF											
Hypromellose (b) (4)	USP											
Polyethylene Glycol (b) (4)	NF											
Vitamin E	USP											
Polyethylene Glycol (b) (4)	NF											
Total Core Tablet Weight												

-- = Not applicable

Table 2: Tapentadol Extended-Release Tablets Composition - Coating

Film Coat	Quality Reference	Function	Dose Strength									
			50-mg		100-mg		150-mg		200-mg		250-mg	
			mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w
(b) (4)	Noncompendial		(b) (4)									
	Noncompendial											
	Noncompendial											
	Noncompendial											
	Noncompendial											
	USP											
	Noncompendial											
	Noncompendial											
	NF											
Propylene Glycol <sup>b</sup>	USP											

<sup>a</sup> Removed during processing

<sup>b</sup> May be used during processing to optimize print quality.

-- = Not applicable

### 2.3.2 Comments on Novel Excipients

Excipients in the proposed drug product are acceptable.

Reviewer's table:

Tamper Resistant formulation (TRF): Per 250 mg tablet		Maximum potency in other approved product *
Polyethylene Oxide	(b) (4)	Up to 543.9 mg
Hypromellose, USP	(b) (4)	Up to 536.8 mg
Polyethylene glycol (b) (4), NF	(b) (4)	Up to 450 mg
Vitamin E, USP	(b) (4)	Up to 2 mg

\* see Inactive Ingredient Guidance

(b) (4)

Reviewer's table

Product identification	Polyvinyl alcohol (%W/W)	Titanium Dioxide (%W/W)	Macrogol/PEG (b) (4) (%W/W)	Talc (%W/W)	(b) (4) aluminum lake (%W/W)	Iron oxide yellow (%W/W)
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(b) (4)

Dr. Bertha noted that: *“the holder has provided the quantitative composition as well as the references to the pertinent food additive regulations and the compendial quality requirements for the components of the four film coating systems. It is also important to note that even though there is no CFR reference for the polyvinyl alcohol that is used as (b) (4) for each of these coating systems, this material is a common excipient in oral, ophthalmic, intravitreal, IM injection, and various types of topical dosage forms. The highest quantity of polyvinyl alcohol reported in an approved solid oral dosage form listed in the Inactive Ingredient Guide is 34.0 mg. This quantity is more than what the N200533 applicant is using as part of these (b) (4) coating systems.”*

**2.3.3 Comments on Impurities/Degradants of Concern**

The applicant is complying with both ICH Q3A and B and there are no specified impurities or degradation products in the drug product.

From batch release data and stability studies at long-term, intermediate, accelerated and stress conditions, no degradation compounds are reported >0.05%. Therefore, no specific degradation compounds are specified and the limit of the unspecified degradation products is the same as the identification/qualification threshold of 0.2%.

**2.4 Proposed Clinical Population and Dosing Regimen**

Nucynta® (50, 100, 150, 200, and 250 mg), an Extended-Release (ER) tablet formulation intended for the management of moderate to severe chronic pain in patients

18 years of age or older. The dosage regimen is up to 250 mg twice daily (MDRHD is 500 mg).

## 2.5 Regulatory Background:

A tapentadol immediate release (IR) tablet formulation has been received FDA approval for the relief of moderate to severe acute pain in patients 18 years of age or older (NDA 22-304, approved 20 November 2008). The Sponsor submitted the IND 61,345 for development of both IR and ER formulation in December 4, 2000. The Sponsor is cross-referencing to NDA 22-304 for nonclinical support of the safety of Tapentadol ER formulation.

(b) (4)

## 3 Studies Submitted

No new nonclinical studies for tapentadol were submitted with this NDA. Eight additional nonclinical studies conducted subsequent to the approval of IR Tapentadol (additional investigations of binding, mechanism of action, nonclinical efficacy and a toxicity study in juvenile rats) were submitted to IND 61,345. (b) (4)

(b) (4) All studies are not considered to provide significant informative value for this NDA.

### 3.1 Studies Reviewed:

No nonclinical studies were submitted or reviewed in this submission. Dr. Kathy Young reviewed nonclinical studies submitted in the cross-referenced NDA 22-304.

### 3.2 Studies Not Reviewed: N/A

### 3.3 Previous Reviews Referenced

The Sponsor cross-referenced to NDA 22-304 for nonclinical support of the safety of Tapentadol ER formulation. The nonclinical program included pharmacology, safety pharmacology, chronic toxicology, genetic toxicology, carcinogenicity and reproductive toxicology studies. See below table, toxicity studies, provided from NDA 22-304.

Study type	Route of administration	Species	GLP compliance
Single-dose toxicity	gavage and i.v.	mouse and rat	yes
Repeat-dose toxicity			
13 weeks	gavage and dietary	mouse	yes
4 weeks	gavage and i.v.	rat	yes
13 weeks	gavage and dietary	rat	yes
26 weeks	gavage	rat	yes
2 week	gavage	dog	yes
4 weeks	i.v.	dog	yes
13 weeks	gavage, i.v. and s.c.	dog	yes
52 weeks	gavage	dog	yes
2 weeks	gavage and s.c.	monkey	yes
Genotoxicity	<i>in vitro</i>	mammalian (2 studies) and non-mammalian cells	yes
	i.v. (2 studies) and gavage	rat	yes
Carcinogenicity	gavage	mouse	yes
	dietary	rat	yes
Reproductive toxicity			yes
fertility and early embryonic development	i.v.	rat	yes
embryo-fetal development	i.v. and s.c.	rat and rabbit	yes
pre- and postnatal development	gavage	rat	yes

## 4 Pharmacology

### 4.1 Primary Pharmacology

*From Dr. Kathleen Young's Review, NDA 22-304*

Tapentadol is an agonist at the mu-opioid and sigma2 receptors, and inhibits norepinephrine reuptake, with minor affinity for the N-methyl-D-aspartate receptor and some antagonist activity at the muscarinic (M1) receptor. Opioid agonist activity was demonstrated *ex vivo*, by inhibition of the twitch reaction in isolated guinea pig ileum that was reversible by the opioid antagonist naloxone. Nonclinical studies conducted *in vivo* demonstrated analgesic activity in models of acute anti-nociception and in inflammatory and neuropathic pain models in mice, rats and rabbits. Tapentadol by the IV, IP and oral routes demonstrated efficacy in the tail-flick, phenylquinone writhing, hot-plate and toothpulp stimulation tests, with an IV potency of approximately 1/4-1/2 times that of intravenous morphine and 3-5 times the potency of intravenous tramadol. By the oral route, tapentadol was approximately equipotent to morphine in analgesic effects in these assays. The maximum effect was observed at 20 minutes in the tail-flick test in rats, and the duration of action by the oral route was 60-90 minutes. Tapentadol showed analgesic potency in models of inflammatory and neuropathic pain of approximately 1/2 that of morphine and 1/4 to equivalent the potency of tramadol by the intraperitoneal and intravenous routes in the paw-pressure test, formalin test, and chronic constriction injury (mononeuropathy) models in rats. The acute antinociceptive effects of intravenous and oral tapentadol were partially blocked by naloxone, indicating a mu-opioid receptor mechanism of action. Tapentadol antinociception was not blocked by the alpha2-receptor antagonist yohimbine and the serotonin-2A-C antagonist ritanserin.

### 4.2 Secondary Pharmacology

*From Dr. Kathleen Young's Review, NDA 22-304*

Secondary pharmacodynamic studies demonstrated drug class effects characteristic of those mu-opioid receptor agonist drugs. Tapentadol inhibited NH<sub>3</sub>-induced cough by in the rat, indicating antitussive activity, and was weakly emetic, inducing retching or vomiting in ferrets and dogs. Local, intradermal injections inhibited dermal twitch response to mechanical stimuli in a concentration-dependent manner in guinea pigs. Tapentadol prolonged barbiturate anesthesia in a study on hexobarbital sleeping time, and inhibited exploration activity in a hole-board test.

### 4.3 Safety Pharmacology

*From Dr. Kathleen Young's Review, NDA 22-304*

Tapentadol administration produced prominent CNS effects in the safety pharmacology studies in rodents, that included decreased activity and awareness, loss of reflexes (including corneal, pinna and hindlimb), and convulsions at the highest doses studied. Motor impairment was also observed at extremely high doses (ED<sub>50</sub> > 100 mg/kg) in a Rota rod test mice. A concentration-effect CNS safety pharmacology study in rat showed convulsions with cyanosis and deaths at 15-20 minutes after IV injection (15 mg/kg) at plasma and CSF parent and metabolite concentrations of approximately 1000 ng/ml, and also at ≥12 hours after dosing in the absence of detectable parent drug and

glucuronide metabolite concentrations in plasma and CSF (sulfate metabolite was assessed and found below the level of detection at all time points). The Sponsor speculated that potential products of parent drug or metabolite enrichment in deeper CNS compartments, not detected in plasma and CSF, may have produced these effects, but this issue was not further addressed.

Tapentadol cardiovascular safety was evaluated in *in vitro*, *ex vivo* and *in vivo* assays. The results of the hERG assay in Chinese Hamster Ovary cells showed reduction of the outward potassium tail current amplitude at all concentrations studied (IC<sub>50</sub> = 36.14 mcM) with 66% recovery after wash-out, suggesting partial reversibility. In *ex vivo* preparations in isolated cardiac tissues, tapentadol showed concentration-dependent negative chronotropic effects in guinea pig atrial muscle and negative inotropic effects at high concentrations in papillary muscle. The action potential duration was prolonged by tapentadol at concentrations of 30-100 mcM in isolated New Zealand White rabbit papillary muscle, and was shortened at 10-100 mcM, with reduced upstroke velocity and action potential amplitude at the highest concentration in Guinea pig papillary muscle. There was a concentration-dependent reduction of heart rate, with slowing of atrioventricular conduction and ventricular depolarization in isolated Langendorff heart preparations in spontaneously beating Guinea pig hearts. Tapentadol increased heart rate and arterial blood pressure in the conscious dog, and decreased blood pressure in anesthetized dog, but had no effects on QT interval in the safety pharmacology studies. However, QT prolongation was observed in the toxicology studies in dog. The main metabolite, tapentadol O-glucuronide had no effects in the hERG assay and *ex vivo* in guinea pig papillary muscle.

Tapentadol respiratory and gastrointestinal depressant effects were consistent with those characteristic of mu-opioid receptor agonist class effects in these systems. Decreased spontaneous respiration rate and CO<sub>2</sub>-induced respiratory stimulation, with corresponding increases in arterial blood CO<sub>2</sub> partial pressure and decreased pO<sub>2</sub> were found in rat. Partial tolerance to tapentadol respiratory depressant effects developed with repeated dosing, that corresponded to observed tolerance to analgesic effects in the tail flick test in another study in rats. Tapentadol-induced inhibition of intestinal fluid transport was observed in isolated Guinea pig ileum, and gut motility was inhibited in mice.

## 5 Pharmacokinetics/ADME

*From Dr. Kathleen Young's Review, NDA 22-304*

Orally administered tapentadol HCl is rapidly absorbed, shows extensive tissue distribution in animals, and crosses the blood brain barrier and placenta. Tapentadol is approximately 20% bound to plasma proteins across species and in human. Oral bioavailability was low in all nonclinical species tested, ranging from 1% in dog to 9% in rat, compared to 32% in human. There was evidence of accumulation with repeated dosing in several, but no in all nonclinical studies. Tapentadol half-life by the oral route was approximately 0.5-1 hour across doses and nonclinical species tested. The metabolic profiles are similar in all species examined including humans, although tapentadol is metabolized to a greater extent in the animal species studied. Tapentadol is primarily metabolized by direct glucuronidation and to a lesser extent by sulfate

formation, with some oxidative P450 metabolism by N-demethylation and hydroxylation. The main circulating metabolite is tapentadol O-glucuronide, resulting in systemic exposure to the glucuronide metabolite of up to 14 times compared to parent drug exposure. No active metabolites were found. Tapentadol had no effects on microsomal cytochrome P450 content, and did not show inhibition of cytochrome P450. Tapentadol is nearly completely excreted in urine as the glucuronide metabolite.

## 6 General Toxicology

*From Dr. Kathleen Young's Review, NDA 22-304*

The target organs of toxicity in the toxicology studies in rat were the central nervous system (CNS) and liver. The LD50 was 1250 mg/kg PO in the single dose study. Tapentadol treatment-related mortality was observed within several hours of dosing and was probably a result of respiratory depression resulting from pharmacological activity by tapentadol in regulatory centers in the brain stem. Acute treatment-related CNS effects observed in rat, most of which were consistent with mu-opioid mechanism of action, included irritability, hyperactivity, cyanosis, Straub tail, lateral recumbency, tremor, increased sensitivity to touch and noise, increased escape response, irregular respiration and convulsions. The convulsions may be related to NE reuptake inhibition; there was reversibility of convulsions with diazepam and phenobarbital, but not by naloxone in 2 single-dose IV studies in rat. Additionally, there was no evidence of tolerance development to the treatment-related convulsions observed in dog; little or no tolerance develops to effects by NE reuptake inhibition whereas tolerance to opioid agonist effects is generally known. Hepatotoxicity was evident by findings of dose related and treatment duration-related increases in the incidence and severity of liver enzymes (ALAT, ASAT, ALP) and liver weights, and histopathology findings of hepatocellular hypertrophy, and in one sub-acute intravenous study, liver necrosis. No Kupffer cell activation or liver fibrosis was found in any study, and the effects in liver were reversible. The toxicology studies in dog revealed target organ toxicity in the central nervous (CNS), cardiovascular (CV), and gastrointestinal (GI) systems. The CNS clinical signs were similar across a range of doses, routes and durations of treatment, and included salivation, restlessness, recumbency, decreased activity, rhinorrhea, panting, labored breathing, and tachypnea. Partial tolerance to these effects was observed, acutely by decreased severity of response between b.i.d. doses, and long term by decreased severity over the treatment period durations. Convulsions, often accompanied by paddling movements, tremors, and twitching were observed in male and/or female dogs given tapentadol by subcutaneous and oral routes, in the studies of 7 days to 1 year duration. There was no evidence of tolerance to tapentadol convulsant effect. Most of the dogs that convulsed were sacrificed in extremis, died during treatment, or received dose reductions following the seizures. However, seizures were observed in one female dog on multiple days throughout the 1-year oral gavage study up to dosing Day 358. QT prolongation was observed in dogs given tapentadol by subcutaneous injection for 3 months, and oral gavage for 13 to 52 months. Reversible hemorrhage in the mesentery, with dark red discolorations in the stomach, small and large intestines were seen in one subcutaneous toxicity study, and activated lymphoid follicles in the gastric mucosa and small intestines were found in an oral gavage study in dogs, that were attributed to GI immune response by the examining pathologist.

***Note: The clinical exposure at the MRHD of 600 mg/day in calculations below appears to use of 0-tau from the multiple dose study state which should be corrected and multiplied by 6. Therefore the safety margins are ~6-fold less than calculated by Dr. Young (see safety margin table in the Executive Summary)***

Key findings in 26 weeks rat toxicity (gavage) study (from Dr. Kathleen Young's review NDA 22-304, page 122-131)

- Target organs were the CNS and liver:
  - Treatment-related effects by CG5503 (tapentadol) were characteristic of class effects by  $\mu$ -opioid receptor agonist agents in rats, with hepatic effects suggestive of adaptive liver metabolism
  - The effects were non-lethal, with the exception of respiratory depression possibly responsible for observed mortality
  - Treatment-related effects were reversible during an 8-week recovery period
- Dose-related **↑ in deaths** without clear cause, resulting in early termination (Week 13) of the surviving rats at the 450 mg/kg/day dose, and addition of 10 rats/sex at 300 mg/kg/day with extension of the dosing period for those rats to 26 weeks to allow for adequate evaluation of reversibility
  - Deaths probably result of **respiratory depression**, a well-known class effect by  $\mu$ -opioid receptor agonist drugs
  - HD terminated early (Week 13) due to excessive mortality
- Clinical signs observed at  $\geq 150$  mg/kg/day
  - Dose-related **↑** excited behavior, recumbency, hunched posture, labored respiration, general poor condition
  - Clinical signs consistent with known effects by  $\mu$ -opioid receptor agonists in rats
- BW & food consumption
  - **Reduced BW** in the males (M) (-6% to -7% compared to controls) and (F) (-4% to -7%) at 450 mg/kg/day and in the M (-6% to -7%) at 300 mg/kg/day
  - **Increased BWG** in the M (14.1%) and F (12.4%) compared to controls during the recovery period
  - **↓** food consumption at 300 and 450 mg/kg/d in M and F and at 150 mg/kg/day in F
- Hematology
  - **↑ leukocyte** count (due to **↑** lymphocytes and segmented neutrophils) in the F at 300 and 450 mg/kg/day
  - **↓ PT and APTT** in the M at 450 mg/kg/day in Week 13
  - **↑ fibrinogen** in the M and F at 450 mg/kg/day in Week 13

- Clinical chemistry
  - ↑ **liver enzymes** (ASAT, ALAT) at 450 mg/kg/day in Week 13
  - Dose-related ↑**ALP and LDH** at 150 and 300 mg/kg/day in Weeks 13 and 26
- Urinalysis
  - ↑ **urine volume** at all doses
  - ↑**specific gravity and osmolality** in F at 450 mg/kg/d
  - Effects reversed during recovery
- Organ weights: ↑ **liver weights** at 300 and 450 mg/kg/day in M & F, and in M at 150 mg/kg/day, reversed during recovery period
- Gross pathology: **enlarged liver** at 150 (2 M), 300 (3 M) and 450 (6 M and 1 F) mg/kg/day
- Histopathology:
  - Centrilobular or diffuse **hepatocellular hypertrophy** at ≥150 mg/kg/day, possibly adaptive in response to increased liver metabolic activity
    - Found in absence of necrosis
    - Possible association with increases in liver enzyme activity, as increased glucuronyl transferase activity found in the evaluation of microsomes
  - Reversible after 8-week recovery period
  - ↑ **fatty change** in liver at 300 mg/kg/day compared to controls
    - Possible relationship to altered lipid handling as a result of decreased food consumption and body weights
    - Reversible after 8-week recovery period
- Dose-related ↑ in exposure to test article in all treated groups
- NOAEL = 75 mg/kg/day
- Systemic exposure at the NOAEL represented approximately **0.8X** in the M (AUC = 391 ng.h/ml) and **1.7X** in the F (AUC = 857 ng.h/ml) the clinical exposure at the MRHD of 600 mg/day in a 70-kg patient on an AUC basis
- Systemic exposure at the NOAEL on a C<sub>max</sub> basis, possibly relevant to the CNS effects observed in the rats, represented approximately 2X in the males and 4.4X in the females the clinical C<sub>max</sub> at the MRHD
- Exposure to the glucuronide metabolite at the NOEL of 75 mg/kg/day represented approximately **9X** the clinical exposure to the metabolite at the MRHD, AUC basis

Key findings in 52 weeks **dog** toxicity (gavage) study (from Dr. Kathleen Young's review NDA 22-304, page 146-162)

- The target organs were the CNS and cardiovascular system
- **Convulsions** at the HD in 2 F (80 mg/kg/d, exposure slightly less than that at the clinical MRHD on an AUC basis, and approximately 2 times the exposure on a Cmax basis)
  - Resulted in sacrifice *in extremis* in one of the dogs
  - Known effect of opioid receptor agonists
  - Reversal by naloxone supports relationship to opioid pharmacological effect
  - Not observed after the recovery period
- **QT, including QTc (Fridericia's and Van de Water's corrections) prolongation** at the HD
  - Observed throughout the study in nearly all of the HD M and F
  - Reversible; not observed after the 4-week recovery period
- Slight, minimal **decrease in partial thromboplastin time** in the HD M and F throughout the treatment period, not reversible (observed at end of recovery)
- Slight **increase in plasma sodium** at the HD, compared to controls but not to baseline measurements, and with no associated changes in other electrolytes
- Minimal to **slight focal gliosis with perivascular mononuclear cell infiltration in the medulla oblongata and/or pons** in 1 HD F and in 2 MD F and 1 MD M, without relationship to convulsions and considered to be spontaneous, in agreement with the pathologist
- No treatment-related effects on P450 content; however, dose-related **increases in O-deethylase activity** were observed in F and dose-related **increases in N-demethylase activity** were observed in M and F. **2-aminophenol glucuronyltransferase activity was decreased** in M and F.
- The NOAEL was 10 mg/kg/day
- The systemic exposure to the parent drug at the NOAEL (AUC = 23.3 mcg.h/ml in the males and 16.6 mcg.h/ml in the females) represented approximately **0.05 times** the clinical exposure ( $\approx 500$  ng.h/ml) at the MRHD of 600 mg/day.
- The peak plasma tapentadol concentrations (Cmax) at the NOAEL (6.8 mcg/L in M and 6.3 mcg/L in F) represented approximately 0.06 times the Cmax ( $\approx 118$  ng/ml) at the MRHD of 600 mg/day.
- Exposure to the O-glucuronide metabolite at the NOAEL represented approximately 1.5 times the clinical exposure at the MRHD, AUC basis
  - Demonstrates lower metabolic transformation to the glucuronide in dog, when compared to rat which showed considerably higher glucuronide exposures

## 7 Genetic Toxicology

Tapentadol was evaluated in a standard battery of genetic toxicity studies and is considered to be equivocal for clastogenicity. A positive response was found in one of two in vitro Chromosome Aberration studies in Chinese hamster V79 cells, showing increased incidence of structural chromosome aberrations at concentrations greater than 1000 mcg/ml in the presence of metabolic activation with S9. No evidence of genetic toxicity by tapentadol was found in the Ames test, the in vivo assay for clastogenicity in rat bone marrow cells, and in rat hepatocytes in the Unscheduled DNA Synthesis assay (from Dr. Young Review, NDA 22-304)

## 8 Carcinogenicity

*From Dr. Kathleen Young's Review, NDA 22-304*

Tapentadol was negative for carcinogenicity in 104-week oral administration studies in mice treated by gavage, and in rats given tapentadol by dietary admixture.

## 9 Reproductive and Developmental Toxicology

*From Dr. Kathleen Young's Review, NDA 22-304*

There was no evidence of adverse effects on fertility and reproductive performance, embryo-fetal malformations and pre- and post-natal development in rats. The results of an embryo-fetal study in Himalayan rabbits given subcutaneous tapentadol showed dose related increases in the incidence of runts and multiple malformations, including thoracogastroschisis, prolapsed organs, amelia, phocomelia, encephalocele, spina bifida, cleft palate, ablepharia, and skeletal malformations. The malformations were observed in fetuses from dams showing severe maternal toxicity, although not all dams showing treatment-related toxicity had malformed fetuses. The incidences of malformations in the rabbits were within the upper limit of historical control range for the laboratory provided by the Sponsor, except for ablepharia, which slightly exceeded the upper historical control range. Tapentadol was found negative for external and skeletal malformations, variations, and retardations in another, intravenous study in rabbits. However, a relationship of the dose-related increased incidences of malformations to tapentadol treatment in the subcutaneous study in rabbits cannot be rejected unequivocally.

## 10 Special Toxicology Studies

*From Dr. Kathleen Young's Review, NDA 22-304*

Tapentadol was negative for immunotoxicity in a 4-week oral study in rats, which examined morphology, distribution, and function of T- and B- lymphocytes, monocytes, and granulocytes. Special histopathology evaluation to investigate treatment-induced neuronal injury, vacuolation and necrosis in areas known to be sensitive to NMDA receptor binding activity in rat brain showed no evidence of morphological lesions by intravenous and oral tapentadol administration for 4 weeks.

## **11 Integrated Summary and Safety Evaluation**

The target organs of tapentadol toxicity observed in the nonclinical studies submitted in NDA 22-304 suggest potential adverse central nervous system (CNS), hepatic, cardiovascular, and gastrointestinal (GI) effects with clinical use. Additionally, there were equivocal signals for potential clastogenicity by a tapentadol metabolite in the evaluation of genetic toxicology in one of two in vitro Chromosome Aberrations assays in Chinese Hamster V79 cells, and for potential adverse effects on human pregnancy and embryo-fetal toxicity including possibly increased risk of malformations in a subcutaneous studying rabbit, but not in the rabbit assay using the intravenous route.

In summary, the non-clinical studies of Tapentadol are not sufficient to support the maximum human exposure to Tapentadol ER nor Tapentadol IR (see the safety margin in the Executive Summary). This lack of full coverage was noted in the Supervisory Memo Addendum for IR formulation by Dr. Adam Wasserman (Appendix 4) and, while the original nonclinical recommendation was to support approval, the nonclinical data is in itself insufficient to support approval.

## 12 Appendix/

### Appendix 1

The study drug (Tapentadol ER) was dosed at Day 1 once daily and from Day 4 until Day 6 twice daily to reach steady state before or around Day 6 at the fifth dose.

**Table 8:** Summary of Descriptive Statistics of the Pharmacokinetic Parameters of Tapentadol (Study R331333-PAI-1036; HP5503/38: Pharmacokinetic Analysis Set)

Pharmacokinetic Parameters (units)	n	Tapentadol TRF 250 mg	
		Mean ± SD	%CV
<b>Day 1</b>			
C <sub>max</sub> , ng/mL	15	88.0 ± 27.8	31.6
t <sub>max</sub> , h	15	5.00 (2.00-12.00)	
AUC <sub>0-12h</sub>	15	651 ± 202	31.1
AUC <sub>∞</sub> , h.ng/mL	15	1070 ± 303	28.3
t <sub>1/2</sub> , h	15	4.4 ± 0.8	17.9
<b>Day 6</b>			
C <sub>max,ss</sub> , ng/mL	17	132 ± 35.1	26.7
t <sub>max,ss</sub> , h	17	5.00 (2.00-10.02)	
AUC <sub>τ</sub> , h.ng/mL	16	1144 ± 339	29.7
C <sub>avg,ss</sub> , ng/mL	16	95.2 ± 28.1	29.5
t <sub>1/2</sub> , h	16	5.2 ± 1.0	18.8
FI, %	16	65.3 ± 27.1	41.4
Acc. Ratio (C <sub>max</sub> )	17	1.60 ± 0.605	26.7
Acc. Ratio (AUC)	14	1.86 ± 0.552	29.7

t<sub>max</sub>: median (min-max)

TRF = tamper resistant prolonged-release formulation, SD = standard deviation, CV = coefficient of variation

**Table 9:** Summary of Descriptive Statistics of the Pharmacokinetic Parameters of Tapentadol-O-Glucuronide  
(Study R331333-PAI-1036; HP5503/38: Pharmacokinetic Analysis Set)

Pharmacokinetic Parameters (units)	n	Tapentadol TRF 250 mg	
		Mean ± SD	%CV
<b>Day 1</b>			
C <sub>max</sub> , ng/mL	15	3669 ± 963	26.3
t <sub>max</sub> , h	15	5.00 (2.02-12.00)	
AUC <sub>0-12h</sub>	15	26527 ± 5623	21.2
AUC <sub>∞</sub> , h.ng/mL	15	42835 ± 9239	21.6
t <sub>1/2</sub> , h	15	4.1 ± 0.9	20.7
<b>Day 6</b>			
C <sub>max,ss</sub> , ng/mL	17	5714 ± 985	17.2
t <sub>max,ss</sub> , h	17	5.00 (4.00-10.02)	
AUC <sub>τ</sub> , h.ng/mL	16	48246 ± 9061	18.8
C <sub>avg,ss</sub> , ng/mL	16	4014 ± 755	18.8
t <sub>1/2</sub> , h	16	4.9 ± 0.9	18.8
FI, %	16	67.5 ± 26.7	39.6
Acc. Ratio (C <sub>max</sub> )	17	1.64 ± 0.338	17.2
Acc. Ratio (AUC)	14	1.82 ± 0.328	18.0

t<sub>max</sub>: median (min-max)

TRF = tamper resistant prolonged-release formulation, SD = standard deviation, CV = coefficient of variation

**Appendix 2**

The information provided for the four (b) (4) tablet coatings is reproduced below from pp. 6122-6125 of the file from the 21-NOV-2008, amendment. (Provided by Dr. Craig Bertha, CMC reviewer).

**PRODUCT IDENTIFIER:** 85F99040  
**PRODUCT DESCRIPTION:** (b) (4) BLUE

%W/W	Ingredients/Compendial Reference	Dye Strength	EEC Number	CFR Reference	CI Number
(b) (4)	POLYVINYL ALCOHOL- (b) (4) (USP, FCC, PhEur, JPE) (Refer to DMF (b) (4) Filed 10/6/2000)		(b) (4)	73.575, 73.1575, 172.820	(b) (4)
	TITANIUM DIOXIDE (USP, FCC, PhEur, JP)				
	MACROGOL/PEG (b) (4) (NF, PhEur, MACROGOL (b) (4) JP)			73.1550	
	TALC (USP, FCC, PhEur, JP)			73.1550	
	FD&C BLUE #2 (b) (4) ALUMINUM LAKE	(b) (4)		82.51, 82.102	

\*\*\*\* CONFIDENTIAL \*\*\*\*

**PRODUCT IDENTIFIER:** 85F91260  
**PRODUCT DESCRIPTION:** (b) (4)

%W/W	Ingredients/Compendial Reference	Dye Strength	EEC Number	CFR Reference	CI Number
(b) (4)	POLYVINYL ALCOHOL- (b) (4) (USP, FCC, PhEur, JPE) (Refer to DMF (b) (4) Filed 10/6/2000)			172.820	
	MACROGOL/PEG (b) (4) (NF, PhEur, MACROGOL (b) (4) JP)				
	TITANIUM DIOXIDE (USP, FCC, PhEur, JP)		(b) (4)	73.575, 73.1575, 73.1550	(b) (4)
	TALC (USP, FCC, PhEur, JP)			73.1550	
	FD&C BLUE #2 (b) (4) ALUMINUM LAKE	(b) (4)		82.51, 82.102	
	IRON OXIDE YELLOW (NF, JPE)			73.1200	

\*\*\*\* CONFIDENTIAL \*\*\*\*

**PRODUCT IDENTIFIER:** 85F90616  
**PRODUCT DESCRIPTION:** (b) (4) BLUE

%W/W	Ingredients/Compendial Reference	Dye Strength	EEC Number	CFR Reference	CI Number
(b) (4)	POLYVINYL ALCOHOL- (b) (4) (USP,FCC,PhEur, JPE)(Refer to DMF (b) (4) Files 10/6/2000) MACROGOL/PEG (b) (4) NF, PhEur, MACROGOL (b) (4) JP			172.820	
	TITANIUM DIOXIDE (USP,FCC, PhEur, JP)		(b) (4)	73.575, 73.1575	(b) (4)
	TALC (USP,FCC, PhEur, JP)			73.1550	
	FD&C BLUE #2/ (b) (4) ALUMINUM LAKE	(b) (4)		82.51, 82.102	

\*\*\*\* CONFIDENTIAL \*\*\*\*

**PRODUCT IDENTIFIER:** 85F90602  
**PRODUCT DESCRIPTION:** (b) (4) BLUE

%W/W	Ingredients/Compendial Reference	Dye Strength	EEC Number	CFR Reference	CI Number
(b) (4)	POLYVINYL ALCOHOL- (b) (4) (USP,FCC,PhEur, JPE)(Refer to DMF (b) (4) Filed 10/6/2000) MACROGOL/PEG (b) (4) NF, PhEur, MACROGOL (b) (4) JP			172.820	
	TALC (USP,FCC, PhEur, JP)		(b) (4)	73.1550	
	TITANIUM DIOXIDE (USP,FCC, PhEur, JP)			73.575, 73.1575	(b) (4)
	FD&C BLUE #2/ (b) (4) ALUMINUM LAKE	(b) (4)		82.51, 82.102	

\*\*\*\* CONFIDENTIAL \*\*\*\*

**Evaluation: Adequate.** The holder has provided the quantitative composition as well as the references to the pertinent food additive regulations and the compendial quality

requirements for the components of the four film coating systems. It is also important to note that even though there is no CFR reference for the polyvinyl alcohol (b) (4) for each of these coating systems, this material is a common excipient in oral, ophthalmic, intravitreal, IM injection, and various types of topical dosage forms. The highest quantity of polyvinyl alcohol reported in an approved solid oral dosage form listed in the Inactive Ingredient Guide is 34.0 mg. This quantity is more than what the N200533 applicant is using as part of these (b) (4) coating systems.

## Appendix 3

**Table 5: Summary of Descriptive Statistics of the Pharmacokinetic Parameters of Tapentadol**

PK parameters	n	Tapentadol IR 100 mg	Tapentadol IR 150 mg
C <sub>trough</sub> , ng/mL	55	55.2 ± 25.2	93.3 ± 50.7
C <sub>tmax,ss</sub> , ng/mL	58	129 ± 42.0	197 ± 89.1
t <sub>max,ss</sub> , h	58	1.45 (0.87-6.00)	1.49 (0.40-6.02)
AUC <sub>τ</sub> , h.ng/mL	58	465 ± 146	729 ± 282
C <sub>avg,ss</sub> , ng/mL	58	78.4 ± 24.3	122 ± 48.0
t <sub>1/2</sub> , h	53	3.7 ± 0.9	3.7 ± 0.9
CL <sub>ss</sub> /F, mL/min	58	3969 ± 1351	3820 ± 1176

t<sub>max</sub>: median (min-max)

Pharmacokinetic Parameters of Tapentadol After First and Repeated Dose Administration of Tapentadol Capsules (Study HP5503/13)

	75 mg <sup>a</sup> (n=10)	100 mg (n=12)	125 mg <sup>a</sup> (n=11)	150 mg <sup>a</sup> (n=11)	175 mg <sup>a</sup> (n=10)
<b>First dose</b>					
C <sub>max</sub> , ng/mL	72.7 ± 36.3	95.1 ± 21.3	124 ± 40.7	135 ± 45.0	125 ± 37.3
AUC <sub>0-6h</sub> , ng.h/mL	229 ± 90.3	299 ± 87.5	413 ± 132	439 ± 121	446 ± 126
t <sub>max</sub> , h	1.50 (0.52-3.00)	1.75 (1.00-4.00)	1.50 (0.50-5.95)	1.50 (1.00-3.00)	2.00 (0.50-3.00)
DN-C <sub>max</sub> , ng/mL	96.9 ± 48.4	95.1 ± 21.3	99.2 ± 32.6	90.0 ± 30.0	71.4 ± 21.3
DN-AUC <sub>0-6h</sub> , ng.h/mL	305 ± 120	299 ± 87.5	330 ± 106	293 ± 80.7	255 ± 72.0
DN-C <sub>max</sub> ratio (90% CI)	reference	105.01 (83.19-132.56)	98.63 (80.88-120.27)	98.37 (77.60-124.70)	76.83 (62.54-94.38)
DN- AUC <sub>0-6h</sub> ratio (90% CI)	reference	100.38 (81.30-123.94)	100.91 (88.01-115.70)	103.64 (83.73-128.29)	84.78 (73.50-97.78)
<b>Repeated doses (steady state)</b>					
C <sub>max,ss</sub> , ng/mL	76.2 ± 31.0	118 ± 33.1	138 ± 64.6	160 ± 61.0	162 ± 42.2
AUC <sub>τ</sub> , ng.h/mL	324 ± 143	494 ± 123	567 ± 199	675 ± 225	737 ± 166
t <sub>max</sub> , h	2.95 (1.93-3.98)	2.95 (0.88-5.98)	2.08 (0.92-3.97)	2.03 (0.98-6.00)	2.00 (1.42-3.13)
t <sub>1/2</sub> , h	3.9 ± 0.4	4.4 ± 0.6	4.0 ± 0.3	4.2 ± 0.7	4.0 ± 0.4
DN-C <sub>max,ss</sub> , ng/mL	102 ± 41.3	118 ± 33.1	110 ± 51.7	107 ± 40.7	92.6 ± 24.1
DN-AUC <sub>τ</sub> , ng.h/mL	432 ± 191	494 ± 123	454 ± 159	450 ± 150	421 ± 94.9
DN-C <sub>max,ss</sub> ratio (90% CI)	reference	118.11 (91.68-152.14)	105.00 (87.14-126.52)	104.36 (80.61-135.09)	88.63 (72.90-107.75)
DN-AUC <sub>τ</sub> ratio (90% CI)	reference	118.94 (94.53-149.66)	108.05 (91.38-127.75)	111.28 (88.05-140.64)	103.01 (86.43-122.77)

<sup>a</sup> Administered as a combination of 25, 50 and 100 mg capsules (batches PD1428, PD1471 and PD1470).  
Data expressed as mean ± SD, except for t<sub>max</sub> median (range).  
DN=dose normalized to 100 mg (post-hoc analysis; in the study report dose-normalization to 75 mg was used);  
τ=dosing interval (6 hours).

CG5503: Clinical Study Report R331333-PAI-1005 (HP5503/13)

**Table 8:** Mean (+/-SD) CG5503 Base Serum Pharmacokinetic Parameters After The First Dose Administration of CG5503 IR  
(Study R331333-PAI-1005; HP5503/13; Pharmacokinetic Dataset)

Parameter (units)	87 (mg) (N=10)	116 (mg) (N=12)	145 (mg) (N=11)	174 (mg) (N=11)	203 (mg) (N=10)
C <sub>max</sub> (ng/mL)	72.7(36.3)	95.1 (21.3)	124 (40.7)	135 (45.0)	125 (37.3)
t <sub>max</sub> (h)	1.50 (0.52-3.00)	1.75 (1.00-4.00)	1.50 (0.50-5.95)	1.50 (1.00-3.00)	2.00 (0.50-3.00)
AUC <sub>0-6h</sub> (h*ng/mL)	229 (90.3)	299 (87.5)	413 (132)	439 (121)	446 (126)
<b>Dose normalized to 87 mg</b>					
C <sub>max</sub> (ng/mL)	72.7 (36.3)	71.3 (16.0)	74.4 (24.4)	67.5 (22.5)	53.5 (16.0)
AUC <sub>0-6h</sub> (h*ng/mL)	229 (90.3)	224 (65.6)	248 (79.5)	220 (60.6)	191 (53.9)

t<sub>max</sub>: median (min-max)Cross-reference: [Attachment 2.3](#) and [Attachment 2.5](#).

Steady state was reached on Day 2, after the third to fourth dose of CG5503 IR ([Table 9](#)) Multiple-dose pharmacokinetic parameters were estimated following the last dose of CG5503 IR on Day 2 (i.e., the 30-hour dose).

**Table 9:** Mean (+/-SD) CG5503 Base Serum Pharmacokinetic Parameters After Multiple-Dose Administration of CG5503 IR  
(Study R331333-PAI-1005; HP5503/13; Pharmacokinetic Dataset)

Parameter (units)	87 (mg) (N=10)	116 (mg) (N=10)	145 (mg) (N=10)	174 (mg) (N=9)	203 (mg) (N=9)
C <sub>max</sub> (ng/mL)	76.2 (31.0)	118 (33.1)	138 (64.6)	160 (61.0)	162 (42.2)
t <sub>max</sub> (h)	2.95 (1.93-3.98)	2.95 (0.88-5.98)	2.08 (0.92-3.97)	2.03 (0.98-6.00)	2.00 (1.42-3.13)
AUC <sub>0-6h</sub> (h*ng/mL)	324 (143)	494 (123)	567 (199)	675 (225)	737 (166)
AUC <sub>last</sub> (h*ng/mL)	539 (259)	838 (222)	928 (295)	1130 (388)	1268 (393)
t <sub>1/2</sub> (h)	3.9 (0.4)	4.4 (0.6)	4.0 (0.3)	4.2 (0.7)	4.0 (0.4)
<b>Dose normalized to 87 mg</b>					
C <sub>max</sub> (ng/mL)	76.2 (31.0)	88.6 (24.8)	82.9 (38.7)	79.8 (30.5)	69.6 (18.1)
AUC <sub>0-6h</sub> (h*ng/mL)	324 (143)	370 (92.3)	340 (119)	338 (113)	316 (71.1)
AUC <sub>last</sub> (h*ng/mL)	539 (259)	629 (167)	557 (177)	565 (194)	543 (168)

t<sub>max</sub>: median (min-max)Cross-reference: [Attachment 2.3](#) and [Attachment 2.5](#).

CG5503: Clinical Study Report R331333-PAI-1005 (HP5503/13)

**Table 10:** Mean (+/-SD) CG5503-O-Glucuronide Serum Pharmacokinetic Parameters After Single-Dose Administration of CG5503 IR  
(Study R331333-PAI-1005; HP5503/13: Pharmacokinetic Dataset)

Parameter (units)	87 (mg) (N=10)	116 (mg) (N=12)	145 (mg) (N=11)	174 (mg) (N=11)	203 (mg) (N=10)
C <sub>max</sub> (ng/mL)	2566 (691)	3104 (868)	3872 (1211)	5212 (1704)	5326 (1567)
t <sub>max</sub> (h)	3.00 (1.00-4.00)	3.00 (1.00-4.00)	3.00 (1.00-5.95)	3.00 (1.00-4.00)	2.50 (1.00-4.00)
AUC <sub>0-6h</sub> (h*ng/mL)	8575 (1249)	10834 (2999)	13619 (4127)	18630 (7028)	18879 (5231)
<b>Dose normalized to 87 mg</b>					
C <sub>max</sub> (ng/mL)	2566 (691)	2328 (651)	2323 (726)	2606 (852)	2283 (672)
AUC <sub>0-6h</sub> (h*ng/mL)	8575 (1249)	8125 (2249)	8172 (2476)	9315 (3514)	8091 (2242)

Cross-reference: [Attachment 2.4](#) and [Attachment 2.6](#)

**Table 11:** Mean (+/-SD) CG5503-O-Glucuronide Serum Pharmacokinetic Parameters After Multiple-Dose Administration of CG5503 IR  
(Study R331333-PAI-1005; HP5503/13: Pharmacokinetic Dataset)

Parameter (units)	87 (mg) (N=10)	116 (mg) (N=10)	145 (mg) (N=10)	174 (mg) (N=9)	203 (mg) (N=9)
C <sub>max</sub> (ng/mL)	3593 (816)	4879 (1003)	5634 (1996)	6667 (1404)	7444 (1994)
t <sub>max</sub> (h)	2.98 (1.93-4.00)	2.99 (1.38-5.98)	2.57 (1.00-4.00)	2.98 (1.53-6.00)	2.92 (1.42-4.00)
AUC <sub>0-6h</sub> (h*ng/mL)	14392 (2960)	21688 (4273)	24189 (9607)	30234 (5738)	34504 (10558)
AUC <sub>last</sub> (h*ng/mL)	22913 (5751)	35984 (5984)	37338 (14618)	50332 (10408)	57254 (21747)
t <sub>1/2</sub> (h)	3.7 (0.2)	4.0 (0.4)	3.9 (0.4)	3.9 (0.6)	3.9 (0.3)
<b>Dose normalized to 87 mg</b>					
C <sub>max</sub> (ng/mL)	3593 (816)	3659 (752)	3380 (1198)	3333 (702)	3190 (854)
AUC <sub>0-6h</sub> (h*ng/mL)	14392 (2960)	16266 (3205)	14513 (5764)	15117 (2869)	14788 (4525)
AUC <sub>last</sub> (h*ng/mL)	22913 (5751)	26988 (4488)	22403 (8771)	25166 (5204)	24537 (9320)

Cross-reference: [Attachment 2.4](#) and [Attachment 2.6](#)

**Table: Summary on exposure to CG5503 base in rats after repeated oral doses (mean values on day 1 and in weeks 4, 13, 26)**

Dose	[mg/kg]	Males				Females			
		75	150	300	450†	75	150	300	450†
<b>On day 1</b>									
C <sub>max</sub>	[µg/L] ±	65	250	623	453	45	167	166	789
	Stand Dev	± 55	± 155	± 447	± 350	± 9	± 59	± 34	± 322
AUC <sub>0-3h</sub>	[µg·h/L] ±	77	255	445	679	79	249	302	1067
	Stand Dev	± 19	± 91	± 161	± 291	± 13	± 41	± 53	± 520
<b>Week 4</b>									
C <sub>max</sub>	[µg/L] ±	117	311	961	411	237	295	507	2934
	Stand Dev	± 32	± 374	± 1308	± 132	± 24	± 56	± 118	± 1632
AUC <sub>0-3h</sub>	[µg·h/L] ±	176	233	434	541	407	398	1075	1986
	Stand Dev	± 52	± 147	± 408	± 182	± 71	± 75	± 201	± 660
<b>Week 13</b>									
C <sub>max</sub>	[µg/L] ±	314	429	1312	1250	558	656	695	848
	Stand Dev	± 18	± 59	± 398	± 1216	± 492	± 204	± 128	± 302
AUC <sub>0-3h</sub>	[µg·h/L] ±	396	375	874	1236	542	844	1032	1530
	Stand Dev	± 223	± 26	± 150	± 764	± 295	± 370	± 268	± 660
<b>Week 26</b>									
C <sub>max</sub>	[µg/L] ±	252	507	1451	nd	520	451	912	nd
	Stand Dev	± 113	± 173	± 8		± 422	± 129	± 1072	
AUC <sub>0-t</sub>	[µg·h/L] ±	391	1060	1987	nd	857	1461	3088	nd
	Stand Dev	± 229	± 366	± 779		± 480	± 432	± 1482	

† = All surviving animals were sacrificed after week 13 due to high mortality.

nd = No data.

**Summary on exposure with CG5503 base in rats after repeated oral doses  
(mean values  $C_{max}$  and  $AUC_{(0-24h)} \pm S.D.$  on days 1 and week 13)**

Dose	[mg/kg/day]	Males			Females		
		60	200	400	60	200	400
Day 1							
AUC	[ng·h/ml]	300 ± 79	1 031 ± 282	4 042 ± 772	289 ± 250	1 307 ± 315	4 854 ± 548
$C_{max}$	[ng/ml]	91 ± 58	301 ± 237	1 281 ± 726	156 ± 136	479 ± 55	1 094 ± 910
Week 13							
AUC	[ng·h/ml]	1 034 ± 528	2 254 ± 106	4 828 ± 1 559	979 ± 382	4 222 ± 226	11 829 ± 2 649
$C_{max}$	[ng/ml]	414 ± 225	758 ± 580	1 244 ± 447	425 ± 232	1 409 ± 145	3 733 ± 1515
$R_{A1}$	[%]	455	252	97	272	294	341
$R_{A3}$	[%]	345	219	119	339	323	244

$R_{A1}$  = ratio of  $C_{max}$  from week 13 to Day 1

$R_{A3}$  = ratio of AUC from week 13 to Day 1

All dosed animals were exposed systemically to CG5503 glucuronide. The exposure to the major metabolite of CG5503, evaluated by  $C_{max}$  and  $AUC_{0-24h}$ , increased linearly with the dose.

**Summary on exposure with CG5503 glucuronide in rats after repeated oral doses  
(mean values  $C_{max}$  and  $AUC_{(0-24h)} \pm S.D.$  on days 1 and week 13)**

Dose	[mg/kg/day]	Males			Females		
		60	200	400	60	200	400
Day 1							
AUC	[ng·h/ml]	90 619 ± 4 709	278 583 ± 45 219	477 399 ± 39 702	94 824 ± 29 234	295 804 ± 32 496	580 852 ± 52 186
$C_{max}$	[ng/ml]	15 329 ± 3 766	26 886 ± 4 447	44 490 ± 10 534	16 848 ± 1 382	35 068 ± 2 952	45 668 ± 11 357
Week 13							
AUC	[ng·h/ml]	106 521 ± 13 153	379 666 ± 62 164	591 322 ± 152 806	144 527 ± 16 825	407 202 ± 33 817	719 230 ± 132 981
$C_{max}$	[ng/ml]	15 911 ± 2 890	33 938 ± 6 402	48 064 ± 5 076	22 853 ± 1 574	47 181 ± 9 639	72 112 ± 14 807
$R_{A1}$	[%]	104	126	108	136	135	158
$R_{A3}$	[%]	118	136	124	152	138	124

$R_{A1}$  = ratio of  $C_{max}$  from week 13 to Day 1

$R_{A3}$  = ratio of AUC from week 13 to Day 1



### Toxicokinetics

All animals were exposed systemically to CG5503. The drug exposure, evaluated by  $C_{max}$  and  $AUC_{0-t}$ , increased superproportionally with the dose. The toxicokinetic study is valid in describing the exposure to the drug since all of the dosed animals were investigated.

The mean exposure data are listed in the following table:

**Table A: Mean  $C_{max}$  and  $AUC_{0-t}$  values of CG5503 base**

Dose CG5503 [mg/kg]	Time [h]	$C_{max} \pm S.D.$ [ng/ml]	$C_{max} \pm S.D.$ [ng/ml]	$AUC_{0-t} \pm S.D.$ [h·ng/ml]	$AUC_{0-t} \pm S.D.$ [h·ng/ml]
		male	female	male	female
10	day 1	13.7 ± 12.6	10.1 ± 3.22	30.9 ± 16.7	17.5 ± 3.85
	day 91	4.19 ± 1.19	4.42 ± 1.34	18.9 ± 3.31	17.1 ± 2.98
35	day 1	26.9 ± 13.6	43.4 ± 11.0	64.9 ± 22.9	86.6 ± 7.25
	day 91	37.1 ± 19.1	40.5 ± 11.1	101 ± 14.2	110 ± 42.3
120/80 <sup>1)</sup>	day 1	701 ± 1192	245 ± 205	846 ± 1089	513 ± 253
	day 91	316 ± 382	338 ± 534	491 ± 447	511 ± 469

1) The dose had to be reduced from 120 mg/kg to 80 mg/kg starting with day 22

**Table: Summary on exposure to CG5503-base in dogs after repeated oral doses on Day 1 and in Weeks 26, 39 and 52**(mean values  $\pm$  standard deviation (S.D.))

Dose	[mg/kg]	Males			Females		
		10	30	80	10	30	80
<b>Day 1</b>							
$C_{max}$	[ $\mu\text{g/L}$ ]	5.9	22.8	106	8.8	19.6	340
S.D.		$\pm 3.9$	$\pm 10.7$	$\pm 90.7$	$\pm 6.5$	$\pm 6.25$	$\pm 549$
$AUC_{0-t}$	[ $\mu\text{g}\cdot\text{h/L}$ ]	13.1	66.6	428	16.4	46.5	417
S.D.		$\pm 3.3$	$\pm 25.2$	$\pm 480$	$\pm 6.4$	$\pm 17.3$	$\pm 513$
<b>Week 26</b>							
$C_{max}$	[ $\mu\text{g/L}$ ]	3.9	32.1	85.3	4.9	50.1	92.6
S.D.		$\pm 2.9$	$\pm 25.1$	$\pm 31.9$	$\pm 1.2$	$\pm 37.8$	$\pm 52.0$
$AUC_{0-t}$	[ $\mu\text{g}\cdot\text{h/L}$ ]	20.1	74.2	235	18.1	76.8	212
S.D.		$\pm 3.6$	$\pm 20.4$	$\pm 42.8$	$\pm 1.4$	$\pm 27.5$	$\pm 75.0$
<b>Week 39</b>							
$C_{max}$	[ $\mu\text{g/L}$ ]	6.0	16.1	272	6.5	36.6	359
S.D.		$\pm 2.9$	$\pm 3.4$	$\pm 287$	$\pm 2.2$	$\pm 39.7$	$\pm 238$
$AUC_{0-t}$	[ $\mu\text{g}\cdot\text{h/L}$ ]	19.9	65.8	509	17.7	64.1	543
S.D.		$\pm 6.3$	$\pm 17.9$	$\pm 359$	$\pm 5.8$	$\pm 43.9$	$\pm 315$
<b>Week 52</b>							
$C_{max}$	[ $\mu\text{g/L}$ ]	6.8	49.0	145	6.3	31.4	221
S.D.		$\pm 6.4$	$\pm 35.8$	$\pm 129$	$\pm 2.4$	$\pm 15.3$	$\pm 255$
$AUC_{0-t}$	[ $\mu\text{g}\cdot\text{h/L}$ ]	23.3	142	303	16.6	61.2	407
S.D.		$\pm 8.7$	$\pm 74.6$	$\pm 103$	$\pm 5.5$	$\pm 22.9$	$\pm 360$

**Table: Summary on exposure to CG5503-glucuronide in dogs after repeated oral doses in Weeks 26 and 52**(mean values  $\pm$  standard deviation (S.D.))

Dose	[mg/kg]	Males			Females		
		10	30	80	10	30	80
<b>Week 26</b>							
$C_{max}$	[ $\mu\text{g/L}$ ]	8141	20937	47993	6895	19699	31737
S.D.		$\pm 2102$	$\pm 3870$	$\pm 8201$	$\pm 2433$	$\pm 5772$	$\pm 13836$
$AUC_{0-t}$	[ $\mu\text{g}\cdot\text{h/L}$ ]	33074	76229	231252	22908	65076	150289
S.D.		$\pm 7880$	$\pm 6710$	$\pm 30616$	$\pm 6805$	$\pm 15891$	$\pm 57276$
<b>Week 52</b>							
$C_{max}$	[ $\mu\text{g/L}$ ]	8522	23363	48027	6604	28643	46821
S.D.		$\pm 1808$	$\pm 6650$	$\pm 7380$	$\pm 2433$	$\pm 9415$	$\pm 21362$
$AUC_{0-t}$	[ $\mu\text{g}\cdot\text{h/L}$ ]	32044	88313	224693	24138	84304	231142
S.D.		$\pm 8146$	$\pm 18485$	$\pm 38779$	$\pm 7936$	$\pm 22197$	$\pm 100293$

H1 Armaghan,

(b) (4)



Some single dose information from the IR NDA:

Parameter	n	Mean ± SD	%CV
t <sub>max</sub> , h	631	1.25 (0.50-6.27)*	
C <sub>max</sub> , ng/mL	631	90.1 ± 36.2	39
AUC <sub>∞</sub> , ng.h/mL	576	417 ± 143	34
t <sub>1/2</sub> , h	576	4.3 ± 0.8	16
CL <sub>R</sub> , mL/min	78	99.0 ± 37.3	38

Data expressed as mean ± SD, except for t<sub>max</sub> where median (range) is provided; n: number of observations.

\* more than 90% of observations was below or equal to 3 hrs.

Cross-reference: post-hoc analysis, data on file

n=24	64 mg (3*21.5 mg)	86 mg (4*21.5 mg)	129 mg (6*21.5 mg)	172 mg (8*21.5 mg)
C <sub>max</sub> , ng/mL	58.6 ± 23.8 [40.6]	95.7 ± 31.5 [32.9]	144 ± 72.7 [50.5]	213 ± 91.2 [42.9]
AUC <sub>last</sub> , ng.h/mL	235 ± 83.9 [35.7]	371 ± 92.2 [24.9]	560 ± 148 [26.4]	873 ± 300 [34.3]
AUC <sub>∞</sub> , ng.h/mL	238 ± 84.2 [35.4]	373 ± 92.0 [24.6]	563 ± 148 [26.4]	878 ± 301 [34.2]
t <sub>max</sub> , h	1.00 (0.75-3.00)	1.00 (0.68-1.50)	1.00 (0.50-3.00)	0.88 (0.50-1.50)
t <sub>1/2</sub> , h	5.22 ± 1.02 [19.6]	5.07 ± 1.05 [20.7]	4.68 ± 0.58 [12.5]	4.75 ± 0.64 [13.5]
DN C <sub>max</sub> , ng/mL	91.5 ± 37.1 [40.6]	111 ± 36.6 [32.9]	112 ± 56.4 [50.5]	124 ± 53.0 [42.9]
DN AUC <sub>last</sub> , ng.h/mL	368 ± 131 [35.7]	431 ± 107 [24.9]	434 ± 115 [26.4]	508 ± 174 [34.3]
DN AUC <sub>∞</sub> , ng.h/mL	372 ± 132 [35.4]	434 ± 107 [24.6]	437 ± 115 [26.4]	511 ± 175 [34.2]

**Dose-normalized (to 86 mg) ratio of 64-, 129- and 172-mg dose vs. 86-mg dose (%) (90% CI)**

AUC <sub>∞</sub> (n=16)*	84.5 (77.2-92.6)	-	104.1 (98.4-110.2)	108.7 (100.6-117.6)
C <sub>max</sub> (n=16)*	80.4 (68.6-94.1)	-	95.6 (81.9-111.5)	97.8 (84.5-113.1)
t <sub>1/2</sub> (n=16)*	102.7 (88.6-119.0)	-	95.2 (89.6-101.8)	90.3 (84.8-96.1)

\* Only subjects receiving active drug in both treatments.

Data expressed as mean ± SD [%CV], except for t<sub>max</sub> median (range). DN=dose-normalized to 100 mg.

	80 mg IR Tablet (PD1707) (n=30)	80 mg IR Capsule (PD1549) (n=30)	Tablet/Capsule Ratio, % (90% CI) (n=30)
C <sub>max</sub> , ng/mL	76.6 ± 22.5	82.4 ± 25.6	93.77 (85.58 – 102.73)
AUC <sub>last</sub> , ng.h/mL	322 ± 84.1	345 ± 107	94.48 (89.78 – 99.43)
AUC <sub>∞</sub> , ng.h/mL	326 ± 85.0	349 ± 108	94.41 (89.73 – 99.34)
t <sub>max</sub> , h	1.00 (0.50 – 4.00)	1.00 (0.50 – 2.02)	
t <sub>1/2</sub> , h	4.0 ± 0.5	4.0 ± 0.5	

Data expressed as mean ± SD, except t<sub>max</sub>: median (range).

	100 mg IR Tablet Fed (PD2213) (n=35)	100 mg IR Tablet Fasted (PD2213) (n=34)	Fed/Fasted Ratio, % (90% CI) (n=34)
C <sub>max</sub> , ng/mL	83.4 ± 28.1 [33.7]	72.8 ± 30.8 [42.4]	115.99 (107.65 - 124.99)
AUC <sub>last</sub> , ng.h/mL	525 ± 154 [29.2]	421 ± 151 [36.0]	125.18 (119.24 - 131.42)
AUC <sub>∞</sub> , ng.h/mL	536 ± 157 [29.3]	429 ± 154 [35.9]	125.18 (119.26 - 131.40)
t <sub>max</sub> , h	3.00 (1.02 – 6.00)	1.50 (1.00 – 4.00)	
t <sub>1/2</sub> , h	3.9 ± 0.4 [10.6]	4.2 ± 0.4 [10.2]	

Data expressed as mean ± SD [%CV], except for t<sub>max</sub> median(range).

**Appendix 4**



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

**Supervisory Pharmacologist Memorandum (#3)**

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

1 page has been Withheld in Full immediately following this page as a duplicate copy of another review for NDA 22304 which can be found at [www.fda.gov](http://www.fda.gov)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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

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/s/

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ARMAGHAN EMAMI  
08/06/2010

ADAM M WASSERMAN  
08/06/2010

While I agree with Dr. Emami the nonclinical data do not support human exposures at the maximum recommended dose I believe the application may be approved. Please see my Supervisory Memo for this NDA.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

**NDA/BLA Number: 200533    Applicant: Johnson & Johnson    Stamp Date: 30 November  
Pharmaceutical Research &    2009  
Development, L.L.C.**

**Drug Name: NUCYNTA™ ER NDA/BLA Type: 505(b)(1)  
(Tapentadol ER)**

On initial overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not Applicable (NA; no nonclinical data required or submitted)
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			NA
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			NA
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Reference NDA 22-304 and IND 61,345
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			NA

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			NA
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?	X		NA
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?**     Yes    

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Kathleen Young, Ph.D.

January 1, 2010

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Reviewing Pharmacologist

Date

Adam Wasserman, Ph.D.

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Team Leader/Supervisor

Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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

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/s/

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KATHLEEN A YOUNG  
03/11/2010

ADAM M WASSERMAN  
03/11/2010